Managing Myositis

A Practical Guide

Rohit Aggarwal
Chester V. Oddis
Editors

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Foreword

Myositis Through the Ages

In this brief essay on the history of myositis, I cannot cover all the descriptions of illnesses that might possibly have been myositis, but such cases can be found in a number of longer and fuller historical reviews. The first myositis case descriptions of the modern era included a paper in 1863 by E. Wagner entitled "Fall einer setten Muskel Krankeit" [Wagner], followed by papers published in the late 1880s by H. Unverricht on "Polymyositis acuta progressiva" and "Dermatomyositis acuta" [Unverricht]. These papers provide the first description of dermatomyositis and its distinction from polymyositis. Indeed, dermatomyositis was often called "Unverricht's disease" until late in the nineteenth century.

In 1903, a young physician from Johns Hopkins, Walter Ralph Steiner, beautifully described a case of dermatomyositis – the first full description in English – which was published as a single-authored paper in an early issue of *The Journal of Experimental Medicine* [Steiner]. Eat your heart out, all you young physicians out there who read this long, lovely paper. It is an example of descriptive medicine at its best and might serve as a guide to all those learning the art of case reports. Steiner's later career was as a bibliophile and autograph collector whose collection is now part of the National Library of Medicine.

In 1916, G. Stertz and H. Kankeleit independently noted the association of myositis and malignancy, thus opening a fascinating and clinically challenging problem for practicing physicians, beautifully summarized recently [Tiniakou and Mammen].

In 1958, John Walton from England and Raymond Adams from Boston, both distinguished neurologists, wrote a monograph called *Polymyositis* that put myositis solidly on the map [Walton and Adams]. It was Copernican in influence. My own copy appears to have been "borrowed" decades ago from the small library in the young National Institute of Arthritis and Musculoskeletal and Skin Diseases, probably when I was a fellow in the 1960s. A quotation from their monograph foreshadows some progress in classification while at the same time illuminating the enigmatic cause of myositis that remains to this day: "In a syndrome such as polymyositis, the pleomorphism of the clinical picture, the inadequacy of present knowledge with regard to aetiology, and the lack of uniformity and specificity of the pathological findings make

any attempt at classification of cases into neatly circumscribed groups a matter of considerable difficulty" (page 27).

The first important therapeutic advance of the modern era that stuck occurred in 1968 when a young Indian rheumatologist, Anand Malaviya, came as a fellow to Robert Schwartz's group at the New England Medical Center. They found that methotrexate was an effective treatment for dermatomyositis [Malaviya, Many, and Schwartz], and it remains a mainstay of treatment almost half a century later. It is instructive to recall that the first use of this family of drugs in rheumatologic disease occurred in 1951 when Richard Gubner and colleagues at the Long Island College of Medicine in Brooklyn published a paper in *The American Journal of the Medical Sciences* demonstrating the efficacy of aminopterin (an anti-folate drug similar to methotrexate) in rheumatoid arthritis – a discovery that was rapidly and almost completely forgotten following the discovery of the efficacy of cortisone in the suppression of inflammation in rheumatoid arthritis [Gubner, August, and Ginsberg]. In the last half century, new drugs and safer versions of old drugs have found a reasonably stable place in the treatment of dermatomyositis and polymyositis.

An important step forward was the publication by Bohan and Peter in 1977 in *Medicine* of a large group of myositis patients who had been carefully studied over many years and the first classification of polymyositis and dermatomyositis, a pioneering and very useful paper [Bohan]. They classified polymyositis as having three or four of the classic features of myositis – proximal, symmetric weakness; a myopathic EMG; elevation of the creatine kinase; and inflammation on a muscle biopsy. Dermatomyositis required four or five of the above features including the pathognomonic DM rash of "Gottron" papules or a heliotrope rash. Over the ensuing decades, there have been modifications of the Bohan and Peter scheme, but it has served as the skeleton of essentially all of the later clinical and pathological groupings.

In the early 1980s, papers by immunologists and neuroimmunologists focused on applying new immunologic methods to muscle inflammation. In 1983, Michael Mathews, a distinguished English biochemist (and the brother of a rheumatologist), and Robert Bernstein (a rheumatology fellow), following leads provided by Nishiki, Reichlin, Lerner, and Steitz, identified a myositis-related serum immunoglobulin protein as an autoantibody directed at an enzyme in the pathway of protein synthesis, histidyl-tRNA synthetase [Mathews and Bernstein]. They called the autoantibody anti-Jo-1 after the myositis patient first found to have it. It has remained one of the best-studied autoantibodies – studies that led to a number of sturdy insights into the origins and pathogenic place of autoantibodies in rheumatologic disease, including clear proof that the anti-Jo-1 autoantibodies could be found before the onset of clinical myositis, several years before similar observations were made in lupus and rheumatoid arthritis.

Following leads from Nishiki, Reichlin, Targoff, and Arnett (all rheumatologists), Lori Love and Fred Miller and their colleagues at NIH in 1991 developed a robust and useful classification of clinical myositis based on autoantibodies. They studied four known myositis autoantibodies at that time: anti-aminoacyl-tRNA synthetases, anti-SRP, anti-Mi-2, and

anti-MAS. The patient groups which were defined by autoantibodies were found also to be divided by clinical symptoms, organ involvement, response to therapy, prognosis, genetic markers, and, very likely, pathogenesis [Love et al].

A significant step forward in diagnosis and disease assessment in myositis was made in 1991 by the NIH group who introduced the use of magnetic resonance imaging (MRI) to find the site and extent of abnormalities such as inflammation, fatty infiltration, and calcification in the skin and muscle [Fraser et al].

In 2001, a group of neurologists in Israel under Zohar Argov found the first mutation in a group of cases of hereditary inclusion body myositis (h-IBM) in Iranian Jews, whose clinical disease spared the quadriceps, had slowly progressive distal and proximal weakness, and a typical muscle pathology including rimmed vacuoles and filamentous inclusions [Eisenberg et al]. The patients were found to have mutations in the gene for UDP-N-acetylglucosamine 2-epimerase/N-acetylmannosamine kinase, and there are ongoing attempts to develop small molecules to heal the effects of the mutation in that protein. This was the first but almost certainly not the last mutation that will be found in IBM since the clinical disease in IBM is actually quite varied.

In the last two decades, there have been studies of gene expression in myositis by Arnett, Hoffman, Greenberg, and Amato, among others; a number of intriguing new autoantibodies (e.g., anti-SAE, anti-MDA5, and anti-TIF1-γ) have been described and linked to interesting clinical syndromes.

There have been several fruitful if imperfect disease models [Katsumata and Ascherman], particularly mice transgenic for MHC Class I developed at NIH [Nagaraju et al], yet a coherent model of pathogenesis of the human disease has not emerged so far, and a “top cytokine” or a “biomarker” has not been identified.

It seems to me that the creation of international groups of physicians and related scientists dedicated to cooperative clinical studies – e.g., PRINTO, IMACS, and MYOGEN – is of major importance. They have led to a welcome standardization of disease description, outcome criteria, and at least some “big enough” treatment trials. Most heartening to me is the growing cooperation between rheumatologists, neurologists, and dermatologists who now work together on myositis and related diseases that we share. Some noted examples of recent advancement in myositis include development of definitions of improvement by IMACS and PRINTO by Rider and Ruperto (Rider 2004), respectively, and two large international, randomized controlled clinical trials. One (Oddis et al. 2013) assessed the efficacy of rituximab in 200 adult and juvenile myositis patients, while another (n = 150 JDM patients) encompassed 54 centers (Ruperto et al. 2016). There are now new data-driven international classification criteria for myositis (Lundberg 2016), revised international myositis response criteria based on a data and consensus-driven process involving rheumatologists, neurologists, and dermatologists (Aggarwal et al. 2016) and the discovery of the antibody against 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) in patients with immune-mediated statin-associated myopathies (Mammen et al. 2011).

Finally, I trust that we will continue to attract new investigators from around the world with new perspectives in areas such as contemporary genetics, definitions of environmental triggers, and new ways of suppressing our diseases.

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Preface

The idiopathic inflammatory myopathies (IIM) are a group of rare, autoimmune, systemic, and highly complex diseases which significantly impact the quality of life and survival of affected patients. The management of myositis is best done by a multidisciplinary team, including, but not limited to, an internist, rheumatologist, neurologist, pulmonologist, dermatologist, physical therapist, occupational therapist, physician assistant, and nurse practitioner as well as trained nurses. This book is written for all such healthcare professionals who wish to gain a practical understanding and knowledge on the optimal management of the many challenging features of myositis. It is also meant to guide medical students, residents, fellows, and other trainees seeking advice in treating myositis patients.

More specifically, this is a practical guide on the day-to-day diagnosis, management, and prognosis of myositis patients, primarily focusing on polymyositis (PM), necrotizing myopathy (NM), and dermatomyositis (DM) but also including juvenile dermatomyositis, cancer-associated myositis, connective tissue disease-associated myopathy, and inclusion body myositis.

Our intent is to present concepts in a straightforward fashion in order to facilitate the assimilation of information for experienced practitioners as well as those lacking prior knowledge of the many manifestations of the IIM. We have emphasized basic concepts and the application of practical information to prevent diagnostic blunders and therapeutic missteps. Further, we hope that the images, figures, tables, algorithms, and flowcharts throughout the book aid in this regard.

Our overarching purpose in writing this practical guide was spawned by the many questions myositis experts receive and the recognition that our medical training and textbooks often lack a practical and unified approach to myositis. We hope this textbook provides an easy-to-read, "one-stop shop" in the care of myositis patients, realizing that most patients receive their care from community clinicians and health professionals rather than myositis experts. It is imperative for those of us with experience and knowledge of IIM to disseminate and train the next generation of clinicians and health professionals.

We are indebted to our myositis patients as well as our students and trainees, who have immensely contributed to our current knowledge and understanding of the disease, motivating and challenging us to better manage all aspects of this enigmatic disorder.

Most of the contributing authors in this book are international myositis experts who have decades of teaching and clinical experience, and we are indebted to them for their efforts in the compilation of this book.

Finally, we gratefully acknowledge the support, encouragement, and patience of our spouses and family members as this task could never have been completed without them.

Thank you for reading this book. We welcome your comments and feedback including suggestions for any future myositis publications and would be pleased to receive them by email at aggarwalr@upmc.edu.

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Introduction to Myositis

1

Adam Schiffenbauer and Frederick W. Miller

Key Points to Remember

- Myositis is a myopathy where chronic inflammation is the prominent feature.
- The idiopathic inflammatory myopathies (IIM) are a family of disorders, thought to be autoimmune in nature, that share chronic inflammation of muscle of unknown cause and often involve other organ systems.
- One of the earliest and most widely used criteria for classifying the IIM has been the Bohan and Peter criteria, but newer ACR-EULAR criteria exist now.
- The IIM have been further classified based on clinical presentation into more homogenous subsets of disease.
- The IIM have also been subdivided into more homogenous phenotypes based on the presence of specific autoantibodies associated with IIM.

Introduction

What Is Myositis?

Patients are considered to have myopathy if they have any form of the many types of muscle diseases, ranging from vascular muscle insufficiency to muscle dystrophies to various other neuromuscular disorders and to inflammatory conditions. When muscle inflammation is the prominent feature of a myopathy, however, then the condition is called myositis. Myositis can result from many different processes, including infections; toxins; endocrine, metabolic, or neurologic disorders; inherited deficiencies in mitochondria or the structural proteins of muscle; and trauma. When all those possible causes have been ruled out, the condition can be referred to as one of the idiopathic inflammatory myopathies (IIM). The IIM are a family of disorders that share chronic inflammation of muscle of unknown cause and often involve other organ systems, including the skin, lungs, joints, gastrointestinal tract, or heart. Because of the chronic inflammation in many tissues, frequent autoantibodies, strong associations with human leukocyte antigens, and response to immunosuppressive medications, these diseases are also often referred to as immune-mediated or autoimmune myopathies.

As later chapters further clarify, however, the causes of these diseases remain unclear. Are the causes possibly hidden within the associated

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genes or environmental exposures? Are they in the cytokines and other proinflammatory biomarkers, or in the distinct autoantibodies, or clinical signs and symptoms, or in the pathology seen on biopsies of many tissues, or perhaps in all of them in different combinations? Only further research and understanding will clarify this, allowing new insights into mechanisms, possible novel treatments, and maybe even the prevention of some types of myositis in the future.

Types of Muscle Disorders (Myopathies)

- Inflammatory myopathies.
- Muscular dystrophies.
- Metabolic myopathies.
- Mitochondrial myopathies.
- Toxin- or drug-induced myopathies.
- Hypothyroidism.
- Hyperthyroidism.
- Infectious myopathies.
- Congenitally absent muscles.
- DNA sequence repeat disease.
- Endocrine disorders.
- Mechanical injury.
- Neuroleptic malignant syndrome.
- Electrolyte imbalances.
- Periodic paralysis disorders.

Types of Inflammatory Myopathies (Myositis)

- Idiopathic inflammatory myopathies.
- Complement deficiency.
- Graft versus host disease.
- Focal myositis syndromes.
- Toxin- or drug-induced myositis.
- Eosinophilia myalgia syndrome.
- Hemophagocytic lymphohistiocytosis.
- Infections.
- Myopathy with muscle fiber necrosis and pipestem capillaries.
- Brachio-cervical inflammatory myopathy.
- Paraneoplastic syndromes.
- Sarcoidosis.

- Inflammatory myopathy with abundant macrophages.
- Inflammatory myopathy and mitochondrial pathology.
- Eosinophilic fasciitis.
- Limb-girdle muscular dystrophies.
- Fascioscapulohumeral dystrophy.

Types of Idiopathic Inflammatory Myopathies

- Polymyositis.
- Immune-mediated necrotizing myopathy.
- Dermatomyositis.
- Clinically amyopathic dermatomyositis.
- Juvenile dermatomyositis.
- Juvenile polymyositis.
- Cancer-associated myositis.
- Myositis associated with another connective tissue disease.
- Inclusion body myositis.
- Granulomatous myositis.
- Eosinophilic myositis.
- Vasculitic myositis.
- Orbital or ocular myositis.
- Focal or nodular myositis.
- Myositis ossificans.
- Macrophagic myofasciitis.

Historical Perspective

It is not known how long the IIM have been affecting human health, but they were recognized clinically and documented by publications in the German literature more than a century and a half ago. The initial descriptions of what we now call polymyositis appear to be those of Wagner in 1863 [1] and 1887 [2], with Potain [3] and Hepp [4] describing similar cases at about the same time, and Unverricht [5, 6] identifying dermatomyositis as a distinct entity shortly thereafter. Many of the first papers describing these diseases, however, indiscriminately used the terms *polymyositis* and *dermatomyositis* without regard

to skin involvement, thus confusing the early literature. The first reported myositis cases in the United States were in 1887 and 1888 [7, 8].

The study and understanding of the IIM, as is the case for many other areas of medicine, has been uneven, with different insights occurring by various groups at different times. Critical milestones in the history of myositis include:

1. A careful review of the then-published myositis cases by Steiner in 1903 [9].
2. Recognition that corticosteroid therapy can be useful [10, 11].
3. The classic review on polymyositis that covers many of the clinical features we recognize today by Walton and Adams [12].
4. Identifying the pathology of childhood dermatomyositis [13].
5. Describing methotrexate use in resistant disease [14].
6. The first systematic criteria and classifications of Bohan and colleagues [15, 16].
7. Defining the distinct clinical entity of inclusion body myositis (IBM) [17–19].
8. The finding of different muscle-infiltrating mononuclear cell subsets in polymyositis versus dermatomyositis [20].
9. The discovery that myositis autoantibodies define distinct genetic, clinical, and prognostic subgroups of patients [21].
10. The development of comprehensive and authoritative texts on myology [22, 23].
11. Identification of genetic risk and protective factors for myositis phenotypes by focused gene [24] and genome-wide approaches [25].
12. The initial understanding of environmental risk factors [26].
13. Careful descriptions of myositis gene expression profiles in different phenotypes [27, 28].
14. International consensus guidelines on clinical trials [29].
15. ACR-EULAR consensus criteria for clinical responses for juvenile [30] and adult [31] myositis.
16. EULAR-ACR classification criteria of idiopathic inflammatory myopathies [46] and [Lundberg IE, Tjärnlund A, Bottai M, Werth VP, Pilkington C, de Visser M, Alfredsson L, Amato AA, Barohn RJ, Liang MH, Singh JA, Aggarwal R, Arnardottir S, Chinoy H, Cooper RG, Dankó K, Dimachkie MM, Feldman BM, Garcia-De La Torre I, Gordon P, Hayashi T, Katz JD, Kohsaka H, Lachenbruch PA, Lang BA, Li Y, Oddis CV, Reed AM, Rutkowska-Sak L, Sanner H, Selva-O'Callaghan A, Song YW, Swierkocka K, Vencovsky J, Ytterberg SR, Miller FW, Rider LG; the International Myositis Classification Criteria Project consortium, the Euromyositis Register, and the Juvenile Dermatomyositis Cohort Biomarker Study and Repository (JDRG) (United Kingdom and Ireland). EULAR/ACR Classification Criteria for Adult and Juvenile Idiopathic Inflammatory Myopathies and their Major Subgroups. Ann Rheum Dis, in press].

Of course, there have been many extensions of those studies that have further refined these findings and often emphasized how these many myositis features differ in various phenotypes, which is an ongoing area of discovery and debate. Hopefully, the many international and multidisciplinary collaborations that have initiated an ongoing emphasis on standardization in the assessment and reporting of myositis and the development of registries and linked biorepositories will allow for much more rapid progress in these areas [32].

The Classification of Myositis

The IIM have been classified in many ways during the time that they have been appreciated. One of the earliest and most widely used set of criteria were developed by Bohan and Peter in 1975 [15]. These criteria defined dermatomyositis and polymyositis by first ensuring that there is no other cause of muscle inflammation and then classifying myositis based on the following criteria: symmetric proximal muscle weakness, a muscle biopsy showing classic findings of myositis, elevated muscle enzymes, electromyography (EMG) with classic findings (short, small, low-amplitude polyphasic motor unit potentials,

fibrillation potentials, even at rest, and bizarre high-frequency repetitive discharges), and the characteristic rashes of dermatomyositis (heliotrope rash, Gottron sign, or Gottron papules). Definite disease is defined as having four of the criteria; probable disease is defined as having three of the criteria; possible disease is defined as having two of the criteria; and if one of the criteria is the characteristic rashes of dermatomyositis, the patient is considered to have dermatomyositis. If the patient does not have these rashes, she/he is considered to have polymyositis.

Those criteria have been refined based on the addition of other phenotypes. The age at disease onset, with the division usually at age 16 or 18 years, categorizes these diseases as either the juvenile-onset or adult-onset form of the disease [33]. The development of cancer around the time of onset of the symptoms of dermatomyositis or polymyositis allows a patient to be categorized as having cancer-associated myositis (CAM) [34, 35]. The exact timing of how close together the diagnosis of IIM and cancer must be for the condition to be called CAM is not well defined and has ranged from 2 to 5 years. Another appreciated subdivision of the IIM has been that some patients meet criteria for IIM and another connective tissue disease and these patients are referred to as connective tissue disease overlap myositis patients.

Another major category of IIM that was appreciated later was inclusion body myositis (IBM). Initially it was diagnosed based on the pathological finding of red-rimmed vacuoles on Gomori trichrome stain [19], which contain classic amyloid and/or 15–18-nm tubulofilaments. More formal criteria for IBM were introduced by Griggs et al. in 1995 [36], which included the clinical features of duration of illness for more than 6 months, age of onset greater than 30 years, and proximal and distal weakness with one of three specific features (finger flexor weakness, wrist flexors weaker than wrist extensors, or quadriceps weakness that is equal to or less than a grade of 4 out of 5 by Medical Research Council testing). The laboratory features include serum creatine kinase less than 12 times the upper limit of normal, the classic muscle biopsy pathology of IBM, and an EMG consistent with an inflammatory myopathy. Using these criteria, a patient's disease is classified as definite IBM if they have the classic muscle biopsy findings of IBM and as possible IBM if they have a biopsy with inflammation and the clinical and laboratory features listed above.

The need to refine these criteria has arisen from appreciation of new subdivisions of IIM, as well as new pathology and laboratory findings that have emerged. The appreciation of patients with the classic rashes of dermatomyositis but who lack the classic muscle findings has led to new designations such as dermatomyositis sine myositis, amyopathic dermatomyositis, hypomyopathic dermatomyositis [37], clinically amyopathic dermatomyositis (CADM), and skin-predominant CADM over time [38, 39]. Several different criteria have been put forth for categorizing these conditions, with the overarching concepts being that there are patients with classic skin manifestations and no signs of muscle involvement (called amyopathic dermatomyositis), and there are patients with classic skin disease and no weakness on exam, but who have other subclinical findings of muscle involvement, such as elevated muscle enzymes, abnormal muscle biopsies, or EMG (hypomyopathic dermatomyositis). The combination of these two entities forms a larger group called CADM.

The so-called immune-mediated necrotizing myopathies (IMNM) are a newer division of the IIM, with their own characteristics [40, 41]. IMNM are similar to polymyositis and dermatomyositis on clinical exam, but have the distinct pathologic feature of myonecrosis with scant or no inflammation on muscle biopsy. There remains controversy as to how to best categorize IMNMs, as many patients with IMNM are still considered by some clinicians to have dermatomyositis or polymyositis.

In addition to these clinicopathologic subtypes of myositis, the discovery of numerous autoantibodies that are associated with myositis (termed myositis-specific autoantibodies or myositis-associated autoantibodies) has led to classification schemes based on autoantibody status [42]. This is justified given that many autoantibody

subgroups are associated with distinct clinical phenotypes and pathology. Just as one could describe a house based on its color or its height so too can a patient with IIM be described by their clinicopathologic parameters or by their autoantibodies. Knowing the autoantibody status of a patient can provide important information about their genetics, histopathology, expected disease manifestations, clinical course, prognosis, and cancer risk. Classification based on autoantibody status offers the prospect of more homogeneous patient groups than classification schema that rely solely on pathology, clinical exam, and basic laboratory evaluation.

In an effort to incorporate these new disease entities and tests, many different sets of classification criteria have been proposed [43–45]. These include initiatives for international, multidisciplinary consensus based on a combined ACR/EULAR set of classification criteria [46]. There is still ongoing work in this area to establish new criteria that best incorporate the many different aspects of these diseases.

Conclusion

Our knowledge of the range and complexity of the spectrum of the IIM has rapidly expanded in recent years. With improved understanding of the clinical, laboratory, and pathogenetic features of this group of diseases, new classification criteria and subgroups have been developed to allow researchers, physicians, and patients to study and communicate better about these illnesses. The development of well-defined and internationally agreed upon new definitions is important to advance research findings in the field as well as for the proper care of patients.

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Myositis Basics/Who Gets Myositis

2

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Key Points to Remember

- The idiopathic inflammatory myopathies (IIM) are thought to result from chronic immune activation following an environmental trigger in genetically predisposed individuals.
- IIM have a bimodal distribution of age of onset, with peaks in adolescence and the sixth and seventh decades of life, and more commonly affect females.
- Inclusion body myositis and cancer-associated myositis are two IIM subtypes where older males are at higher risk, in contrast to other IIM subtypes.
- The strongest genetic risk factors for IIM lie in the major histocompatibility complex (MHC) on chromosome 6, a highly variable region which encodes many proteins that present antigens to the immune system.

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- Genetic risk factors identified outside the MHC region implicate both the innate and adaptive immune responses in IIM.
- Some genetic risk factors are unique to specific clinical IIM subgroups, potentially suggesting that different pathophysiologies are implicated, whilst other genetic risk factors overlap between the IIM and other seropositive autoimmune rheumatic diseases.
- Several environmental risk factors, including ultraviolet radiation exposure, occupational exposures, smoking and certain medications, have been implicated in IIM aetiology, but further studies are needed to determine causality.
- A number of viral and bacterial infectious triggers have been suggested, but data is rather limited and preliminary.

Introduction

This chapter will address the prevalence and incidence of idiopathic inflammatory myopathies (IIM) and their major subtypes. We will focus on modifiable (radiation, smoking, drugs) and non-modifiable risk factors (age, gender, ethnicity) that predispose an individual to develop IIM and what is currently known about environmental and genetic associations and interactions.

Prevalence and Incidence of Myositis and Its Subtypes

The rarity of IIM and the recent advances in our understanding of their many clinical subtypes and multisystem nature, where affected patients may present to many differing medical specialties, have made the undertaking of epidemiological studies and interpretation of previous studies a considerable challenge. As testament to this, the most widely used diagnostic criteria for IIM, those of Bohan and Peter [1], were developed and validated prior to the description of recently described clinical subtypes and before access became available to myositis-specific antibodies or magnetic resonance imaging. In the rare IIM disease spectrum, undertaking epidemiological studies has the potential to shed light on important factors involved in the disease process.

A systematic review of previous epidemiology studies indicates an annual IIM incidence of around 8 per million, ranging from 1.16 to 19 per million in different geographical areas of the world. The combined prevalence of IIM overall is around 14 per 100,000, ranging from 2.4 to 33.8 per million [2]. When taken collectively, there is no apparent geographical or spatial variation, although associations have been found for particular clinical subsets discussed below. Two studies subsequent to this review from Quebec and the USA cited similar incidence and prevalence rates [3, 4].

There has been a trend for increasing incidence and prevalence figures for IIM over time, which may be due to wider recognition, more accurate disease recording or a true increase in disease burden. The most common IIM subtypes in adults are dermatomyositis (DM), anti-synthetase syndrome and polymyositis (PM), but much of the epidemiological data collected is specific to particular

Table 2.1 Incidence and prevalence estimates of IIM and their subtypes

	Incidence estimates	Prevalence estimates
Overall IIM	8 (1–19) per million	14 (2–33) per 100,000
DM	No subtype-specific data Comprises ~20% of IIM (modulated by latitude)	No subtype-specific data Comprises ~20% of IIM (modulated by latitude)
PM	No subtype-specific data	No subtype-specific data
IBM	2–6 per million	5 per million (9–71 per million in adults >50 years old)
JDM	2–4 per million	2.5 per 100,000
IMNM	No subtype-specific data Comprises ~20% of IIM	No subtype-specific data Comprises ~20% of IIM
CAM	20–30% of DM and 10–20% PM have a malignancy	20–30% of DM and 10–20% PM have a malignancy

IIM idiopathic inflammatory myopathy, *DM* dermatomyositis, *PM* polymyositis, *IBM* inclusion body myositis, *JDM* juvenile DM, *IMNM* immune-mediated necrotising myopathy, *CAM* cancer-associated myositis

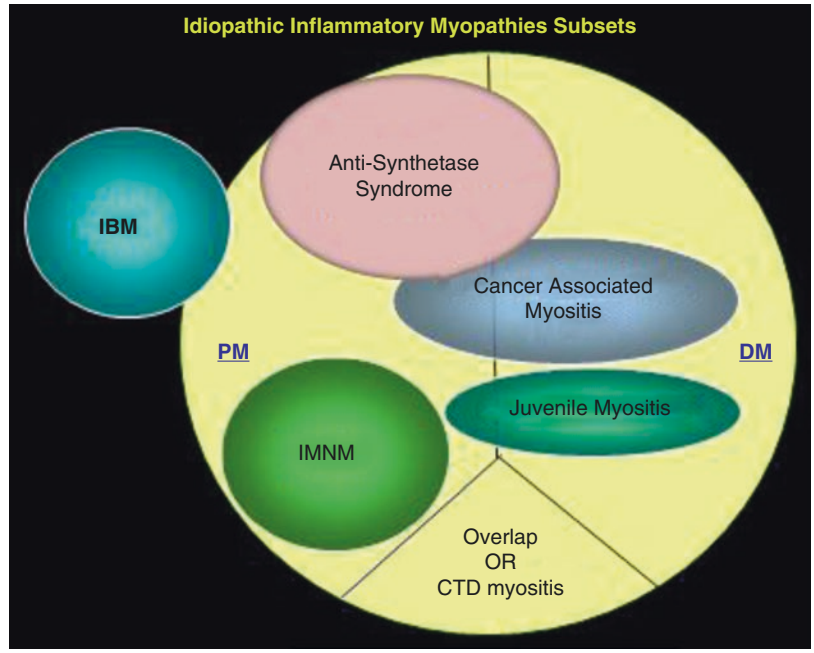

Fig. 2.1 IIM subsets, area of each subset approximates to its relative frequency compared to overall IIM prevalence

subtypes which will be briefly discussed further and is summarised in Table 2.1. Figure 2.1 shows a conceptual representation of how the subtypes overlap and relate to each other.

Inclusion Body Myositis Inclusion body myositis (IBM) represents a small IIM subset, and various diagnostic criteria (including the Griggs, Mastaglia and ENMC criteria) have been employed in different studies, which has had an impact on the interpretation of results obtained [5–7]. The estimates of prevalence and incidence vary considerably. The prevalence of IBM is around 5 per million of the general population, but this rises substantially when studying an older population (50 years and older) to between 9 and 71 per million [8–12]. The incidence of IBM has been less frequently investigated, but a recent Norwegian study calculated an annual incidence of 2–6 per million [13].

Cancer-Associated Myositis An association between IIM and cancer has long been recognised, and contemporary epidemiological research has helped further investigate this relationship. Approximately 20–30% DM patients and 10–20% of PM patients have an underlying cancer [14, 15]. A recent estimate of the standardised incidence rates for malignancy were 2.0 in DM, 1.3 in PM and 1.0 in IBM, somewhat lower than earlier estimates [16]. The cancer risk is highest in older males with dermatomyositis with most cancer diagnoses being made within 1 year on either side of the diagnosis of an incident IIM. Particular autoantibodies (anti-TIF1γ, anti-NXP2, anti-SAE) are associated with adult DM and cancer [17, 18]. These antibodies do not associate with cancers in juvenile DM.

Juvenile Dermatomyositis Although different studies have used different age ranges of disease onset to define their cases, the annual incidence of juvenile DM appears similar to that of adults, at between two and four per million [19–22]. One study estimated the prevalence from their data at 2.5 per 100,000 persons [19].

Immune-Mediated Necrotising Myopathy Overall it has been estimated that immune-mediated necrotising myopathy (IMNM) makes up around 20% of all IIM and the incidence and prevalence can be roughly extrapolated from this figure in reference to the epidemiology figures for IIM collectively,

reported above [23]. One study in particular has shown a statistically significant increase in IMNM incidence over time, which may in part be due to a general increase in relevant environmental exposures such as statin therapy [24].

Age, Gender, Racial/Ethnic and Geographical Differences

The age at IIM disease onset has a bimodal distribution, with peaks in both childhood and in adulthood. However, IIM can affect all age groups. The peak for adults is in the 55–64 age group, with roughly two-thirds of patients being female. Therefore, the gender demographics of the IIM are broadly similar to those of many other autoimmune diseases, including rheumatoid arthritis. An exception is IBM, where affected patients are characteristically older (disease onset typically in the seventh decade and with a delay in diagnosis of around 5 years) and with a male gender preponderance [25].

Although individual studies may support an impression of racial and ethnic differences in the epidemiology of certain IIM subtypes, for example, the high incidence of anti-MDA5 positive clinically amyopathic DM in Japan, it is difficult to directly compare studies undertaken in different regions employing varied methodologies [26]. IIM are internationally prevalent, but different geographical areas have slightly different distributions of autoantibody subsets which could relate to referral bias in the comparison of different studies. There is little evidence to support the notion of spatial clustering as a consequence of rural or urban habitation, or of seasonal clustering when cases are analysed as a whole (with the possible exception of juvenile DM, discussed below).

There is little data on the epidemiology comparing differing ethnicities within the same geographical areas. A population subset of a single study from the US found 43% of their myositis incident cases were African American compared to 38% Caucasian and 5% Hispanic [4]. However, these data likely mostly reflect the characteristics of the general Medicaid program population rather than a particular risk in African Americans. Further investigation may shed more light on this issue.

Points to Remember
Age: Bimodal, 2–16 years and 30–70 years
Gender: Female>male (2:1), except IBM where male > female
Ethnicity/race: None confirmed

Risk of Myositis in Family Members of IIM Patients

There are rare reports of familial co-occurrence in IIM [27, 28]. However, due to the low incidence of the disease, the number of published multi-case family studies is extremely limited, with the exception of familial IBM. Increased rates of other autoimmune diseases, such as autoimmune thyroid disease, rheumatoid arthritis and type 1 diabetes, have been reported in the first-degree relatives of IIM sufferers, with an overall prevalence of 21.9% compared to 4.9% in non-autoimmune families [29]. Similarly, type 1 diabetes and systemic lupus erythematosus are more common than would be expected in the family members of patients with juvenile DM [30]. This aggregation of autoimmune disease within IIM families may suggest that shared environmental and/or genetic factors contribute to disease risk. The familial recurrence rate, and the rate of disease concordance in monozygotic compared to dizygotic twins, can be used to estimate the *genetic heritability*, the proportion of phenotypic variation that is attributable to genetic factors. In other autoimmune diseases, genetic factors have been shown to play a large role in disease susceptibility; for example, in type 1 diabetes and rheumatoid arthritis, the genetic heritability is approximately 88% [31] and 66% [32], respectively. However, due to the rarity of IIM, few

Points to Remember
First-degree relatives of IIM patients have an increased risk of autoimmune disease in general but not specifically for developing myositis.

family or twin studies have been carried out, therefore disease heritability remains unknown.

The Role of Environmental and Genetic Factors in the Development of Myositis

Although the aetiology and pathogenesis of IIM is poorly understood, autoimmune diseases are known to be complex disorders that result from chronic immune activation following specific environmental exposures in genetically predisposed individuals. Several environmental risk factors, including occupational exposures and infectious agents, have been implicated in IIM. The variety of these environmental insults may contribute to the clinical heterogeneity observed in IIM.

Points to Remember
All risk factors seem to increase risk for one or another subtype of IIM, but none is sufficient alone or necessary to cause the disease.

Environmental Risks: The Role of Noninfectious Risk Factors

Several environmental factors have been associated with IIM, although causality has not yet been proven. A role for ultraviolet radiation (UV) exposure has been postulated to act through immunomodulatory effects. The direct absorption of UV radiation by DNA and production of reactive oxygen species may lead to changes in the production of various immune mediators, which, in turn, suppress systemic immune responses, promoting defects in cellular immunity. Hence, the prevalence of DM, as a proportion of DM and PM, as well as the presence of the DM-specific autoantibody, anti-Mi-2, has been shown to increase from north to south with latitudinal gradient [33, 34]. Seasonal effects on incidence and prevalence also have been reported in some studies of juvenile onset DM [2]. In individuals who are current or previous smokers, the frequency of the most common adult myositis-specific autoantibody, anti-Jo-1, is increased, particularly in individuals who carry a specific genetic variant (*HLA-DRB1*03)* [35]. The latter observation suggests an interaction between genes and environment that increases susceptibility to develop one of the IIM, an effect similarly observed for smoking in rheumatoid arthritis [36, 37]. Moreover, the likelihood of developing anti-HMGCR antibody-positive immune-mediated necrotizing myopathy as a result of exposure to lipid-lowering statins is increased in adults who are positive for the genetic variant *HLA-DRB1*11* [38]. The finding that there is an increased incidence of a range of different cancers in IIM, particularly in those individuals with DM and especially those with another DM-specific autoantibody, anti-TIF1γ [39], suggests that environmental factors may act as both carcinogens and inflammatory triggers. Whilst the reason for this association between myositis and cancer is still unknown, a model has been suggested whereby a mutation in the individual's tissue triggers an autoimmune cytolytic antitumour response, which in some patients successfully eliminates the cancer but may fail in those who develop cancer-associated dermatomyositis [40]. Contrary to adults, anti-TIF1γ autoantibodies are one of the most common autoantibodies in juvenile DM, but are not associated with malignancy in juveniles, suggesting that the increased risk of cancer with anti-TIF1γ represents a complex interplay of exposure and genetics. Although there are no known dietary risk factors for IIM, naturally occurring statins are present in certain foods, for example, high concentrations of lovastatin are found in oyster mushrooms, which may act to influence risk in some individuals [41] (Table 2.2).

Environmental Risks: The Role of Infectious Agents

Although a variety of infectious agents have been linked to the development of IIM, as dem-

Table 2.2 Environmental risk factors for IIM (causality not proven)

Noninfectious risks (strong associations)
UV exposure for DM
Smoking in anti-Jo-1 + patients, especially in those with *HLA-DRB1*03*
Statin in anti-HMGCR + patients, especially in those with *HLA-DRB1*11*
Cancer in DM, especially in those with anti-TIF1γ autoantibody
Infectious risks (weak and inconsistent associations)
Epstein-Barr virus
Retroviruses such as influenza, hepatitis and HIV
Enteroviruses, such as coxsackieviruses
Bacteria such as streptococcal, *Mycobacterium tuberculosis* and *Staphylococcus aureus*

onstrated by case reports and epidemiological studies (see Gan and Miller, 2011, for review [42]), the associations are neither strong nor consistent. A potential role of microbial pathogens, including viruses, bacteria, fungi and parasites has been suggested. Associated viruses include Epstein-Barr virus; retroviruses such as influenza, hepatitis and HIV; and enteroviruses, such as coxsackieviruses, whilst bacteria include streptococcal infection, *Mycobacterium tuberculosis* and *Staphylococcus aureus.* A potential role of infectious agents in the development of IIM is supported by their use to induce myositis in experimental animal models. Recent studies of the *microbiome*, the combined genetic material of the microorganisms in a particular environment, for example, in the human gut or on the skin, allow the role of the host microenvironment in the development of autoimmunity to be investigated [43]. In addition, novel experimental approaches are being developed to screen serum from individuals with IIM and other diseases for signatures of past or current infections. However, it is not established yet whether any identified infection is primary or secondary to the development of autoimmunity, and for some individuals the lack of obvious clinical disease and consequent delays in diagnosis makes it more difficult to identify responsible temporal environmental exposures.

Genetic Risk Factors in Idiopathic Inflammatory Myopathies

Numerous studies have been carried out over the last decade to identify genetic risk factors that predispose individuals to develop IIM. To identify genes involved in disease, these association studies compare the frequency of genetic variants in individuals with disease compared to healthy individuals (case-control studies). Most of these studies have focused on the more prevalent IIM clinical subgroups, due to the rarity of even the most common subgroups, causing sample size and consequent power issues when trying to identify statistically meaningful results.

The strongest genetic associations identified in IIM are within the major histocompatibility complex (MHC) on chromosome 6; the highly variable region which contains many of the genes that encode proteins that present antigens to the immune system to trigger an immune response. Genetic variants within this region confer susceptibility to numerous autoimmune diseases, including rheumatoid arthritis, systemic lupus erythematosus and Sjögren syndrome. The largest published genetic study to date in IIM included samples from 2566 affected individuals of European ancestry collected through the Myositis Genetics Consortium (MYOGEN). The results identified that multiple variants within the MHC region may contribute independently to IIM risk [44, 45]. This increased genetic risk may be due to specific amino acids on the *HLA* genes that change the structure of the peptide-binding groove, thus affecting the ability to bind autoantigenic peptides and present them to the immune system. These specific amino acid associations differentiate IBM from PM and DM [45].

Genetic risk factors outside of the MHC region also have been implicated in IIM, including a variant of the *PTPN22* gene [44]. This results in an arginine to tryptophan amino acid change at position 620, a risk factor which also has been established for several autoimmune diseases other than IIM. Associations with genes involved in the adaptive immune response, such as *STAT4* and *UBE2L3,* which are known regulators of T and B cell differentiation, respectively,

implicate other key pathogenic mechanisms in IIM [44]. A region on chromosome 3 also has been implicated in IBM, where a frameshift mutation in CCR5 is thought to be the causal variant [45]. Whilst some of these associations are unique to different clinical IIM subgroups and may suggest different pathophysiologies between the subgroups, other associations confirm extensive genetic overlap between IIM and other seropositive rheumatic autoimmune diseases, such as rheumatoid arthritis, Sjögren syndrome and systemic sclerosis [46].

Specific MHC associations also have been identified within myositis-specific autoantibody defined subgroups (Table 2.3), in agreement with the finding that many myositis-specific autoantibodies are mutually exclusive. These association signals may be stronger than for clinically defined subgroups, and the serotype/phenotype associations are described in detail in later chapters of this handbook (Role of autoantibodies in myositis). Many studies are ongoing to better understand the links between genotypes and serotypes to better predict clinical phenotypes, and therefore better predict treatment responses in IIM.

Notably, in IIM a relatively small number of genetic risk variants have been identified, in contrast to other more common autoimmune diseases, such as rheumatoid arthritis. This observation may simply reflect statistical power problems due to sample size in a disease spectrum as rare as IIM, as well as the marked heterogeneity of these complex diseases. Also, many of the genetic variants identified have a relatively small effect on disease risk individually, and only 5.5–16% of the phenotypic variance in IIM can be explained by genetic risk factors identified from the most recent genetic studies. Although most of the largest genetic studies in IIM to date have focused on populations of European ancestry, some of these associations have been replicated in other ethnic groups, such as Han Chinese and Japanese, suggesting some common aetiology between ethnicities [47, 48].

Overall, there is likely to be a complex interaction between genetic and environmental factors in IIM initiation and progression. Whilst it is not yet known how these genetic variants contribute to disease pathogenesis in IIM, integrating genetic and environmental data will potentially lead to increasingly refined models of disease pathogenesis. These will be necessary to provide earlier disease detection, improved diagnostic accuracy and prediction of disease progression, and to identify clinically meaningful patient subgroups for stratified treatment approaches. Such insights would clearly have the potential to improve therapeutic outcomes in these difficult diseases (Table 2.3).

Table 2.3 Genetic risk factors in IIM

MHC variants
Confers highest risk
Examples: *HLA-DRB1*03* in anti-Jo-1 antibody, *HLA-DRB1*11* in anti-HMGCR antibody
Non-MHC region
PTPN22 gene
STAT4 gene
UBE2L3 gene
Frameshift mutation in CCR5 (chromosome 3)

Conclusion

Substantial work already has been undertaken towards establishing the epidemiology of IIM (Table 2.1) and non-modifiable risk factors such as gender and age for IIM, and different subtypes are well known. As current research stands, relatively few environmental and genetic associations have been identified, particularly for IIM subtypes, and no common causal link has been established. Further work will lead to discovery of additional genes and the putative environmental triggers involved in initiating disease pathogenesis, and identify persons at risk of IIM to enable limitation or prevention of disease development.

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3 Evaluating the Patient with Suspected Myositis

Rohit Aggarwal and Chester V. Oddis

Key Points to Remember

- Polymyositis is often overdiagnosed given the many neuromuscular disorders that mimic polymyositis.
- Myositis typically presents with an acute or subacute onset including bilateral symmetrical proximal muscle weakness, except for inclusion body myositis.
- Electromyography is highly sensitive but not specific for myositis, primarily serving to differentiate between myopathy and neuropathy.
- Most suspected myositis patients require a muscle biopsy to confirm the diagnosis except in the anti-synthetase syndrome and clinically amyopathic dermatomyositis.
- One must exclude thyroid disorders and drug-induced myopathy before making the diagnosis of myositis.
- There are five different muscle enzymes, and the AST, ALT, and LDH may be more abnormal than the CK or aldolase in some subsets.
- Muscle MRI is increasingly utilized in the evaluation of myositis.

Introduction

The evaluation of a patient with suspected muscle weakness begins with a comprehensive history and physical examination to generate the initial differential diagnostic considerations. Special consideration should be given to conditions that closely resemble idiopathic inflammatory myopathy (IIM, myositis) as noted in Table 3.1. Following the history and physical examination, laboratory and imaging studies can help to narrow the potential diagnoses, while electromyography (EMG) and/or muscle or skin biopsy may be necessary to confirm the diagnosis (Table 3.2). The most common setting for a misdiagnosis or delayed diagnosis is seen in cases of polymyositis (PM) or sometimes in necrotizing myopathy (NM), due to a large number of PM mimics (Table 3.2) [1]. That is, when a rash of dermatomyositis (DM) is present, the diagnosis is more obvious due to high specificity of the classic DM rashes, but with a suspected myositis and no rash, the differential diagnosis is considerably expanded to include many other myopathies (Table 3.1). Inclusion body myositis (IBM) can be

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Table 3.1 Conditions that mimic idiopathic inflammatory myopathies (IIM)

Endocrine myopathies
Hyperthyroid, hypothyroid
Drug or toxic myopathies
Alcohol, colchicine, antimalarials, statins, etc.
Metabolic myopathies
Mitochondrial myopathies
Muscular dystrophies
Infectious myositis
Neuropathies/neurologic syndromes: Myasthenia gravis, ALS, GBS
Paraneoplastic syndromes
Other connective tissue disorders
Miscellaneous: Amyloidosis, sarcoidosis

Table 3.2 Key studies to consider in a patient with muscle weakness

History and physical examination
Proximal symmetric muscle weakness (could also be distal and asymmetric in IBM)
Characteristic rashes of dermatomyositis
Laboratory
Muscle enzyme elevation
Myositis autoantibodies
Imaging: Muscle MRI
Specialized testing:
Myopathic EMG
Muscle/skin biopsy

Table 3.3 Clinical features to consider while establishing diagnosis of myositis in a patient

Clinical features that point toward a myositis diagnosis
Family history of autoimmunity
Symmetric, chronic, proximal > distal weakness (not seen with IBM)
Muscle atrophy after long-standing symptoms
Lack of neuropathy, fasciculations, or cramping
Enzyme elevation (5–100× upper limit of normal)
Rash, fever, arthritis, and other systemic autoimmune rheumatic disease symptoms
Response to prior therapy (not seen with IBM)
Autoantibody positivity (e.g., ANA, ENA, myositis-associated and myositis-specific antibodies)
Inflammatory signal on muscle MRI
Clinical features that point away from a myositis diagnosis
Family history of a similar pattern of muscle weakness
Asymmetric and distal muscle weakness (characteristic of IBM)
Early muscle atrophy (characteristic of IBM) or muscle hypertrophy at any time
Neuropathy, fasciculations, or cramping
Muscle enzymes >100× upper limit of normal
Lack of any systemic autoimmune features
No response to therapy (Also seen in IBM)
No abnormal autoantibodies
Normal or only atrophic muscle MRI signal
Rhabdomyolysis
Endocrinopathy or drug-associated

challenging to diagnose and is often misdiagnosed as PM due to significant overlap in patterns of muscle weakness especially early in the disease course. As alluded to above, dermatomyositis (DM) and its related subsets including clinically amyopathic dermatomyositis (CDAM), cancer-associated DM, or juvenile DM (JDM) can usually be recognized based on the typical Gottron rashes (papules and/or sign) or a heliotrope rash. Further, there are certain clinical features that should lead the clinician toward or away from an IIM diagnosis (Table 3.3).

History

Myositis is a heterogeneous systemic disease, meaning that patients can first present with extramuscular symptoms involving the lungs, joints, skin, vascular, and other systems, with or without involving muscle. These include characteristic DM rashes such as vasculitic ulcers and ischemic digits, mechanic's hands, dyspnea and cough (often misdiagnosed as "double pneumonia" in community hospitals), arthritis (sometimes misdiagnosed as rheumatoid arthritis), or Raynaud phenomenon, etc. However, in most cases, patients will eventually develop muscle involvement (except in clinically amyopathic DM or some cases of the anti-synthetase syndrome) leading to mild to severe muscle weakness, myalgia, exertional muscle fatigue, or elevated muscle enzymes. The clinician must recognize the difference between muscle weakness, fatigue, myalgia, and asymptomatic hyperCKemia, when patients first present with muscular symptoms (Table 3.4). Patients with myositis (except clinically amyopathic form or anti-synthetase syndrome) should have objective muscle weakness on physical examination, which should not be confused with fatigue, myalgia, etc. (Table 3.4) [2–4]. Neurological symptoms such as sensory loss, paresthesias, or fasciculations or

Table 3.4 Definitions of key presenting symptoms that may aid in establishing accurate diagnosis of myositis

Symptom/ sign	Definition	Associated disease organ	Association with myositis
Muscle weakness	Inability to perform a single repetition of a specific task requiring use of a muscle	Muscle, nerve, central nervous system (CNS)	Necessary to confirm myositis diagnosis
Fatigue	Inability to continue performing a specific task after multiple repetitions	General systemic complaint seen with many diseases	Commonly seen; not specific
Myalgia	Muscle pain at rest or associated with activity	Muscle (metabolic or inflammatory), nerve-related; central pain syndromes (fibromyalgia)	Less common feature of myositis; occasionally in DM
Arthralgia	Joint pain at rest or associated with activity	Joint (mechanical or inflammatory), central pain syndromes (fibromyalgia)	Anti-synthetase or overlap myositis syndrome
Sensory loss	Partial or complete loss of sensation (numbness)	Nerve and CNS	Not seen in myositis
Muscle enzyme elevation	Elevation of CK, aldolase, transaminases, lactate dehydrogenase above the upper limit of normal	Various muscular and nonmuscular causes [discussed in chapter 4 (asymptomatic hyperCKemia)]	Often seen with muscle weakness in myositis but possibly normal in some myositis subsets such as DM, IBM and JDM

muscle twitches on history or physical examination should point away from a myositis diagnosis.

Demographic Considerations

Demographic features are helpful in differentiating between various myositis subtypes. In general, IIM is a disease of middle age (e.g., 30–60 years), except for JDM (<18 years of age at onset) and IBM (typically over age 50 but often diagnosed several years later). In the young adult with muscle weakness, one must consider muscular dystrophies and metabolic myopathies even though these disorders can present later in adulthood (see Chap. 23 for detail). Like most other autoimmune rheumatic diseases, females are twice as likely to be affected than males with the exception of IBM where males are more commonly affected. All races and ethnicities are affected by IIM.

Pattern and Progression of Muscle Weakness

After establishing the presence of muscle weakness, clinicians should elucidate the onset, progression, and pattern of muscle weakness. A subacute (weeks to months) onset of muscle weakness is generally seen in autoimmune myositis, but IBM clearly has an insidious (years) onset where the patient actually has difficulty dating the onset of their muscle symptoms. In fact, a diagnosis delay of 10 years is commonly observed with IBM. The rate of progression of weakness is similarly long (years) in IBM, whereas patients with other subsets of myositis often progress in weeks to months. Although autoimmune muscle weakness may change over time or with treatment, it is generally chronic in nature, whereas patients with intermittent symptoms of weakness may more likely have a metabolic myopathy. Most forms of IIM except for IBM lead to proximal symmetric muscle weakness usually involving the shoulder and hip girdle. Patients have difficulty in getting up from a low chair or climbing stairs or getting in and out of a car, in lifting objects, or in activities like bathing or combing their hair. IBM patients can certainly have proximal symmetric muscle weakness, perhaps more commonly associated with quadriceps atrophy, but often have distal and asymmetric muscle weakness patterns including subtle or prominent foot drop or finger flexor weakness. Focal or regional muscle weakness with or without associated sensory loss often points away from a diagnosis of myositis.

Extra-Muscular Features of Myositis

The evaluation of any myositis patient must include a detailed assessment of extra-muscular manifestations (Table 3.5). Clinicians must inquire regarding dyspnea and cough as patients may fail to consider respiratory symptoms as related to their muscle weakness. Cardiac involvement is less common, but palpitations, chest discomfort, or any nonspecific cardiac complaints should not be ignored. All patients should be asked about dysphagia, gastroesophageal reflux, choking episodes, or aspiration. If these symptoms are present, an esophagogram should be done. Lower gastrointestinal involvement is uncommon in IIM, except for JDM (GI ulcerations) and overlap syndromes with systemic sclerosis (dysmotility) [5]. Joint pain and swelling including a bilateral symmetric polyarthritis of the small joints of hands and feet can be a presenting symptom especially in the anti-synthetase syndrome, and in some cases, the patient may have been previously misdiagnosed with rheumatoid arthritis. Raynaud phenomenon can be similarly seen in the anti-synthetase syndrome and other forms of myositis, perhaps even leading to fingertip ischemic pain or tenderness, or digital pits in some forms of myositis (overlap syndromes, anti-MDA5). Constitutional complaints of low-grade fever and malaise are quite common. DM rashes commonly include Gottron papules or sign, a heliotrope rash, V-neck rashes, a "shawl sign," periungual erythema, nailfold capillary abnormalities, palmar papules, cutaneous ulcerations and calcinosis, a "holster sign," or other nonspecific rashes of the upper arms. These are discussed in detail in Chap. 6.

Social, Family, and Medication Assessment

It is essential to ascertain a detailed family, social, and medication history in the evaluation and management of suspected myositis. A family history of other autoimmune (rarely myositis) diseases is common including autoimmune thyroid disease. However, a family history of muscle disease or weakness points toward a metabolic myopathy, muscular dystrophy, or some other heritable myopathy. The social history may uncover an environmental exposure as well as important functional and work status issues and patient support systems. The medication history is critical including the use of illicit drugs such as cocaine or excessive alcohol intake. Further,

Table 3.5 Extra-muscular manifestations of myositis

Organ	Symptoms	Evaluation	Association
Lung	Dyspnea and cough, dysphonia	High-resolution CT chest, pulmonary function tests (PFTs)	ILD, respiratory muscle weakness, pulmonary hypertension. One of the most common organ systems affected after muscle and skin
Cardiac	Palpitations, heart failure, dyspnea	Echocardiogram, Holter monitor, cardiac MRI	Cardiomyopathy, clinically uncommon but can be severe in some cases
Upper GI	Dysphagia, gastroesophageal reflux, choking, recurrent aspiration, dysphonia	Pharyngeal dysphagia seen on esophagogram	Common in severe myositis and IBM, difficult to treat
Joints	Polyarthritis of small joints of the hand	Clinical and radiographic imaging; check RF, CCP, and anti-synthetase autoantibodies	Commonly seen in anti-synthetase syndrome but can occur in other overlap myositis subsets
Vascular	Raynaud phenomenon, fingertip ulcers/ischemia	Clinical assessment	Severe DM (vasculitis) and anti-synthetase syndrome
Constitutional	Fever, malaise, fatigue, etc.	Clinical assessment, rule out infections	All forms of IIM
Skin	DM rashes	Skin biopsy may be required	DM, clinically amyopathic DM, anti-synthetase syndrome

Table 3.6 Common medications and drugs causing muscle weakness

Common medications and drugs causing muscle weakness
Alcohol
Illicit drugs (e.g., cocaine)
Statins
Glucocorticoids
Hydroxychloroquine
Antithyroid agents
Antibiotics
Chemotherapeutic agents
Cimetidine
Fibric acid derivatives (gemfibrozil)
Over-the-counter supplements

there is a long list of myotoxic medications including supplements as outlined in Table. 3.6 that can lead to muscle weakness either as an adverse event or interaction with other medications (Table 3.6).

Physical Examination

A detailed physical examination including a neurological assessment is necessary. This includes a careful skin exam, pulmonary auscultation for crackles (i.e., pulmonary fibrosis), and the assessment of the many systemic manifestations discussed in the above extra-muscular features section. This is critical for prognostic and classification purposes. Bilateral, symmetric proximal muscle weakness is noted in most IIM subsets, except for IBM where asymmetric and distal muscle weakness is common. Atrophy is usually a late finding of chronically active disease, except in patients with IBM where it is often noted at the time of diagnosis. Severe proximal muscle weakness is seen in anti-SRP-associated NM, where muscle atrophy may also be noted particularly in the lower extremity and gluteal musculature. A detailed neurological examination is a must to rule out upper and lower motor neuron diseases. Muscle strength should be quantitated objectively using manual muscle testing (MMT) or a hand-held dynamometer so as to accurately follow muscle weakness and to assess response to treatment. There are various reported techniques to document an MMT score (e.g., MMT-8 or MMT-9, in which eight or nine different upper and lower extremity and axial muscles are evaluated) [6]. The patient must have objective muscle weakness for a clinical diagnosis of IIM except in the case of clinically amyopathic DM or the anti-synthetase syndrome, where non-muscle organ involvement can dominate the clinical picture.

Laboratory Evaluation

The laboratory assessment follows next (Table 3.7), and several muscle enzymes should be ordered including the creatine kinase (CK), aldolase, aspartate transaminase (AST), alanine transaminase (ALT), and lactate dehydrogenase (LDH) as any one or more of these enzymes may be elevated in myositis [7, 8]. Some myositis subsets such as JDM may more frequently have elevation of the AST or ALT rather than the CK or aldolase. Moreover, in JDM and many cases of DM and IBM, all muscle enzymes may indeed be normal or near normal despite active myositis and significant muscle weakness [9, 10]. On the other hand, active disease with PM or NM should be associated with an elevated CK. In some cases a very high CK (>50–100 times the upper limit of normal), as well as borderline CK elevations (<5 times the upper limit of normal), may prompt consideration of a metabolic myopathy or muscular dystrophy. Of prognostic importance is the assessment of myositis autoantibodies [11–13]. The phenotypic associations of all of the myositis autoantibodies and their role in diagnosis, management, and prognosis are discussed in detail in Chaps. 18–22. The ANA, although routinely done, can be normal in up to 50% of some subsets of myositis patients [14]. Initial laboratory testing should also include thyroid function testing, given the common myopathic features seen with both hypothyroidism and hyperthyroidism.

Table 3.7 Common laboratory testing in myositis

Laboratory testing	Types and associations
Muscle enzymes	CK, AST, ALT, LDH, aldolase; <5 or >50–100 x upper limit of normal, points toward other myopathies
Myositis-specific antibodies	Anti-synthetase antibody, anti-TIF1-γ, anti-MDA5, anti-NXP2, anti-Mi-2, anti-SRP, anti-HMGCR, and anti-SAE; highly specific for diagnosis
Myositis-associated autoantibodies	Anti-Ku, anti-RNP, anti-PM-Scl, anti-SSA/B; associated but not specific
ANA and cytoplasmic staining	ANA is not useful in myositis; cytoplasmic pattern on immunofluorescence is seen more commonly in myositis especially in anti-synthetase syndrome
Complete blood count, basic metabolic profile, liver function tests	Done routinely at baseline
Hepatitis B and C, tuberculosis screening	Done routinely before starting immunosuppression
TSH, T3, T4	Rule out thyroid disorders
RF, anti-CCP, autoantibodies for systemic sclerosis (Scl-70, centromere, RNA pol III), lupus and Sjogren antibodies (dsDNA, Sm/RNP, anti-SSA/B)	Rule out overlap syndrome like rheumatoid arthritis, systemic sclerosis, systemic lupus erythematosus, Sjogren syndrome

The need for a complete blood count and metabolic panel is obvious with testing for hepatitis B and C and screening for tuberculosis prior to initiating immunosuppressive therapies. In some patients with polyarthritis, an RF and anti-CCP should be ordered as these RA-associated autoantibodies can be seen in some myositis subsets including the anti-synthetase syndrome.

- Elevated "LFTs" may indicate muscle disease and not liver disease.
- A TSH should be done at the time of the initial evaluation of myositis.

Imaging Studies

In myositis patients with polyarthritis, plain radiographs of the involved joints should be done as a baseline assessment and to document the extent of joint damage. The radiographic study of choice to evaluate muscle disease is muscle MRI, which is discussed in detail in Chap. 16. Muscle MRI is primarily done for distinguishing active muscle disease vs. muscle damage as the latter is characterized by fibrous and fatty replacement or muscle atrophy [15]. The MRI can be used as guidance for selecting the site of muscle biopsy. As radiologists and clinicians are gaining experience in evaluating muscle MRI, distinct imaging patterns are being identified with different myositis subsets. Also, in clinical trials, muscle MRI may be used to evaluate treatment efficacy. Generally, muscle MRI is done on proximal lower extremity (thigh) and hip girdle muscles. One must remember that "inflammatory" changes in muscle MRI, although supportive of active myositis, are non-specific as muscle dystrophy, metabolic myopathies, or other myopathic syndromes may manifest abnormal muscle MRI changes similar to autoimmune myositis syndromes.

In patients with any pulmonary symptoms, or in asymptomatic patients with a high risk of ILD (e.g. the anti-synthetase syndrome or anti-MDA5 positivity), it is necessary to order a high-resolution chest CT (HRCT), pulmonary function tests, and an echocardiogram. In myositis patients with documented ILD, the HRCT is only repeated to assess progression (i.e., at the time of flare) or treatment response [16]. In patients with dysphagia or gastroesophageal reflux, the esophagogram can distinguish the etiology as it relates to pharyngeal dysfunction or esophageal dysmotility.

Muscle MRI is increasingly utilized in assessing myositis patients; however, more studies are needed to determine its optimal use.

Specialized Tests

Electromyography and Nerve Conduction Study

Electrodiagnostic testing for myositis consists of a nerve conduction study (NCS) and needle electromyography (EMG), which help to narrow the differential for muscle weakness as well as evaluate the severity and pattern of muscle involvement [17]. The role of EMG and NCS in the evaluation of myositis as well as its interpretation is discussed in Chap. 12. Briefly, NCS is usually normal in myositis and helps to rule out neurological and neuromuscular junction pathology in patients with muscle weakness. EMG is highly sensitive for myositis but lacks specificity for IIM, given that many dystrophic and metabolic myopathies may show similar irritable/inflammatory myopathic patterns on EMG. EMG will confirm a myopathy and provide a reasonable site for muscle biopsy. The presence of fibrillation potentials or positive sharp waves in a myopathic EMG indicates significant inflammation or necrosis, features usually seen in myositis.

EMG is highly sensitive, but non-specific in myopathic syndromes.

Muscle Biopsy

A discussion of the clinical and histopathological features of muscle biopsy in IIM is addressed in Chap. 13. Muscle biopsy is the confirmatory diagnostic test in most cases of suspected myositis, and all major subtypes of IIM have distinctive findings on histopathology [18]. In patients with a clinical suspicion of PM, NM, and IBM, a muscle biopsy is absolutely necessary due to the extensive number of myositis mimics. In contrast, a muscle biopsy in DM is recommended but may not be critical for diagnosis in the presence of any one of the pathognomic or characteristic DM rashes (e.g. Gottron sign or papules or the heliotrope rash), and classic proximal symmetrical muscle weakness with elevation of muscle enzymes. In JDM, a muscle biopsy is also often not done in the presence of typical skin findings especially if muscle MRI is supportive of the diagnosis. Similarly a clinically amyopathic DM diagnosis can be made without muscle biopsy, but a skin biopsy is often helpful in this myositis subset. The selection of the site for muscle biopsy is important to increase the yield and is usually done on the contralateral side of the EMG or based on muscle MRI findings [19, 20]. A muscle biopsy can be helpful to rule out other neuromuscular etiologies including steroid myopathy, muscular dystrophies, and even metabolic myopathies with appropriate stains. Finally, a muscle biopsy can differentiate between weakness from chronic damage and active disease as well as evaluate treatment responses in clinical trials.

Muscle biopsy is a must in polymyositis, necrotizing myopathy, and inclusion body myositis for confirmation of diagnosis.

Conclusion

The evaluation of patients with suspected myositis incorporates the art and science of medicine including history and physical examination considerations and the potential for confirmatory muscle and/or skin biopsy. Muscle enzymes are elevated in many conditions other than myositis and can even be normal in certain myositis subsets. Given various mimics of PM and NM, special attention is required to carefully rule out other differential diagnostic considerations before making a definitive PM or NM diagnosis. Myositis autoantibody testing can be very helpful given its high specificity and moderate sensitivity. EMG should be interpreted cautiously as it is highly sensitive, but non-specific for myositis. Muscle MRI is increasingly utilized for the determination of a site for muscle biopsy as well as to differentiate activity vs. damage and to help in diagnosis by the identification of patterns of muscle involvement.

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Asymptomatic HyperCKemia

4

Siamak Moghadam-Kia and Rohit Aggarwal

Key Points to Remember

- Patients with asymptomatic hyperCKemia should have repeat CK testing after avoiding exercise for 7 days.
- CK elevation should be assessed relative to the revised threshold of 97.5% for gender and ethnicity.
- Further workup is recommended if the serum CK is more than 1.5 times the upper limit of normal.
- Non-neuromuscular causes should be initially ruled out.
- Macro CK, endocrinopathies, and drugs (e.g., statins) are important non-neuromuscular causes of asymptomatic hyperCKemia.
- An EMG/NCS or muscle biopsy can be considered after discussion with the patient given the low diagnostic yield (25–30%).
- Neuromuscular causes need to be ruled out with comprehensive genetic testing prior to muscle biopsy evaluation.
- Dystrophies and metabolic myopathies are important neuromuscular causes of asymptomatic hyperCKemia.
- If the EMG/NCS and muscle biopsy are both normal, then idiopathic hyperCKemia is the appropriate diagnosis with a good long-term prognosis.

Introduction

Serum creatine kinase (CK) concentrations have been widely used as the primary muscle enzyme marker for diagnosis and follow-up of inflammatory myopathy and other muscle diseases [1]. Asymptomatic hyperCKemia is a diagnostic dilemma and is defined as the persistent elevation of the serum CK with no or minimal muscle-related signs and symptoms such as myalgia and/or weakness. Some patients with asymptomatic hyperCKemia may experience minimal non-specific muscle symptoms such as muscle spasms, cramps, and fatigue that do not interfere significantly with activities of daily living. Asymptomatic hyperCKemia can occur in the setting of neuromuscular or non-neuromuscular etiologies. Neuromuscular etiologies

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include diseases such as muscular dystrophy and metabolic myopathy, whereas non-neuromuscular etiologies refer to other diseases with neuromuscular symptoms such as endocrine disorders, metabolic disturbances, or muscle trauma.

Etiology of Asymptomatic HyperCKemia

Most patients presenting to a rheumatologist with asymptomatic hyperCKemia may actually have a normal CK for their age, gender, and ethnicity. Serum CK levels above a reference laboratory's upper limit of normal (ULN) are seen more frequently in African-American patients [2]. Among other nonneuromuscular causes of hyperCKemia, the most common include strenuous exercise, generalizedseizures, macro CK, medications, malignant hyperthermia susceptibility, toxins, and renal insufficiency [3–5]. Only after non-neuromuscular etiologies have been ruled out, should neuromuscular etiologies be considered.

Some patients may have an abnormal electromyogram/nerve conduction study (EMG/NCS) and/or muscle biopsy, which may lead to the diagnosis of a specific neuromuscular disorder such as muscular dystrophy or metabolic myopathy [6]. Such patients may be in the preclinical stage of disease and may or may not subsequently develop muscle weakness or other neuromuscular symptoms [7].

In a report of 114 asymptomatic or minimally symptomatic individuals with incidentally noted persistent hyperCKemia, 57 subjects (50%) had EMG or muscle biopsy abnormalities but a specific diagnosis (e.g., dystrophinopathy, metabolic myopathy, susceptibility to malignant hyperthermia, and congenital myopathy) was only found in 21 individuals (18.4%). Approximately 32% of the subjects had a completely normal EMG and muscle biopsy [8]. In a more recent case–control European study, the frequency of muscular symptoms and function, neuromuscular diseases, and risk factors were compared between 120 subjects with persistent hyperCKemia and 130 age- and sex-matched controls with normal CK [9]. In men, weight, body mass index (BMI), and muscle symptoms were significantly higher in those with persistent hyperCKemia compared to the controls. In women, no differences were noted between the two groups, but three women with persistent hyperCKemia were diagnosed with a myopathy.

Problems with the "Normal" Laboratory CK

A reference laboratory's normal CK can be misleading as most clinical laboratories use the central 95% CK observations in Caucasian individuals. This often translates to 0–200 U/L, for the reference range of serum CK, assuming that the CK values have a Gaussian (or bell-shaped) distribution. Using the aforementioned reference range, an abnormal CK occurs in up to 10–19% of healthy males and 3–5% of healthy females [10]. However, the actual distribution of the serum CK in healthy individuals is significantly skewed toward higher values and has a non-Gaussian distribution [11, 12], such that using the central 95% of values will lead to the over-reporting of (asymptomatic) hyperCKemia [10]. Given the skewed and non-Gaussian distribution of CK, using the central 97.5% of the observations for defining a normal CK will lead to a much lower false-positive CK reporting compared to using the 95% cutoff. Therefore, the 97.5% cutoff should be used for defining hyperCKemia in clinical reference laboratories.

CK levels vary by age, gender, and ethnicity, and studies have shown a mild age-related decrease in CK [11]. Further, gender and ethnicity play a role as the mean serum CK is highest in black males, followed by black females and white males and lowest in white females as reported in one study [13]. Possible reasons for this heterogeneity of serum CK distribution among racial and gender groups include differences in muscle mass, total body mass, or inherited differences in the permeability of the sarcolemma to CK [14]. Taken together, using

the 97.5% cutoff as discussed above as well as gender and ethnicity, the proposed upper limit of normal values for CK as recommended in one study was approximately 200 for white females, 300–400 for black females, 500–600 range for white males, and approximately 800 for black males [12, 15].

Physical Activity, Exercise, and CK Levels

A transient rise in the CK occurs after exercise, particularly eccentric exercise or heavy manual labor. This CK elevation can be asymptomatic or associated with myalgia. Serum CK levels may increase as high as 10–30 times the upper limit of normal within 8–24 hours of strenuous physical activity or exercise. CK levels then begin to drop at 24–48 hours after exercise and slowly decline over the next 3 days [16, 17]. The degree of CK elevation correlates with the type, intensity, and duration of the exercise, with untrained individuals having greater CK elevations after exercise [16–19]. Therefore, one should repeat the serum CK after rest and exercise avoidance for 3–7 days when assessing asymptomatic hyperCKemia.

Non-neuromuscular Etiologies of Asymptomatic HyperCKemia

Once "asymptomatic hyperCKemia" has been established using the aforementioned parameters, the next step is to assess for any non-neuromuscular etiology. These include endocrine disorders (hyperthyroidism, hypothyroidism, acromegaly), electrolyte disturbances (hyponatremia, hypokalemia, hypophosphatemia), muscle trauma due to seizure or iatrogenic muscle injury (intramuscular injections, needle electromyography, intraoperative muscle injury), viral illness, macro CK, medications such as statins, malignant hyperthermia susceptibility, renal insufficiency, cardiac causes, pregnancy (uncommon), and malignancy [3–5]. Cardiac causes need to be ruled out using the history and physical, EKG, and/or cardiac troponins. Myotoxic medications are important and common etiologies of CK elevation, necessitating a careful medication history for both prescription medications and supplements including herbal agents. Table 4.1 outlines the important non-neuromuscular etiologies of asymptomatic hyperCKemia.

Table 4.1 Non-neuromuscular disorders causing asymptomatic hyperCKemia

Non-neuromuscular etiologies of asymptomatic hyperCKemia	
Infections	Viral illness
Medications	HMG-CoA reductase inhibitors (statins)
	Fibrates
	Antiretrovirals
	Beta-blockers
	Clozapine
	Angiotensin receptor blocking agents
	Hydroxychloroquine
	Isotretinoin
	Colchicine
Endocrine disorders	Hypothyroidism
	Hyperthyroidism
	Acromegaly
Metabolic disturbances	Hyponatremia
	Hypokalemia
	Hypophosphatemia
Muscle trauma	Strenuous exercise
	Seizures
	Intramuscular injections
	Needle electromyography
	Intraoperative muscle injury
Others	MacroCK
	Renal insufficiency
	Malignant hyperthermia susceptibility
	Celiac disease
	Cardiac disease
	Pregnancy
	Malignancy

Macro CK

Macro CK accounts for approximately 4% of asymptomatic hyperCKemia [5, 20]. Macro CK is a CK enzyme complex with a higher molecular

weight than usual CK, and includes two types. Macro CK type 1 is the most common and consists of CK complexes with immunoglobulin seen in about 0.43–1.2% of the general population and associated with systemic autoimmune diseases [5, 20]. Macro CK type 2 is composed of CK with an undetermined protein and has been associated with malignancies. Being a complex enzyme, macro CK has reduced clearance resulting in higher CK levels. Current standard CK assays used in most clinical laboratories do not differentiate between CK and macro CK. Macro CK can be detected by CK isoenzyme electrophoresis, while macro CK types 1 and 2 can then be distinguished by protein G affinity chromatography [5, 20].

Statins

Statins, inhibitors of hydroxy-methyl-glutaryl-Co-A reductase (HMGCR), are the most common medications currently used to lower serum cholesterol for both primary and secondary prevention of coronary disease and cerebrovascular disease. Although generally safe and well-tolerated, statin use is an important and common non-neuromuscular cause of hyperCKemia associated with a variety of muscle-related symptoms including myalgia and muscle weakness [21, 22]. The frequency of hyperCKemia in patients using statins ranges from 0.9% to 4.9% with most elevations 2–10 times the upper limit of normal [23]. The CK often declines after stopping statins, but it may require weeks to months to normalize. However, if the patient has an asymptomatic elevation of the CK secondary to a statin, one can continue the statin if there are no symptoms, particularly if the CK remains less than five times the upper limit of normal with monitoring. The broad range of statin-associated hyperCKemia could be partially attributable to heterogeneous genetic susceptibility in different individuals. Genome-wide scanning has demonstrated a single-nucleotide polymorphism (SNP) located within SLCO1B1 on chromosome 12 that was strongly associated with an increased risk of statin-associated myopathy. Genotyping and identifying common variants in SLCO1B1 may help direct statin therapy more safely and effectively in the future [24]. Other mechanisms of CK elevation include altered muscle membrane fragility due to decreased cholesterol content, inhibition of isoprenoid production (a necessary step in the synthesis of membrane proteins), and depletion of ubiquinone leading to mitochondrial dysfunction.

The frequency and severity of muscle problems, including hyperCKemia, vary among the different statins. The risk of muscle injury is lowest with pravastatin and fluvastatin [25]. In three large, prospective controlled trials [West of Scotland Coronary Prevention Study (WOSCOPS), the Cholesterol and Recurrent Events (CARE), and the Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID)], with more than 112,000 person-years of experience, pravastatin therapy (40 mg per day) demonstrated no laboratory or clinical evidence for myopathy [26]. Rosuvastatin (20 mg daily) use in 17,802 apparently healthy men and women (with low-density lipoprotein [LDL] cholesterol levels of less than 130 mg/dl), had similar muscle toxicity to placebo [27]. Pravastatin, fluvastatin, rosuvastatin, and pitavastatin are not extensively metabolized by CYP3A4 and therefore are associated with a lower risk of drug–drug interactions.

More recently, a subset of statin-associated myopathy called statin-associated immune mediated necrotizing myopathy (IMNM) has been described. This is very different from the above, milder statin-associated muscle complaints and is characterized by marked CK elevations, prominent muscle weakness and a lack of improvement in both the serum CK and muscle symptoms even after statin discontinuation [28, 29].

Elevations of CK are reported with other drugs such as colchicine, fibrates, niacin, hydroxychloroquine, as well as with alcohol or cocaine use (Table 4.1).

Endocrine Disorders

Hypothyroidism is commonly accompanied by mild to moderate elevations of the serum CK [30]. Muscle involvement in hypothyroidism is frequently associated with muscle cramps and mild muscle weakness with more marked CK elevation rarely occuring after vigorous exercise [31]. Thyroid hormone replacement therapy typically results in CK normalization within 1–2 months [32]. Although the serum CK is normal in patients with hyperthyroidism in most clinical scenarios, it can rarely be associated with severe hyperCKemia and associated rhabdomyolysis [33]. Among other endocrine disorders, acromegaly can also be associated with mild CK elevation and myopathic symptoms [34].

Neuromuscular Etiologies of Asymptomatic HyperCKemia

Once non-neuromuscular etiologies of hyperCKemia have been ruled out, the next step is to evaluate for neuromuscular causes of hyperCKemia. Table 4.2 lists the common neuromuscular causes for asymptomatic hyperCKemia that include muscular dystrophies, metabolic and mitochondrial myopathies, infectious myopathy, and rarely, IIM.

In one study, IIM was reported in approximately 5% of patients presenting with asymptomatic chronic hyperCKemia where the CK exceeded 500 IU/L [35]. Anti-synthetase syndrome, an IIM subset, can present with mildly elevated serum CK and interstitial lung disease. Another subset of IIM, hypomyopathic dermatomyositis, can present with mild hyperCKemia with normal muscle strength [35, 36]. Inclusion body myositis (IBM) is characterized by an insidious onset and slowly progressive course and can be associated with mild hyperCKemia (typically less than 10 times the upper limit of normal) [37]. Mild elevation of the serum CK may be seen with other systemic rheumatic diseases including rheumatoid arthritis, systemic lupus erythematosus, Sjogren syndrome, mixed connective tissue disease (in association with anti-U1RNP), and myositis/systemic sclerosis overlap syndromes (often in association with anti-PM-Scl antibody positivity) [38–41]. HyperCKemia can also occur in systemic vasculitides and sarcoidosis [42–44].

Table 4.2 Neuromuscular disorders causing asymptomatic hyperCKemia

Neuromuscular etiologies of asymptomatic hyperCKemia	
Inflammatory myopathies	Dermatomyositis and polymyositis
	Clinically amyopathic dermatomyositis
	Anti-synthetase syndrome
	Inclusion body myositis
Dystrophinopathies	Duchenne/Becker
	Limb girdle
	Others: Myotonic, myofibrillar
Metabolic/mitochondrial disorders of the muscle	CPT2 deficiency
	Muscle phosphorylase deficiency (McArdle)
	Acid maltase deficiency (Pompe's disease)
	Myoadenylate deaminase deficiency
	Mitochondrial myopathies
Others	Sarcoid myopathy
	Familial hyperCKemia
	Congenital conditions

Infectious myopathies can occur in the setting of localized or generalized muscle involvement including HIV or other viral infections, bacterial, mycobacterial, fungal, and parasitic infections [45, 46]. Extreme elevations of serum CK can occur in acute viral myositis. A case of Coxsackie B virus infection was reported to be associated with a serum CK level exceeding 500,000 IU/L leading to acute renal failure [47].

Among muscular dystrophies, the most common conditions associated with serum CK elevation are the sex-linked recessive disorders of Duchenne or Becker dystrophies and the limb-girdle dystrophies and myotonic dystrophy [48, 49]. Female carriers of dystrophin mutations may have hyperCKemia as well, which generally does

not exceed three times the upper limit of normal [6]. In Duchenne or Becker dystrophies, serum CK levels are elevated in infancy and generally peak by the age of 2. The CK levels progressively decline and may normalize in adult patients as more *myofiber* loss with *fibrosis* and *fat replacement* occurs [6].

Metabolic/genetic myopathies, especially carnitine palmitoyltransferase II (CPT II) deficiency, muscle phosphorylase deficiency (McArdle disease), acid maltase deficiency (Pompe's disease), myoadenylate deaminase deficiency, and mitochondrial myopathies, may also present with hyperCKemia [50–53]. Partial CPT deficiency has been described in patients heterozygous for CPT gene point mutations. In metabolic myopathies, there is often exercise intolerance in childhood as well as recurrent muscle cramps including myalgia and mild serum CK elevation or even myoglobinuria and rhabdomyolysis in early adulthood. The serum CK level may or may not normalize between the recurrent episodes.

IIM must be considered in the setting of an elevated serum CK since treatment is available and effective. In many adult dystrophies or metabolic myopathies, no treatment is available but the clinical course is often benign, particularly if the presentation is exclusively hyperCKemia. In some cases, extensive and expensive (i.e. biochemical muscle enzyme analysis and sarcolemmal protein staining) and at times invasive procedures such as electromyography and muscle biopsy may be required, which need to be discussed with the patient given the limited diagnostic yield and ineffective treatment options in many cases. Genetic testing using novel genetic sequencing techniques including targeted gene panels, whole-exome sequencing, or whole genome sequencing can avoid the need for invasive workup and should be pursued before muscle biopsy.

Idiopathic HyperCKemia

The term "idiopathic hyperCKemia" was first used by Rowland et al. and was defined as a persistent elevation of the serum CK concentration (generally 3–10 times higher than the upper limit of normal) in the absence of significant muscle-related symptoms and no clinical evidence of neuromuscular disease including a normal neuromuscular exam, EMG/NCS and muscle biopsy [54, 55]. Some individuals with idiopathic hyperCKemia have minimal abnormalities of muscle cells on muscle biopsy, including changes in fiber size and distribution. However, these non-specific changes generally do not affect muscle function. Although patients with idiopathic hyperCKemia often have no family history of neuromuscular disease, this syndrome may be familial. In one retrospective study, hyperCKemia was familial in 13 of 28 subjects when the serum CK was measured in other relatives [56]. These 13 families had a total of 41 individuals with elevated CK levels, with a higher male prevalence of hyperCKemia. The familial subset of idiopathic hyperCKemia is genetically heterogeneous and inherited as an autosomal dominant trait in at least 60% of cases with higher penetrance in men.

The long-term prognosis of idiopathic hyperCKemia is favorable. In one study, 55 subjects with idiopathic hyperCKemia were followed for 7 years [52]. The diagnosis remained unchanged in most cases with persistent CK elevations and no or minimal symptoms. Nearly 10% were diagnosed with neuromuscular disorder (one with limb-girdle dystrophy, one dystrophinopathy carrier, and two as possible spinal muscular atrophy carriers), 5% developed malignancy, and approximately 10% developed non-neuromuscular disorders. The CK level normalized in 12 patients. No follow-up differences in CK levels were noted between subjects with minimal EMG and/or muscle biopsy abnormalities and those with normal findings at first examination.

Diagnostic Yield of Muscle Biopsy and EMG/NCS in Asymptomatic HyperCKemia

An abnormal EMG/NCS is seen in about half the cases of asymptomatic hyperCKemia (Table 4.3). Although an EMG/NCS distinguishes between primary neuropathic and myopathic disorders, the sensitivity and specificity is low for a definitive and distinct diagnosis. Nevertheless, a completely normal EMG/NCS has a modest negative predictive value and is strong evidence against a severe neuromuscular disorder. EMG/NCS is also used as a guide for muscle biopsy. Most changes noted on an abnormal EMG/NCS are non-specific, and in a very few neuromuscular disorders with an elevated CK, such as motor neuron disease, Charcot–Marie–Tooth disease, and myotonic dystrophy, an EMG/NCS alone could be sufficient for diagnostic purposes.

There is wide variation in the frequency of muscle biopsy abnormalities and subsequent diagnostic yield in asymptomatic hyperCKemia [57–61]. On average, a muscle biopsy (including special stains for sarcolemmal proteins for muscular dystrophy and biochemical muscle enzyme analysis for metabolic myopathies) is abnormal in one-fourth of the cases (Table 4.3). However, most muscle biopsy abnormalities include non-specific myopathic changes that are not diagnostic for any specific neuromuscular disease.

The likelihood of making a diagnosis in subjects with asymptomatic hyperCKemia using both EMG/NCS and muscle biopsy is slightly higher at about 28% (Table 4.3).

The European Federation of Neurological Society guidelines on the muscle biopsy for asymptomatic hyperCKemia suggest that a biopsy may be performed in a patient with hyperCKemia if one or more of the following is present: an abnormal (myopathic) EMG, a CK more than three times the ULN, a patient age less than 25 years, or a history of exercise intolerance [16].

Conclusion: Diagnostic Approach to Asymptomatic HyperCKemia

A proposed algorithm is provided in Fig. 4.1 for the diagnostic evaluation of the asymptomatic patient with an elevated serum CK. The initial step is to determine whether the serum CK is truly abnormal and of clinical significance. The European Federation of Neurological Society guidelines recommend using the 97.5% CK cutoff for age, gender, and race [16]. They further recommend consideration of a cutoff of 1.5 times the ULN to decrease unnecessary workups and aggressive investigations with only a small reduction in sensitivity. This equates to an approximate level of 300 IU/L in white females, 500 in white males, 600 in black females, and 1200 in black males in one study [16]. CK levels generally decline with age, so hyperCKemia in young individuals is more likely to be due to an

Table 4.3 Yield of EMG, muscle biopsy, EMG, and muscle biopsy in asymptomatic hyperCKemia

EMG		Muscle biopsy		EMG and muscle biopsy	
Study	Percentage leading to diagnosis (%)	Study	Percentage leading to diagnosis (%)	Study	Percentage leading to diagnosis (%)
Brewster et al. [3]	29	Brewster et al. [3]	0	Brewster et al. [3]	71
Joy and Oh et al. [7]	74	Joy and Oh et al. [7]	79	Joy and Oh et al. [7]	79
Fernandez et al. [34]	40	Fernandez et al. [34]	49	Lilleng et al. [11]	4
Simmons et al. [56]	45	Simmons et al. [56]	30	D'Adda et al. [51]	11
Malandrini et al. [57]	41	Filosto et al. [60]	0	Fernandez et al. [34]	55
Prelle et al. [8]	57	Malandrini et al. [57]	8	Simmons et al. [56]	30
Dabby et al. [58]	29	Prelle et al. [8]	18	Malandrini et al. [57]	8
Reijneveld et al. [59]	30	Dabby et al. [58]	8	Prelle et al. [8]	18
Average of all studies	46	Reijneveld et al. [59]	14	Dabby et al. [58]	8
		Average of all studies	23	Average of all studies	28

identifiable etiology. One should repeat the serum CK after 3–7 days of rest if there is any doubt that the hyperCKemia could be related to overexertion [15].

Next, one should rule out non-neuromuscular etiologies (Table 4.1) including macro CK, which can be identified by CK electrophoresis. If non-neuromuscular causes are adequately investigated and ruled out, a workup for neuromuscular etiologies can be considered. The utility and low yield of a further workup for a treatable muscle condition must be discussed with the patient in these scenarios. Evaluation for possible neuromuscular disorders would include an EMG/NCS and muscle biopsy. However, current comprehensive genetic testing should be pursued before invasive muscle biopsy. The combined use of EMG/NCS and muscle biopsy may yield a definitive diagnosis in only 30% of such cases. If the EMG/NCS and muscle biopsy are both normal, idiopathic hyperCKemia is the appropriate diagnosis to be considered, which typically has a benign prognosis.

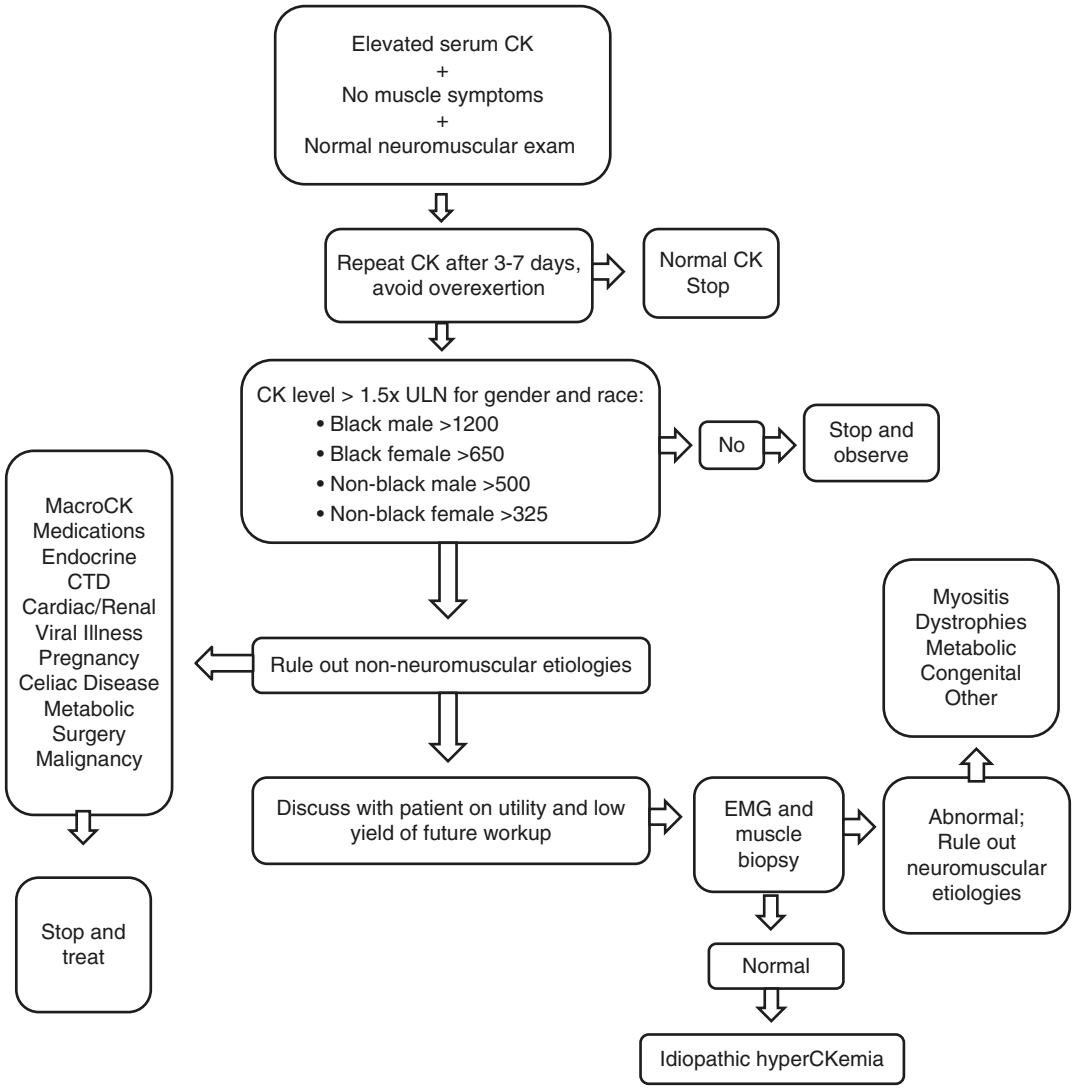

Fig. 4.1 Diagnostic approach to asymptomatic hyperCKemia

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Clinical Features of Myositis: Muscular Manifestations

5

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Key Points to Remember

- Muscle weakness, not pain, is the main symptom in myositis.
- Weakness in polymyositis (PM), dermatomyositis (DM), and immune-mediated necrotizing myopathy (IMNM) is proximal and symmetric.
- Weakness in IBM is more often asymmetric and distal involving mainly quadriceps and forearm flexors.
- Manual muscle testing for muscle strength is crucial for disease assessment.
- Edema on muscle MRI means active disease, and when not seen in the presence of significant weakness may suggest acquired muscle damage due to the previous disease or a glucocorticoid-induced myopathy.
- Dysphagia is common and due to upper esophagus muscle involvement.
- A number of conditions may mimic myositis, and careful detailed workup is needed, particularly in treatment-resistant cases.

Introduction

Muscle weakness is the predominant symptom in myositis, regardless of the subtype [1]. Without the presence of objective muscle weakness, it is nearly impossible to make a diagnosis of polymyositis or dermatomyositis except in patients with amyopathic or hypomyopathic dermatomyositis (together called clinically amyopathic dermatomyositis). Although patients with clinically amyopathic dermatomyositis have no muscle weakness, some who are initially amyopathic may later become weak in the course of their disease. Weakness is generally symmetrical and primarily proximal in distribution, except in IBM which is characteristically asymmetric with distal muscle involvement [2]. The onset of weakness is usually subacute or insidious with a very slowly progressive course over years which is especially frequent in IBM. In some patients with IMNM, the onset of weakness can be relatively acute.

Muscle weakness is required to make a diagnosis of polymyositis and dermatomyositis (except clinically amyopathic dermatomyositis).

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Patterns of Muscle Weakness

Patients complain of difficulty walking up the hill or in climbing stairs due to involvement of the iliopsoas and gluteus muscles. They have the inability to stand up from an armless chair, get up from the squatting position, or get up off the toilet. Patients may fall and require assistance to stand up. Those with severe weakness may need a walker or wheelchair to ambulate, especially those with long-standing IBM. Upper extremity weakness leads to difficulty in raising one's hands to comb their hair or shower with the inability to reach for overhead objects. Patients with severe weakness cannot feed themselves due to the inability to move their hands to the level of the mouth. This may be achieved with the help of the other hand, but assistance with feeding may be necessary from another person. Weakness is often similar in both the upper and lower parts of the body, but disproportional weakness may be present with muscles either in the shoulder or pelvic girdle more involved. Neck flexor weakness is common with difficulty lifting the head from a pillow. Distal muscle strength in PM-DM and IMNM is usually preserved with the exception of severe cases. However, distal muscle weakness is the rule with IBM patients who manifest weakness in forearm flexors, distal finger flexors, ankle dorsiflexors, as well as the triceps and quadriceps. Muscle weakness in IBM is also asymmetric, and such patients complain of compromised fine finger movements leading to poor handwriting or difficulty buttoning.

DM and PM: Proximal >> Distal weakness, bilateral and symmetrical.

IBM: Distal > Proximal and asymmetrical.

Most Common Muscles Involved in PM/DM

Lower extremity

- Iliopsoas (hip flexors)
- Gluteus medius (hip abductor)
- Gluteus maximus (hip extensor)

Upper extremity

- Deltoid

Axial

- Neck flexor
- Paraspinal muscles (only detected on EMG)

Myalgia Versus Weakness

Muscle weakness is usually painless, although some patients may complain of myalgia, more so at the onset of the disease. This is common with necrotizing myositis (NM), whether statins are the cause or in those with the anti-SRP autoantibody. However, when muscle pain is prominent, this should prompt the search for an alternative diagnosis such as fibromyalgia, polymyalgia rheumatica, neuropathies or metabolic myopathies, or other inflammatory disorders. In patients with myositis and the anti-synthetase syndrome, pain may be related to a concomitant arthritis. Therefore, a careful history, physical examination, and other investigations regarding myalgia vs. muscle weakness are necessary. In most instances, simply asking patients about their predominant symptom of pain vs. weakness may yield the answer.

Myalgia without muscle weakness is never polymyositis or dermatomyositis.

Muscle Examination

The physical examination in PM-DM and IMNM demonstrates upper extremity weakness mainly in the deltoid muscle but also affecting the biceps

or triceps, with much less wrist or hand weakness. Hip flexors and gluteal muscles are predominantly affected in the lower extremity, followed by involvement of the quadriceps and hamstring with minimal ankle or foot problems. The pattern of weakness is always proximal > distal except with IBM where distal involvement is severe and often detected by the time of initial evaluation. Typically in IBM the finger flexors and quadriceps muscle weakness is prominent and often more severe than other proximal or distal muscles [3]. Muscle weakness is bilateral and symmetrical except in IBM where asymmetrical involvement is common. Core muscles and spinal muscles are considered proximal muscles, and when affected there is difficulty in getting up from a lying position. Neck flexor weakness with relative sparing of the neck extensors is often observed and should always be assessed on muscle testing in myositis.

Muscle inflammation and disuse during the disease course may lead to muscle fiber damage and muscle atrophy with replacement by adipose tissue that may not be obvious on physical examination. While in PM, DM, and IMNM the atrophy is primarily proximal and symmetric, there is more prominent asymmetrical forearm flexor and quadriceps muscle atrophy in IBM (Fig. 5.1). NM patients often develop early atrophy from severe weakness and given their younger age may be confused with muscular dystrophies where atrophy is common.

Proximal and distal muscle strength is assessed mainly by manual muscle testing (MMT) in adults and older children using either the 0–5 MRC scale or 0–10 Kendall scale, both of which are interchangeable. In the juvenile population the Childhood Myositis Assessment Scale (CMAS) tool is frequently used, which is a combination of muscle strength, physical function, and muscle endurance measurement [4]. Recently, a candidate core-set of fitness and strength tests for patients with childhood or adult idiopathic inflammatory myopathies was developed [5]. It includes a treadmill exercise stress test, an incremental cycle ergometer test, 6-minute walk test (6MWT), handgrip strength, MMT, and CMAS in children and measurements of muscle endurance in adults using the functional index (FI-2). The MMT, CMAS, and FI-2 have been validated and shown to be reliable in people with IIM.

Atrophy
IBM: Early, can be a presenting feature
PM/DM: Late, chronic refractory disease
IMNM: May be early

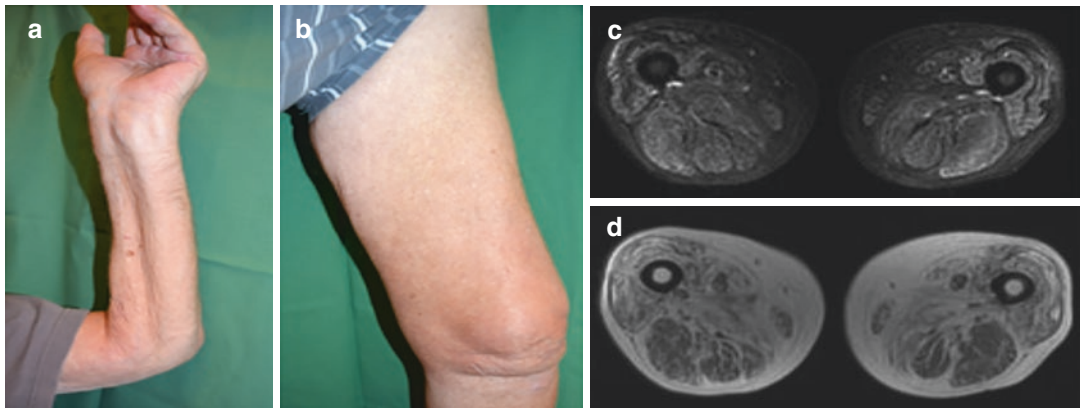

Fig. 5.1 Patient with inclusion body myositis. (**a**, **b**) Typical muscle atrophy in forearm and in quadriceps. (**c**) STIR (short tau inversion recovery) sequence in magnetic resonance imaging of thigh muscles showing persisting inflammation after 4 years of IBM duration. Almost all muscles have increased signal intensity that represents muscle edema induced by inflammation. (**d**) T1W (T1-weighted image) in magnetic resonance imaging shows fatty infiltration and muscle atrophy

Dysphagia and Dysphonia

Dysphagia occurs in 12–54% of patients with PM, DM, and IMNM, although it is less common in patients with anti-HMGCR-positive IMNM. Dysphagia is usually associated with more severe disease and carries a poor prognosis [6]. It is more frequent in the acute than in the late chronic phase of the disease. In IBM dysphagia is even more prevalent, occurring in up to 60% of patients. Symptoms vary from mild swallowing problems with dry food or reflux-like symptoms to severe impairment, which confers a risk of aspiration and may require nasogastric feeding or parenteral nutrition. Nasal regurgitation may also occur. A troubling consequence of dysphagia includes malnutrition and weight loss, ultimately leading to failure to thrive, and a major complication is aspiration of esophageal contents into the airways with subsequent development of pneumonia or lung abscess.

Dysphagia results from involvement of the striated portion of the upper esophagus and hypopharynx by the same myopathic process that afflicts the peripheral skeletal musculature [7]. Dysphagia in myositis is due to upper esophageal involvement, whereas the dysphagia of scleroderma results from dysmotility in the distal two-thirds of the esophagus.

Normal pharyngoesophageal muscle tone is lost, so patients complain that a food bolus cannot be properly propelled into the esophagus. The cricopharyngeus muscle, which is situated at the entrance to the upper esophagus, consists primarily of striated muscle fibers. When this muscle is impaired, it leads to severe difficulties in swallowing and long-term diminished elasticity, and contracture in the muscle may result in fibrosis with permanent impairment (Fig. 5.2).

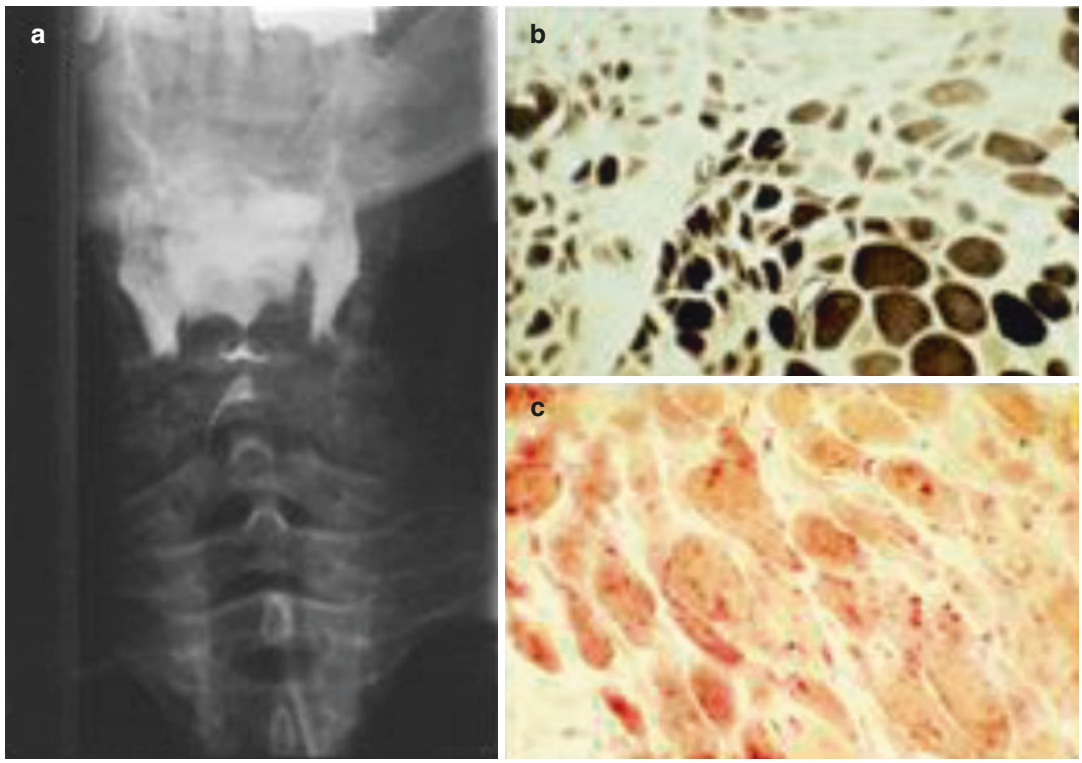

Fig. 5.2 Dysphagia due to upper esophagus muscle involvement in dermatomyositis. (**a**) Anteroposterior view of upper esophagus taken during swallowing of contrast material demonstrating total obstruction at the cricopharyngeal level. (**b**) Mosaic pattern of cricopharyngeal muscle. Fiber atrophy involves both types of fibers, and perifascicular atrophy is visible (ATPase, pH 10.4 × 200). (**c**) Intermysial fibrosis in the cricopharyngeal muscle with lysosomal activation in muscle fibers and intermysial elements (acid phosphatase, ×200)

Cricopharyngeal myotomy was described to help in this situation [8], but some patients may improve after rigid esophagoscopy if fibrosis of the muscle is the predominant cause. When severe dysphagia is present, there is a significant risk for airway aspiration often precluding swallowing studies due to the risk of barium aspiration. This is particularly dangerous in immunosuppressed myositis patients who are more susceptible to infections. When performed, contrast swallow X-ray film reveals obstruction at the cricopharyngeal level. A contrast liquid that can be easily absorbed if aspirated should be preferably used. Esophageal manometry is a reasonable alternative and shows ineffective esophageal motility, absence contractility, and increased upper esophageal sphincter pressure [9]. Recently, real-time MRI was successfully used for the evaluation of dysphagia in IBM [10].

Dysphagia
Avoid barium esophagography in severe dysphagia.
Alternatives: manometry or real-time MRI.
Upper endoscopy to rule out cancer.

Trismus is an infrequently reported symptom of polymyositis [11] but frequently reported when patients are specifically queried.

Pharyngeal muscle weakness may result in hoarseness or dysphonia. Patients complain of a voice change, which has a nasal quality. In rare cases, breathing difficulties due to diaphragmatic or thoracic muscle weakness may require assisted ventilation.

Muscle Damage and Steroid Myopathy

Assessing the cause of muscle weakness in myositis is critical to determine the appropriate treatment approach. That is, muscle weakness caused by inflammation (disease activity) must be distinguished from weakness due to muscle damage that results from fibrosis and fatty replacement. The former requires more immunosuppression, whereas muscle damage will not respond to anti-inflammatory treatment. Exercise and rehabilitation should be started early to improve function and to mitigate muscle damage and atrophy. Normal levels of creatine kinase (CK) or other muscle enzymes, a lack of response to increased immunosuppression, atrophy on muscle examination, and minimal to no activity found in electromyography (lack of insertional activity, positive sharp wave, and fibrillations) may point to the lack of ongoing inflammation and more to damage as the prevailing cause of the weakness. However, it is important to note that muscle enzymes may be normal in 20%–25% patients with active DM and JDM, whereas in PM and IMNM, they are nearly always elevated in active disease and often parallel disease activity. Magnetic resonance imaging should be considered in the assessment of muscle weakness in selected individuals and to distinguish activity from damage to the muscles (Fig. 5.3). Active inflammation shows characteristic features, while damage shows more fatty infiltration and atrophy [12]. In some cases a muscle biopsy may be necessary to guide subsequent therapy.

Another problematic situation relates to glucocorticoid myopathy that must be distinguished from myositis disease activity. In this situation, muscle enzymes are often normal, and there are less fibrillation potentials on EMG testing (Fig. 5.4), and muscle MRI can again be employed to assess for inflammation within the muscle tissue (Fig. 5.5). However, in some instances, more rapid glucocorticoid tapering will simply confirm the cause. Rarely, muscle biopsy will be required but if done will often demonstrate type 2 atrophy in steroid myopathy (Fig. 5.6).

Differentiate active myositis from muscle atrophy and/or steroid myopathy.

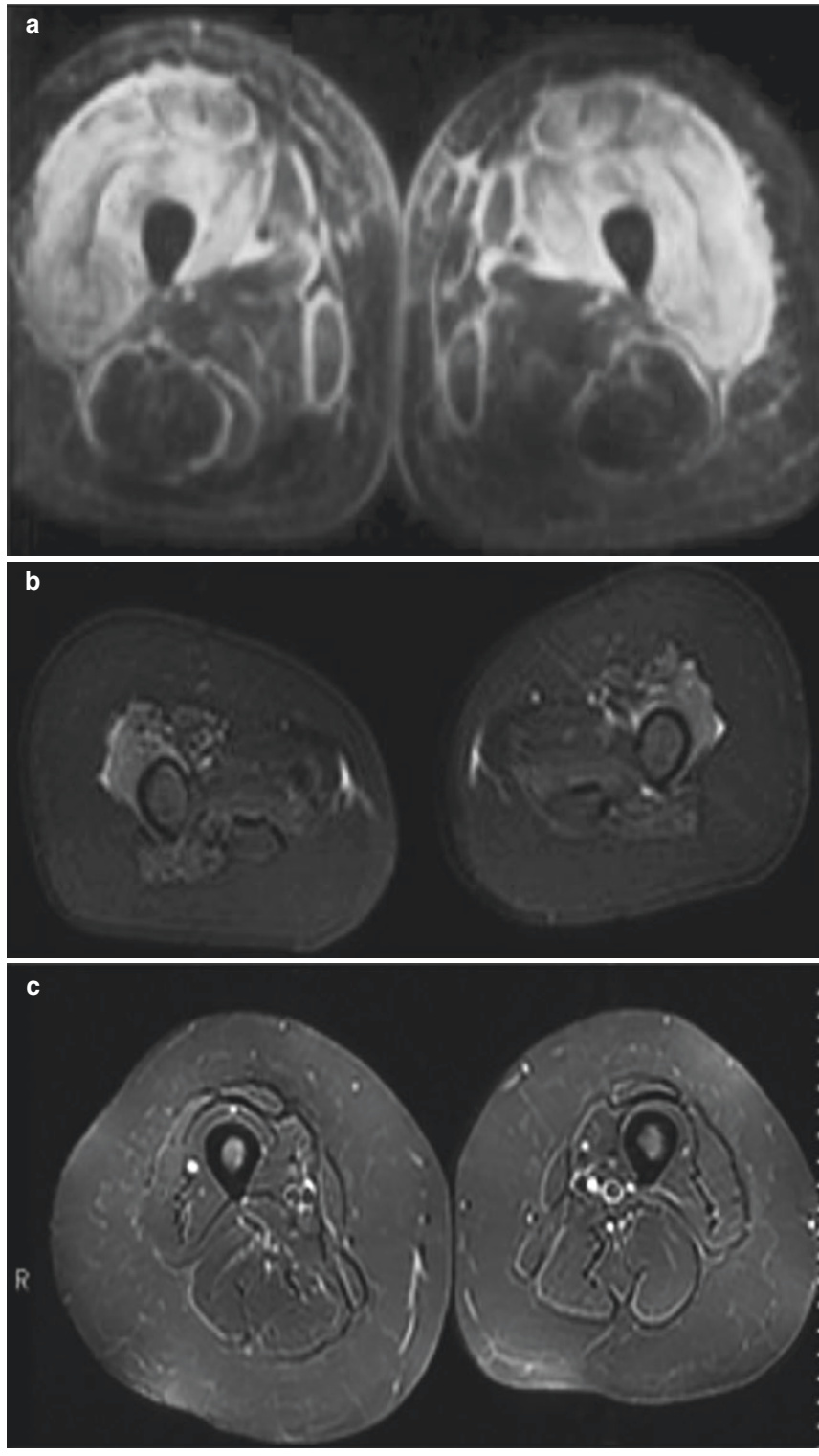

Fig. 5.3 Muscle MRI with axial STIR sequence of the thighs. (**a**) Inflammation with edema of extensors and fluid in fascial compartments in a patient with active dermatomyositis without muscle atrophy. (**b**) Localized muscle edema in extensor compartment in a patient with long-standing ongoing active disease with severely atrophic muscles. (**c**) No signs of edema on MRI in a patient with polymyositis and persistent weakness due to muscle atrophy

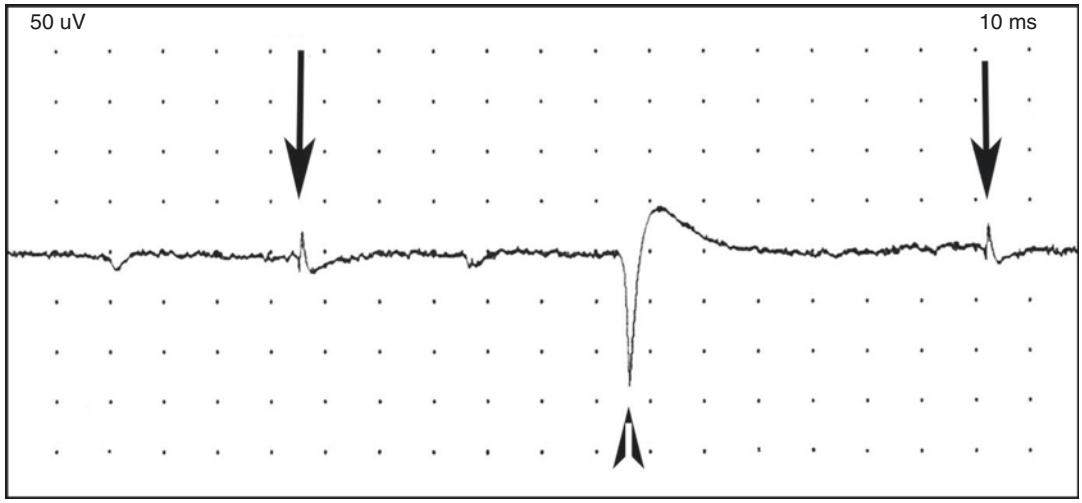

Fig. 5.4 In resting muscle, a positive sharp wave (arrowhead) and fibrillation potentials (long arrows) are shown. Lack of fibrillation potentials are seen in steroid myopathy

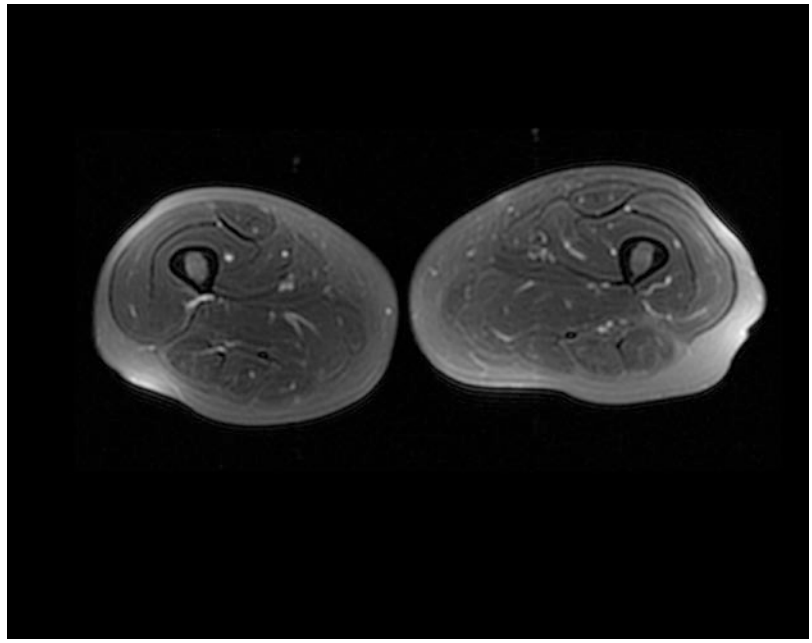

Fig. 5.5 MRI (T2-weighted image with fat suppression) in a patient with glucocorticoid-induced myopathy. A 46-year-old patient was investigated for severe muscle weakness. His history included long-term treatment with medium to high doses of methylprednisolone given for resistant bronchial asthma. Muscle MRI showed mild atrophy of thigh muscles without any signs of inflammation. Glucocorticoid-induced myopathy was confirmed by muscle biopsy that showed typical atrophy of type II muscle fibers and no other changes. After partial glucocorticoid tapering to 12 mg methylprednisolone daily, muscle strength improved significantly

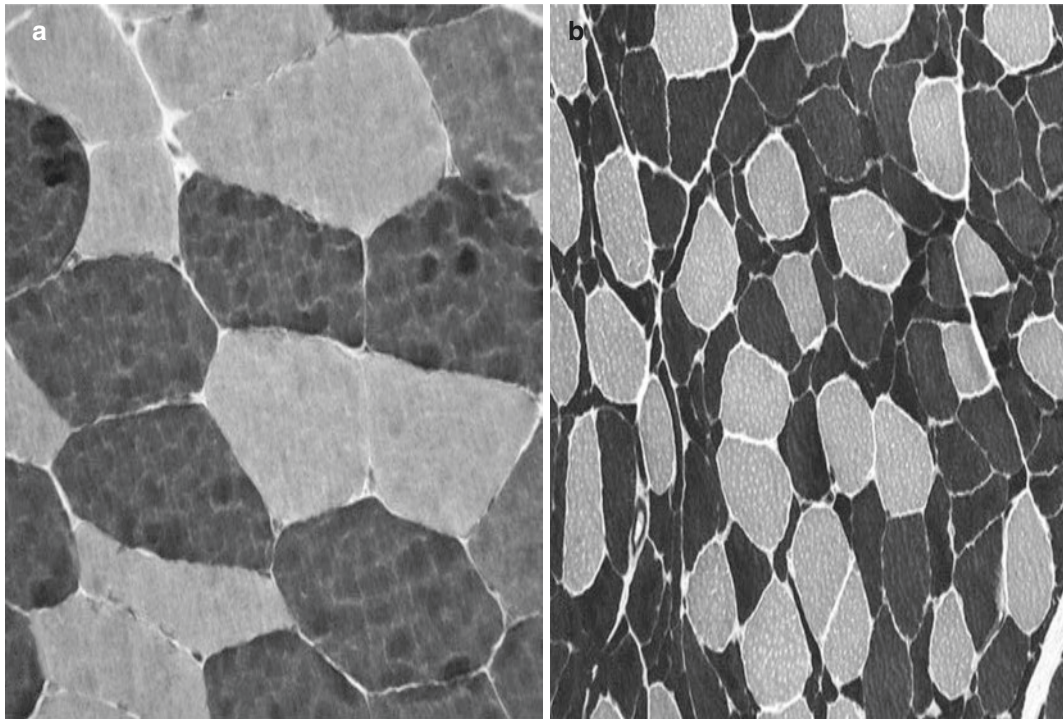

Fig. 5.6 Muscle histology, ATPase pH 9.4 (**a**) Normal size myofibers with dark-stained type 2 myofibers and light-stained type 1 fibers. (**b**) Atrophy affecting type 2 fibers exclusively

Red Flags for Myositis Diagnosis

Red Flags for Polymyositis and Dermatomyositis

- Family history of muscle weakness
- Asymmetric and significant distal weakness
- Muscle pain as a main symptom
- Sudden onset of muscle weakness
- Episodic muscle weakness after exercise, fasting, or illness
- Ocular and facial muscle involvement
- Early muscle atrophy or hypertrophy
- Presence of myotonic discharges on EMG or clinical myotonia
- Neuropathy, fasciculations, or cramping
- Muscle enzymes <2× or > 100× normal limits
- Lack of extramuscular: rash, arthritis, ILD, etc
- No response to therapy, especially initial response to glucocorticoids
- Absence of myositis autoantibodies
- Use of drugs associated with myopathies

There are certain muscle manifestations that are not usually associated with inflammatory myopathy and, if present, should prompt consideration of a different diagnosis [13]. Ocular and facial muscles are not affected in PM-DM and IMNM. However, as already mentioned, trismus may be observed due to impaired elasticity and persisting contractions in masticatory muscles. Mild facial muscle weakness is common in patients with IBM. Deep tendon reflexes in the upper extremities and patella are usually preserved in inflammatory myopathy

but diminish or disappear early in muscular dystrophies [14]. However, reflexes may be lost in severely weakened and damaged muscles such as IBM. Muscle pseudohypertrophy and the early development of muscle atrophy are characteristic features of muscular dystrophies [15] except in IMNM where early atrophy may develop due to the severity of muscle weakness. Dystrophinopathies usually manifest in children, and occasionally some patients with Becker dystrophy (incomplete dystrophin deficiency), facioscapulohumeral muscular dystrophy (FSHD), or female carriers of the Duchenne muscular dystrophy gene may present in adulthood. FSHD may be associated with inflammatory infiltrates in muscle biopsy, but the pattern of muscle weakness with facial involvement differs significantly from that of polymyositis [16]. Inflammatory infiltrate and upregulation of MHC class I may be seen in dysferlinopathy, and proper evaluation of muscle biopsy with staining for dysferlin is crucial to make the correct diagnosis. Myotonia, which is characterized by failure of muscle relaxation after activation, is usually not a feature of IIM and should prompt testing for any disease associated with this symptom, such as myotonic dystrophy type 2. Visible muscle fasciculations are caused by lower motor neuron involvement and may be seen in patients with amyotrophic lateral sclerosis. Predominant distal weakness is more typical for neuropathy and is not a feature of PM-DM or IMNM, although it can be observed in IBM. Episodic muscle symptoms, which develop only when the level of physical exertion or state of nutrition requires muscles to rely on the defective energy pathway, are characteristic of metabolic myopathies. Patients with myophosphorylase deficiency (McArdle's disease) typically experience an increase in exercise capacity after brief resting, which is called the second-wind phenomenon. Sudden onset of muscle weakness, rhabdomyolysis, muscle pain at rest, or severe muscle cramps are not typical for IIM and should prompt a search for a toxic or endocrine myopathy or other diagnoses [17]. The presence of myoglobinuria or CK levels higher than 100 times of the upper limit of normal are uncommon in IIM and should point to a different etiology.

Patients should be carefully asked for any medication they take, and particular attention needs to be paid to drugs with known myopathic potential. If no other symptoms except muscle weakness is present, it can still be IIM, but as the absence of extramuscular symptoms is rare in inflammatory myopathy (with the exception of IMNM), special care is required in diagnosing such cases. Similarly, if no response to treatment is encountered, then a different diagnosis should be considered. More than 70% of patients with IIM have myositis-specific or myositis-associated autoantibodies in their serum, and the absence of any positivity in autoimmune serology should be taken into consideration in making a diagnosis in such patients.

Disease Course

In IIM, the disease course is often subacute or chronic, and if treatment is delayed then ongoing inflammation may lead to muscle atrophy. As noted above, the disease course may be more rapid with NM related to anti-SRP or anti-HMGCR autoantibodies, where severe necrosis leads to significant weakness. If treatment is delayed, damage may rapidly ensue followed by atrophy, joint contractures, and substantial functional disability. Some patients, particularly with dermatomyositis, can have mild disease with the return of muscle strength in several months and may not require any subsequent treatment or, perhaps, only low maintenance therapy. In contrast, IBM progresses very slowly, often over many years, and simulates muscular dystrophy or slowly progressive motor neuron disease [18]. It does not respond to any known medications, but exercise, rehabilitation, and compensatory measures should be considered to maximally preserve functional capacity.

Conclusion

Muscular manifestations in IIM span from acute, severe immobilizing weakness in NM and progressive weakness in IBM, to mild or no muscle weakness in clinically hypomyopathic or amyopathic DM. Although muscle pain may be present, it is not a common symptom and points to an alternative etiology. Disease onset is usually acute or subacute in NM, subacute in DM and PM, and chronic in IBM. Except for IBM, proximal muscles are mostly involved with symmetric distribution. Muscle biopsy is essential for the diagnosis of most subtypes of myositis, except in some DM cases. Serum muscle enzymes parallel the disease activity but may be only slightly elevated or even normal in some active cases, particularly in DM or advanced PM. MRI is a useful technique to identify edema, atrophy, fibrosis, and fatty infiltration and may guide the selection of the muscle for the biopsy site. Signs and symptoms may overlap with different muscular, neurological, endocrine, toxic, and metabolic diseases, and careful diagnostic workup is necessary for correct diagnosis.

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6 Clinical Features of Myositis: Skin Manifestations

Peter B. Chansky and Victoria P. Werth

Key Points to Remember

- Dermatomyositis (DM) is a unique autoimmune disease within the family of idiopathic inflammatory myopathies that presents with characteristic cutaneous findings.
- Skin disease can present as activity (potentially reversible) with erythema, scale, erosions, or ulcerations or evolve into damage (irreversible chronic lesions) with poikiloderma or calcinosis cutis.
- Classic cutaneous manifestations of DM include the "heliotrope" rash on the eyelids, "Gottron papules or sign" on the hands/extensor surfaces, psoriasiform-like plaques on the scalp, "V sign" on the upper chest, "shawl sign" on the upper back or posterior neck/shoulders, "mechanic's hands" on the lateral or palmar sides of the fingers, "holster sign" on the lateral thighs, and nailfold changes.
- Calcinosis cutis is highly prevalent in children with juvenile DM and is associated with the anti-NXP-2 antibody in both adults and children.
- The anti-MDA5 antibody, seen in a subtype of clinically amyopathic DM, can present with palmar papules, severe cutaneous ulceration, ischemic digits, and a rapidly progressive and potentially fatal interstitial lung disease.
- Mechanic's hands are seen with antisynthetase and anti-PM-Scl autoantibodies, while anti-Mi-2 is associated with the classic rashes of DM.
- DM patients with the anti-TIF1-γ antibody often present with hyperkeratotic palmar papules, psoriasiform lesions, and telangiectatic and hypopigmented patches ("red on white").
- When considering a diagnosis of DM, it is critical to consider a broad differential because of the potential for overlapping symptoms with other connective tissue diseases.

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Introduction

Dermatomyositis (DM), unique among the idiopathic inflammatory myopathies (IIM), exhibits a set of distinctive and bothersome cutaneous findings. The classic skin manifestations of DM are not seen in patients with polymyositis or necrotizing myopathy and are broadly described as being active or resulting from disease damage causing scarring. Activity reflects a potentially reversible process and is represented by varying degrees of erythema, scale, and erosion or ulceration. Damage, an irreversible finding, describes chronic skin lesions that result from scarring of active skin lesions, often represented by the presence or absence of poikiloderma and calcinosis cutis. Erythema, a sign of skin inflammation and irritation, ranges in severity from pink to red to dark red/violet and is usually the first cutaneous finding in DM. Scale (visible hyperkeratosis of the stratum corneum) is also a marker of elevated disease activity that can occur with or without erythema. Lichenification (thickening of the epidermis) indicates worsening disease activity that results from chronic and excessive rubbing due to pruritus. Poikiloderma, a characteristic dermatologic finding in both DM and cutaneous lupus, describes the stereotypical features of hypopigmentation, hyperpigmentation, telangiectasia, and epidermal atrophy, often occurring in a photo-distributed pattern. Calcinosis cutis refers to calcium deposits within the skin and is another sign of damage from cutaneous DM. Overall, the skin lesions of DM are irritating and extremely pruritic—leading to a significantly impaired quality of life [1–3]. It may help differentiate DM rashes from CLE, as they are generally less pruritic.

The cutaneous signs of DM readily occur in specific anatomic locations that are almost pathognomonic for the disease. The two most common and pathognomonic rashes of DM are the "heliotrope" rash on the eyelids (30–60% of cases) and "Gottron papules or sign" on the hands or other extensor surfaces (60–80% of cases). These rashes are included in both Bohan and Peter's classification criteria as well as the newer EULAR/ACR classification criteria for IIM [4, 5]. Most DM rashes are symmetric, helping to differentiate them from local skin reactions or infections.

Description of Individual DM Rashes

An overview of the most common cutaneous manifestations in DM is illustrated in Fig. 6.1. The face is often affected with generalized facial erythema and the hallmark "heliotrope" rash (Fig. 6.2). The facial erythema is a photosensitive phenomenon that resembles the "malar rash" seen in lupus but is distinguished in patients with DM by the involvement of the nasolabial fold (Fig. 6.2). The textbook "heliotrope" rash refers to a localized pink-to-dark red/violet eruption or erythema on the eyelids, with the upper eyelid mostly involved, and can be associated with significant periorbital edema (Fig. 6.2). This finding is particularly bothersome to patients, as it is easily visible and can be quite pronounced. Moreover, the scalp is another site of involvement and usually presents with widespread erythematous scaly psoriasiform-like plaques that can be very pruritic (Fig. 6.3). These plaques are easily mistaken for seborrheic dermatitis or psoriasis and may contribute to a misdiagnosis or delayed diagnosis of DM. Furthermore, nonscarring alopecia on the scalp is also a common manifestation in patients with DM.

The upper chest and neck/shoulder region are also common areas of DM involvement. Photodistributed erythema and poikiloderma on the upper chest are referred to as the "V sign" (Fig. 6.4), while a similar finding on the upper back and posterior neck/shoulders is referred to as the "shawl sign" (Fig. 6.5). These sun-exposed areas can initially present as activity with erythema and pruritus that later develops into damage or poikiloderma.

The hands and extensor surfaces of the upper and lower extremities can be additional sites of cutaneous involvement. Raised, erythematous papules or plaques with or without scaling of the knuckles of the dorsum of the hand describes the textbook presentation known as "Gottron pap-

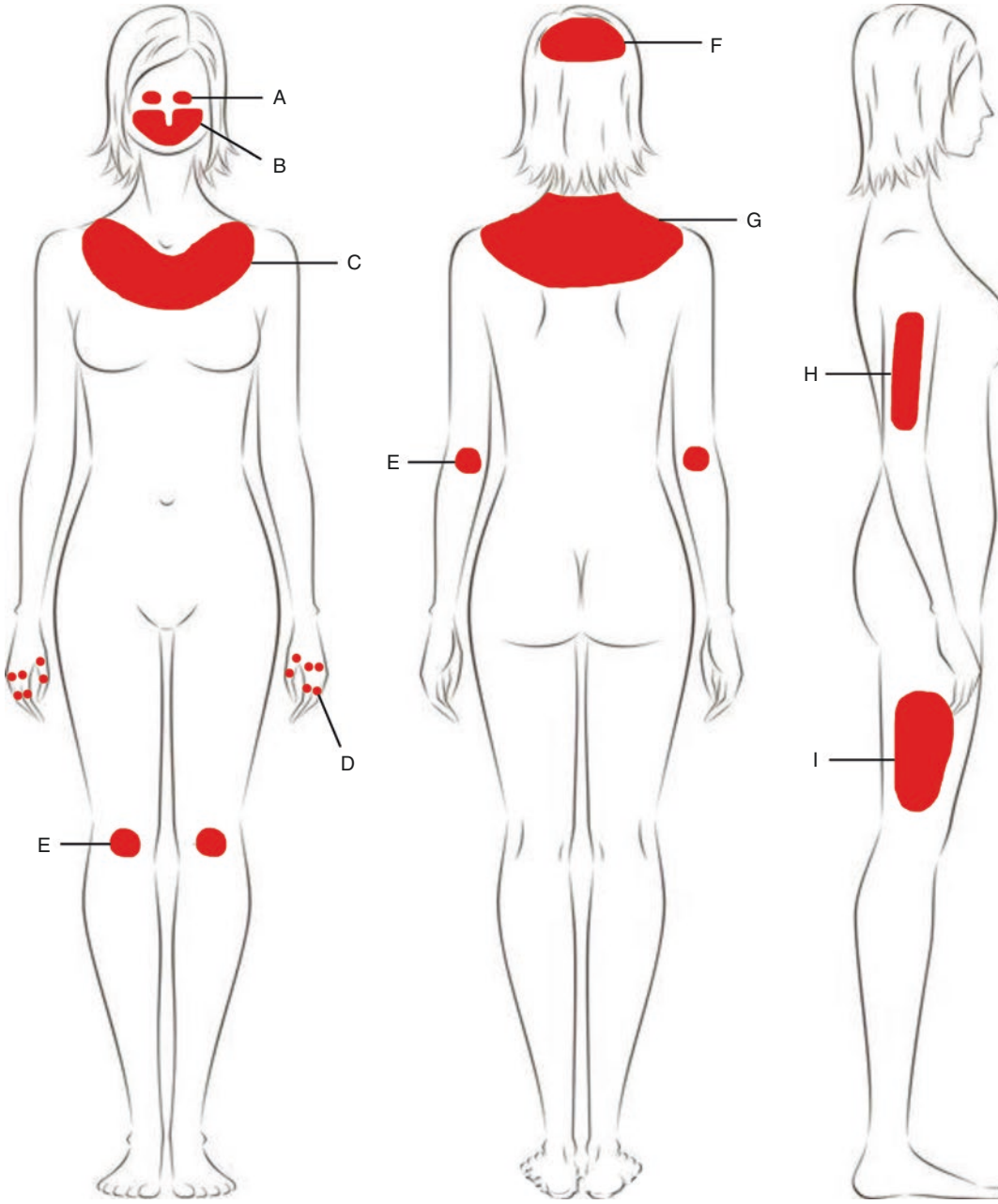

Fig. 6.1 Distribution of involvement in cutaneous DM ((**a**) heliotrope rash, (**b**) facial erythema involving nasolabial folds, (**c**) "V sign," (**d**) "Gottron papules," (**e**) "Gottron sign" on the knees and elbows, (**f**) scalp involvement, (**g**) "Shawl sign," (**h**) extensor erythema on lateral upper extremity, (**i**) "Holster sign" on lateral thigh)

ules" (Fig. 6.6). This eruption commonly involves the metacarpophalangeal joint, proximal interphalangeal joint, and distal interphalangeal joint, running linearly over the joints and tendons of the hand. In some patients, the erythema can occur on the dorsum of the hand and between the joints on the fingers. In particularly severe cases, patients may present with erosions, ulcerations, and scale. When erythematous, scaly macules are found in the same distribution over the joints of

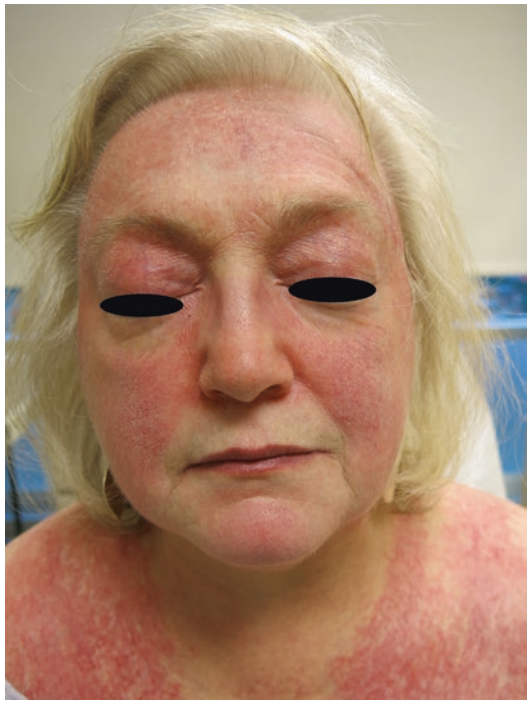

Fig. 6.2 Facial erythema with "heliotrope rash" and eyelid edema

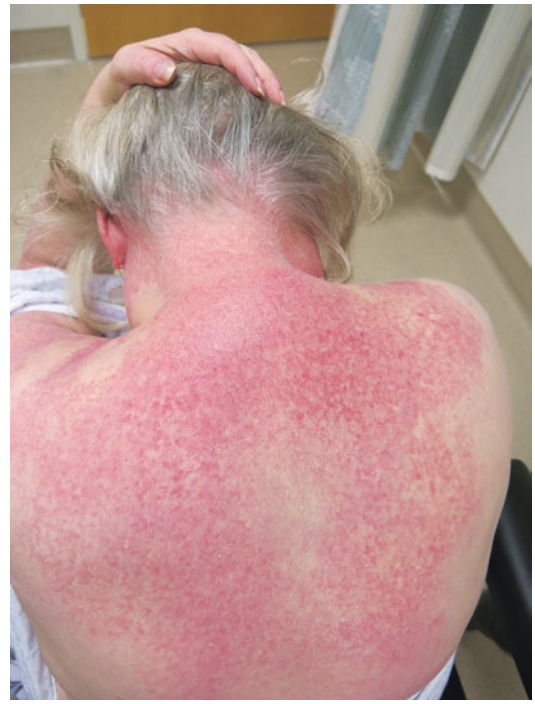

Fig. 6.5 Erythema and poikiloderma on the upper back ("Shawl sign")

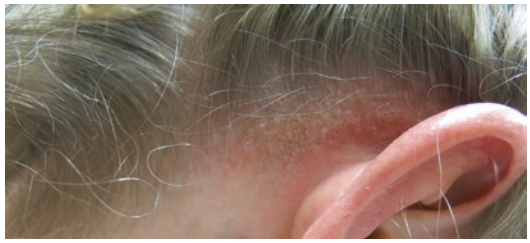

Fig. 6.3 Scaly, psoriasiform-like plaques on the scalp

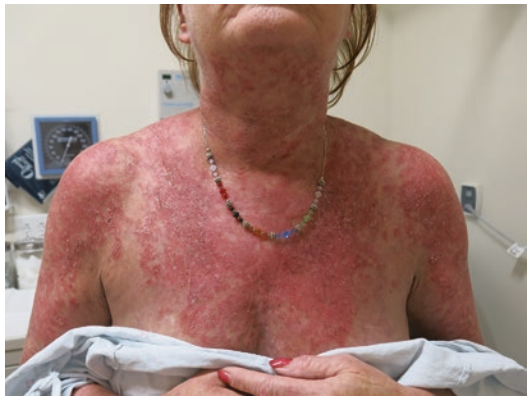

Fig. 6.4 Photodistributed erythema and poikiloderma on the chest ("V sign")

the hands or over the extensor surface of the elbows, knees, and ankles, it is known as "Gottron sign" (Fig. 6.7).

Finally, the lateral and palmar sides of the fingers may exhibit hyperkeratosis, lichenification, erythema, and scale known as "mechanic's hands" (Fig. 6.8). These features combine to produce horizontal fissuring, cracking, and lines on the skin that resemble the coarse hands of someone working in an industrial job or labor-intensive industry and occur most commonly on the radial aspect of the index and middle fingers and the ulnar aspect of the thumb. "Mechanic's hands" are frequently observed in patients with anti-synthetase autoantibodies and are reported in up to 70% of these patients [6] but have also been seen in patients possessing anti-PM-Scl autoantibodies as well as patients with classic and amyopathic DM without lung involvement.

The lower extremities can also be affected in DM. Erythema and scale on the lateral thighs is known as the "holster sign" (Fig. 6.9). These areas can exhibit poikiloderma. A similar, less

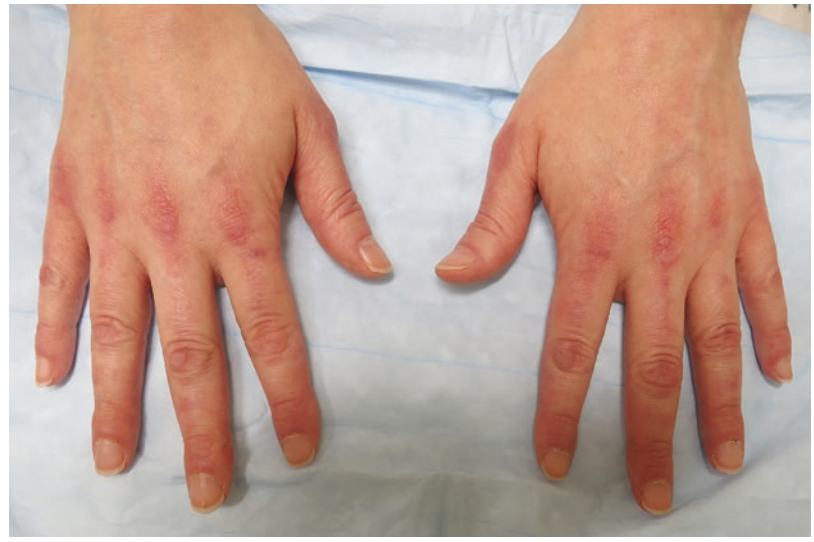

Fig. 6.6 Erythematous papules on dorsal knuckles ("Gottron papules")

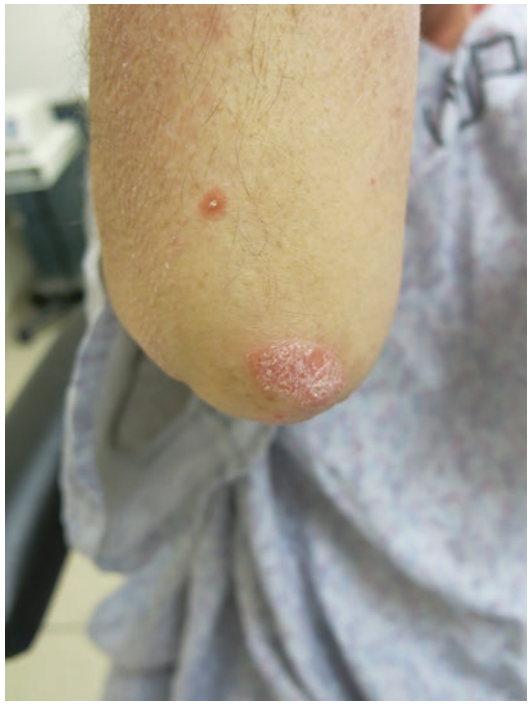

Fig. 6.7 Erythematous scaly plaque on the elbow ("Gottron sign")

common rash can be seen on the upper arms (Fig. 6.10). It is not well understood why this dermatologic finding presents in a traditionally sun-protected area of the body.

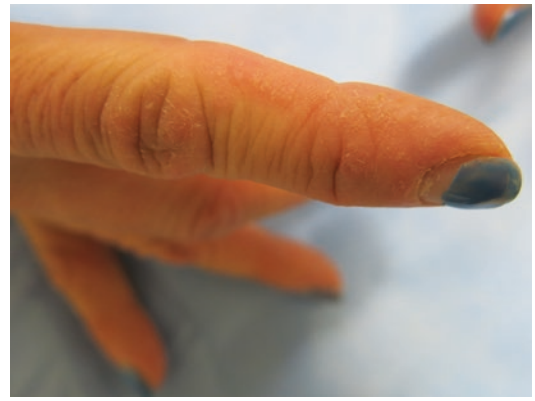

Fig. 6.8 Hyperkeratosis, lichenification, erythema, and scale on the sides of the finger ("mechanic's hands")

The presence of nailfold changes such as cuticular dystrophy, visible telangiectasias, and nailfold capillary dilation and dropout is also characteristic of DM (Fig. 6.11). Overgrowth of the nail beds can give the cuticles a classic "ragged" appearance. The nailbed capillary network may become dilated and visible with either the naked eye or a dermatoscope. Consequently, the enlarged vessels produce erythema around the cuticles termed periungual erythema, which, together with overgrowth, can be quite bothersome for

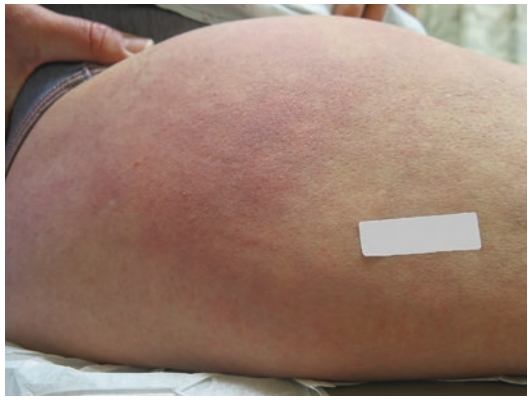

Fig. 6.9 Erythema and scale on the lateral thigh ("Holster sign")

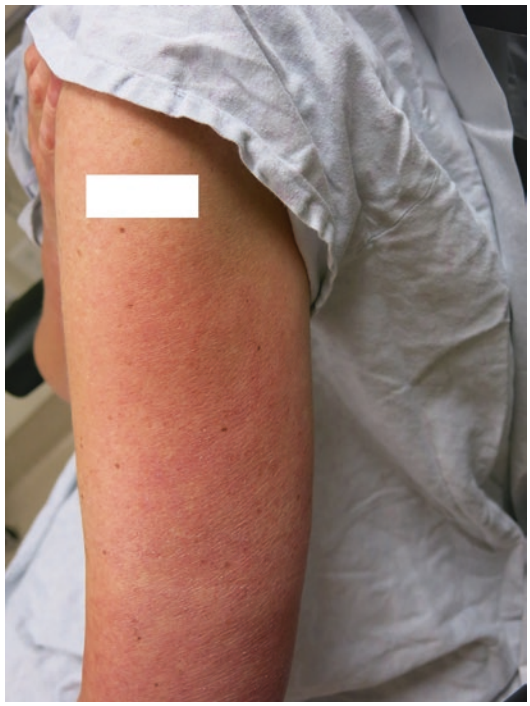

Fig. 6.10 Extensor erythema on the lateral upper arm

patients. The severity of the nailfold changes reflects disease activity, particularly in juvenile DM [7].

In several small studies, cutaneous ulceration as the early presentation of DM has been reported to reflect more severe disease or an underlying malignancy [8–10]; however, many DM patients with ulcers do not have cancer. Ulcerations can be associated with cutaneous vasculitis, calcinosis, panniculitis, or local microtrauma.

Fig. 6.11 Cuticular dystrophy ("ragged" cuticles) and visible telangiectasias on distal fingers

Calcinosis Cutis and Other Uncommon Rashes

Calcinosis cutis—the accumulation of calcium into hard nodules beneath the skin—occurs in intracutaneous, subcutaneous, fascial, or intramuscular locations, with a predilection for sites subjected to repeated microtrauma (the elbows, knees, flexor surfaces of the fingers, and buttocks). It is reported in up to 70% of children with juvenile DM (JDM) but is far less prevalent (approximately 20%) in adult DM patients [11–13]. Calcinosis usually develops in the upper extremities, such as the shoulders, arms, and hands, and is particularly resistant to treatment. It is linked to the duration of untreated disease as well as disease severity [14] and an increased risk for malignancy when associated with the anti-NXP-2 antibody [15]. Calcinosis leads to pain and functional compromise, particularly if the deposits are large and adjacent to a joint. Subsequent complications include extrusion of calcium deposits, ulceration, and infection of the overlying skin. Calcinosis cutis is also seen in other systemic autoimmune rheumatic disorders such as the limited form of systemic sclerosis (CREST). Thus, this physical exam finding requires a broad differential diagnosis. In JDM and DM, calcinosis is associated with anti-NXP-2 antibody.

Beyond the classic cutaneous findings discussed above, DM can also present with other less frequent skin manifestations. These include flagellate erythema, vesicular and bullous lesions, panniculitis, small vessel vasculitis, ichthyosis, widespread erythroderma, subcutaneous edema, and lipoatrophy. Flagellate erythema describes a specifically linear and streak-like distribution on the skin.

Rashes Associated with Clinically Amyopathic Dermatomyositis

A unique subtype of DM is clinically amyopathic DM (CADM), seen in approximately 20% of all DM cases in the USA [16]. These patients may have subtle signs of muscle involvement such as mildly elevated muscle enzymes and/or mild myopathic EMG or muscle biopsy abnormalities. Some CADM patients possess a unique autoantibody, termed anti-MDA5 antibody. This autoantibody has a characteristic cutaneous phenotype that includes palmar papules (Gottron papules but on the palmar side of the hand) (Fig. 6.12) with severe cutaneous ulcerations (Fig. 6.13) and ischemic digits sometimes leading to gangrene. It is very important to recognize these rashes, as up to 50% of such patients may present with or develop severe, rapidly progressive ILD, which portends a poor prognosis [17].

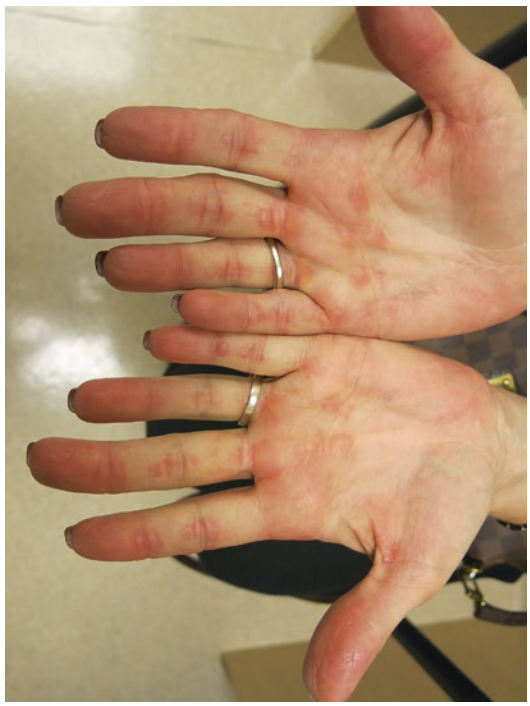

Fig. 6.12 Palmar papules associated with anti-MDA5 subtype of DM

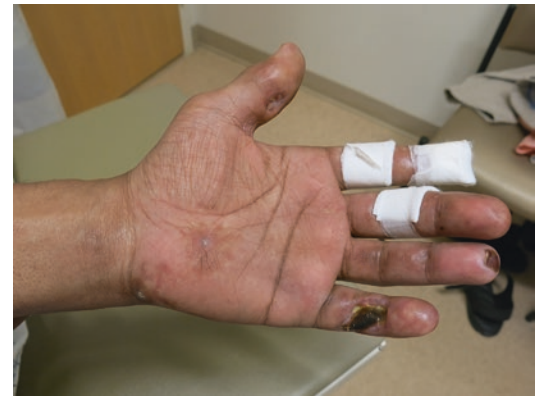

Fig. 6.13 Cutaneous ulceration associated with anti-MDA5 subtype of DM

Autoantibody Association of the Dermatomyositis Rashes

DM is associated with specific rashes and certain autoantibodies as seen with MDA-5 as described above. Similarly, mechanic's hands are seen with anti-synthetase and anti-PM-Scl autoantibodies, while anti-Mi-2 is associated with the classic rashes of DM including the heliotrope rash, Gottron's changes, the "shawl" and "V-neck" sign, cuticular overgrowth, and photosensitivity. Furthermore, DM patients with anti-TIF1-γ antibodies are more likely to demonstrate certain DM-specific cutaneous rashes including hyperkeratotic palmar papules, psoriasiform lesions, and the unique finding of telangiectatic and hypopigmented patches ("red on white") [18].

Differential Diagnosis

Ultimately, establishing a diagnosis of DM requires an astute dermatologist or a rheumatologist or neurologist with training or experience in DM, who can recognize many of the subtle features and characteristic distributions of the cutaneous manifestations of this disease. Overlapping

symptoms of other systemic autoimmune rheumatic disorders, such as rheumatoid arthritis, mixed connective tissue disease, Sjogren syndrome, systemic sclerosis, and subacute cutaneous lupus erythematosus, can contribute to a confusing clinical picture and an incorrect diagnosis.

A broad differential is important whenever considering a diagnosis of dermatomyositis. The appearance of a heliotrope rash must be evaluated for an allergic contact dermatitis or periorbital eczema. The facial erythema and malar rash seen in DM could be a sign of systemic lupus erythematosus (SLE). The differential for periungual erythema and visible nailfold telangiectasias includes scleroderma and less commonly SLE. The finding of photodistributed poikiloderma could also be seen in SLE, scleroderma, and rarely cutaneous T-cell lymphoma. The finding of erythematous scaly plaques on the extensor surface of the elbows, knees, and scalp could also present as psoriasis. Lastly, one must include the diagnosis of multicentric reticulohistiocytosis (MRH) and knuckle pads whenever considering the finding of Gottron papules on the joints of the dorsal hand.

The role of skin biopsy and its interpretation is discussed separately and may not be required in a typical DM case with classic rashes and confirmed muscle involvement. However, given the broad differential presented by the DM rashes discussed above, and in cases of less typical DM rashes, a skin biopsy may confirm one's clinical suspicion (Table 6.1).

Table 6.1 Characteristics of typical DM rashes

DM rash	Typical location	Frequency	Clinical association	Common differential	Figure
Gottron papules	Dorsum of the hands over MCP, PIP, and DIP joints, B/L	Common, ~70% [19]	Pathognomonic rash of DM	MRH, knuckle pads	Figure 6.6
Palmar papules	Palms, B/L	Rare	Associated with anti-MDA5 antibody	Callus	Figure 6.12
"V sign"	Upper chest, B/L	Common, ~83% [20]	All types of DM	Photodistributed drug eruption, SLE	Figure 6.4
"Shawl sign"	Upper back, posterior neck, and shoulders B/L	Common, ~63% [20]	All types of DM	Photodistributed drug eruption, SLE	Figure 6.5
"Holster sign"	Lateral thigh, B/L	Less common, ~28% [20]	All types of DM	Bruise, SLE	Figure 6.9
Nailfold capillary changes with cuticular overgrowth	Cuticles of fingernails, B/L	Common, capillary changes ~70%, cuticular overgrowth ~35% [20]	All types of DM	Scleroderma, SLE	Figure 6.11
Calcinosis	Shoulder girdle, elbows, hands, B/L	20–70% [11–13]	Associated with JDM and anti-NXP-2 autoantibodies	Scleroderma (CREST)	N/A
Mechanic's hands	Lateral and palmar side of the digits of the hand, B/L	Common, ~48% [20]	Associated with anti-synthetase and anti-PM-scl autoantibodies	Hand dermatitis, allergic contact dermatitis	Figure 6.8
Ulceration	Dorsal and/or ventral side of the hand and digits, B/L	Rare	Associated with anti-MDA5 antibody	Scleroderma, diabetes, chronic infection	Figure 6.13
Scalp	Scalp, all quadrants	Common, ~70% [20]	All types of DM	Psoriasis, seborrheic dermatitis	Figure 6.3
Heliotrope	Eyelids, B/L	30–60% [19, 20]	All types of DM	Contact dermatitis, eczema	Figure 6.2

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Clinical Features of Myositis: Lung Manifestations

7

Sonye K. Danoff

Key Points to Remember

- Lung involvement is common in autoimmune myositis and is a leading cause of morbidity and mortality.
- Interstitial lung disease (ILD) is the most common manifestation and can present with variable severity from asymptomatic to acute respiratory failure and death.
- Lung involvement can be a presenting symptom in myositis, so one must consider autoimmune myositis in the assessment of ILD.
- Initial symptoms of lung involvement may be mild and non-specific including persistent cough and shortness of breath with exertion.
- All patients with myositis, particularly those at high risk for ILD (e.g., anti-synthetase and anti-MDA5 antibody positive patients), should be evaluated for myositis-associated lung disease.
- Treatment is determined by the etiology of underlying lung involvement but most commonly includes immunosuppression for ILD and diaphragmatic weakness.
- Patients with lung involvement require careful, ongoing monitoring as the disease course can be variable and occasionally fulminant.

Introduction

The lung is a common target in autoimmune myositis, affecting up to 90% of patients with anti-synthetase antibodies [1]. While interstitial lung disease (ILD) is frequently noted, there are other pulmonary manifestations directly and indirectly associated with myositis that impact lung function leading to pulmonary symptoms. These include venous thromboembolic (VTE) disease, pulmonary artery hypertension (PAH), diaphragmatic dysfunction, pneumomediastinum, and infection [2]. Further, myositis can be complicated by obstructive sleep apnea (OSA) [3] and coronary artery disease (CAD) [4], both of which may contribute to dyspnea as well as fatigue. Thus, evaluating the myositis patient with possible lung involvement requires a methodical approach (Table 7.1).

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Table 7.1 Lung involvement in myositis

	Frequency and associations
Interstitial lung disease	Most common (50–90%), associated with anti-synthetase syndrome and anti-MDA5 autoantibodies [5]
Rapidly progressive interstitial lung disease	Common (10–50%), associated with anti-MDA5, more common in Asian countries [6]
Diaphragmatic weakness	Less common (10–20%), associated with severe muscle disease [7]
Pulmonary artery hypertension	Less common (10%), associated with anti-synthetase syndrome and higher mortality [8]
Venous thromboembolism	Uncommon [9]
Pneumomediastinum	Rare, associated with dermatomyositis [10]
Pulmonary infection	Major contributor to inhospital mortality [11]
Chronic acid reflux/ aspiration pneumonia	Commonly associated with esophageal dysmotility in myositis, often leading to ILD pattern on CT chest or worsening of underlying ILD [12]

Lung as the First Organ Manifestation In addition to being the initial organ targeted in myositis, lung involvement is often the dominant feature. Consequently, patients with myositis-associated ILD fall into two groups: (1) those with known myositis and (2) those with ILD of no known etiology. In the first group, lung involvement may represent an autoimmune feature, a complication of myositis therapy, or an infectious complication [2]. In the second group, the more significant issue is the recognition that the ILD is indeed autoimmune in nature and then determining the most likely clinically associated disease [13]. That is, ILD in myositis patients is a challenge to diagnose in patients without muscle involvement and may only be considered by an experienced clinician. Patients with clinically amyopathic disease presenting as ILD are difficult for pulmonologists (and other specialists) to identify, leading to both misdiagnoses and a delay in diagnosis. Further, some patients are never recognized as having autoimmune ILD failing to receive potentially lifesaving immunosuppressive therapy.

> Interstitial lung disease can be the presenting and predominant clinical feature in myositis.

Common Clinical Presentations of Lung Disease The presence of lung involvement is variable, ranging from subtle symptoms with mild dyspnea on exertion or fatigue to fulminant respiratory failure [5]. In this scenario, one must also consider cardiac causes of dyspnea, especially CAD [4], or myocardial involvement from myositis [14] as well as obstructive sleep apnea [3]. The most common cause of dyspnea in myositis is ILD and/or diaphragmatic weakness leading to restrictive physiology. ILD increases morbidity and mortality in myositis [15] and comes in many forms, including usual interstitial pneumonitis (UIP), organizing pneumonia (OP), or non-specific interstitial pneumonia (NSIP) [2]. One must consider chronic acid reflux and aspiration pneumonitis (especially in myositis patients with esophageal dysmotility) with worsening dyspnea in patients with or without known ILD. Treatment of underlying acid reflux is often a reasonable strategy. Fortunately, ILD is often treatable and the prognosis is better when recognized and treated early. Diaphragmatic weakness can occur with or without ILD and is a challenge to diagnose if both are present [7]. The treatment of both ILD and diaphragmatic weakness includes appropriate immunosuppression with careful attention to common comorbidities such as infection, thromboembolic disease, pulmonary artery hypertension, and pneumomediastinum.

Asymptomatic Lung Involvement

The precise prevalence of lung involvement in myositis is unknown, in part because of asymptomatic lung involvement in some patients. These patients

may be identified during evaluation for other comorbid conditions such as CT imaging done for cancer screening or screening for ILD in patients with antibodies known to be associated with ILD. CT scanning may demonstrate minimal interstitial changes, and pulmonary function testing (PFT) may only show a slight reduction in lung volumes or diffusing capacity (DLCo). Nevertheless, these patients should be carefully followed for progression, despite needing no specific therapy given their asymptomatic lung disease.

Chronic Cough

A dry, persistent cough is a common feature in ILD [16], but a chronic cough in myositis patients should be approached as in any patient. More acute, infectious coughs (typically viral) should be treated with cough suppressants, but if this treatment fails, then consideration should be given to asthma, postnasal drip, and reflux. A more chronic cough leads to consideration of ILD, but esophageal dysmotility and gastroesophageal reflux disease (GERD) are common comorbidities in myositis patients [12], so addressing these comorbidities is reasonable. A persistent cough after treatment for reflux certainly warrants chest CT imaging.

- Chronic cough is a common presenting symptom of ILD.
- Chronic gastroesophageal reflux disease and aspiration should be considered in the differential for worsening dyspnea as well as chronic cough.

Rapidly Progressive ILD

This rare lung manifestation is characterized by progression of pulmonary symptoms to respiratory failure in a matter of weeks to months. This pattern has been described in patients with the MDA5 autoantibody but can be seen with virtually any antibody known to be associated with ILD in myositis patients [6]). An interesting feature in many such patients is the lung-dominant nature of their disease in the setting of subtle signs and symptoms of myositis. Features to watch for include Raynaud phenomenon, skin rashes, muscle weakness, or laboratory abnormalities showing elevated muscle or liver enzymes. Typically, the results of myositis-associated autoantibody testing is not always available at the time of diagnosis, so treatment must be undertaken with the provisional diagnosis of myositis-associated ILD. Additional testing to further support this diagnosis includes an electromyogram, muscle MRI, or a muscle biopsy consistent with inflammatory myopathy.

Rapidly progressive ILD is commonly associated with anti-MDA5 antibody.

List of common clinical features

Asymptomatic	Commonly noted during cancer screening or ILD screening of high-risk patients
Progressive dyspnea on exertion	Most common manifestation of ILD and diaphragmatic weakness
Rapidly progressive dyspnea on exertion	Less common but severe feature of ILD and primarily associated with specific autoantibodies
Chronic cough	Common ILD feature
Dyspnea, productive cough, and fever	Consider infection especially if immunocompromised
Acute dyspnea	Consider VTE, pneumomediastinum, aspiration pneumonia, or drug (e.g., methotrexate) toxicity
Exercise desaturation	Consider PAH

Diaphragmatic Weakness Isolated diaphragmatic weakness is common and is associated with reduced lung volumes and a preserved DLCo on PFT. However, PFT is difficult to interpret in the setting of concomitant ILD. Diaphragmatic weakness can be evaluated by supine and upright PFT which will show a drop of >5% in Forced vital capacity (FVC) in the supine position [17]. Fluorographic sniff testing is less helpful since

both diaphragms are involved, and paradoxic movement of the diaphragm is not seen as would occur with unilateral paralysis. Finally, the maximal inspiratory pressure (MIP) and maximal expiratory pressure(MEP) can be measured, but these tests require patient cooperation and may be difficult to interpret.

Diaphragmatic weakness is a common cause of dyspnea in myositis.

Infectious and Medication Toxicity Infection and medication-associated lung involvement are complicating features of myositis to be considered. In immunosuppressed patients, infection must always remain high on the differential and includes common viral and bacterial pathogens followed by opportunistic infections (e.g., Pneumocystis) including fungal and mycobacterial causes. Infection is a major cause of inhospital mortality [11]. Drug-associated lung injury must also be considered. Methotrexate, a first-line agent in myositis, can cause pneumonitis with cough, which is generally resolved by stopping the medication. Biological agents have been implicated in lung toxicity as well [18]. Thus, concomitant therapeutic agents and infection must always be considered when lung disease is seen in myositis patients.

Must rule out infection and treatment toxicity in patients with worsening dyspnea even in setting of known lung disease.

Pneumomediastinum Pneumomediastinum can be a dramatic and early presenting feature in myositis, and its presence should raise the suspicion for this autoimmune disease, especially dermatomyositis [10]. While dramatic, this finding is a marker of underlying ILD and can typically be followed conservatively until resolution. It may worsen after the use of high-dose glucocorticoids for the treatment of ILD.

Pneumomediastinum is associated with dermatomyositis.

Pulmonary Artery Hypertension (PAH) The prevalence of primary PAH in myositis is unclear, but it should be considered in patients with myositis-scleroderma overlap syndromes and anti-synthetase syndrome. It is reasonable to screen these patients with an echocardiogram at baseline and periodically thereafter. Clinically, development of primary or secondary PAH should be considered (1) in the setting of worsening dyspnea without evidence of high-resolution chest CT (HRCT) progression or (2) with a drop in DLCo out of proportion to a drop in the lung volumes. The presence of an elevated pulmonary artery systolic pressure (PASP) on an echocardiogram as well as right ventricular (RV) dilatation or dysfunction should trigger a thorough evaluation for pulmonary hypertension while at the same time considering thromboembolic disease.

PAH should be considered in anti-synthetase and myositis-scleroderma overlap syndromes.

Diagnosis, Evaluation, and Management The assessment of ILD is more thoroughly discussed in Chap. 26, and the management of ILD is reviewed in Chap. 32. Briefly, the diagnosis of lung disease typically derives from patient-reported symptoms (dyspnea on exertion, cough, chest discomfort, fatigue), physical examination findings (crackles, tachypnea, tachycardia), or screening studies completed to detect cancer or lung involvement (e.g., in anti-synthetase syndrome). An ILD diagnosis is confirmed by typical high-resolution chest CT (HRCT) scan findings that also provide information on the different patterns of lung involvement (see Chap. 26). Pulmonary function testing pro-

vides the requisite quantitative assessment realizing that it is possible to have typical ILD features in the setting of normal pulmonary function tests. Similarly, the 6 Minute Walk Test (6MWT) distance and the degree of oxygen desaturation with exercise can provide useful information on the impact of lung disease on a patient's functional capacity. Bronchoalveolar lavage may be necessary to rule out infection, especially in patients with worsening dyspnea on immunosuppressive agents or the patient with fever and an elevated white blood cell count. A lung biopsy may be required in patients with no definitive autoimmune diagnosis or in those lacking a myositis-specific autoantibody known to be associated with ILD or when other competing causes of dyspnea should be considered.

Treatment is determined related to the etiology of the lung disease. For ILD and diaphragmatic weakness, immunosuppression is necessary which includes prophylaxis against opportunistic infection. Supplemental oxygen in the setting of exercise desaturation can improve exertional capacity and limit the risk for hypoxemic vasoconstriction leading to PAH. Routine vaccination to prevent common bacterial and viral infections should always be done. A comprehensive assessment of cardiac function including echocardiography and an exercise stress test is indicated in many patients to evaluate PAH and CAD, respectively. Finally, functional rehabilitation programs including pulmonary rehabilitation are likely an underutilized intervention but provide both physical and emotional benefits.

Conclusion

Lung involvement, particularly ILD, is common in myositis, and chronic cough and dyspnea on exertion are hallmark features. Identifying the nature of the lung disease is essential for directing appropriate therapy and eliminating alternative etiologies. Since there are a range of pulmonary manifestations, a systematic approach including careful history, medication review, physical examination, as well as pulmonary-specific testing including high-resolution chest CT scans and pulmonary function testing are indicated. The early detection and treatment of myositis-associated lung involvement is critical for optimal patient outcomes.

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Clinical Features of Myositis: Cardiac Manifestations

8

Sangmee Bae and Christina Charles-Schoeman

Key Points to Remember

- Clinically evident heart problems such as symptomatic arrhythmias and congestive heart failure are reported in anywhere from 3% to 10% of patients with IIM, and the incidence of asymptomatic cardiac disease in IIM patients is even higher.
- Initial evaluation of cardiac status with assessment of traditional CV risk factors as well as echocardiogram and EKG, especially if high cardiovascular risk is recommended in IIM patients.
- Cardiac MRI and technetium99m-pyrophosphate scintigraphy are noninvasive imaging tools that can be utilized.
- Comprehensive screening of cardiac function in all IIM patients should be undertaken if patients present with any cardiac or even nonspecific unexplained symptoms.
- cTnI is more specific for myocardial damage and should be used to evaluate the myocardium in IIM, whereas cTnT and CK-MB are nonspecific and elevated with elevation of CK.
- Immunosuppressive therapies in conjunction with traditional cardiac medications and risk mitigation can be used for the treatment of cardiac disease in IIM. Severe cases may require pacemaker or defibrillator placement.

Introduction

Cardiac involvement in idiopathic inflammatory myopathies (IIM) was first reported in the late nineteenth century by Oppenheim [1] but until the late 1970s was considered to be a rare disease manifestation. However, with the introduction of sensitive, noninvasive techniques to assess cardiac involvement, heart disease is now a well-recognized clinical manifestation of IIM [2–4]. In earlier reports, the cardiac manifestations in IIM were primarily described as being occult or subclinical, mostly manifesting as conduction abnormalities [5]. However, as additional data on various noninvasive testing have accumulated, it has become evident that the heart muscle is frequently affected in patients with IIM, and more importantly, cardiovascular events are one of the major causes of morbidity and mortality [6–9]. To date, there have been no large epidemiological studies on cardiac involvement in IIM, and thus, the exact frequency of heart involvement is still unknown. In smaller cohort studies, the reported incidence of cardiac involvement varies between

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6% and 72% dependent on patient selection, the definition of heart involvement, and the diagnostic modalities used for screening [10–12]. Clinically evident heart problems are reported in 3–10% of patients with IIM, of which symptomatic arrhythmias and congestive heart failure constitute a large portion [13].

Pathophysiology

Distinct histopathological features are noted in the skeletal muscle of polymyositis (PM) and dermatomyositis (DM) patients [14]. Similarly, autopsy studies of DM and PM patients demonstrate inflammatory infiltration of the myocardium that resembled the inflammation in the skeletal muscle [15]. Diffuse, severe mononuclear inflammatory infiltrates and fibrosis localized to the endomysium and the perivascular areas were reported with associated degeneration of cardiac myocytes. Such findings were also noted in the conduction system including the SA-AV node and His-Purkinje conduction system, suggesting a mechanistic link to the clinically observed conduction abnormalities including complete heart block [15, 16].

A recent case report compared detailed histopathological findings of both the heart and the skeletal muscle of a DM patient undergoing heart transplantation [17]. A distribution of muscle fiber damage/atrophy in the peripheral areas of the cardiac muscle was noted to be similar to the perifascicular distribution in the DM skeletal muscle. Intense perimysial alkaline phosphatase reactivity was also noted in the cardiac and skeletal muscles. Finally, overexpression of membrane attack complex (MAC) on capillaries, another hallmark finding of DM, was present in both the cardiac and skeletal muscles of the same patient further supporting a similar pathogenesis.

- Cardiac muscle shows similar histopathological findings as skeletal muscle in DM.
- Inflammatory infiltrates and fibrosis are seen in the endomysium, perivascular, and perifascicular regions of the cardiac muscle as well as in the conduction system.

Clinical Manifestations

Clinically significant cardiac involvement constitutes a small portion of patients with DM/PM. Table 8.1 represents proportions of clinical symptoms in compiled IIM cohorts in a systematic review. The most commonly reported cardiac problem is congestive heart failure seen in 5–12% of patients [2, 4, 5, 16, 18]. Symptoms such as dyspnea, orthopnea, and palpitations are reported in 5–20% of IIM patients [4, 12, 16], but it is difficult to differentiate between a primary cardiac cause and concurrent respiratory muscle weakness due to skeletal muscle involvement [19].

Ischemic heart disease is important in IIM, and angina pectoris has previously been reported in 4–18% of IIM patients [4, 5]. Interestingly, autopsy studies have demonstrated significantly more coronary artery disease than reported clinically as angina, with coronary atherosclerosis including intimal proliferation, medial sclerosis, luminal narrowing, and evidence of remote infarction in up to 44% of patients [5, 15, 18]. In prospective IIM cohorts, MI was seen in 4.6–6.8%, which is similar to the reported age-matched prevalence in the US population [13]. However, a

Table 8.1 Clinically evident cardiac involvement

Prospective cohort	$n = 195$ patients (%)	Retrospective cohort	$n = 290$ patients (%)
Dyspnea	21 (10.8)	Combined dyspnea, chest pain, edema, and palpitations	14.8 (5.1)
Angina	15 (7.7)		
Palpitations	10 (5.1)		
Peripheral edema	13 (1.5)		
Systolic murmur	227 (13.8)	Systolic murmur	3 (1)
S4 gallop	15 (7.7)		
S3 gallop	1 (0.5)	S3 gallop	4 (1.3)
Arrythmia	27 (13.8)	Arrhythmias	7 (2.4)
CHF	11 (5.6)	CHF	34 (11.7)
MI	9 (4.6)		
Myocarditis	5 (2.6)		
Complete heart block	1 (0.5)		
Pericarditis	2 (1)	Pericarditis	2 (0.6)

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recent large Canadian population study noted an incidence rate of MI being significantly higher than in the general population (22.5 vs. 5.5 events per 1000 person-years) with hazard ratios being the highest within the first year of IIM diagnosis [20]. Vasospastic angina has also been reported to be associated with signs of generalized vasculopathy such as Raynaud phenomenon [21].

Symptoms of arrhythmias and conduction defects such as palpitations, dizziness, and syncope have also been reported in up to 13.8% of IIM patients in prospective cohorts [13]. Such signs may suggest developing fibrosis of the conduction system and should be monitored carefully. Although the mild rhythm disorders do not commonly have clinical significance, there are several reports of patients requiring permanent pacemaker placement and others having fatal arrhythmias [4, 18]. Taken together, this data reinforces the need for increased awareness and monitoring of cardiac involvement in IIM patients. Comprehensive screening of cardiac function in all IIM patients should be undertaken if patients present with any cardiac or even nonspecific unexplained symptoms.

Subclinical Heart Involvement

Subclinical cardiac involvement is reported much more commonly than clinically evident cardiac manifestations, and the reported incidence varies between 13% and 72% of IIM patients depending on the selected noninvasive testing [22]. However, the clinical and prognostic significance of these subclinical cardiac abnormalities are not well known such that routine screening is not recommended beyond initial cardiac evaluation in the asymptomatic patient. Abnormal EKG findings are the most commonly observed findings including atrial or ventricular premature beats, atrial/ventricular tachycardia, atrial fibrillation, A-V conduction block, high-grade heart block, bundle branch block, PR prolongation, abnormal Q waves, nonspecific ST-T wave changes, and left ventricular hypertrophy [4, 18]. Echocardiography is useful in detecting structural heart disease and cardiac function even in the absence of clinical symptoms. In patients with IIM, there are reports of atrial enlargement, ventricular hypertrophy, valvular changes such as thickening and stenosis, global or segmental hypokinesis, reduced systolic or diastolic function, and pericardial involvement [22]. Newer techniques such as tissue Doppler imaging [23] allow detection of earlier manifestations such as left ventricular diastolic dysfunction (LVDD) when conventional measurements may be unremarkable [24]. The incidence of LVDD seems to be significantly higher in IIM patients compared to the general population [25].

- Initial evaluation of cardiac status with assessment of traditional CV risk factors, echocardiogram, and EKG is recommended in IIM patients.
- No routine follow-up screening is currently recommended beyond initial cardiac evaluation in an asymptomatic patient.
- Comprehensive cardiac workup is recommended in a patient with cardiac or nonspecific, unexplained symptoms.

Diagnostic Modalities

Clinically relevant cardiac manifestations may be present even without overt symptoms, which is why noninvasive testing is recommended at the time of diagnosis.

1. *Electrocardiogram (EKG)*

EKG or Holter abnormalities are detected in 32–72% of IIM patients, which is significantly more frequent than the general population. The most well-described finding is a conduction abnormality, with the most frequently observed being left anterior hemi-block and right bundle branch block [18]. SA or AV nodal dysfunction related to extensive fibrotic damage of the conduction system can be seen and may even result in high-

Table 8.2 ECG abnormalities in IIM patients

Prospective cohort	*n* = 243 patients (%)	Retrospective cohort	*n* = 433 patients (%)
First-degree AV block	9 (3.7)	First-degree AV block	6 (1.4)
Second-degree AV block	1 (0.4)		
Third-degree AV block	3 (1.2)	Third-degree AV block	8 (1.8)
Bundle branch blocks	3 (1.2)	Bundle branch block	12 (2.7)
Left anterior fascicular block	5 (2)		
Conduction abnormality, not specified	38 (15.6)	Arrhythmias, nonspecific	7 (1.6)
Supraventricular tachycardia	8 (3.3)	ECG abnormalities, nonspecific	28 (6.4)
Atrial fibrillation/flutter	3 (1.2)		
Premature atrial contraction	6 (2.5)		
Premature ventricular contraction	46 (18.9)		
Nonsustained ventricular tachycardia	1 (0.4)		
ST-T abnormalities	11 (4.5)	ST-T abnormalities	64 (14.7)
Q waves	2 (0.8)	Q waves	3 (0.7)
Left ventricular hypertrophy	18 (7.4)		
Left atrial hypertrophy	4 (1.6)	Left atrial hypertrophy	2 (0.4)
Right ventricular hypertrophy	2 (0.8)	Right ventricular hypertrophy	1 (0.2)

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degree heart block, which has been reported in 1–2% of patients. Other rhythm abnormalities include premature atrial or ventricular contractions, atrial dysarrhythmias, ventricular tachyarrhythmias, longer QRS, and supraventricular tachycardia [25]. Nonspecific ST-T wave changes are also seen frequently in 4–15% of patients [22] (Table 8.2).

As rhythm and conduction abnormalities are the most commonly reported cardiac manifestations in IIM patients, experts recommend routine ECG at time of diagnosis. ECG and telemetry monitoring should also be done when patients present with symptoms such as palpitations or syncope. Findings such as high-degree heart block or tachyarrhythmias may require therapeutic intervention such as a permanent pacemaker or defibrillator placement.

- Baseline EKG should be done in all patients diagnosed with IIM.
- EKG abnormalities are common in IIM patients, but most are not clinically significant.
- No association between myositis disease activity and EKG abnormalities has been found in the studies to date.
- Severe arrhythmias in IIM patients may occur and require telemetry for diagnosis and pacemaker/defibrillator placement.

To date, the degree of systemic disease activity does not seem to correlate with the presence of ECG abnormalities [15, 16]. In a cohort of 77 IIM patients, there was no association between the presence of ECG abnormalities and CK levels, severity of IIM, presence or absence of various clinical phenomenon (i.e., arthritis, Raynaud phenomenon, rash, ILD, malignancy), disease duration, or treatment. Furthermore, ECG findings frequently progressed during clinical remission [18].

2. *Echocardiogram*

Few prospective, detailed echocardiographic studies are available in the literature, which report echocardiographic abnormalities in 14–62% of myositis patients [4, 11, 23, 26]. Left

ventricular diastolic dysfunction (LVDD) by tissue Doppler imaging (TDI) is the most frequently reported abnormality, noted in up to 48% of IIM patients, which is significantly higher than in the general population (30%) [24, 25, 27]. LVDD may be reflective of increased chamber stiffness due to fibrosis and is usually the first sign of systolic and diastolic heart failure. TDI estimates the velocity of contraction and relaxation of myocardial segments during a cardiac cycle. The use of TDI has increased sensitivity and specificity for systolic and diastolic dysfunction when compared to traditional echocardiography [28] and has been shown to be a useful tool to detect preclinical cardiac impairment in several studies [24, 25, 27, 29]. Two prospective controlled studies of echocardiographic measurements on 46 IIM and 51 DM patients with age- and gender-matched healthy controls confirmed a higher frequency and/or severity of LVDD in IIM [24, 27]. In contrast to diastolic dysfunction, compromise of systolic function noted by decreased LV ejection fraction on echocardiogram is rarely noted except when severe cardiac involvement and typical CHF symptoms are present.

Finally, other observed findings noted on echocardiography include mitral valve prolapse (7–23%), hyperdynamic LV function, left atrial and/or left ventricular enlargement, left ventricular hypertrophy, septal hypertrophy, thickened valve leaflet, valve prolapses/stenosis/regurgitation (most frequently in the mitral and aortic valve), pericardial effusions (which were all hemodynamically insignificant), and pulmonary hypertension [30]. However, reported incidences are observational from prospective patient cohorts, and it is unclear if such findings are more common in IIM compared to healthy controls.

- Left ventricular diastolic dysfunction (LVDD) is reported more frequently in IIM patients compared to matched healthy controls.

3. *Cardiac Magnetic Resonance (CMR)*

CMR provides not only anatomical imaging but also the ability to detect features of myocardial tissue such as inflammatory edema, irreversible necrosis or scarring, and contractile dysfunction [31]. Contrast-enhanced MRI technique using gadolinium diethylene-triaminepantaacetic (Gd-DTPA) is able to differentiate between myocardial infarction and inflammatory tissue from myocarditis. Early contrast enhancement with high signal intensities detected within the first minutes of injection indicates myocardial hyperemia; however, late gadolinium enhancement (LGE) [32] is highly sensitive for irreversible injury demonstrated as areas with high signal intensity in the equilibrium phase (>10 min post injection) [33]. The pattern and regional distribution of LGE is helpful in distinguishing the etiology of myocardial disease, whereas the severity or extent of LGE is associated with a worse prognosis [34, 35]. Inflammatory myocarditis may have a patchy distribution and can be subepicardial, sparing the subendocardium, which is distinct from ischemic lesions that always involve the subendocardium [36]. As IIM patients have an increased risk of both inflammatory myocarditis and ischemic events, CMR can be considered to differentiate between the two with the differences in regional distribution. This suggests CMR as a useful tool in diagnosis as well as monitoring of myocardial inflammation in IIM [37–39].

CMR may also be a useful tool in early detection of subclinical cardiac involvement in IIM by determining the extent of unrecognized myocardial scarring [39]. CMR is also sensitive to changes in the cardiac muscle following treatment. In a study of four patients with IIM and myocarditis, after 6 months of treatment with glucocorticoids, the area of early and delayed contrast enhancement on CMR was substantially reduced and correlated with improvement of cardiac symptoms [38].

- Cardiac MRI is a useful noninvasive tool for detection of inflammation vs. myocardial damage in IIM.

4. *Technetium99m-Pyrophosphate (99mTc-PYP) Scintigraphy*

Cardiac uptake of ^{99m}Tc-pyrophosphate (99mTc-PYP) in particular has been suggested as a mode of detecting inflammatory activity of the myocardium in IIM patients. A study of 30 DM/PM patients reported abnormal 99mTc-PYP uptake in 57% of patients suggesting that it may assist in early detection of cardiac involvement [40]. Patients with high uptake scores had poor cardiac outcome, and autopsy showed perivascular and interstitial mononuclear infiltrates and degenerative muscle fibers within the myocardium [40]. Smaller studies also have used 99mTc-PYP in the detection of cardiac outcome in IIM and reported uptake in 50–76% of patients [41–43]. However, without large comparative studies with a control group, the clinical usefulness of scintigraphy in IIM-related myocarditis is yet to be proven, and further studies are warranted. False-positive results may be seen with hyperparathyroidism, prior myocardial infarction, dystrophic cardiac calcification, and ventricular aneurysms.

5. *Endomyocardial Biopsy*

Endomyocardial biopsies allow histologic confirmation of inflammatory myocarditis and are the gold standard for diagnosis. However, biopsies are rarely performed in routine clinical practice given the invasive nature and concern for complications such as vascular injury, puncture site complications, or prolonged bleeding [44] and should only be considered at a center where it is performed routinely. A case of endomyocardial biopsy in a patient with abnormal contrast enhancement on Gd-DTPA CMR showed interstitial fibrosis, edema, cellular cluster, and hypertrophy, suggestive of inflammatory damage [45].

- Endomyocardial biopsy is the gold standard for myocarditis due to connective tissue disease, but is not commonly done due to the risk of complications related to an invasive procedure.

6. *Biochemical Markers*

Cardiac enzymes in patients with IIM must be interpreted with caution, as elevations may be from damaged or regenerating skeletal muscle. Creatine kinase isoenzymes include the CK-MM form, which is mainly from the skeletal muscle, and the CK-MB isoform, which is thought to be restricted to the myocardium. Although cardiac enzymes are reported to be specific for myocardial damage and ischemia, there have been reports of elevated CK-MB levels and CK-MB/CK ratios in IIM patients even in the absence of cardiac symptoms or ECG changes [46–48]. This is also true for cardiac troponins, which are typically thought to be highly specific for myocardial ischemia [49, 50]. It is thought that as regenerating muscle fibers resemble fetal muscles and express similar genes, CK-MB and cTnT isoforms (which are known to be expressed in the skeletal muscle during fetal development) are re-expressed in damaged or regenerating skeletal muscle. Hence, elevated CK-MB and cTnT may be misleading in IIM patients and result in unnecessary investigations for coronary artery disease.

Cardiac troponin isoform I (cTnI) is only expressed in the heart during fetal development and unlikely to be found in a noncardiac muscle [51, 52]. In a study of 49 patients with IIM, CK elevations had a high correlation with cTnT but not with cTnI, suggesting cTnI is the most reliable serum marker to detect myocardial damage in patients with IIM [53, 54]. A study by Erlacher and colleagues also measured various "cardiac" enzymes in IIM patients without clinical evidence of cardiac involvement and showed CKMB elevation in 51%, cTnT in 41%, and cTnI in only 2.5% of patients. CTnT, but not cTnI, was correlated with disease severity scores and skeletal muscle damage markers [55].

- CK-MB and cTnT may be elevated in myositis without cardiac involvement
- cTnI is more specific for myocardial damage and should be used to evaluate the myocardium in IIM

Management

1. *Glucocorticoids and Immunomodulatory Agents*

There are no randomized trials to evaluate the treatment effects for DM/PM-specific heart disease. Glucocorticoids and immunosuppressive therapy are used to control the underlying disease process as active disease is thought to be driving the cardiac disease. However, reports of response in the cardiac manifestations to immunosuppressive therapy are conflicting. In a study of four patients with IIM-related myocarditis, two of four (50%) patients who presented with symptoms of heart failure had resolution of their symptoms after 2 months of immunosuppressive therapy, and cardiac MRI normalized in all four patients after 6 months, suggesting a beneficial role for systemic immunosuppression [38]. In contrast, other studies assessing abnormal EKGs, complete heart block, and abnormalities on autopsy in IIM cohorts suggested that cardiac involvement was independent of skeletal muscle disease activity or treatment [16, 18, 56].

Systemic immunosuppressive agents other than glucocorticoids that have been used in treating cardiac disease in IIM include cyclophosphamide, cyclosporine, methotrexate and azathioprine, but the impact of individual agents remains unknown. Intravenous immunoglobulin (IVIG) has shown good immunomodulatory effects in IIM and is frequently used for cutaneous and skeletal disease. There are no studies of its use in IIM cardiac disease, but in pediatric acute myocarditis, IVIG was shown to improve LV function and survival in the first year after treatment [57]. When considering IVIG in patients with IIM cardiac involvement, it is important to consider co-management with cardiology and close monitoring of their volume status with appropriate adjustments in their diuretics given the risk of volume overload with IVIG. Subcutaneous immunoglobulin also may be of benefit with lower risk of volume overload in such cases [58].

2. *Traditional Cardiac Medications*

For clinically evident cardiac involvement, patients are managed similarly to non-IIM patients in regard to their cardiac manifestations. Antiarrhythmics, antianginals, and heart failure medications are considered depending on the clinical presentation. When there is myocardial involvement with clinically significant CHF, pharmacological treatment includes beta-blockers, aspirin, diuretics, angiotensin-converting enzyme (ACE) inhibitors, or angiotensin-II receptor blockers (ARBs) [59]. IIM patients also have a higher risk of vascular involvement leading to ischemic episodes in which case anti-anginals such as calcium channel blockers and nitrates may be used.

3. *Pacemaker and Cardiac Implantable Cardiac Defibrillator*

Conduction abnormalities including high-degree heart block are seen in IIM patients with cardiac involvement, and there are several reports of patients requiring a temporary or permanent pacemaker placement (PPM) with variable outcomes [18, 56, 60]. In the general population, PPM success rates are reported between 88% and 92%, but success rates in IIM patients are yet to be determined [59]. Some reports have shown a successful outcome, whereas others have noted mortality from progressive conduction abnormalities resulting in sudden cardiac death (SCD) despite PPM placement. Most cases that require PPM placement were below the AV node with SA node dysfunction noted infrequently [60].

Cardiac resynchronization therapy with an implantable cardiac defibrillator (ICD) may be considered in patients with symptomatic ventricular tachycardia or ventricular fibrillation which can be fatal. In non-IIM patients, cardiac resynchronization therapy with ICD is indicated for patients with impaired LV function (LV ejection fraction <35%) and left bundle branch block in NYHA functional classes II to IV [61]. There are no studies regarding ICD placement in patients with

IIM-related myocarditis, and further investigation is needed to address the benefits and timing of ICD placement in IIM-related cardiomyopathy.

4. *Management of Traditional Cardiovascular Risk Factors*

There is increasing evidence of a higher prevalence of traditional cardiovascular risk factors (obesity, hypertension, dyslipidemia) in patients with IIM [62–65]. One retrospective study of 344 patients with IIM reported a high prevalence of hypertension (62%) and diabetes (49%) [62], and other cross-sectional studies have shown an increased frequency of dyslipidemia, glucose intolerance, and obesity [63–65]. A Canadian population study showed an increased myocardial infarction frequency but not ischemic stroke in DM and PM patients compared to age-/gender-matched control group selected from the general population [66]. Age/sex/entry time-matched hazard ratios (HR) for MI among PM and DM patients compared with the control cohort were 5.2 and 3.5, respectively. For stroke, the HR for PM was 2.46 and for DM was 1.81 (not statistically significant). The incidence of MI and stroke were highest in the first year of diagnosis.

Several contributing factors have been proposed to explain the increased atherosclerosis in patients with IIM. Long-term use of glucocorticoids is known to increase glucose intolerance and dyslipidemia and accelerate the development of atherosclerosis. The Danish study demonstrated that present use of glucocorticoids correlated with severe coronary artery calcification [65]. Physical inactivity caused by the disease itself as well as the constant low-grade inflammation may also lead to increased development of atherosclerosis and metabolic syndrome, as suggested in patients with RA and SLE [67, 68].

Such results support increased vigilance in cardiovascular prevention and aggressive treatment of modifiable CV risk factors in IIM. Structured exercise programs have been well established as beneficial to skeletal muscle disease in IIM [69, 70], but the increased physical activity and improvement in aerobic capacity may also be beneficial in improving cardiovascular outcomes. Statins are completely contraindicated in patients with immune-mediated necrotizing myopathy related to the anti-HMGCR antibodies [71, 72]. Approximately 10% of patients developed some worsening muscle symptoms associated with statin use with the majority of symptoms improving after holding therapy, suggesting that particular attention should be paid to statin use in some myositis patients.

5. *Cardiac Transplantation*

Severe cardiac involvement in IIM requiring cardiac transplantation is rare, and only a few cases of cardiac transplant in IIM have been reported. Successful cardiac transplantation was first reported in 1999 in a patient with dilated cardiomyopathy related to polymyositis [73]. A recent report described a case of a patient with treatment refractory DM with severe cardiomyopathy with cardiogenic shock who underwent a successful orthotropic heart transplant doing well at 25 months post-transplant [17].

Cardiac Management

- Immunosuppressive/immunomodulatory therapies
  - Glucocorticoids
  - Other immunosuppressive agents including cyclophosphamide, cyclosporine, methotrexate, azathioprine, etc.
  - IVIG or SQIG
- Traditional cardiac medications
  - Beta-blockers, aspirin, diuretics, ACE inhibitors, or ARBs
  - Antiarrhythmic drugs
- Risk factor modification
  - Smoking
  - Obesity
  - Diabetes/insulin resistance
  - Hypertension
  - Dyslipidemia
  - Steroids
- Pacemaker and cardiac implantable cardiac defibrillator
- Cardiac ablation
- Cardiac transplantation[1]

[1]Angiotensin-converting enzyme (ACE), angiotensin-II receptor blockers [74].

Prognosis

Patients with DM/PM have increased mortality compared to the general population with cardiopulmonary disease as the leading cause of death, ranging between 5% and 20% [8, 10, 12, 75]. Congestive heart failure and/or myocarditis, myocardial infarction, and complete heart block were most frequently noted in a systematic review including 33 retrospective and prospective IIM cohorts (30%, 18%, and 10%, respectively) (Table 8.3) [13]. Unlike viral myocarditis, which leads to spontaneous recovery with minimal or no sequelae, cardiac involvement in IIM portends an overall poor prognosis of the disease [59]. Prospective studies are needed to evaluate the effect of various cardiac and immunomodulatory therapies/strategies on survival in IIM patients.

Conclusions and Recommendations

Cardiac involvement is increasingly recognized in patients with IIM as a poor prognostic factor as well as a major cause of morbidity and mortality. When clinically evident, patients may present with congestive heart failure, arrhythmias, or coronary artery disease, but most patients will have subclinical involvement that is only evident on further testing. Experts recommend that all patients with a diagnosis of IIM undergo a detailed cardiac history and a screening EKG and echocardiogram on initial evaluation. Tailored cardiac therapy should be used in conjunction with immunosuppression, and patients require continued monitoring even when the skeletal disease is in remission (Fig. 8.1.).

Table 8.3 Causes of cardiac mortality

Prospective cohort	$n = 102$ patients	Retrospective cohort	$n = 550$ patients
CHF	4	CHF	3
MI	7	MI	2
Myocarditis	4	Myocarditis	1
Pericarditis	2	High-degree AV block/bundle branch block	5
Endocarditis	1	Arrhythmia	4
		Cardiac arrest	2
		Nonspecific cardiac cause of death	9
		HOCM	1

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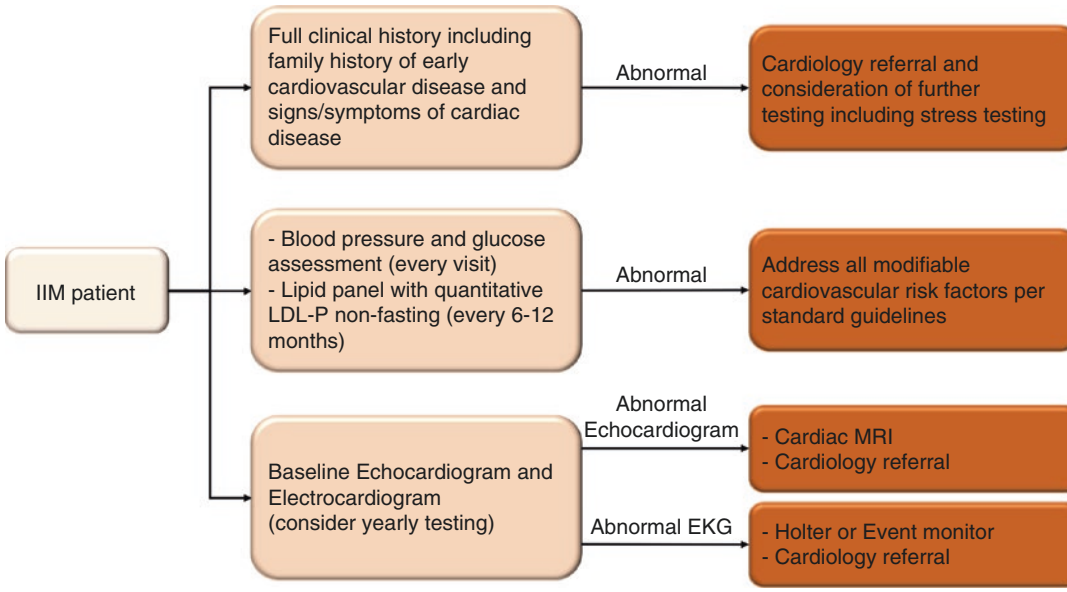

Fig. 8.1 Evaluation of cardiac involvement in IIM. * Co-management by Cardiology and Rheumatology for all IIM patients with cardiovascular disease

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9 Clinical Features of Myositis: Arthritis, Raynaud Phenomenon, Constitutional

Kristina E. N. Clark and David A. Isenberg

Key Points to Remember

- Effects of idiopathic inflammatory myopathies are not confined to muscles.
- Arthritis typically manifests in patients with anti-synthetase syndrome, where it most commonly presents with subluxation without erosions.
- Patients with anti-synthetase syndrome and rheumatoid factor or anti-cyclic citrullinated peptide antibodies are more likely to have an arthritis with erosions, a distribution which is rheumatoid-like.
- Raynaud phenomenon is more prevalent in patients with anti-synthetase syndrome, and nail-fold capillaroscopy can provide diagnosis, prognosis and treatment response.
- Fever is most commonly described in anti-synthetase syndrome.
- Myalgia is a frequently reported symptom, specifically in statin users and those with necrotising myopathy.

Introduction

Idiopathic inflammatory myopathies (IIM) represent a group of heterogeneous systemic autoimmune disorders that encompass not only muscle and skin disease but many extramuscular features including arthritis, Raynaud phenomenon (RP) and constitutional symptoms. These features often predate muscle weakness and will be discussed in this chapter.

Arthritis and Arthralgia

Arthritis and arthralgias are common in patients with myositis occurring in up to 90% of patients [1, 2] at some point in their disease course, with a higher incidence in those with anti-synthetase syndrome (anti-SS). Arthralgia is the presenting symptom in 21–31% [3, 4] of patients with anti-SS but increases to 88% if patients also have anti-cyclic citrullinated peptide (anti-CCP) antibodies [3]. This group of patients may represent a rheumatoid arthritis/anti-SS overlap, more overt in some cases than others. Three general patterns of joint involvement have emerged. The most common symptom is a symmetrical polyarthritis mainly affecting metacarpophalangeal (MCP) joints, proximal interphalangeal (PIP) joints, wrists and knee joints, while 25% have isolated arthralgias, and about 15% develop a subluxing arthropathy mainly affecting the distal interphalangeal joints (DIP) [5].

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Within the subgroup of anti-SS, there is a higher prevalence of arthritis in patients with the Jo-1 autoantibody. Up to 75% of patients with this antibody will develop arthritis or arthralgia and is the presenting clinical feature in 24% of patients [2, 6]. The majority of patients with anti-Jo-1 anti-SS and arthritis develop a symmetrical polyarthritis without erosions (most commonly affecting the small joints of the hands) (66%) [7]. A subluxing arthropathy is described in nearly 20% of patients [3, 5, 8] and is rarely found in other forms of IIM [9].

Patients with anti-Jo-1 anti-SS and a subluxing arthropathy exhibit a predominately deforming non-erosive arthropathy, mainly affecting the interphalangeal joint of the thumb and DIPs. This can be associated with periarticular calcinosis, although calcinosis in this subgroup is rare [8]. Patients with subluxing arthropathy tend to experience a longer time interval between joint onset of symptoms and diagnosis of anti-SS compared to the symmetrical polyarthritis and arthralgia of anti-SS patients [5]. Subluxing or deforming non-erosive arthropathy is also seen in patients with anti-Jo-1 sine myositis, although the frequency is low [10].

Although the commonest anti-SS autoantibody to be associated with arthralgia is anti-Jo-1, this symptom is also commonly described in patients with anti-EJ and anti-KS. Anti-PL-7 makes up 2–5% of the anti-synthetase spectrum and leads to an erosive arthritis in around 60% of patients [2, 11]. Arthritis and arthralgia symptoms are less commonly seen in patients with any of the other antibodies associated with the anti-SS.

Rheumatoid Factor (RF) and Anti-CCP Positivity in Idiopathic Inflammatory Myopathies

RF and anti-CCP antibodies are positive in about 45% and 30% of patients with anti-SS, respectively [9]. These patients are significantly more likely to develop an inflammatory arthropathy during their disease course (100% vs. 41% anti-CCP positive vs. negative) [3]. The number of joints involved is also significantly higher in patients with anti-SS and anti-CCP (+) than those with just anti-SS [3].

It is the combination of anti-Jo-1 anti-SS and anti-CCP/RF, which seems to have the strongest association with an inflammatory erosive arthropathy. At disease onset, anti-CCP and RF are positive in anti-Jo-1 (+) patients with arthritis in about 30% and 13.5%, respectively [3], whereas only 8% of patients without arthritis at disease onset were positive for RF, and 1.5% were positive for anti-CCP. The majority of these patients with anti-CCP and RF autoantibodies will develop an inflammatory arthropathy later during the course of their disease. As a result, nearly a third of patients with anti-SS and anti-CCP are misdiagnosed as having rheumatoid arthritis for up to 2 years [3].

The question as to whether this subgroup of patients with Jo-1 autoantibodies and anti-CCP represents a distinct subgroup or an overlap condition remains to be settled. There are strong similarities in this subgroup with rheumatoid arthritis (erosions and distribution of joint involvement), with some arguing that the anti-CCP (+) status gives more rise to earlier joint involvement rather than two overlapping conditions. It is clear that when diagnosing an inflammatory arthritis, anti-SS must remain in the differential regardless of anti-CCP status.

Radiographic Findings of Arthritis

Plain radiographs most frequently demonstrate a non-destructive arthropathy in anti-SS [9]. Two distinct groups of destructive radiographic findings have been described. The first group is characterised by erosions in the PIP and MCP group, with ankyloses of the wrist, and are more likely to be anti-CCP and RF positive [6]. The other group is almost exclusively anti-Jo-1 positive and demonstrates subluxation at the CMC joint of the thumbs with periarticular calcification, and these findings are independent of anti-CCP or RF status [9]. Radiographic erosions are seen more frequently in patients with anti-SS and anti-CCP or RF positivity [3, 7]. In patients who are anti-Jo-1 positive with erosions on their

plain radiograph, 53% are IgM RF positive and 27% anti-CCP positive [7].

It is important, therefore, for any patient who presents with an inflammatory arthropathy or arthralgias to be assessed and tested for both rheumatoid arthritis and an accompanying inflammatory myopathy. This is particularly relevant given the joint symptoms can predate the muscle weakness by several years.

Raynaud Phenomenon (RP)

Raynaud phenomenon (RP) affects up to 40% of patients with IIM and is a more prominent symptom in dermatomyositis (DM) over polymyositis (PM) (39% vs. 19%) [12]. Among all myositis patients, those with anti-SS are most typically affected. The non-Jo-1 anti-SS patients (anti-PL7, PL12, EJ, OJ, KS and Zo) are more likely to have RP as a presenting symptom compared to a minority of anti-Jo-1 (+) patients (25% vs. 7%, respectively) particularly patients with anti-PL-12 and anti-PL-7 antibodies [13–15]. RP can precede any other symptoms of myositis by a median of 13 months (IQR 12–48 months) [7]. Up to 40% of anti-Jo-1 (+) patients will develop RP during their disease course [7].

Of patients with DM, it is those with anti-transcriptional intermediary factor-1ɣ antibodies who are less likely to have RP, arthritis or arthralgia compared to other patients with DM [16].

Nail-fold capillaroscopy and thermography are useful for early diagnosis and provide prognostic value, with abnormal findings being identified in 42–90% of patients with IIM [17, 18]. These abnormalities include disorganised vascular array, enlarged and giant capillaries, capillary loss and a scleroderma-like pattern, with these findings being documented at a higher frequency in patients with DM when compared to PM [17]. Capillaroscopic alterations are more specific for patients with DM, especially microhaemorrhages and capillary enlargement, and these alter with disease activity and severity [18]. Shorter disease duration is associated with more severe changes in all IIM patients on nail-fold capillaroscopy, as well as a scleroderma pattern of capillary loss in DM patients [17].

Abnormalities in nail-fold capillary findings have been shown to be associated with systemic changes. Paraneoplastic myositis is associated with its own characteristic capillaroscopy pattern, while patients with interstitial lung disease have a significantly higher capillary score [18]. DM patients with a scleroderma pattern of nail-fold capillary changes are more likely to have a higher creatine kinase on serum testing and a higher VAS score of muscle disease activity [19]. Muscle disease activity was also associated with loss of capillaries, whereas cutaneous disease was associated with haemorrhages.

Improvement in nail-fold capillaroscopy findings such as irregularly enlarged capillaries, haemorrhages and loss of capillaries is seen with global disease response to immunosuppression [19, 20]. Thus, monitoring for these changes may have some use in evaluating disease activity and response to treatment.

Constitutional Symptoms

Constitutional symptoms (comprising fever, weight loss, fatigue and myalgia) occur in 40–70% of patients with IIM, specifically those with anti-SS (particularly anti-Jo-1 (+)) and those with necrotising myopathy [21, 22].

Fever

Overall, fever is not a common finding in myositis, except in all forms of anti-SS [15]. In anti-SS, fever is a presenting symptom in 25% of patients and is reported in up to 40% of patients during their disease course [7, 15]. It often manifests during disease relapse in those with an established diagnosis of anti-SS. Fever is commonly associated with the juvenile variant of DM, which is discussed more completely in Chap. 10 [23].

Weight loss is more commonly reported in anti-SS than in other forms of IIM [24], where it corresponds to disease activity in 50% patients.

Fatigue

Fatigue is a major symptom that patients feel needs to be addressed further [25]. In a small subset of patients, it is the presenting symptom of IIM (up to 3.5%) [13]. IIM patients report significantly lower scores on health assessment questionnaires compared to healthy controls. This appears to be a reflection of subjective reduced physical functioning, body pain, impaired social functioning and mental health [26] and is independent of disease activity.

Other studies have supported this finding that fatigue is independent of disease activity in the adult IIM population. Both VO_2 peak and tests of endurance and strength were unrelated to patient-reported fatigue measures [27, 28].

Forty-four percent of patients with JDM report a significant sleep disturbance, which is strongly correlated with fatigue scores using the PedsQL questionnaire [29]. However, fatigue was associated with disease activity in the juvenile population. Increasing fatigue had a significant negative impact on quality of life. Fatigue appears to also be related to disease-modifying antirheumatic drug (DMARD) use in this cohort, most specifically methotrexate use; however, it is unclear whether this is purely due to the medication or due to severity of disease requiring DMARD use.

Myalgia

Myalgia is defined as muscle pain without elevation of creatine kinase levels in the serum. Patients with both PM and DM have a 75% cumulative risk of developing myalgia during their disease course [12]. Those particularly vulnerable are patients on statins (up to 10% of statin users) and those with a necrotising myopathy (over 40%) [22, 30], and this represents one of the leading causes of statin discontinuation. Myalgia is also associated with younger age of IIM disease onset [31] .

There is a suggestion (not yet confirmed) that patients with statin-induced myalgia have a distinct molecular signature of mitochondrial stress and affected muscles show altered gene expression of immunity and inflammation and altered cellular signaling, compared to asymptomatic patients on a statin [32].

Significantly lower vitamin D levels have been reported in patients with statin-induced myalgia compared to those without any symptoms; however, low vitamin D levels do not predict those who will become symptomatic prior to treatment initiation [33, 34]. Rather, low vitamin D is associated with an increase in myalgia symptoms in those who develop statin-induced myopathy.

Conclusion

Extramuscular manifestations of IIM remain a prominent feature. Arthritis, RP and fever are features most commonly reported in anti-SS and can predate any symptoms of active myositis by over 12 months. This emphasises the importance of keeping IIM within the differential of a patient presenting with an inflammatory arthritis, RP or fever even in the absence of typical muscle weakness or DM rashes. The extramuscular manifestations can serve to risk-stratify patients, as well as provide an early opportunity for diagnosis of IIM prior to the onset of characteristic features of muscle weakness.

Conflicts of Interest There are no conflicts of interest to be declared.

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Clinical Features of Myositis: Juvenile Dermatomyositis

10

Adam M. Huber

Key Points to Remember

- Juvenile idiopathic inflammatory myopathies are rarer than their adult counterparts.
- Patients usually present with signs of weakness and, in juvenile dermatomyositis, typical cutaneous features.
- In younger children, weakness may be manifest as changes in function (such as difficulty climbing stairs) and endurance.
- The use of magnetic resonance imaging has markedly increased in diagnosis, while electromyography has largely fallen from favor.
- Muscle biopsy is done less than in the past, although recent recommendations advocate an increase. Muscle biopsy should be done when cutaneous lesions are absent or when disease is otherwise atypical.
- Myositis-specific autoantibodies (MSAs) are different in children than in adults.
- Juvenile idiopathic inflammatory myopathies are not associated with malignancy.

Introduction

Juvenile idiopathic inflammatory myopathies (JIIM) are rare, autoimmune myositis syndromes affecting children with an onset prior to the 16th birthday. Juvenile dermatomyositis (JDM) is the most common form, with an incidence of 2.5 per million children per year [1] and representing approximately 90% of JIIM patients [2]. Juvenile polymyositis (JPM) is about 1/10 as common, with other primary forms of juvenile myositis, such as amyopathic JDM, focal myositis, macrophagic myofasciitis, inclusion body myositis, and orbital myositis being even rarer [3]. Myositis may also be seen in association with other autoimmune or inflammatory illnesses, such as juvenile systemic lupus erythematosus or mixed connective tissue disease. These are likely more common than JPM, but reliable estimates are not available.

In general, the clinical features of JIIM resemble those of the corresponding disorder in adults, although there are some differences in how weakness presents and in frequencies of some skin manifestations, such as calcinosis, vasculitis, and cutaneous ulcerations. Moreover, there are significant differences in underlying pathophysiology [4] and the relative frequencies of myositis-specific autoantibodies (MSA) [5], which are clinically important.

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Muscle Disease

As in adults, muscle involvement is a cardinal feature of JIIM. This is characterized by proximal muscle weakness of the hip and shoulder girdle and the axial muscle groups, with associated limitations in physical function and endurance. While older children are likely to have similar complaints as adults, in younger children weakness may be more difficult to recognize. Young children are unlikely to complain of weakness. More frequently, changes in physical function or endurance may be observed by parents, teachers, or other care providers. It may be noted that children are having more difficulty climbing stairs, rising from a squatting position, or getting up off a low chair or the floor. More global changes may also be seen, where children are able to play for shorter periods of time or completely stop activities that were previously favorites.

Muscle pain may be present, although not in all patients, and correlates poorly with the degree of muscle weakness. Distal weakness may be observed, particularly if proximal weakness is severe, but should always be less than the degree of proximal weakness. Distal weakness that is similar or exceeds the proximal weakness should stimulate consideration of alternate diagnoses, such as various myopathies or muscular dystrophies. The extent of muscle weakness can range from profound, such as in patients who are bedbound or require ventilator support, to virtually imperceptible. In a rare subset of patients with amyopathic/hypomyopathic JDM, typical cutaneous features of JDM exist without detectable muscle involvement [3]. Between one quarter and one third of these patients will develop typical muscle disease on follow-up [6]. Confirmation of muscle disease may be obtained with assessment of serum muscle enzymes, muscle biopsy, electromyography, and magnetic resonance imaging, the latter being an increasingly preferred investigation [7]. Documentation and monitoring of the extent of muscle weakness can be achieved using validated and standardized clinical testing, including confrontational manual muscle testing [8], the Childhood Health Assessment Questionnaire [9], and the Childhood Myositis Assessment Scale [10].

Skin Disease

Cutaneous manifestations represent another defining feature of JDM, although they are not typically seen in other forms of JIIM (Table 10.1). As in adults, Gottron papules and the heliotrope rash are the most common and are considered pathognomonic [2, 11, 12]. Gottron papules consist of red to violaceous patches distributed over the metacarpophalangeal, proximal interphalangeal, and distal interphalangeal joints, as well as the elbows, knees, and medial malleoli (Fig. 10.1). They are usually raised with silvery superficial scaling which may be mistaken for psoriasis. The term Gottron sign is used for lesions in the typical distribution that are not raised/scaly. Associated ulceration and/or atrophy is not uncommon. The heliotrope rash refers to a blue-to-red discoloration around the eyes, often associated with visible swelling (Fig. 10.2).

There are a number of other skin and mucous membranes lesions that can be seen [11, 12]. Malar or facial erythema is common and resembles that seen in lupus. Often, the nasolabial folds are not spared, which may help to distinguish JDM patients from those with lupus. Induration or scaling may be seen. Linear extensor erythema is redness, sometimes with scaling over the extensor

Table 10.1 Common cutaneous manifestations of juvenile dermatomyositis [2, 7, 14, 25, 28][a]

Gottron papules or sign	44–91%
Heliotrope	58–87%
Periungual telangiectasia	41–79%
Malar/facial erythema	29–74%
Photosensitivity	47%
Calcinosis	4–40%
Linear extensor erythema	37%
Cuticular overgrowth	35%
Mucous membrane lesions	30%
V or shawl sign	5–29%
Skin ulceration	5–23%
Edema	15%
Lipoatrophy/lipodystrophy	5–10%
Raynaud phenomenon	5–9%
Mechanic's hands	7.5%

[a]Some variation is related to whether studies reported feature as present at diagnosis or throughout course. Some features are not consistently reported across studies and represent a single report

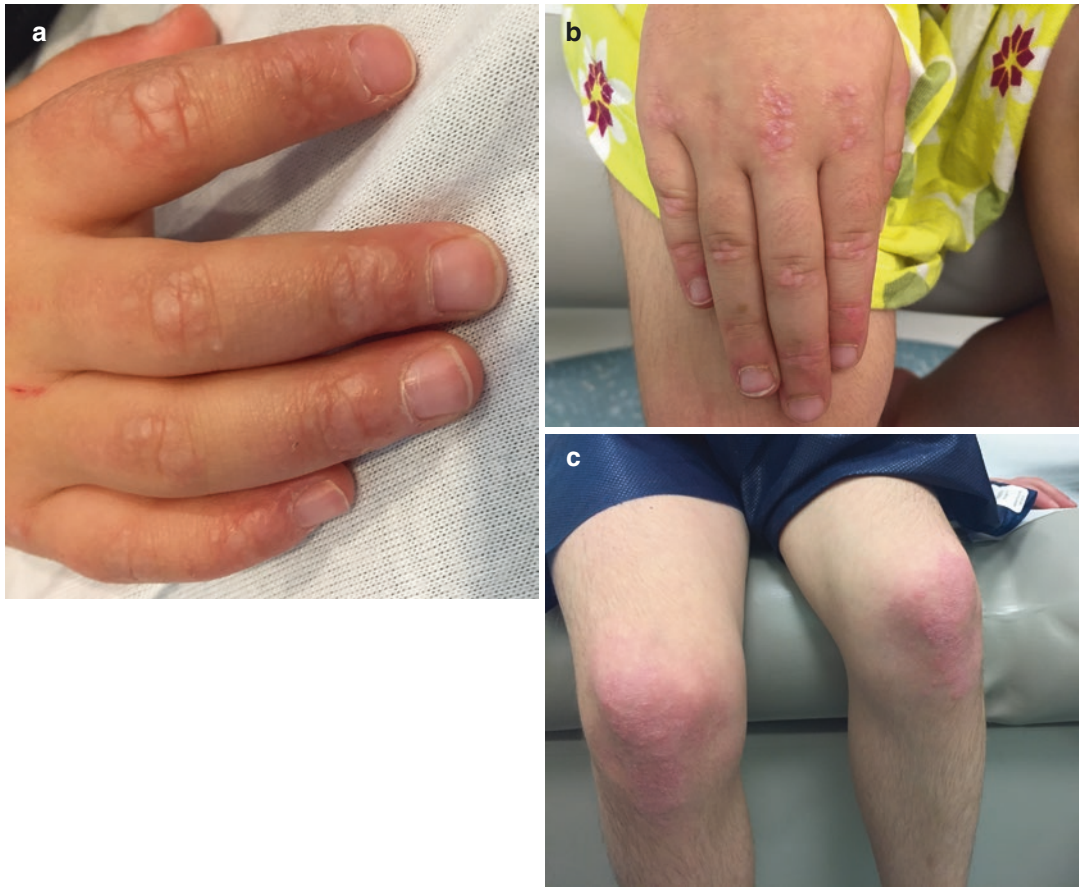

Fig. 10.1 Gottron papules. Note the distribution over metacarpophalangeal, proximal, and distal interphalangeal joints. Note also the pallor and atrophic appearance of the lesions. Erythema and scaling are not demonstrated here. (**a**) Gottron papules. Note the pallor and atrophic appearance of the lesions on metacarpophalangeal, proximal, and distal interphalangeal joints. Erythema and scaling are not demonstrated here. (Image courtesy: Laura Tasan). (**b**) Gottron papules on hands. Note the distribution of erythematous papules over metacarpophalangeal, proximal, and distal interphalangeal joints. (Image courtesy: Aarat Patel). (**c**) Gottron papules on knee. Note the erythematous papules on both knees. (Image courtesy Aarat Patel)

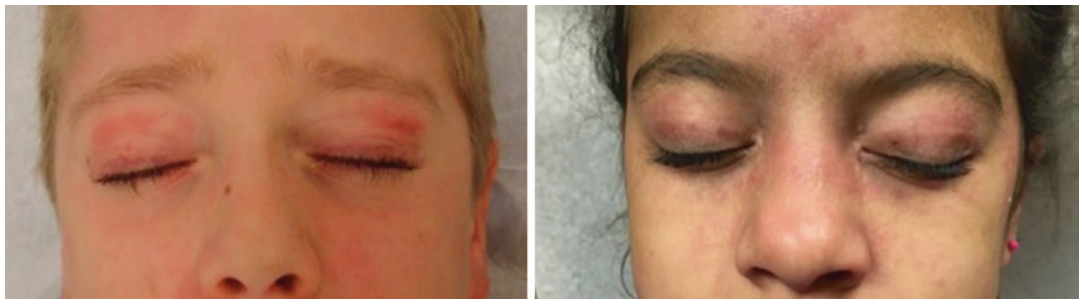

Fig. 10.2 Heliotrope rash on eyelids: Note the erythematous or violaceous papules on upper eye lids. (Images courtesy: Kathryn (Cassie) Torok)

surfaces of the hands, forearms, thighs, or feet. V-sign and shawl sign rashes are less common than in adults and consist of erythema of the upper chest and upper back, respectively. Other erythema can also be seen in areas that are both sun-exposed, indicating photosensitivity, and non-sun exposed, including erythroderma, which by definition involves more than 50% of the body surface area. Other lesions are related to the underlying vasculopathic nature of JDM. Livedo reticularis is a fixed, net-like pattern of red or blue discoloration that does not disappear with warming. It may represent vasculitic involvement and can be associated with skin ulceration. Skin ulceration, caused by localized ischemia and infarction, can also be seen in isolation. It is typically associated with more severe disease, such as vasculitis of the bowel, and may be associated with a poorer prognosis [13].

Abnormalities of the digital nailfolds are an important feature of JDM (Fig. 10.3). They can be seen in other illnesses, such as lupus or scleroderma. These changes can be observed in the clinic with modest magnification provided by an ophthalmoscope or dermatoscope. Features include dilatation and tortuosity of capillary loops, areas of capillary loop dropout, and hemorrhages. Other skin lesions involving the hands include mechanic's hands (fissuring and scaling on the palmar and lateral aspects of digits, seen in children with anti-synthetase autoantibodies), overgrowth of the cuticles, vasculopathic lesions on the palms and soles (red to purple macules or patches) (Fig. 10.4), and mucinous papules (edematous and tender papules and plaques on the palmar surface of the digits). Finally, localized or generalized subcutaneous edema, alopecia, and panniculitis (inflammation of the subcutaneous fat) can all be manifestations of active disease in JDM.

Several cutaneous lesions are associated with damage in JDM [11, 12], the most important of which is calcinosis. It is much more common in JDM than in adults with DM, affecting approximately 40% of children [14]. The appearance can vary widely, from simple subcutaneous nodules to deeper nodular deposits, to calcification along fascial planes, to the most severe manifestation, exoskeletal deposits that act to encase broad areas of soft tissue (Fig. 10.5). These lesions can exist in combination, and severity can range from minimal to profound. Clinically, calcinosis often presents with masses, sometimes with superficial ulceration and drainage of toothpaste-like material, but may also only be identified with radiographic imaging. Calcinosis is cosmetically problematic but can also be associated with pain and functional limitations and in some circumstances may reflect inadequately treated disease [14].

Lipodystrophy, localized or generalized loss of adipose tissue, is also much more common in JDM than in adult disease [15]. While potentially disfiguring, it is also important as a potential marker of underlying insulin resistance, risk of

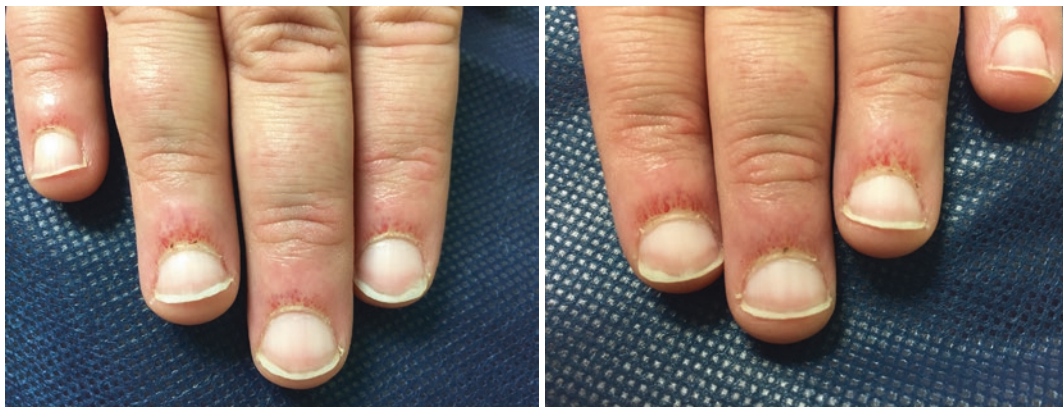

Fig. 10.3 Nailfold capillary loop abnormalities. Note dilated, tortuous, disorganized nailfold capillaries with drop out (absence of capillaries) at the nailfold bed in bilateral fingers of the child. (Image courtesy: Aarat Patel)

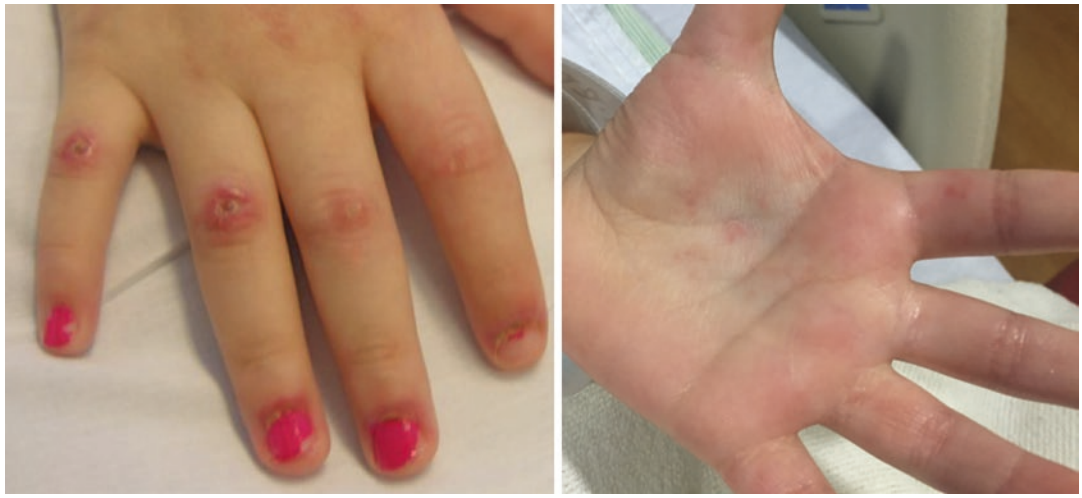

Fig. 10.4 Vasculitis on hands: Note the erythematous ulcerative lesion on proximal interphalangeal joint and erythematous lesion on the palm. (Images courtesy: Kathryn (Cassie) Torok and Laura Tasan)

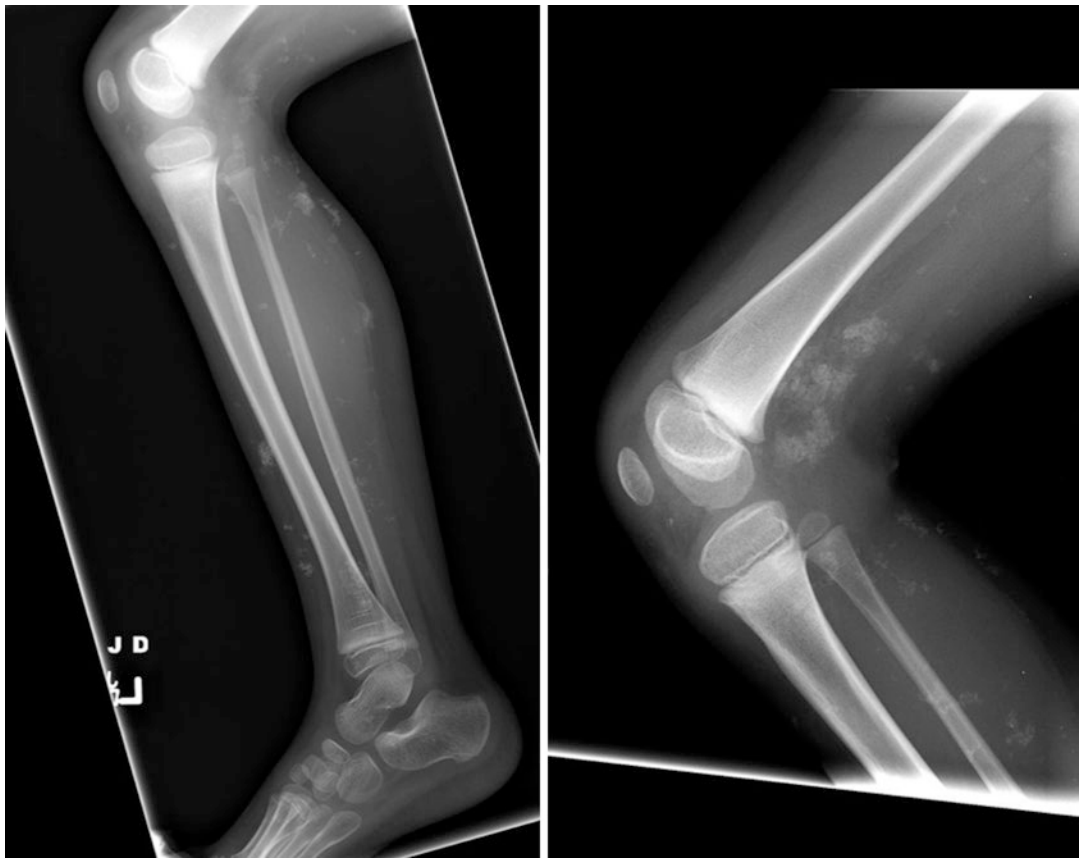

Fig. 10.5 Calcinosis in leg: Note the white random patches in subcutaneous areas showing up on X-rays in a JDM patient with calcinosis. (Image courtesy: Kathryn (Cassie) Torok)

diabetes, and hyperlipidemia. Acanthosis nigricans, areas of skin thickening and hyperpigmentation, is also seen in JDM and is associated with similar risks. Skin atrophy and depressed scars are also sometimes present, often as sequelae of the active lesions previously described [11, 12].

Extra-muscular Disease Features

Extramuscular, non-cutaneous manifestations of the JIIM can also be seen in children, although less frequently than in adults (Table 10.2). The most important of these is pulmonary involvement. As in adults, progressive pulmonary fibrosis can be seen in association with anti-synthetase and anti-melanoma differentiation-associated protein (MDA)-5 autoantibodies but fortunately only affects 3–8% of patients [16, 17]. Hypoventilation due to diaphragmatic and/or intercostal weakness is also seen, although typically only in patients with profound weakness. Dysphonia and/or dysphagia can be seen with varying degrees of weakness. Aspiration due to pharyngeal weakness is a risk and is not well correlated with clinical muscle weakness or symptoms of swallowing dysfunction, warranting careful evaluation in all patients [18].

Gastrointestinal involvement is a concern in JDM, primarily due to the potential for bowel vasculitis [2]. This may be associated with intussusception, massive bleeding, or perforation and is an important (although rare, 0.2–4%) cause of morbidity and mortality in early disease [13]. It may be associated with anti-MJ autoantibodies [17]. Vasculitis in the bowel may be associated with skin findings such as ulcers—these patients warrant extremely close observation. Other, less severe gastrointestinal features can also be seen including abdominal pain, dyspepsia, and constipation.

Systemic symptoms such as fever, fatigue, and weight loss can be seen [2]. Arthritis is also quite common, particularly at presentation and affects 40% or more of children [19]. It appears to be more common in those with anti-synthetase autoantibodies but is widely seen. In the longer term, this may be associated with the development of contractures, although these are more likely related to chronic muscle damage. Involvement of other organ systems such as cardiac, renal, or central nervous system is described, but generally very rare. However, in the right clinical context, this must be considered.

Myositis-Specific Autoantibodies

As in adults, MSA-defined clinical phenotypes have become important in the understanding of JIIM [20] (Table 10.3). This is a relatively recent phenomenon, as historically, few patients with JIIM had recognizable MSA [21]. The identification of new MSA, particularly anti-transcriptional intermediary factor (TIF1)-gamma, anti-nuclear matrix protein (NXP)-2 (previously anti-MJ), and anti-MDA5, means that 60–70% of patients tested have an MSA [20]. Other MSAs such as anti-synthetase, anti-Mi-2, anti-signal recognition particle (SRP), and anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) autoantibodies are more common in adult IIM but infrequent (<5%) in JIIM. For some of these, the associated phenotype is similar to that seen in adults. For example, patients with

Table 10.2 Key extra-muscular features to consider in juvenile idiopathic inflammatory myopathies [2, 7, 17, 19, 25, 28]

Clinical feature	Frequency (%)	Autoantibody association[a]
Interstitial lung disease	3–8	Anti-synthetase autoantibodies Anti-MDA5 autoantibody
Gastrointestinal ulceration/bleeding	0.2–4	Anti-NXP2 (Anti-MJ) autoantibody
Arthritis	34–66	Anti-synthetase autoantibodies
Dysphagia/dysphonia	18–40	Anti-NXP2 (Anti-MJ) autoantibody Anti-SRP autoantibody
Systemic symptoms (fever, fatigue, weight loss)	29–85	Anti-synthetase autoantibodies

[a]Many of these associations should be considered preliminary

Table 10.3 Comparison of autoantibody phenotypes in adult and juvenile idiopathic inflammatory myopathy

	Juvenile dermatomyositis [16]		Adult dermatomyositis [5, 16, 29–32]	
Anti-tRNA synthetase	<5%	Myositis, arthritis, mechanics hands, Raynaud, fever, interstitial lung disease	25–40%	Myositis, arthritis, mechanics hands, Raynaud, fever, interstitial lung disease
Anti-Mi2	<5%	"Classic skin disease," moderate muscle disease, good response to therapy	20%	"Classic skin disease," moderate muscle disease, good response to therapy
Anti-SRP	<5%	Immune-mediated necrotizing myopathy, severe muscle disease, high muscle enzymes, no rash	5%	Immune-mediated necrotizing myopathy, severe muscle disease, high muscle enzymes, no rash
Anti-HMGCoA Reductase	<5%	Immune-mediated necrotizing myopathy, severe muscle disease, high muscle enzymes, no rash	6%	Immune-mediated necrotizing myopathy, severe muscle disease, high muscle enzymes, no rash
Anti-MDA5	7–10%	Myositis, minimal skin disease, oral and skin ulcers, fever, interstitial lung disease	7–13%	Myositis, minimal skin disease, fever, interstitial lung disease
Anti-TIF1-gamma	23–30%	Severe rash (including V-sign and shawl-sign), photosensitivity, skin ulceration, edema, lipodystrophy, chronic course	15–38%	Severe rash (including V-sign, shawl-sign), malignancy
Anti-NXP2 (MJ)	12–23%	Muscle cramps and atrophy, joint contractures, more severe weakness, increased GI ulceration and bleeding, increased calcinosis, chronic course	17%	Severe rash (including V-sign, shawl-sign), malignancy

anti-Jo1 or other anti-synthetase autoantibodies have a phenotype that typically includes moderate muscle disease, typical skin lesions (such as mechanic's hands), arthritis, and a markedly increased risk of interstitial lung disease [16]. This phenotype is not common in JIIM. Patients with anti-Mi2 autoantibodies, again less common in JIIM, have what appears to be "classic" JDM, with typical skin lesions, muscle weakness, and a generally excellent response to therapy [16]. Anti-SRP and anti-HMGCR autoantibodies are associated with a JPM phenotype with minimal or no rash, severe muscle disease with marked weakness and very high muscle enzymes and a poor response to therapy. These children, as in adults, have muscle necrosis on biopsy and are now classified as immune-mediated necrotizing myopathy [16]. Fortunately, this phenotype is also very rare in JIIM.

Patients with anti-MDA5 autoantibodies also appear to have a similar phenotype in children to adults, associated with less severe muscle disease, more severe skin disease, more arthritis, and an increased risk of interstitial lung disease [16]. Anti-MDA5 disease accounts for 5–10% of pediatric JIIM. Anti TIF1-gamma autoantibodies are the most common MSA in JIIM, accounting for 22–36% of patients [16]. The phenotype in children includes prominent rash, photosensitivity, and an increased tendency for the rash to be chronic. In stark contrast with adults, anti-TIF1-gamma autoantibodies are not associated with an increased risk of malignancy in JIIM. Anti-NXP2 (previously anti-MJ) autoantibodies are the second most common MSA in JIIM, observed in 20–23% of children [16]. Patients tend to have more severe muscle disease and a poorer response to therapy. These patients are also distinguished by an increased risk of developing calcinosis, which may be associated with increased disease chronicity [22].

Diagnosis of Juvenile Dermatomyositis

Making a diagnosis of JIIM is similar to the process in adults. While not intended as diagnostic criteria, the Bohan and Peter criteria [23, 24] remain relevant. A more practical approach has also been taken recently, requiring the presence

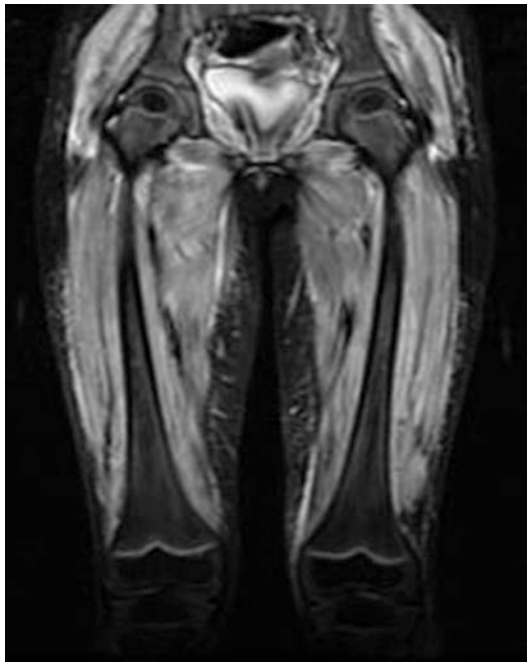

Fig. 10.6 Magnetic resonance image of the hip girdle muscles in a child with juvenile dermatomyositis. (Image courtesy: Kathryn (Cassie) Torok)

of typical skin disease and evidence of muscle disease, whether weakness, biopsy, electromyography (EMG), or magnetic resonance imaging (MRI) [7]. In general, EMG has largely fallen out of favor, due largely to the difficulty in performing this test in children. MRI has become a key investigation and is performed in most children with suspected JIIM [7] (Fig. 10.6). Muscle biopsy rates have fallen to only 50%, often replaced with MRI [7, 25]. However, biopsy is necessary in patients without skin features or with atypical features that may suggest an alternate diagnosis, such as non-inflammatory myopathies or dystrophies. In addition, recent work has documented correlations of muscle biopsy with both JIIM phenotype and outcome [26, 27]. Knowledge of which patients are at higher or lower risk of poor outcomes may influence treatment decisions, identifying those in need of more aggressive therapy and those who may be treated less aggressively. These results may lead to an increase in biopsy as a part of initial evaluation.

Additional evaluation of new JIIM patients should include an investigation of the pulmonary and cardiac systems, a detailed assessment of swallowing function (even in the absence of symptoms [18]), and assessment of other organ systems as appropriate (e.g., gastrointestinal evaluation in patients with abdominal pain). Finally, while evaluation for malignancy is of great importance in adults presenting with IIM, this is not the case in children. While there are a few case reports documenting malignancy in JIIM, routine evaluation is not recommended in the absence of atypical features.

Conclusion In summary, JIIM have many similarities to their adult counterparts. However, there are important differences including more frequent calcinosis, cutaneous ulcerations, vasculitis, gastrointestinal involvement, and joint contractures. The diagnostic workup often includes MRI, which is utilized more commonly than an EMG and/or muscle biopsy. The distribution of autoantibodies is more likely to include anti-TIF1-gamma and anti-NXP2 autoantibodies. JIIM are complex illnesses and require multidisciplinary pediatric care from an experienced team. Thus, referral to appropriate tertiary center is strongly recommended.

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11 Making the Diagnosis of Myositis: Definition and Classification of Myositis

Valérie Leclair and Ingrid E. Lundberg

Key Points to Remember

- Myositis is a group of multisystemic diseases that can initially present with isolated arthritis, interstitial lung disease, or dermatomyositis (DM) rashes.
- Myositis-specific autoantibodies are associated with specific disease phenotypes.
- In myositis, early diagnosis is important to prevent organ damage such as muscle atrophy and lung fibrosis.
- In adults, major myositis subsets include dermatomyositis, clinically amyopathic dermatomyositis, polymyositis, overlap myositis, immune-mediated necrotizing myopathy, anti-synthetase syndrome, and sporadic inclusion body myositis.
- New classification criteria for myositis have been endorsed in 2017 by the EULAR/ACR.

Introduction

For decades, the diagnosis and classification of myositis were dependent on the presence of muscle weakness along with electromyographic changes, muscle enzyme elevation, and skeletal muscle inflammation on muscle biopsy. Further, typical skin rashes supported the diagnosis of dermatomyositis (DM). However, the past 10 years has seen a shift in the perception of myositis toward a disease characterized by multiple organ involvement with some patients manifesting no clinically evident muscle weakness. The identification of several new myositis-specific autoantibodies (MSA), often associated with distinct clinical phenotypes, has further shaped our understanding and classification of myositis as a spectrum of related diseases (Fig. 11.1).

When to Suspect Myositis

Myositis is characterized by symmetrical muscle weakness predominating in proximal limb muscles including the neck flexors. The muscle weakness is typically of low *endurance* rather than of low *resistance* type, at least at disease onset. Symptoms develop progressively over weeks (subacute) to months (chronic), with a very slow and insidious onset (i.e., years) with concomitant

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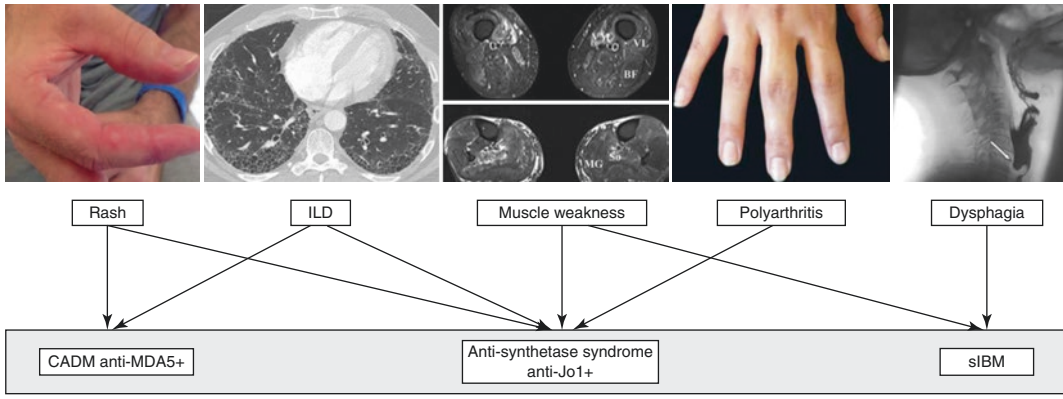

Fig. 11.1 Examples of different clinical presentations of myositis. CADM clinically amyopathic dermatomyositis, ILD interstitial lung disease, sIBM sporadic inclusion body myositis

muscle atrophy of the knee extensors or weak finger flexors in the subset of sporadic inclusion body myositis (sIBM). Another classical presentation is the presence of a skin rash typical of DM such as Gottron papules/sign or the heliotrope rash. Myositis patients may be initially referred to an early arthritis clinic for an inflammatory arthritis mimicking rheumatoid arthritis, in a pulmonology clinic with symptoms of interstitial lung disease (ILD), or in a dermatology clinic with atypical skin rashes (Box 11.1). Lack of recognition of these atypical presentations may delay diagnosis and treatment leading to irreversible organ damage. The frequency of such patients presenting with predominantly extramuscular involvement is highly variable. For example, in a cohort of anti-Jo-1-positive subjects from Spain, isolated arthritis was noted in 18%, isolated ILD in 32%, and isolated myositis in 27% [1].

There are significant limitations when using health-care registries based on World Health Organization (WHO) classification systems to identify myositis patients as there are no International Classification of Diseases (ICD) codes for newly described myositis phenotypes such as the anti-synthetase syndrome, amyopathic DM, or autoimmune necrotizing myopathy. Therefore, myositis experts must be unified in an initiative to revise the WHO classification system and promote the inclusion of specific ICD codes for these new myositis subsets. Collaborations to create large international longitudinal registry-based studies (e.g., EuroMyositis—www.euromyositis.eu) including patients fulfilling standardized classification criteria as well as early cases failing to meet such diagnostic or classification criteria are required. More importantly, clinicians must work in multidisciplinary teams including rheumatologists, neurologists, pulmonologists, immunologists, and dermatologists to diagnose and treat early cases to prevent disease-related morbidity in the muscle, skin, joints, and lung. That is, pulmonary fibrosis patients being seen by a pulmonologist should be systematically screened for systemic autoimmune rheumatic disease symptoms such as muscle weakness, muscle enzymes elevation, mechanic's hands or DM-associated rashes, Raynaud phenomenon, and polyarthritis, with a low threshold for rheumatology consultation and

When to Suspect Myositis Spectrum of Diseases

- Muscle weakness, low muscle endurance, or muscle enzyme elevation
- Seronegative polyarthritis
- Typical DM rashes or palmar papules even in the absence of muscle weakness
- ILD associated with Raynaud phenomenon, mechanic's hands, arthritis, or fever
- Dysphagia

MSA screening. Likewise, patients presenting with a DM rash without objective muscle weakness may have clinically amyopathic DM, and such patients may benefit from a high-resolution computerized tomography of the lungs and MSA screening given the association of anti-MDA5 antibody with rapidly progressive ILD [2]. Similarly, patients presenting with "seronegative" (i.e., rheumatoid factor and anti-CCP negative) rheumatoid arthritis may have anti-synthetase syndrome with polyarthritis as the initial presentation.

Classification Criteria

Classification criteria are developed for research purposes in order to enroll a uniform cohort of subjects such that different published studies can be adequately compared. They require very high specificity even with a potential loss of sensitivity. *Diagnostic criteria*, on the other hand, aim at identifying a wider spectrum of disease cases including early cases with incomplete presentation to those with severe, advanced features and thus need to be both sensitive and specific. It is essential not to confuse classification with diagnosis, as by using classification criteria for diagnostic purposes, one may delay diagnosis and proper treatment of an individual with myositis that does not yet fulfill classification criteria. Accurate and early diagnosis is paramount to adequate myositis management.

In 1975, Bohan and Peter published the most widely used criteria for myositis, intended for both diagnosis and classification, which continued to be used to date (Table 11.1) [3]. Many large subsequent studies utilized these criteria. These were mainly based on expert opinion and included a proposal of five subgroups of myositis shown in Box 11.2. Although these criteria could differentiate PM or DM from systemic lupus erythematosus and systemic sclerosis with a sensitivity of 93% and specificity of 93% [4], the criteria lacked specificity for PM, leading to misclassification of metabolic myopathies, muscle dystrophies, and sIBM as PM. Moreover, the exclusion of other myopathies, a prerequisite to Bohan and Peter classification, was not well defined. Criteria were highly specific and worked better for DM given the requirement of characteristic rashes (heliotrope rash or Gottron papules). However, patients with less characteristic DM rashes, but all other features consistent with DM, could not be classified as having DM. Importantly, sIBM had not been recognized at the time these criteria were published. Therefore, earlier studies clearly classified sIBM as PM based on Bohan and Peter classification. In addition, the MSA were not yet discovered, and newer technologies, such as muscle MRI and sophisticated muscle immunohistochemical staining, were not available for classification purposes (Box 11.3).

Table 11.1 Bohan and Peter criteria for DM and PM [3]

First, rule out all other forms of myopathy
1. Symmetrical weakness, usually progressive, of the limb-girdle muscles
2. Muscle biopsy evidence of myositis
Necrosis of type I and type II muscle fibers, phagocytosis, degeneration and regeneration of myofibers with variation in myofiber size, endomysial, perimysial, perivascular, or interstitial mononuclear cells.
3. Elevation of serum levels of muscle-associated enzymes (CK, LDH, and transaminases)
4. EMG triad of myopathy
(a) Short, small, low-amplitude polyphasic motor unit potentials
(b) Fibrillation potentials, even at rest
(c) Bizarre, high-frequency repetitive discharges
5. Characteristic rashes of dermatomyositis

Definite PM, all first four elements; probable PM, three of the first four; possible PM, two of the first four. Definite DM, rash *plus* three other; probable DM, rash *plus* two other; possible DM, rash *plus* another

CK creatine kinase, *LDH* lactate dehydrogenase, *EMG* electromyography

Bohan and Peter Five Subgroups of Myositis

- Primary idiopathic PM
- Primary idiopathic DM
- DM or PM associated with neoplasia
- Childhood DM or PM associated with vasculitis
- DM or PM associated with collagen-vascular disease

In the last decades, several groups have attempted to refine the approach of myositis classification and define various myositis subsets, proposing mostly classification criteria based on expert opinion and rarely based on data. In Table 11.2, selected criteria sets for PM/DM/IMNM are compared [3, 5–10]. Most of those include the presence of proximal muscle weakness, elevation of muscle enzymes, myopathic changes on EMG, inflammation on muscle biopsy, MSAs, and the characteristic rashes of DM. The European Neuromuscular Center (ENMC) criteria, developed by a group of myologists in 2004, provide detailed clinical, histopathologic, and laboratory criteria including MSA and muscle MRI [9]. The eight phenotypes described were definite PM, probable PM, definite DM, probable DM, amyopathic DM, possible DM sine myositis, nonspecific myositis, and, for the first time, immune-mediated necrotizing myopathy (IMNM). They defined IMNM with the same clinical and laboratory criteria as PM or DM but with the presence on muscle biopsy of predominantly necrotic muscle fibers with sparse inflammatory cells. However, these histopathological features are not specific for IMNM and can also be found in patients with, e.g., cancer-associated myopathies or muscle dystrophies. This subgroup of patients with IMNM, also termed necrotizing autoimmune myopathy (NAM), has been associated with the presence of one of two specific autoantibodies [anti-signal recognition particle (anti-SRP) and anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase (anti-HMGCR)], suggesting involvement of the immune system in this subset of myositis. It is clinically important to identify IMNM cases as they are often difficult to treat and may need more aggressive or alternative immunosuppressive treatment as discussed in Chap. 24.

Box 11.3 Shortcomings of Bohan and Peter Classification Criteria

- Lack of specificity of PM
- Lack of newer entities such as CADM, anti-synthetase syndrome, and immune-mediated necrotizing myopathy
- Lack of DM rashes other than heliotrope and/or Gottron papules
- Absence of myositis-specific autoantibodies (MSA)
- Absence of well-defined exclusion criteria

Cancer-associated myositis is another subgroup of myositis. It is well recognized that, in adults, DM more than PM is associated with the presence of a malignancy, but this is not well established for other myositis subsets. There is no general agreement on the definition of cancer-associated DM, but one frequently used is the occurrence of malignancy within 3 years from DM diagnosis. Recently, two MSAs have been linked with cancer-associated DM, anti-transcriptional intermediary factor 1-gamma

Table 11.2 Summary of selected proposed criteria for PM, DM, and/or IMNM

	Bohan and Peter [3]	Tanimoto [6]	Targoff [7]	Dalakas [8]	ENMC [9]	EULAR/ACR [5]
Year of publication	1975	1995	1997	2003	2004	2017
Muscle weakness	X	X	X	X	X	X
Muscle pain		X				
Muscle biopsy[a]	X	X	X	X	X	X
EMG	X	X	X	X	X	
Muscle enzymes[b]	X	X	X	X	X	X
Rash	X	X	X	X	X	X
MSA		X	X		X	X

Modified from [10]
EMG electromyography, *MSA* myositis-specific autoantibodies
[a]Inflammation on muscle biopsy
[b]Elevation of muscle enzymes

(anti-TIF1-gamma), and antinuclear matrix protein 2 (anti-NXP2). Please see Chap. 21 for a more comprehensive discussion of these autoantibodies. There is still controversy as to whether these autoantibodies represent an epiphenomenon associated with neoplasia or if these antibodies are truly pathogenic. Their presence in adult DM patients should however prompt clinicians to be thorough in their malignancy screening.

Myositis may appear as a disease on its own but may also present in patients diagnosed with another rheumatic disorder either at the same time or one following the other. Myositis associated with another systemic autoimmune rheumatic disorder (SARD), or overlap myositis, refers to these myositis patients that also fulfill criteria for another SARD. The most common rheumatic disorders overlapping with myositis are systemic sclerosis and Sjögren syndrome, followed by systemic lupus erythematosus. Mixed connective tissue disease (MCTD) is a rare autoimmune condition associated with anti-U1RNP antibody, where myositis is regarded as one of the characteristic clinical manifestations such that this condition represents an overlap syndrome. More rarely, patients with rheumatoid arthritis also develop myositis. Whether myositis in patients with overlap syndrome is different from myositis as a single entity is still unknown.

The EULAR/ACR Myositis Classification Criteria

To overcome the limitations of Bohan and Peter's classification criteria as well as other proposed criteria (empirically derived, based on small/single-center cohorts, lack of appropriate controls/validation), a group of international myositis experts including adult and pediatric rheumatologists, neurologists, dermatologists, epidemiologists, and biostatisticians developed data and consensus-driven new myositis classification criteria following the recommendations endorsed and published by EULAR/ACR [5, 11, 12]. These criteria were developed and validated using a collaborative data-driven methodology. Data on 93 variables were collected from 976 myositis patients and 624 patients with conditions mimicking myositis (74% adults, 26% children). Two models, with or without muscle biopsy results, were developed to better reflect some clinical settings such as pediatrics, where muscle biopsy may not be regarded as standard of care. Based on statistical performance and best specificity and sensitivity, a set of 16 variables weighted depending on their importance was identified (Table 11.3). The final score, which is the sum of scores achieved for various individual clinical features, corresponds to a certain probability of having myositis, which gives flexibility to the investigators to decide on threshold, depending on the types of study they are conducting (e.g., clinical trial vs. epidemiological). The criteria are based on two steps: (1) to identify a myositis patient compared to a non-myositis patient and (2) to identify subgroups of myositis (Fig. 11.2). A web-based calculator has been developed and can be used off-line in electronic devices. These proposed criteria have been endorsed by the European League Against Rheumatism (EULAR) and by the American College of Rheumatology (ACR) and demonstrate strong sensitivity and specificity for a probable myositis diagnosis of 93% and 88%, respectively, when biopsy results are included. Nevertheless, there are limitations as the heterogeneity of myositis limited the number of the rare subgroups (e.g., IMNM, hypomyopathic DM, and juvenile PM) that could be recruited, and therefore the criteria cannot be used to define these subsets. Moreover, only one MSA, anti-Jo-1, was documented in enough subjects to be included as a final variable, so with the wider study of other MSAs and their clinical phenotypes, these autoantibodies could be incorporated in future EULAR/ACR classification criteria. Muscle MRI, only available in 38% of cases, was also excluded from the analysis. Thus, these criteria will soon require revision using a cohort with further data on MSAs, MRI, as well as validation on an external cohort with myositis cases and comparators.

Table 11.3 2017 EULAR/ACR myositis classification criteria for adult and juvenile myositis

When no better explanation for the symptoms and signs exists, these classification criteria can be used		
	Score	
Variable	No muscle biopsy	With muscle biopsy
Age of onset of first symptom assumed to be related to the disease ≥18 years and <40 years	1.3	1.5
Age of onset of first symptom assumed to be related to the disease ≥40 years	2.1	2.2
Muscle weakness		
Objective symmetric weakness, usually progressive, of the proximal upper extremities	0.7	0.7
Objective symmetric weakness, usually progressive, of the proximal lower extremities	0.8	0.5
Neck flexors are relatively weaker than neck extensors	1.9	1.6
In the legs, proximal muscles are relatively weaker than distal muscles	0.9	1.2
Skin manifestations		
Heliotrope rash	3.1	3.2
Gottron papules	2.1	2.7
Gottron sign	3.3	3.7
Other clinical manifestations		
Dysphagia or esophageal dysmotility	0.7	0.6
Laboratory measurements		
Anti-Jo1 autoantibody present	3.9	3.8
Elevated serum levels of CK *or* LDH *or* ASAT/AST/SGOT *or* ALAT/ALT/SGPT	1.3	1.4
Muscle biopsy features—the presence of:		
Endomysial infiltration of mononuclear cells surrounding, but not invading, myofibers		1.7
Perimysial and/or perivascular infiltration of mononuclear cells		1.2
Perifascicular atrophy		1.9
Rimmed vacuoles		3.1

Modified from [5]
Anti-Jo-1 anti-histidyl-tRNA synthetase, *CK* creatine kinase, *LDH* lactate dehydrogenase, *AST/ALT* aspartate aminotransferase/alanine aminotransferase

IBM Diagnostic/Classification Criteria

In the last decades, sIBM diagnostic criteria have shifted from Griggs et al. criteria [13], with a strong emphasis on histopathological variables to an approach based more on clinical phenotypes (Table 11.4). The MRC Centre for Neuromuscular Disease [14] and the ENMC [15] have both developed new sets of diagnostic criteria, with the goal of capturing sIBM patients at an earlier stage of their disease to allow them to access specialized care rapidly and to be included in clinical trials. This can be particularly challenging as clinical manifestations in IBM are often subtle at onset with suggestive pathological findings appearing later in the disease evolution. The ENMC criteria also reflected the advances in immunostaining of abnormal protein aggregates and the recognition of MHC-1 expression as well as mitochondrial abnormalities as markers of sIBM. Some of these newer stains as well as electron microscopy (EM) are not routinely used, making those criteria difficult to apply outside of specialized centers. By investigating the sensitivity and specificity of differ-

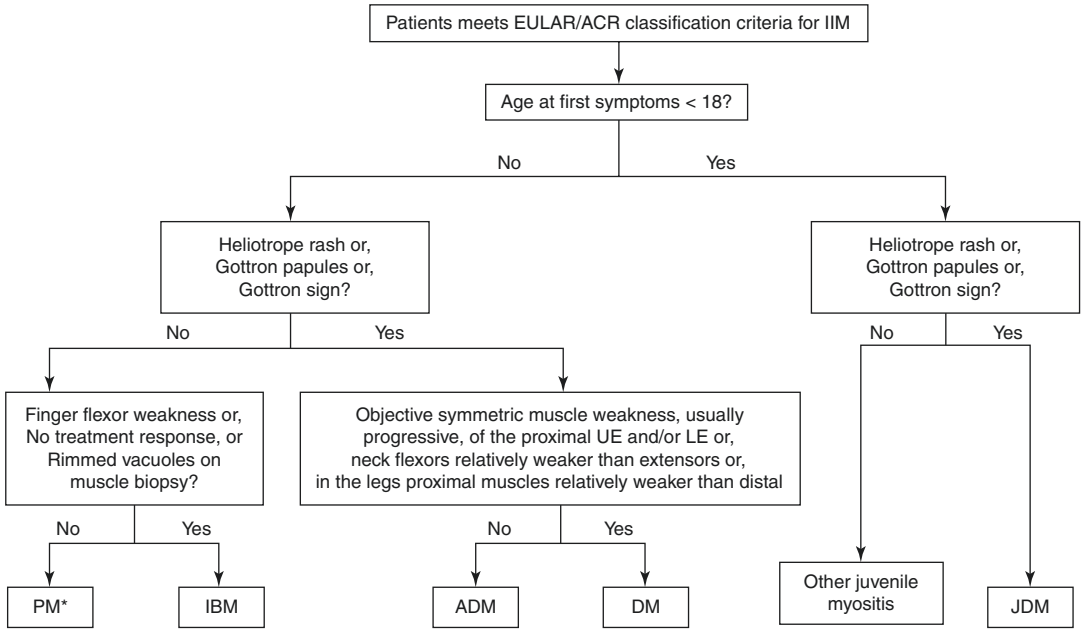

Fig. 11.2 Subgroups of myositis according to the 2017 EULAR/ACR classification criteria [5]. *The polymyositis (PM) subset includes immune-mediated necrotizing myopathies (IMNM). IBM inclusion body myositis, ADM amyopathic dermatomyositis, DM dermatomyositis, JDM juvenile dermatomyositis

Table 11.4 Modified IBM diagnostic criteria [14]

	Clinical features	Pathological features
Clinically defined IBM	Duration of weakness >12 months Age >35 years Weakness of finger flexion > shoulder abduction *and* of knee extension > hip flexion	Invasion of non-necrotic fibers by mononuclear cells *or* rimmed vacuoles *or* increased MHC-1 but no intracellular amyloid deposits or 15–18 nm filaments
Possible IBM	Duration of weakness >12 months Age >35 years Weakness of finger flexion > shoulder abduction *or* of knee extension > hip flexion	Invasion of non-necrotic fibers by mononuclear cells *or* rimmed vacuoles *or* increased MHC-1 but no intracellular amyloid deposits or 15–18 nm filaments
Pathologically defined IBM		Invasion of non-necrotic fibers by mononuclear cells *and* rimmed vacuoles *and* either intracellular amyloid deposits *or* 15–18 nm filaments

ent "categories" of sIBM criteria defined as Boolean algebraic combinations of features (e.g., definite, probable) in patients diagnosed with sIBM by neuromuscular specialists, it was demonstrated that the available criteria for sIBM have a high specificity (>97%) but that some pathologic and clinical items, such as muscle strength comparison between different muscle groups, had a low sensitivity [16]. Those less sensitive items would exclude many patients with otherwise clinically typical sIBM from trials. The authors instead proposed a triad of data-derived criteria with 90% sensitivity and 96% specificity as shown in Box 11.4.

Box 11.4 Triad of Features Highly Specific for sIBM

- Finger flexor or quadriceps weakness
- Endomysial inflammation
- Invasion of non-necrotic muscle fibers *or* rimmed vacuoles on histopathology

Conclusion

In summary, myositis is a heterogeneous group of diseases where muscle weakness may predominate. However, it is now clear that multiple organs are also commonly affected and that extramuscular involvement such as pharyngeal muscle weakness, skin rash, ILD, arthritis, and cardiac involvement should be systematically screened for. The detection of MSA is a new useful tool that both supports diagnosis and orients the clinicians to different myositis subgroups characterized by specific organ manifestations. New classification criteria for adult and juvenile myositis as well as myositis subgroups have been developed and recently endorsed by the EULAR and the ACR.

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12 Making the Diagnosis of Myositis: Electrodiagnostic Testing

David Lacomis

Key Points to Remember

- Nerve conduction studies are typically normal in patients with idiopathic inflammatory myopathies.
- Electromyography (EMG) findings of myopathy are sensitive but not specific for idiopathic inflammatory myopathy.
- EMG can provide excellent guidance for the selection of muscle biopsy site in idiopathic inflammatory myopathy.
- Myopathic findings on EMG are typically short-duration, low-amplitude, polyphasic motor unit potentials.
- Idiopathic inflammatory myopathies have myopathic findings on EMG in symmetric proximal more than distal muscle of upper and lower extremities except in inclusion body myositis where asymmetry and distal muscles weakness could be seen as well.
- Irritative myopathy, typically seen in inflammatory and necrotizing myopathies, includes finding of increased insertional activity and spontaneous discharges (fibrillation potentials and positive sharp waves).

Introduction

Electrodiagnostic (EDx) testing is an important part of the evaluation of a patient with a suspected inflammatory myopathy. It is very useful in localizing causes of neuromuscular weakness to a component of the motor unit which consists of an anterior horn cell and its motor axons, neuromuscular junctions, and innervated muscle fibers.

In patients with possible myositis, the goals of EDx testing are (1) to identify the presence and distribution of electrodiagnostic features of myopathy, (2) to determine if there are EDx features more suggestive of myofiber necrosis or inflammation, (3) to aid in selecting a muscle for biopsy, and (4) to determine if there is another cause of weakness such as neuropathy or radiculopathy.

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Planning the Study

There are two parts to EDx testing, namely, the *nerve conduction study (NCS)* and *needle electromyography (EMG)*. Frequently, both parts are simply called an EMG. In patients with suspected myopathy, the NCS is usually performed on a motor and sensory nerve in an arm and a leg [8, 10]. The muscles selected for needle EMG should be chosen based on the suspected diagnosis and pattern of weakness identified via manual muscle testing performed by the electromyographer. Generally, in myopathic processes, proximal more than distal muscles should be preferentially examined on EMG. Usually, sampling is performed unilaterally on a wide distribution of arm and leg muscles and on a paraspinal muscle. We prefer to study thoracic paraspinal muscles, since thoracic paraspinal muscles are less likely to harbor confounding findings due to radiculopathy compared to the lumbar or cervical paraspinal musculature. In the limbs, the study is performed unilaterally so that a potential open biopsy could be obtained contralaterally without the risk of EMG needle-induced artifact occurring in the biopsy specimen and with the hope that the disease is symmetric.

Nerve Conduction Study

Nerve conductions are usually normal in myopathy. In pure muscle diseases like myositis, sensory responses should *always* be normal since they involve stimulation and recording only from unaffected sensory nerves. Abnormal sensory responses indicate dysfunction in the large fiber sensory pathway at or distal to the dorsal root ganglion. The motor responses, which are elicited by the stimulation of a mixed (sensorimotor) or purely motor nerve and recorded over the innervated muscle as compound muscle action potentials (CMAPs), are occasionally abnormal in myopathies, since the CMAP reflects conduction through the motor nerves but also through neuromuscular junctions *and muscle fibers*. If there has been significant loss of muscle or an abnormality in depolarization of the muscle membrane, CMAP amplitudes may be reduced. However, since motor responses are usually recorded from distal muscles which are not affected in most myopathic processes, CMAPs are usually normal in myopathy. Occasionally, in myopathies with distal involvement including IBM or in severe, diffuse myopathic disorders, low CMAPs are encountered. Low CMAP amplitudes, however, are more typical of motor neuronopathy, motor axon loss processes, and Lambert-Eaton myasthenic syndrome. Note CMAPs should not be confused with motor unit potentials (MUPs) that are recorded by needle electromyography and are generated only from muscle fibers within a motor unit. Other parameters of interest in NCS are latency and conduction velocity. Latencies are prolonged due to demyelination as may be seen with focal conditions like carpal tunnel syndrome or more diffuse disorders such as chronic inflammatory demyelinating polyneuropathy. Conduction velocities are substantially slowed in demyelinating processes like CIDP, but they are only mildly affecting in axonal neuropathies when there is significant loss of large myelinated axons.

> NCS are typically normal in inflammatory and necrotizing myopathies.

Needle Electromyography

Needle EMG is the most important component of EDx testing in myopathy [4] with abnormalities more likely to occur in weaker muscles. In addition, it is important to study the paraspinals especially when limb muscles are electrically normal, since these most proximal muscles tend to be preferentially affected in inflammatory myopathy and have the highest yield as far as detecting fibrillation potentials (discussed below).

There are four parts to needle EMG examination. The first is examining the muscle at rest for insertional activity which is an electrical discharge due to mechanical irritation of myofibers. After needle movement stops, the electromyogra-

pher monitors the muscle for 1–2 seconds looking and listening for spontaneous discharges (see below) with the muscle still at rest. The presence of increased insertional activity and spontaneous discharges is sometimes referred to as an "irritable" EMG [11]. Next, the patient is asked to activate the muscle by contraction at about 20% of total force with the goal of firing a few motor unit potentials (MUPs), and their morphology is assessed. Last, the patient is asked to maximally contract the muscle to evaluate recruitment of MUPs (all described below).

Insertional Activity

Insertional activity consists of a burst of spikes from myofiber injury that stop when needle movement ceases. It can be prolonged in irritative myopathic processes such as inflammatory and necrotizing myopathies. However, insertional activity is also prolonged in the presence of denervation, other causes of muscle membrane dysfunction, and severe neuromuscular junction disorders (Fig. 12.1).

Insertional activity may be *reduced* if there is significant myofiber loss, fibrosis, and fatty infiltration as seen in IBM, anti-SRP, and other severe forms of chronic myopathies or with reduced muscle membrane depolarization as in periodic paralysis (Table 12.1).

Abnormal spontaneous activity in the form of positive (downward deflection) sharp waves and fibrillation potentials occurs as regular depolarizations from single muscle fibers when there is loss of innervation or with defects in the muscle membrane as may occur with myofiber necrosis, inflammation with muscle membrane dysfunction, channelopathies, and severe neuromuscular junction disorders (Fig. 12.2) [4–6].

Therefore, positive sharp waves and fibrillation potentials are not specific for either myopathic or neurogenic conditions. However, their presence with other myopathic changes on EMG suggest either an inflammatory myopathy such as PM/IBM or a necrotizing myopathy (NM) (i.e., seen with anti-SRP, statin-associated myopathy, or paraneoplastic syndromes). Importantly, fibrillation potentials do *not* occur in steroid myopathy, and they are usually absent in a number of myopathic disorders including congenital

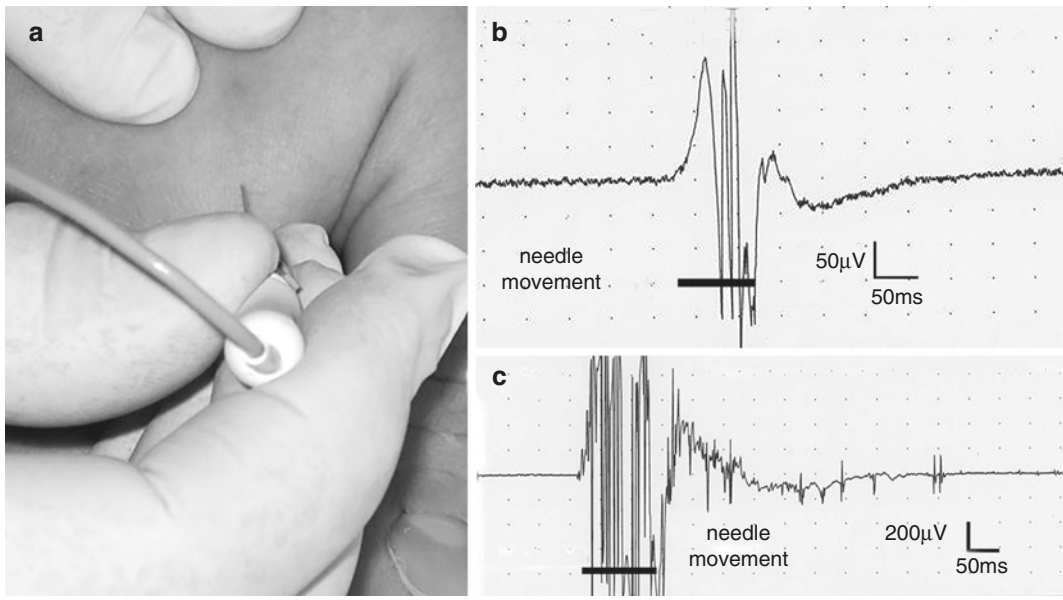


Fig. 12.1 Insertional activity. (**a**) A needle EMG electrode is inserted into a relaxed first dorsal interosseous (hand) muscle. (**b**) Needle movement (*bar* denotes timeline) is associated with a burst of spikes. (**c**) With increased insertional activity, the spikes continue for about 500 ms after needle movement *(bar)* ceases

Table 12.1 Major EMG findings and their associations

EMG component	Finding	Pathological association	Disease examples
Insertional activity	Increased	Muscle inflammation or necrosis, muscle membrane dysfunction Denervation (motor axon or neuron dysfunction) Severe neuromuscular junction disorders	PM, DM, IBM, NM, toxic myopathy (*not* steroid myopathy), some dystrophies, Pompe disease Axonal neuropathy, motor neuron diseases, radiculopathy Botulism
	Decreased	Significant myofiber loss, fibrosis, and fatty infiltration or reduced muscle membrane depolarization	Advanced IBM, dystrophies, end-stage myopathy of any cause Periodic paralysis
Spontaneous activities	Fibrillation potentials and positive sharp waves Fasciculation potentials Myotonic discharges Complex repetitive discharges	Same as for increased insertional activity Axonal degeneration Motor neuron degeneration Muscle membrane dysfunction; channelopathy Chronic myopathic and neurogenic changes; myofiber splitting	Same as for increased insertional activity Motor neuron diseases, e.g., ALS, axonal neuropathy, radiculopathy Myotonic dystrophies; myotonic congenitas; Pompe disease; toxic myopathy, e.g., statin; focal myositis Any chronic myopathy, some toxic myopathies, Pompe disease, radiculopathy
Motor unit potential	Short duration, low amplitude	Myofiber loss, degeneration, and atrophy	Any myopathy; neuromuscular junction disorders, e.g., myasthenia gravis; early motor axonal regeneration
	Long duration, high amplitude	Reinnervation after axonal or motor neuronal injury, advanced or end-stage myopathy	Chronic axonal neuropathies, radiculopathy, motor neuron disease, IBM, advanced muscular dystrophy
	Polyphasia	Ongoing reinnervation of myofibers, myofiber regeneration	Subacute radiculopathy, axonal neuropathy; most subacute to chronic but not end-stage myopathies
Recruitment	Increased or early	Myofiber degeneration or loss	Myopathy of almost any cause and usually at least moderate severity
	Decreased	Neurogenic: demyelination with conduction block or axonal or motor neuronal loss or degeneration, end-stage myopathy, neuromuscular junction dysfunction (severe)	Guillain-Barré syndrome, ALS, axonal neuropathy, radiculopathy, advanced dystrophy, severe myasthenia

Abbreviations: *IBM* inclusion body myositis, *PM* polymyositis, *DM* dermatomyositis, *NM* necrotizing myopathy, *ALS* amyotrophic lateral sclerosis

myopathy, some muscular dystrophies, and some metabolic myopathies.

Fasciculation potentials also occur at rest and are random spontaneous depolarizations of the motor unit. They have the morphologic appearance of a motor unit potential (MUP) (see below Fig. 12.5) [4]. Fasciculation potentials are *not* seen in myopathic processes, and their presence would suggest a disorder of motor neurons or motor axons.

Complex repetitive discharges are polyphasic action potentials that fire spontaneously from groups of individual myofibers (Fig. 12.3). They appear and end abruptly, have a motor boat engine or machinery type of sound, and are due to short circuit (ephaptic transmission) within muscle fibers that often exhibit chronic histopathologic changes. Complex repetitive discharges are associated with more chronic myopathic (e.g., IBM) or neurogenic processes.

Myotonic discharges are spontaneous, rapid firings from single muscle fibers and consist of waxing and waning or purely waning positive sharp waves or spikes that sound like a revving motorcycle (Fig. 12.4). They are associated with muscle membrane disturbances, especially myotonic dystrophies, myotonia congenita, and

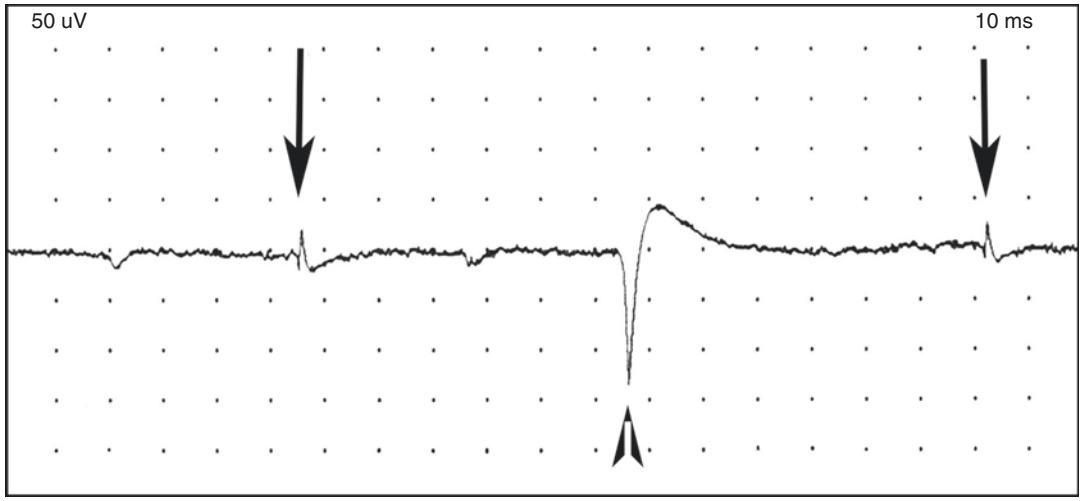
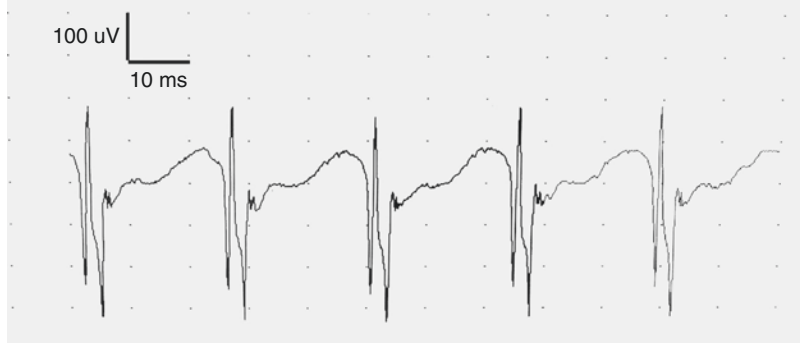


Fig. 12.2 In resting muscle, a positive sharp wave (arrowhead) and fibrillation potentials (long arrows) are shown

Fig. 12.3 Complex repetitive discharge consists of a regularly firing complex (polyphasic) waveform that occurs at rest and begins and ends abruptly



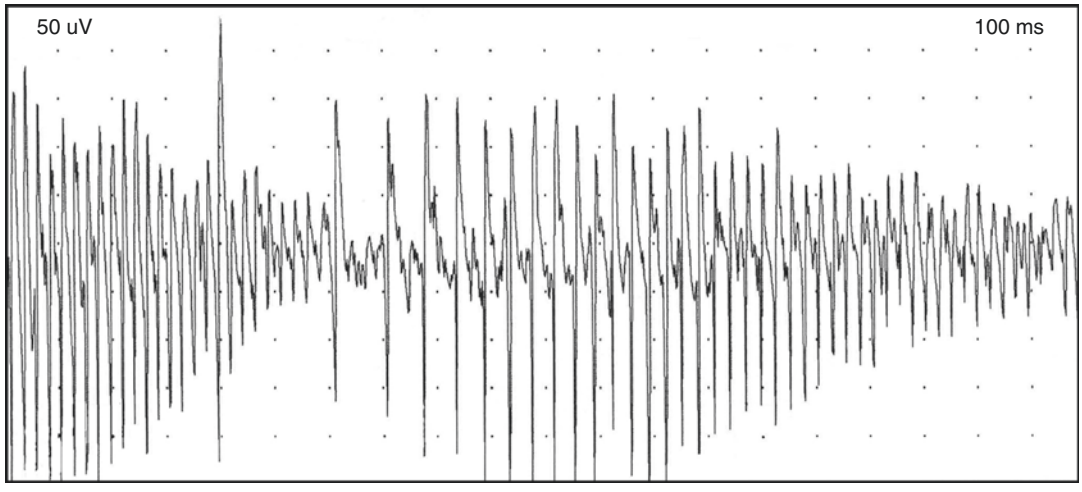


Fig. 12.4 Myotonic discharge. This is a spontaneously occurring spike discharge that changes in amplitude (manifest as variations in height) and firing rate (seen as variations in distance between spikes)

other muscle channelopathies in which patients usually have at least grip myotonia. Occasionally, they appear more focally in inflammatory myopathies; in some toxic myopathies such as statin, colchicine, and hydroxychloroquine myopathy; and in Pompe disease (acid maltase deficiency) without clinical myotonia [1, 10, 14, 16].

Voluntary Contraction: Motor Unit Potential (MUP) Assessment

In myopathic processes, there is atrophy and loss of muscle fibers, and depolarization of myofibers within the motor unit may not be normally synchronous, especially with ongoing myofiber regeneration. Therefore, the resultant MUPs that fire with voluntary contraction are of short duration and low amplitude and polyphasic (Fig. 12.5). These findings in proximal muscles of upper (deltoid, biceps brachii, and triceps) and lower extremity (iliopsoas, quadriceps, and thigh adductors), in association with fibrillation potentials, positive sharp waves, or both, help to make a diagnosis of inflammatory or necrotizing myopathies. Distal involvement, e.g., finger and forearm flexors and tibialis anterior, typically also occurs with IBM along with prominent quadriceps abnormalities.

Recruitment

The other component of the EMG is the assessment of recruitment. Recruitment refers to the number and rate of firing of MUPs. In myopathies, there may be loss or dysfunction of muscle fibers. In order to generate the same amount of force compared to a normal muscle, a *myopathic muscle* undergoes *increased or early, rapid recruitment* in which a larger number of MUPs fire at normal rates. In mild myopathies, recruitment is usually normal. In contrast, *neurogenic disorders* result in loss or blocking of motor units, so fewer MUPs can be activated, and these MUPs fire at a faster rate to compensate for the reduced number of MUPs, i.e., *reduced recruitment*.

All of the inflammatory and necrotizing myopathies share electrodiagnostic findings.

EMG Findings in Myositis

There is an increase in insertional activity along with positive sharp waves, fibrillation potentials, or both in the affected muscles which tend to be proximal muscles. The paraspinal muscles have the highest yield [13, 18]. The findings may be patchy and vary in degree. They are present in almost all patients with inclusion body myositis (IBM) and autoimmune necrotizing myopathy and in 45–75% of patients with DM and PM [7, 10–12, 15, 18]. In addition, short-duration, low-amplitude, and polyphasic MUPs that may recruit early—increased recruitment— are commonly seen in a similar distribution. In IBM, there is asymmetric muscle weakness and the quadriceps is often preferentially affected, and this is not necessarily the case in any of the other autoimmune myopathies. Also, in IBM, there tends to be more distal involvement, especially in forearm and finger flexors. Mainly because IBM is a more chronic myopathy with more advanced remodeling of the motor unit with a clinical or subclinical neurogenic component, there tends to be a "mixed" population of MUPs with typical short-duration, low-amplitude MUPs being seen frequently along with a mixture of normal and sometimes long-duration, high-amplitude MUPs [15]. Long-duration MUPs are those that are more typical and common with neurogenic disorders and are not seen alone in IBM [2].

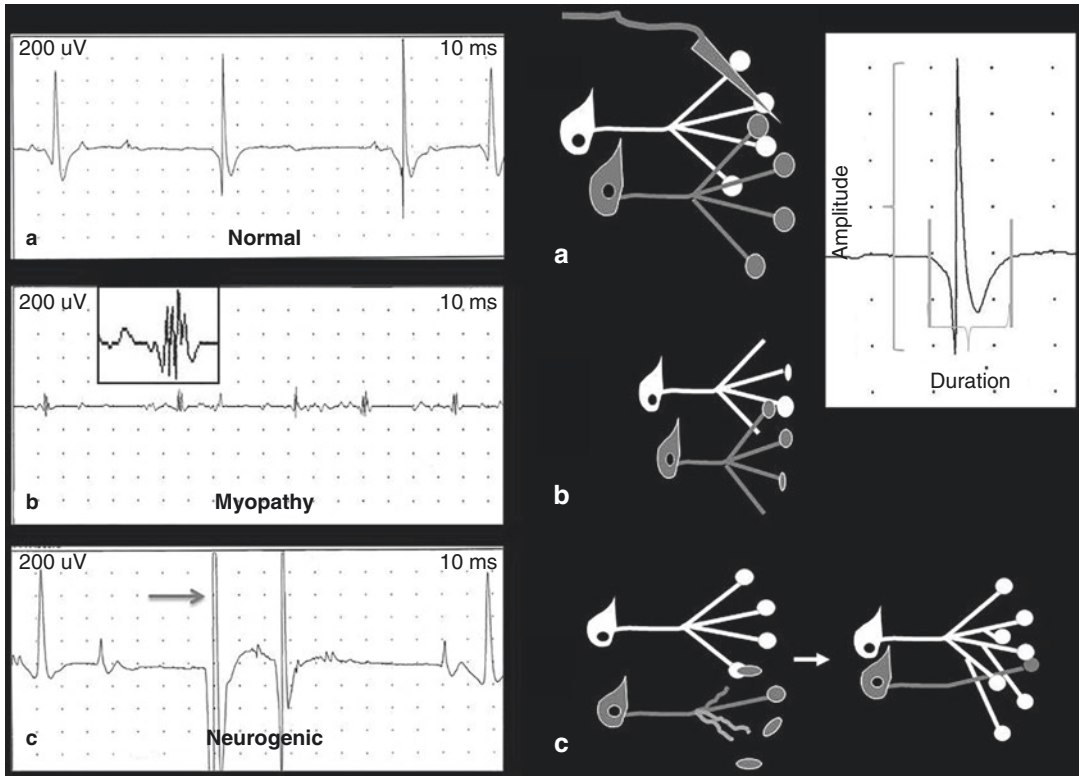


Fig. 12.5 Motor unit potentials (MUPs). (**a**) Normal MUPs are shown. The cartoon in the middle denotes a needle electrode in the neighborhood of muscle fibers from two different motor units—from the gray and white anterior horn cells. On the far right is a zoomed image of a normal MUP. The amplitude is shown as the height from the peak to peak. The duration is the width of the MUP from one baseline crossing to the other denoted by the gray bars. (**b**) In myopathies, there is loss and dysfunction of muscle fibers from motor units resulting in smaller, low-amplitude, short-duration motor unit potentials. In the inset, a complex, polyphasic MUP is shown in which there are multiple turns of the waveforms that cross the baseline. (**c**) In neurogenic processes, MUPs become longer (wider) and higher in amplitude (see arrow) due to reinnervation which is depicted on the right. The lower gray motor unit has lost axons resulting in denervation of muscle fibers. On the far right, the motor unit depicted in white becomes enlarged as those healthy axons reinnervate the previously denervated fibers resulting in the enlarged motor unit potentials

A so-called mixed population of MUPs can also be occasionally seen in other longstanding myopathies, including dystrophies and chronic refractory PM/NM/DM, and it is not specific to IBM. Myotonic discharges occasionally occur in inflammatory myopathies, but they are usually seen in a focal or regional distribution as opposed to the myotonic myopathies in which they tend to be more widespread. Complex repetitive discharges (CRDs) are thought to occur with muscle fiber splitting and also occur in chronic inflammatory myopathies.

The Needle Examination Report

When reading the EMG report, first note which muscles were studied and if they were representative of the symptoms, signs, and suspected condition. Also, note whether there is a notation in the summary if the patient was not cooperative and if there were other limitations like extremity edema. Figure 12.6 illustrates the results of a needle EMG examination from a patient with DM.

Needle EMG Examination:

	Insertional	Spontaneous Activity			Volitional MUAPs					Max Volitional Activity		
Muscle	Insertional	Fibs	+Wave	Other 1	Other 2	Duration	Amplitude	Poly	Hz	Recruitment	Rate	Other
Tibialis anterior.L	NI	0	0	None		NI	SI	0	NI	Normal	NI	
Gastrocnemius (Medial head).L	NI	0	0	None		NI	NI	0	NI	Normal	NI	
Vastus lateralis.L	NI	0	0	None		SD	NI	Some	NI	Normal	NI	
Iliopsoas.L	Inc	0	1+	None		SD	SD	Many	NI	SI	NI	
Biceps femoris (long head).L	NI	0	0	None		Few short	NI	0	NI	Normal	NI	
1st dorsal interosseous.L	NI	0	0	None		NI	SD	0	NI	Normal	NI	
Flexor digitorum superficialis.L	NI	0	0	None		NI	NI	Some	NI	Normal	NI	
Biceps brachii.L	Inc	0	0	None		SD	SD	Many	NI	Normal	NI	
Triceps brachii.L	Inc	2+	2+	None		SD	SD	Many	NI	SI	NI	
Deltoid.L	Inc	0	2+	Myoton		SD	NI	0	NI	Normal	NI	
T10 paraspinal.L	Inc	2+	2+	None		SD	SD	Many	NI	Normal	NI	

Abbreviations: NI = normal, Fibs = fibrillation potentials, MUAP = motor unit action potential, Poly = polyphasic, SI = slightly increased, MI =moderately increased, SD = slightly decreased, MD= moderately decreased, MUP = motor unit potential, PSW = positive sharp waves, CMAP = compound motor unit potential, SNAP = sensory nerve action potential, NCS = nerve conduction study, RNS = repetitive nerve stimulation

Fig. 12.6 EMG findings in a patient with dermatomyositis. See text for description

Note the list of examined proximal and distal upper and lower extremity muscles and the thoracic paraspinal muscle. Insertional activity (second column) was increased in the iliopsoas and thoracic paraspinal muscle and in the three proximal arm muscles. Fibrillation potentials (third column), positive sharp waves (fourth column), or both were present in the same muscles with increased insertional activity. In the fifth column, other spontaneous discharges are noted. The only muscle with a different type of discharge was the deltoid in which myotonic discharges (Myoton) were noted. During voluntary activation, motor unit action potential (MUAP)/ motor unit potential (MUP) morphology was assessed, and the findings were recorded in the next three columns. Slightly decreased (SD) duration MUPs and slightly decreased amplitude MUPs were mostly present in proximal arm and leg and in thoracic paraspinal muscles. The presence and relative frequency of polyphasia are noted in the ninth column and were mostly abnormal in muscle groups with slightly decreased duration and/or amplitude MUPs. The firing frequency (Hz) was considered normal subjectively. Recruitment (far right) was normal except for being slightly increased (SI) in the triceps and iliopsoas. These findings are consistent with a proximal-predominant myopathic process with electrodiagnostic features of muscle inflammation, necrosis, or membrane irritability also known an irritable myopathy.

The abbreviations used in our reports are given below the table. Some labs will use other connotations for short, long, high, low, increased, or decreased. They may use down arrows for short (duration) or low (amplitude) or decreased (recruitment) and up arrows for long, high, or increased. Some use a combination of plus and negative signs instead.

> Fibrillation potential activity can be suppressed by the use of glucocorticoids which stabilize muscle membranes. Therefore, it is ideal to perform EMG testing on patients prior to initiation of glucocorticoids.

Caveats and Correlations

In patients who are weak and have undergone electrodiagnostic testing to differentiate steroid myopathy from inflammatory myopathy, the presence of fibrillation potentials, positive sharp waves, and increased insertional activity is consistent with active myositis rather than steroid myopathy which is not associated with fibrillation potentials [6].

The sensitivity of EMG in predicting myopathic change histologically is 50–67% [3,

Table 12.2 Summary of EMG findings in myopathies and axonal neuropathy

Disorder	Insertional activity	PSW, Fibs	Motor unit potential (MUP) morphology	Recruitment	Other
DM, PM, IBM, necrotizing myopathy[a]	Inc	+	SD, LA, Poly	Inc or Nl	Mixed[b] MUPs in IBM and very chronic/refractory PM/DM
Steroid myopathy	Nl	0	SD or NL	Nl	
Statin toxic myopathy	Inc	+	SD, LA, Poly	Inc or Nl	May have myotonia
Hydroxychloroquine, colchicine myopathy	Inc	+	SD, LA, Poly	Inc, Nl, or Dec	May have myotonia and axonal PN changes
Axonal PN	Inc	+	LD, HA, Poly	Dec	Abnormalities worsen distally; may have regional fasciculations
Motor neuron disease	Inc	+	LD, HA, Poly	Dec	Fasciculation potentials—often diffusely
Radiculopathies	Inc	+	LD, HA, Poly	Nl or Dec	Abnormalities follow myotomal distribution

PSW positive sharp waves, *fibs* fibrillation potentials, *PN* peripheral neuropathy, *Inc* increased, *Nl* normal, + present, 0 absent, *SD* short duration, *LA* low amplitude, *LD* long duration, *HA* high amplitude, *Poly* polyphasic
Footnote:
[a]Increased insertional activity, PSW, and Fibs indicate active inflammation or necrosis in PM/DM/IBM/NM. They may be absent in partially treated cases, milder cases, as well as inactive disease process
[b]Mixture of short-duration and low-amplitude and normal- or long-duration and high-amplitude MUPs

17]. A positive predictive value as high as 82% has been reported [9]. If patients have weakness, an elevation in CK, and myopathic EMG changes, the sensitivity and specificity are even higher at >74% and 77%, respectively, with regard to predicting myopathy histologically. [17]

Differential Diagnosis

A summary of the EMG findings for the major myopathic processes relevant to those who see patients with myositis is shown in Table 12.2. Note the overlap in many categories and the distinction between inflammatory myopathies, steroid myopathy, toxic myopathy, and axonal polyneuropathy (PN). The findings in motor neuron disease are similar to axonal neuropathy except that fasciculation potentials are usually more widespread. In radiculopathies with axon loss, the findings are also similar to axonal PN, but the abnormalities follow a myotomal distribution, whereas they are usually worse distally with PN. Following acute axon loss, fibrillation potentials follow in 2–3 weeks, and the MUP changes of reinnervation (polyphasia with high amplitudes and long durations) usually evolve over 1–6 months or so depending on the lesion.

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13 Making the Diagnosis of Myositis: Muscle Biopsy and Interpretation

David Lacomis

Key Points to Remember

- Muscle biopsies are very helpful in confirming myositis in many patients with muscle weakness, elevated muscle enzymes, and irritable myopathic findings on electromyography.
- Muscle biopsy should be performed on an affected, but not end-stage, typically proximal muscle contralateral to the side of EMG testing (except if EMG and muscle biopsy are done on the same day).
- Classic muscle biopsy findings in dermatomyositis are perifascicular atrophy and myofiber degeneration, perimysial and perivascular inflammation, and upregulation of MHC-1 and deposition of membrane attack complex in capillaries especially in the perifascicular region.
- Classic muscle biopsy findings in polymyositis are endomysial inflammation with cytotoxic T cells surrounding and typically invading intact myofibers, nonspecific chronic myopathic changes, and upregulation of MHC-1, especially in myofibers that are attacked by inflammatory cells.
- Classic muscle biopsy findings in inclusion body myositis are chronic myopathic changes, myofiber invasion by cytotoxic T cells similar to PM, the presence of amyloid-like material, and, in most cases, rimmed vacuoles that are reactive to some markers of autophagy, such as p62.
- The classic muscle biopsy finding of necrotizing myopathy is acute myofiber necrosis (degenerating myofibers and myophagocytosis) with or without myofiber regeneration with little or no lymphocytic inflammatory infiltrate.

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Introduction

Histopathologic examination of skeletal muscle is an important component of the evaluation of a patient with suspected myopathy, especially inflammatory myopathy.

The yield of muscle biopsy is high when patients have weakness, electromyogram (EMG) findings of myopathy (see Chap. 12), and an elevated serum creatine kinase (CK). In such patients, the likelihood of confirming a myopathy histopathologically is >74%, and the likelihood of identifying the specific type is 77% [19].

On the other hand, the yield in the setting of myalgias with no weakness, normal CK, and a normal EMG is essentially nil [5]. With asymptomatic elevations in CK, the yield is usually less than one-third in patients who undergo comprehensive histopathologic and biochemical studies for metabolic and other forms of myopathy, and the final diagnoses are almost never inflammatory myopathy [20]. In general, the yield of biopsy increases with higher CK levels and with EMG findings of myopathy.

Selecting a Muscle Biopsy Site

If the pathologic process is of recent onset (days to few months), it is reasonable to biopsy the most severely affected muscle when feasible. Manual muscle strength testing is used to screen for weakness, and electrodiagnostic testing (discussed in Chap. 12) can identify electrical features of myopathy with or without features of an irritative process. Causes of irritability include muscle necrosis, inflammation, or sarcolemmal membrane dysfunction. Increased insertional activity as well as fibrillation potentials and other spontaneous discharges are such irritative features on EMG. In addition, imaging, mainly magnetic resonance imaging (MRI), can detect muscle edema findings that can be targeted for biopsy [24].

If an EMG was performed within several weeks of a planned biopsy, examined muscles should be avoided for sampling, since needle-induced muscle necrosis can confound the histopathologic findings. The contralateral, nonstudied muscle would then be a reasonable choice for biopsy. On the other hand, if an EMG is performed on the day of the muscle biopsy as in the case of needle muscle biopsy [10], then the muscle biopsy could be performed on the same studied muscle. If the pathological process is more chronic (several months to years), one must be careful to avoid biopsy of a muscle that demonstrates severe weakness and/or atrophy on clinical exam. Such a muscle could be fibrotic and likely to reveal "end-stage" changes of muscle fiber loss, endomysial (within muscle fascicles) and perimysial (between fascicles) fibrosis, and fatty infiltration. Both EMG and MRI can be useful in identifying muscles that may be "end-stage." On EMG, such muscles may have decreased insertional activity, and it may be difficult to identify motor unit potentials (MUPs) due to loss of myofibers. In addition, the muscle may feel gritty to the electromyographer during needle passage. MRI shows evidence of fatty infiltration and muscle atrophy in advanced disease.

The lower extremity sites that are often utilized for muscle biopsy include thigh muscles, especially the vastus lateralis and rectus femoris. In dermatomyositis (DM) and polymyositis (PM), the quadriceps may not be a good choice (personal observation) especially when the hip flexors are more affected than knee extensors. The gastrocnemius, occasionally a site preferred by a general surgeon, should be avoided given the high false-negative results due to being a distal muscle. In the upper extremity, the deltoid and biceps brachii are the most commonly biopsied muscles. In patients with chronic myopathies with distal muscle involvement, a distal muscle may be appropriate for biopsy, especially if the proximal muscles are likely to harbor "end-stage changes." For example, in inclusion body myositis (IBM), the quadriceps is often a good choice early in the course but not in the later stages due to fibrosis. In later stages of the disease, the biceps brachii or

possibly a distal leg muscle, such as the tibialis anterior, may be a better choice.

The muscle is typically obtained by an open biopsy, but some centers perform percutaneous needle biopsies or large-bore needle biopsies, e.g., using a Bergstrom needle [10, 22]. In a few centers, biopsy by conchotome is performed [4]. The choice should be guided by the expertise of the physician performing the biopsy and by the histology laboratory. Small needle biopsies are much more difficult to process than open biopsies and do not provide enough tissue for biochemical studies used for the diagnosis of metabolic myopathies, but they are usually adequate for frozen and paraffin sections required for inflammatory myopathies.

Processing the Specimen

Specimens should be processed for both frozen (cryostat) and paraffin sections. Some tissue should be placed in electron microscopy (EM) fixative, but EM is rarely necessary for diagnosis, and it is not useful for screening. If only one preparation is to be performed, it should be frozen section analysis. This is because rimmed vacuoles (discussed below) can only be seen in frozen sections, and other abnormalities involving organelles such as mitochondria are mainly seen with histochemical evaluation of frozen tissue.

The battery of stains may vary among laboratories; but, typically, hematoxylin and eosin (H&E), Gomori trichrome, oxidative stains, adenosine triphosphatase (ATPase), and nonspecific esterase are performed. H&E staining is performed for routine histopathologic evaluation including assessment of myofiber sizes, location of nuclei and inflammatory cells, myofiber degeneration and regeneration, and vacuolation. Gomori trichrome highlights ragged red fibers in mitochondrial myopathy as well as abnormal myofibrillar alterations including nemaline rods (Table 13.1). Oxidative stains include nicotinamide adenine dinucleotide tetrazolium reductase (NADH-TR), succinic dehydrogenase (SDH), and cytochrome oxidase (COX). NADH-TR is particularly useful in identifying darkly staining angulated atrophic fibers suggestive of denervation as well as nonspecific myofibrillar alterations in which the mitochondria are no longer homogeneously distributed. Such alterations include nonspecific moth-eaten fibers. Target fibers, which look like a bull's eye, are indicative of a neurogenic process and are also identified with NADH-TR. Oxidative stains, especially SDH and COX, are also useful in identifying features of a mitochondrial myopathy (discussed below). The adenosine triphosphatase (ATPase) reactions are used to differentiate myofiber histochemical types and to evaluate patterns of

Table 13.1 Common histochemical stains and their utility

Histochemical stain	Common pathologic findings	Commonly associated diagnoses
Gomori trichrome	Ragged red fibers, nemaline rods, rimmed vacuoles	Mitochondrial myopathy, nemaline myopathy, multiple others including IBM
Nicotinamide adenine dehydrogenase	Target fibers and small dark fibers, central cores	Neurogenic change, central core myopathy
Adenosine triphosphatase	Type 2 fiber atrophy fiber-type grouping	Steroid myopathy, neurogenic change (reinnervation)
Periodic acid Schiff	Reactive aggregates, usually in vacuoles	Glycogen storage disease
Oil-red-O or Sudan black	Increased number and size of lipid droplets	Lipid storage diseases
Cytochrome oxidase	Absent reactivity in myofibers	Mitochondrial myopathy
Succinic dehydrogenase	Increased reactivity	Mitochondrial myopathy
Nonspecific esterase	Hyperreactive atrophic fibers	Denervation atrophy
Acid phosphatase	Reacts with macrophages Vacuolar reactivity	Myophagocytosis (nonspecific); Lysosomal activity, for example, Pompe disease

atrophy such as type 2 vs. neurogenic and to evaluate for grouping of fiber types as is seen with reinnervation. Nonspecific esterase is hyperreactive in atrophic denervated fibers, and it also identifies motor endplates and reacts with lysosomal elements and macrophages that contain esterases. Acid phosphatase highlights lysosomes and macrophages. Amyloid staining, such as Congo red, is also useful in both IBM and amyloidosis. Some centers will perform stains for glycogen and lipid routinely, and others do so as needed, to identify metabolic myopathies related to storage disorders. Phosphorylase, phosphofructokinase, and myoadenylate deaminase reactivity can also be assessed histochemically in patients with suspected metabolic myopathies. They are nonreactive when the enzyme is absent.

Immunohistochemistry can be performed for various proteins including major histocompatibility complex (MHC) class I or II, transactive response (TAR) DNA-binding protein 43 (TDP-43), autophagic vacuole markers such as p62 (sequestosome-1), lymphocyte subsets, macrophages, and C5b-9 membrane attack complex (MAC). A number of immunostains are available for muscular dystrophies, and some such as dysferlin antibody are more pertinent, since dysferlinopathy may be associated with an inflammatory infiltrate [13].

Electron microscopy is performed on specimens fixed in Karnovsky's fixative (glutaraldehyde and paraformaldehyde) or glutaraldehyde and embedded in plastic (Epon). Semi-thick (1 micron) sections are reviewed by the pathologist, and thin sections are then cut from the area of interest followed by ultrastructural imaging. EM is mostly useful in identifying "inclusions" such as abnormal filaments, myofibrillar alterations such as nemaline rods, and the contents of vacuoles such as autophagic debris, glycogen, or filaments. Mitochondrial abnormalities and complex lipid or glycogen aggregates may be seen with EM. Usually, there is already suspicion that these abnormalities may be present based on light microscopy, but the finding is uncertain and needs to be confirmed ultrastructurally. Since only a small number of myofibers are assessed, EM is not a screening tool. It is performed on a small number of muscle biopsies, primarily serving as a confirmatory study.

> It is important that the pathologist is aware of the clinical history so that the proper staining is performed on each case.

Remaining frozen tissue can be stored indefinitely at -180 °C, but most centers limit the duration due to freezer space. Paraffin blocks and glass slides can be stored indefinitely. Digital and whole slide imaging may also be available.

Interpretation of Muscle Biopsy Findings

In any of the inflammatory myopathies, it is common to find evidence of muscle fiber degeneration and regeneration. Most of the histopathologic changes can be seen on a frozen H&E-stained section. When muscle fibers degenerate and become necrotic for any reason, they appear pale initially and are then infiltrated by macrophages in a process termed *myophagocytosis* (Fig. 13.1).

Regenerating myofibers develop plump, vesicular nuclei. On H&E stain, they exhibit basophilic cytoplasm due to increased RNA activity (Fig. 13.1). Some regenerating myofibers react with alkaline phosphatase. After regeneration, nuclei may become internalized, losing their peripheral eccentric location. In myopathic processes, the fiber shapes may be more rounded than polygonal, and even atrophic fibers may be rounded. In chronic myopathies, atrophy and hypertrophy commonly occur over time leading to significant fiber size variation along with internalization of nuclei. Myofibers may exceed 100 microns in diameter in chronic myopathies (normal myofibers are usually about 40–60 microns in diameter). Larger myofibers may split. Fibrosis—scarring—can appear around muscle fibers (endomysial fibrosis) and between fascicles (perimysial fibrosis). These late chronic changes of fibrosis as well as fatty

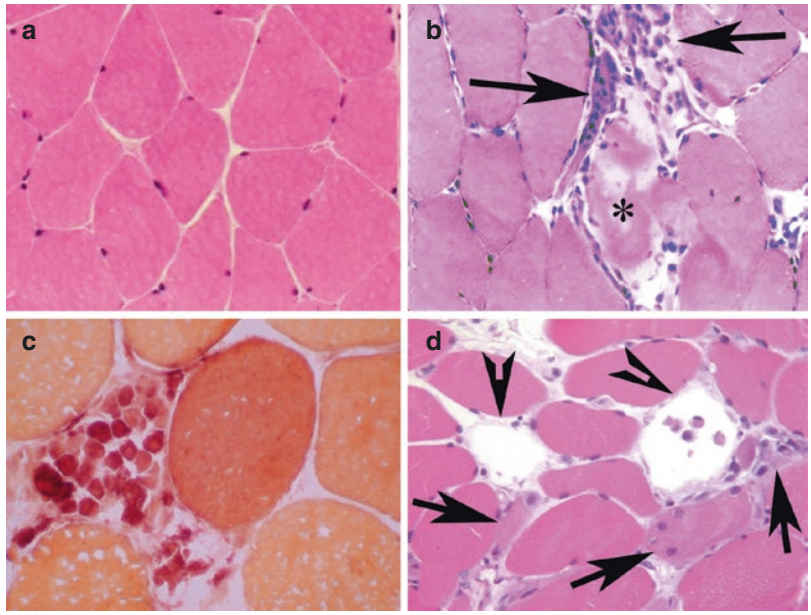

Fig. 13.1 Myofiber degeneration and regeneration. (**a**) Normal muscle for comparison. Myofibers stain homogeneously and are polygonal in shape. The nuclei are eccentric in location (H&E, frozen). (**b**) An acutely necrotic, pale, disintegrating/degenerating myofiber (*) and myofibers containing macrophages undergoing myophagocytosis *(arrows)* are seen. (**c**) Numerous darkly staining macrophages are apparent in a myofiber undergoing myophagocytosis (nonspecific esterase). (**d**) Regenerating myofibers are basophilic *(arrows)* and have plump nuclei. Remnants of necrotic fibers (ghost fibers) are also seen *(arrowheads)*

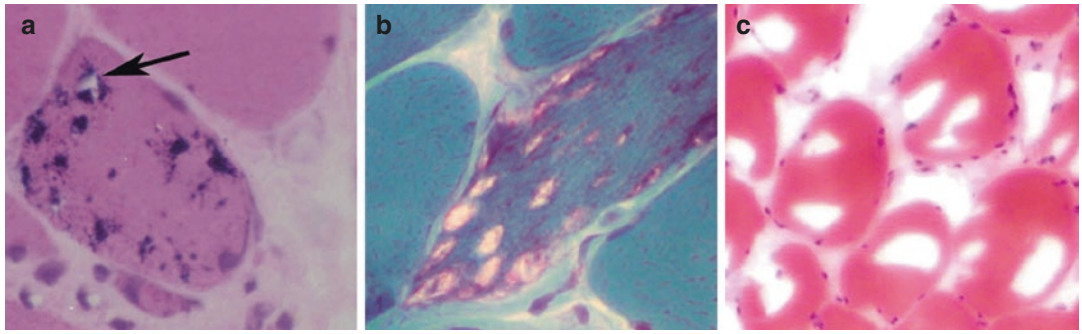

Fig. 13.2 Rimmed vacuoles. (**a**) The arrow points to a rimmed vacuole. The myofiber has other blue granular deposits associated with tiny vacuoles that are not obvious (H&E, frozen). (**b**) Gomori trichrome stain reveals rimmed vacuoles lined with red granules. (**c**) Freeze artifact is shown for comparison

infiltration are more typical of a dystrophy, but they are also common with IBM.

The presence of rimmed vacuoles is sought with H&E and Gomori trichrome stains. Vacuoles are clear spaces, and rimmed vacuoles have a lining of granules that are blue with H&E and red with Gomori trichrome (Fig. 13.2). Vacuoles related to freeze artifact have no lining, are usually seen diffusely, and have no contents. They have no significance but need to be distinguished from pathologic vacuoles. Vacuoles containing storage material such as glycogen or lipid are clear on H&E. However, glycogen reacts with PAS, and lipid reacts with oil-red-O or Sudan black. Vacuoles, typically nonrimmed, may also occur as part of myofiber

degeneration. They may be due to autophagy and react with acid phosphatase and p62 as well as other markers of autophagy.

Mitochondrial abnormalities are detected mainly with Gomori trichrome as ragged red fibers (Fig. 13.3). With succinic dehydrogenase, the cytoplasm stains darkly as "ragged blue."

With involvement of mitochondrial DNA, there are usually myofibers that do not react with cytochrome oxidase (COX) and are reported as COX-negative fibers.

Myofiber atrophy can be seen with any stain, but ATPase is used to identify the fiber types involved. Some laboratories use fast (type 2) and slow (type 1) myosin immunostains for fiber typing instead of ATPase. Atrophy from denervation, namely, neurogenic atrophy, affects both type 1 and type 2 fibers, and the atrophic fibers tend to be angulated. Denervated fibers may stain darkly with NADH-TR and esterase. Target fibers are best seen with NADH-TR. With reinnervation, there is grouping of type 1 and 2 fibers as opposed to the normally occurring checkerboard pattern of fiber types. Atrophy limited to type 2 fibers (Fig. 13.4) is commonly seen with steroid myopathy, but it may be seen with other conditions such as disuse and endocrinopathies. Atrophy from any cause is also associated with the presence of nuclear clumps.

The localization and nature of an inflammatory infiltrate can be identified with routine stains and further characterized by immunohistochemistry. First, the distribution of the inflammation should be identified as being in the perimysial or endomysial compartments or both (Fig. 13.5).

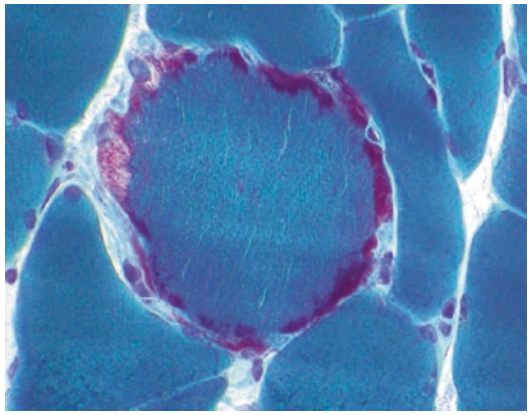

Fig. 13.3 A ragged red fiber is shown from a patient with IBM (Gomori trichrome, frozen section)

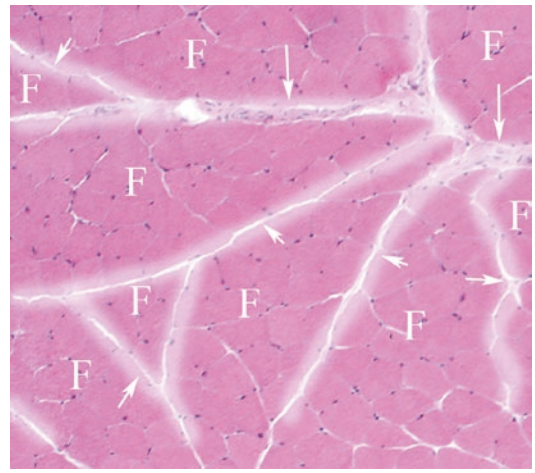

Fig. 13.5 Organization of muscle. The muscle is arranged in fascicles (*F*). The fascicles are surrounded by perimysial connective tissue that is highlighted in white. In some regions, the perimysial connective tissue that is between fascicles is thicker (*long arrows*) than in other areas (*short arrows*). The endomysium is the region within the fascicles, and inflammatory cells within that compartment are endomysial in location. Endomysial connective tissue surrounds each myofiber

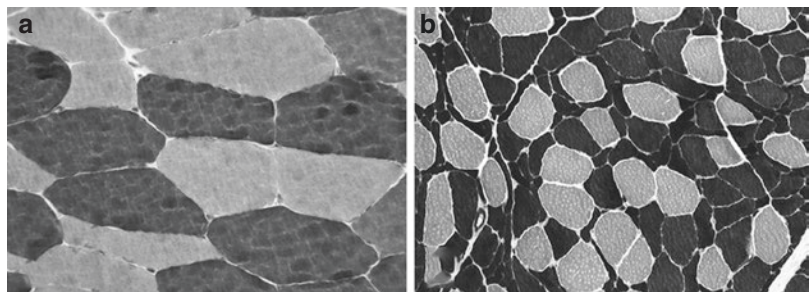

Fig. 13.4 ATPase reacted sections at pH 9.4. (**a**) Normal sizes with darkly staining type 2 myofibers and lighter type 1 fibers. (**b**) Atrophy affecting type 2 fibers exclusively

Next, the cell types, e.g., lymphocytes vs. macrophages, should be evaluated. If desired, lymphocyte subsets can be assessed with immunostains for pan-T (CD3), helper T (CD4), and cytotoxic T (CD8) cells, B cells (CD20), macrophages (CD68), and dendritic cells. There are markers for numerous other cells including more specific markers for plasmacytoid dendritic cells and plasma cells.

Invasion of non-necrotic fibers by lymphocytes (Fig. 13.6), mainly cytotoxic T cells, is termed *myofiber invasion*, and this occurrence is associated with polymyositis (PM) and IBM, but it is not seen with dermatomyositis or autoimmune necrotizing myopathy. It rarely occurs in some dystrophies. Immunostaining for major histocompatibility complex (MHC) class I can be performed as a very sensitive marker for an inflammatory process, but it is nonspecific. MHC I immunoreactivity is normally seen in capillaries but not on muscle fibers. It is seen in the sarcolemma (muscle membrane), cytoplasm, or both in myofibers in autoimmune myopathies (shown later), but it sometimes appears in other processes such as dystrophies. MHC class II is not normally found on myofibers, and myofiber immunoreactivity for MHC II may be more specific for myositis, but it is less sensitive than MHC I [18].

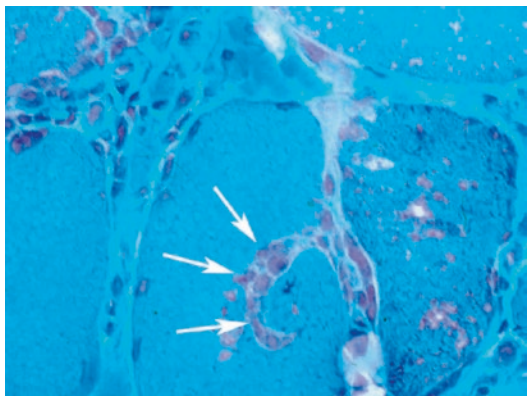

Fig. 13.6 Myofiber invasion. Lymphocytes *(arrows)* are invading a non-necrotic myofiber (IBM, Gomori trichrome, frozen)

How to Read the Muscle Biopsy Report

The report should include a brief history if available, the site of biopsy, a list of stains, and a microscopic description of the findings such as those discussed above. Any limitations, such as freezing artifact, should be noted. The final diagnosis should list the main category of pathologic change such as myopathy, neurogenic atrophy, type 2 fiber atrophy, no diagnostic change, etc., and provide a more specific diagnosis if possible such as inclusion body myositis, inflammatory myopathy, necrotizing myopathy, or mitochondrial myopathy. Often, there is a final diagnosis and comment that provides a differential diagnosis that typically requires clinical correlation.

Dermatomyositis (DM)

In patients with DM, skeletal muscle biopsies usually show atrophy of perifascicular myofibers along with myofiber degeneration changes such as vacuolation and myofibrillar disorganization as well as regeneration mostly in perifascicular myofibers (Fig. 13.7).

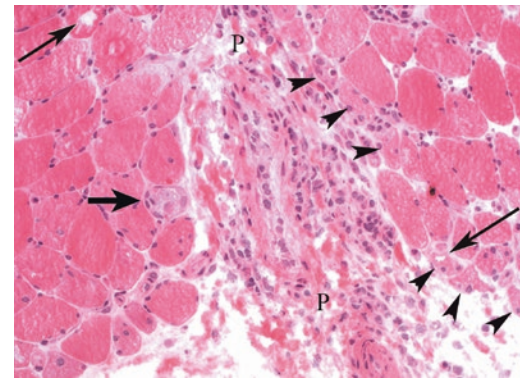

Fig. 13.7 An H&E-stained frozen section from a patient with DM shows a region of perimysial (*P*) expansion, fragmentation, and mononuclear cell inflammation. The two adjacent fascicles exhibit perifascicular atrophy *(arrowheads)*. There are vacuolated fibers *(long arrows)*. A basophilic fiber that is starting to regenerate is highlighted by the short arrow

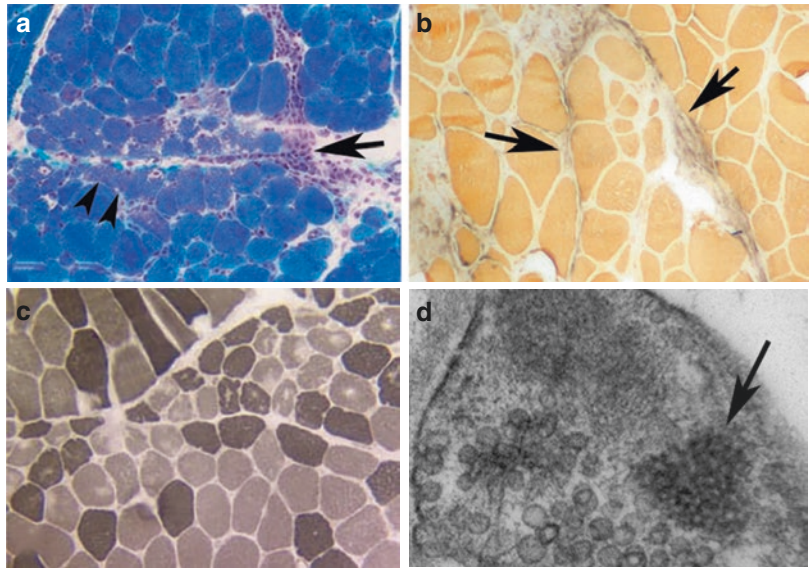

Fig. 13.8 Dermatomyositis. (**a**) There is perimysial inflammation (*arrow*) with abnormal purplish reactivity in atrophic perifascicular myofibers (see *arrowheads* for examples) with Gomori trichrome. (**b**) Alkaline phosphatase reacts (dark staining) with perimysial connective tissue (*arrows*). (**c**) ATPase highlights atrophy in perifascicular fibers, and there is reduced or patchy reactivity in perifascicular fibers (bottom fascicle) and throughout the middle fascicle (frozen sections in **a**–**c**). (**d**) Electron microscopy reveals a tubuloreticular inclusion (*arrow*) in a muscle capillary endothelial cell

The disrupted myofibers often have a purplish appearance with Gomori trichrome (Fig. 13.8). Expansion, edema, and fragmentation of the perimysial connective tissue are commonly seen, and the connective tissue may react with alkaline phosphatase (Fig. 13.8). The pathology is no different in DM patients with cancer than in those without it, and the findings in adult and juvenile DM are similar.

The inflammatory infiltrate is present in the perimysium and is usually around blood vessels (perivascular), but it may extend to the endomysium. The inflammatory cells usually consist of macrophages, dendritic cells, and CD4+ more than CD8+ lymphocytes as well as some B cells [2, 8]. Lymphoid follicles are sometimes seen, especially in patients with juvenile dermatomyositis (JDM). These follicles contain more CD4+ than CD8-reactive T cells or B cells [12]. There is another typical finding seen in 60% or more of biopsies, namely, deposition of membrane attack complex (MAC) in endomysial capillaries especially in regions of perifascicular atrophy and degeneration (Fig. 13.7) [11]. The deposition of MAC is thought to be an early change. Over time, there may be loss of capillaries, which can be identified with endothelial cell markers such as *Ulex europaeus* or CD31 (Fig. 13.9).

There is upregulation of MHC1 in the sarcolemma or cytoplasm of predominantly perifascicular myofibers (Fig. 13.7), and this finding may be seen even in hypomyopathic DM in the absence of other histopathological changes of DM [6]. Although EM is not usually performed in patients with possible DM, if obtained, it may reveal tubuloreticular inclusions in capillary endothelial cells (Fig. 13.8).

Polymyositis (PM)

In PM, the most important finding is the presence of endomysial inflammation with cytotoxic T cells that surround and typically invade intact fibers (Fig. 13.10) along with the presence of nonspecific myopathic changes described above. There is upregulation of MHC I in myofibers, especially those surrounded and invaded by inflammatory cells. The inflammatory infiltrate is present predominantly in the endomy-

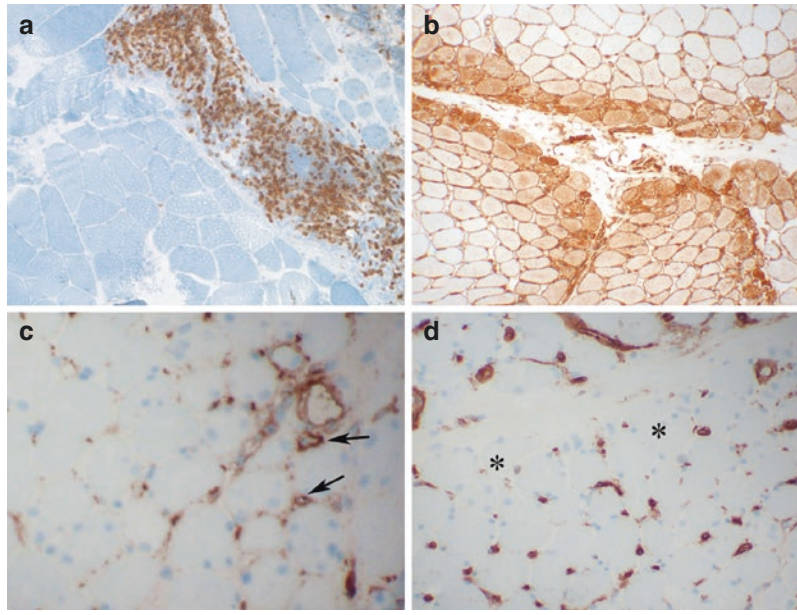

Fig. 13.9 Dermatomyositis. (**a**) A follicular focus of perimysial T cells is seen (CD3). (**b**) MHC I reacts strongly with the cytoplasm of perifascicular myofibers; all fibers have sarcolemmal membrane reactivity. There should be no reactivity in normal myofibers. (**c**) Membrane attack complex deposition is seen *(see arrows for examples)*. Capillaries should be nonreactive. (**d**) Immunoreactivity for the endothelial cell marker CD31 reveals many normally reactive capillaries and regions *(*)* of capillary loss or attenuation

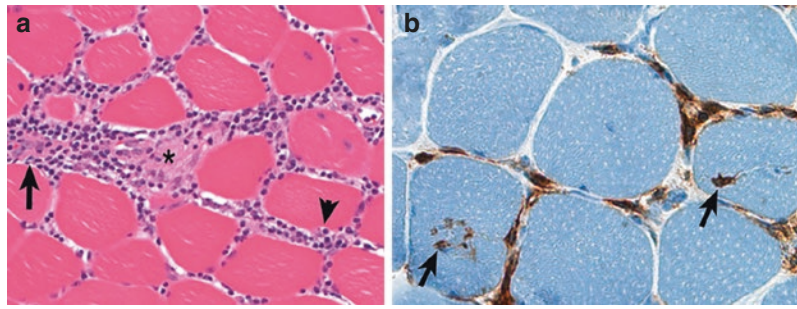

Fig. 13.10 Polymyositis (**a**). H&E-stained paraffin section reveals a region of perimysial lymphocytic inflammation *(arrow)* as well as endomysial inflammation surrounding myofibers and early fiber invasion (*arrowhead*) (**b**). CD8 immunostain highlights cytotoxic T cells *(arrows)* invading non-necrotic fibers (frozen section)

sium, but perimysial inflammation also occurs. In addition to CD8-positive cytotoxic T cells, there may be lesser number of T helper and B cells as well as macrophages and dendritic cells [2, 8]. There is no perifascicular atrophy or capillary pathology. The pathology is no different in PM patients with cancer or overlapping connective tissue diseases.

If there is endomysial inflammation *without* myofiber invasion of PM or clinical or histopathologic features of DM, the pathological diagnosis may be best termed *nonspecific (unspecified) myositis* rather than PM [8, 23]. Such patients may actually have early IBM or a long list of other myopathies, including limb-girdle muscular dystrophy (LGMD) [14] that may have inflammation histologically and potentially mimic polymyositis (see partial list below). In such cases, the clinical diagnosis of PM is generally accepted after ruling out potential PM mimics.

Myopathies with inflammation that may mimic PM:

- Inclusion body myositis
- LGMD 2B (dysferlinopathy)
- Facioscapulohumeral dystrophy
- LGMD 2A (calpainopathy)
- LGMD 2I (Fukutin-related protein deficiency)
- LGMD 2E (beta-sarcoglycanopathy)
- Autoimmune necrotizing myopathy

The type 2 limb-girdle muscular dystrophies are autosomal recessive; therefore, most of these patients have a negative family history. In general, patients with histopathologic findings of "nonspecific myositis" and a questionable response to immunotherapy warrant periodic reevaluation for PM mimics.

Inclusion Body Myositis (IBM)

On H&E-stained specimens, rimmed vacuoles appear to be empty and are lined by basophilic granules as mentioned earlier. The granules usually stain red with Gomori trichrome and vary in frequency (Fig. 13.2). Eosinophilic cytoplasmic inclusions (cytoid bodies) may be seen in rare myofibers. These bodies have a dense central core and a paler halo. They stain darkly with Gomori trichrome and are nonspecific (Fig. 13.12). There may be evidence of mitochondrial abnormalities manifest as ragged red fibers on Gomori trichrome stain and ragged blue fibers with succinic dehydrogenase (Fig. 13.12). They may be nonreactive/negative with cytochrome oxidase. There is usually "neurogenic" change histologically which manifests as myofiber atrophy affecting both type 1 and 2 fibers, and the atrophic fibers often stain darkly with NADH-TR and may be hyperreactive with nonspecific esterase. Capillaries are normal.

Upregulation of MHC I is present especially in myofibers undergoing invasion by inflammatory cells (Fig. 13.12). The inflammatory infiltrate is composed of T cells, especially CD8 reactive T cells. However, other cells may be seen including plasma cells, dendritic cells, and macrophages. Abnormal clonal expansion of either cytotoxic T lymphocytes or natural killer cells has been reported in some patients with IBM and T cell large granular lymphocytic leukemia. The majority of abnormal cells show a CD3+, T cell receptor Ab+, CD8+, CD57+, CD16+, CD4-, CD27-, and CD28- phenotype [7].

In addition, there is evidence of a degenerative component with Congo red positivity (Fig. 13.12), amyloid-like material being seen in a minority of myofibers, as well as the presence of cytoplasmic inclusions that react with a number of markers including TDP43 (Fig. 13.12), p62 (Fig. 13.13), tau, beta amyloid, and SMI-31. SMI-31 reacts with a phosphorylated epitope in extensively

In IBM, there is usually histopathologic evidence of a chronic myopathy unless the biopsy is performed earlier than usual in the course. Such chronic findings may include a large variation in myofiber sizes with hypertrophy and atrophy as well as an increase in internalized nuclei, endomysial fibrosis, fiber splitting, and fatty infiltration (Fig. 13.11). In addition, myofiber invasion by cytotoxic T cells is typically seen similar to PM. A characteristic finding is the presence of the rimmed vacuole that occurs in variable numbers but not in all cases (Fig. 13.12).

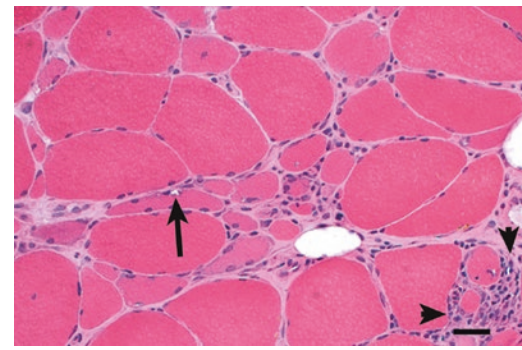

Fig. 13.11 Inclusion body myositis. There are atrophic and hypertrophic fibers. A rimmed vacuole is highlighted (*arrow*). There is a focus of endomysial inflammation (denoted by *short arrows*). Other findings are endomysial fibrosis, a few internalized nuclei, and several bluish regenerating fibers adjacent to the fiber with the rimmed vacuole. (H&E, frozen, bar = 50 microns)

phosphorylated neurofilament H and, to a lesser extent, with neurofilament M.

Electron microscopy is usually performed on a minority of patients to help confirm the diagnosis if light microscopic studies are equivocal. For example, if there are features of a chronic inflammatory myopathy without the presence of rimmed vacuoles or sarcoplasmic inclusions suggestive of IBM (see above), EM may be useful. The EM findings of IBM include the presence of 18 nm filamentous inclusions in vacuoles or in the nuclei (Fig. 13.14).

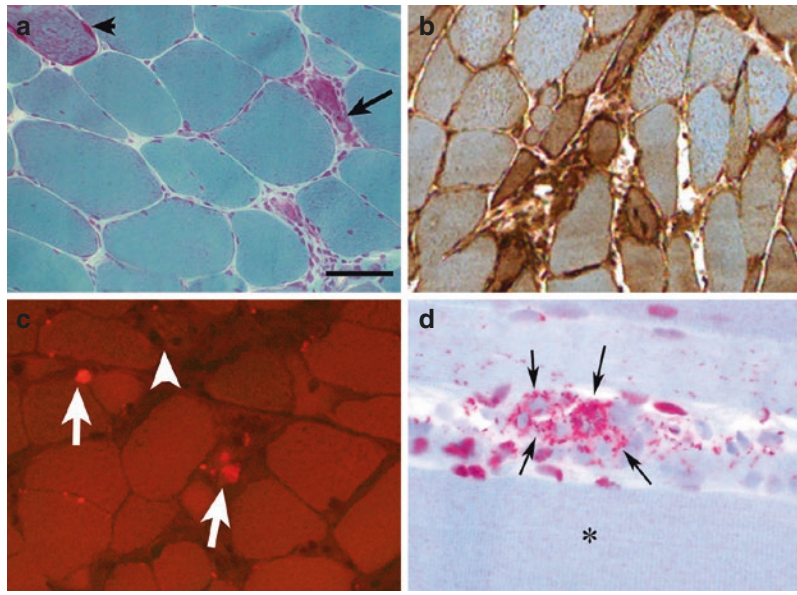

Fig. 13.12 Inclusion body myositis. (**a**) A ragged red fiber is seen *(short arrow)* along with a cytoid body *(arrow).* There is diffuse myofiber hypertrophy. (Gomori trichrome, bar = 80 microns). (**b**) There is diffusely abnormal MHC I immunoreactivity especially in the central myofibers surrounded by inflammatory cells. (**c**) *Congo* red viewed with Texas red fluorescence filters reveals probable amyloid inclusions *(arrows),* while some vacuoles do not react (*arrowhead*) (**a**–**c** frozen sections) (**d**). A longitudinal paraffin section reacted with TDP-43 reveals a vacuolated myofiber with many reactive rod-like inclusions *(arrows).* TDP-43 normally reacts with nuclei, but some of the nuclei adjacent to the arrows are nonreactive. A normal myofiber (*) is also seen

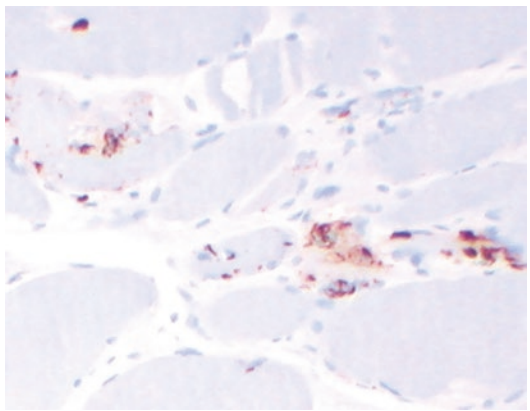

Fig. 13.13 p62 in IBM. Several myofibers contain vacuoles with contents reactive with p62 immunostaining (paraffin section)

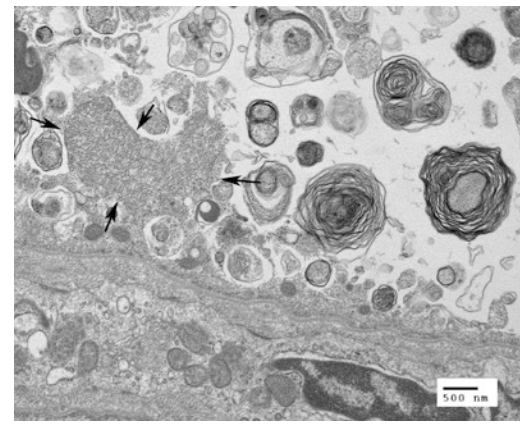

Fig. 13.14 Ultrastructural image of a vacuole containing autophagic debris and a collection of filaments *(outlined by arrows)*

Necrotizing Autoimmune Myopathy

In necrotizing autoimmune myopathy, the main finding is myofiber necrosis, which acutely manifests as pale/degenerating myofibers and myophagocytosis followed by regeneration with little or no lymphocytic inflammation (Fig. 13.1). There may or may not be upregulation of MHC I on myofibers, and MAC deposition in capillaries is occasionally seen [3].

Patients with myopathy and antibodies to *signal recognition particle (SRP)* may have features of a necrotizing myopathy acutely or subacutely, but they may develop dystrophic-type changes over time (Fig. 13.15). Such dystrophic changes would include a variation of myofiber sizes with endomysial fibrosis. There may be clustered, rounded, atrophic myofibers. There is usually a paucity of lymphocytic inflammation in all stages [9, 16]. Sarcolemmal deposition of MAC is occasionally noted as well as MAC deposits in capillaries. There may or may not be upregulation of MHC I on myofibers.

In patients with necrotizing autoimmune myopathy with *HMGCR autoantibodies* with or without statin exposure, there is usually myophagocytosis with little or no lymphocytic inflammation (Fig. 13.1). Upregulation of MHC I and capillary deposition of MAC are seen in about half of the biopsy specimens obtained from these patients [3]. The histopathologic changes of autoimmune necrotizing myopathy *associated with cancer* are nonspecific.

Antisynthetase Syndrome

Patients with antisynthetase syndrome have perimysial-predominant pathologic findings similar to DM even in the absence of cutaneous manifestations of DM. Pestronk noted the perimysial predominant pathology which he termed immune myopathy with perimysial pathology (IMPP) [17]. Inflammatory cells, mainly lymphocytes and macrophages, are present in the perimysium, and there is also evidence of perimysial expansion and injury (Fig. 13.16).

Perifascicular-predominant myofiber necrosis is usually present with sarcolemmal deposition of MHC I on myofibers in a perifascicular-predominant pattern. Perifascicular myofiber necrosis may be more prominent than in DM [15]. It has been reported that EM may reveal myonuclear actin filament aggregates [21].

A summary of histopathologic findings in the autoimmune myopathies is provided in Table 13.2.

Steroid and Other Toxic Myopathies

Patients being evaluated for active myositis may also be treated with potentially myotoxic agents such as glucocorticoids and hydroxychloroquine; therefore, brief mention about the pathology associated with these agents is worthwhile.

Glucocorticoid use is associated with atrophy of type 2 (Fig. 13.5c) or specifically type 2b myofibers. There is no associated myofiber degenera-

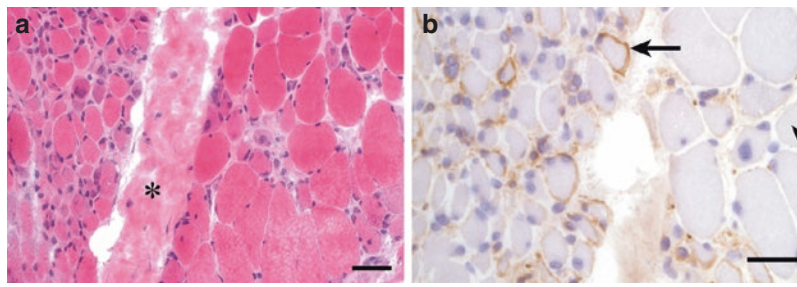

Fig. 13.15 Anti-SRP myopathy. (**a**) There is fibrosis of perimysial connective tissue (*), and many myofibers are atrophic, especially in the fascicle on the left that also exhibits endomysial fibrosis and myofiber regeneration (bluish fibers). (**b**) Membrane attack immunoreactivity is seen in the sarcolemma of some myofibers (see *arrow* for example), and a capillary (dot at *arrowhead*) is also reactive (frozen sections, bar = 40 microns)

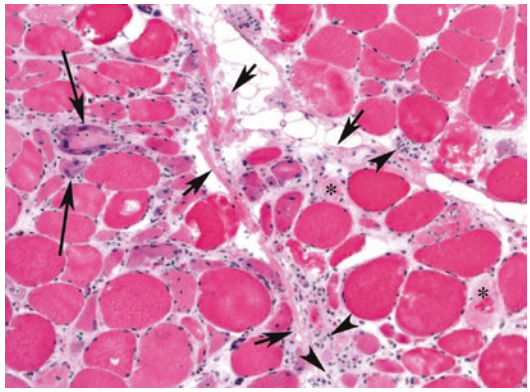

Fig. 13.16 Synthetase syndrome (anti-OJ antibody). An H&E-stained frozen section shows parts of three fascicles with disruption of the perimysial connective tissue (*short arrows*), some perimysial inflammation (*arrowheads*), and myofiber atrophy that is more prominent at the edge of fascicles. Some bluish regenerating fibers are apparent (*long arrows*). There are rare, pale, necrotic fibers *(*)*

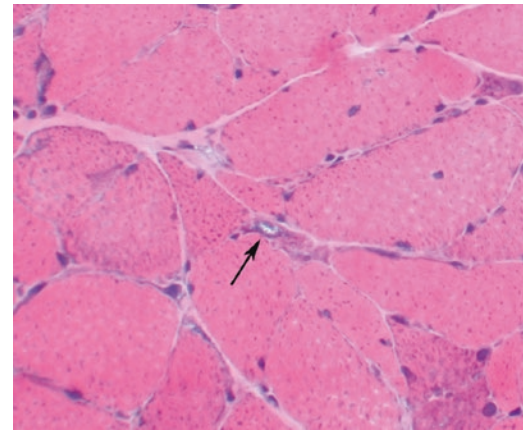

Fig. 13.17 Hydroxychloroquine myopathy. H&E-stained frozen section reveals an atrophic myofiber containing a rimmed vacuole (*arrow*). Several adjacent myofibers have internalized nuclei

Table 13.2 Summary of histopathologic findings in autoimmune myopathies

Disorder	General	Inflammation	MHC I	Other
Dermatomyositis	Perifascicular atrophy, myofiber degeneration and regeneration, perimysial expansion and fragmentation	Perimysial and perivascular CD4 > CD8 lymphs, B cells, macs, dendritic cells	Perifascicular predominant	Capillary microangiopathy (MAC deposition and capillary loss)
Polymyositis	Myofiber degeneration and regeneration, myofiber invasion	Endomysial > perimysial, CD8 > CD4 lymphs	Endomysial, esp. invaded fibers	
Inclusion body myositis	Chronic myopathic changes, rimmed vacuoles, myofiber invasion, mitochondrial changes	Endomysial CD8 > CD4; plasma cells	Endomysial, esp. invaded fibers	Inclusions TDP-43, p62, SMI-31+, and amyloid, EM: filamentous inclusions
Autoimmune necrotizing myopathy	Myofiber necrosis with myophagocytosis; myofiber regeneration	Little or no lymphocytic inflammation	Variable	+/− MAC on capillaries

MHC1 major histocompatibility complex class I, *macs* macrophages, *lymphs* lymphocytes, *MAC* membrane attack complex, *EM* electron microscopy

tion or regeneration, nor is there inflammation. There is no increased reactivity of atrophic fibers with nonspecific esterase or NADH-TR as is seen with neurogenic atrophy, nor is there any fiber type grouping.

Hydroxychloroquine and chloroquine may cause a vacuolar myopathy with or without neuropathic changes [1]. The vacuoles are generally rimmed (Fig. 13.17). There may be other associated nonspecific myopathic changes. Inflammation is not usually present. In these cases, EM can be diagnostic when it shows the presence of electron dense, complex lipid inclusions that have a curvilinear shape (Fig. 13.18).

Metabolic Myopathies and PM Mimics

Adult acid maltase deficiency (form of Pompe disease) can be a polymyositis mimic. Patients

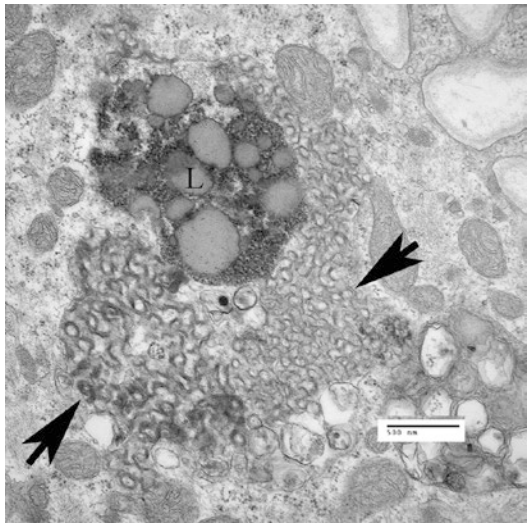

Fig. 13.18 Ultrastructural study of a skeletal muscle biopsy specimen from a patient with hydroxychloroquine myopathy reveals curvilinear inclusions outlined by the arrows and a complex lipid deposit (L). (Bar = 500 nm)

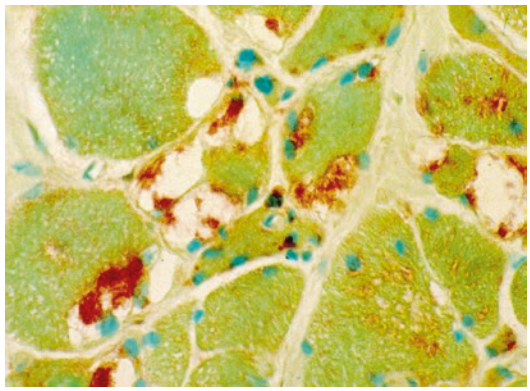

Fig. 13.19 Adult Pompe disease. Red acid phosphatase reactivity is present in vacuoles (frozen section)

can have various patterns of weakness including proximal-predominant weakness, elevations in serum CK, and myopathic EMG changes (see Chap. 12). Histopathologically, they have a vacuolar myopathy. The vacuoles may be rimmed, and they have autophagic features in which they usually stain intensely with acid phosphatase (Fig. 13.19) as well as other markers including p62.

The vacuoles and sometimes other parts of myofibers have increased glycogen as seen with the PAS stain. The glycogen is mostly, but not necessarily, completely digested with diastase. Electron microscopy identifies membrane-bound sacs of granular material which is glycogen.

Most other glycogen storage diseases such as McArdle disease (phosphorylase deficiency) present with exercise-induced muscle pain or cramping and sometimes cause rhabdomyolysis. Histopathologically, muscle specimens usually show a variable number of myofibers containing clear vacuoles at the periphery of myofibers (subsarcolemmal blebs). The vacuoles may contain glycogen (Fig. 13.20), but sometimes, the glycogen drops out during preparation. It is usually digested completely by diastase. In phosphofructokinase deficiency, the findings are similar, but sometimes the glycogen is not completely digested. In both of these disorders, histochemical staining for the deficient enzyme can be performed, and it should be absent. Of course, it is necessary to have an appropriate normal control to be sure the stain is functioning. It is also useful to confirm the findings either with a biochemical assay or genetic testing.

Lipid storage diseases are quite rare. Carnitine palmityl transferase deficiency usually presents with exercise-induced muscle pain. Histologically, the findings can be minimal to none. Sometimes, small round clear vacuoles are seen on H&E stain, and lipid is identified in the vacuoles using either oil-red-O or Sudan black.

There are a large number of muscular dystrophies. In some, inflammatory cells may be seen, mimicking myositis (see list above in the PM section). Inflammation is commonly seen with dysferlinopathy and also in calpainopathy in which eosinophils are relatively common. Inflammatory cells may be seen in the muscle biopsies of patients with facioscapulohumeral dystrophy. MHC I may also be upregulated to some extent in muscular dystrophies, while MHC II is usually not [18]. Membrane attack complex reactivity may be present on the surface of myofibers but not in capillaries. Other features of muscular dystrophy are those of a chronic myopathy with atrophic and hypertrophic fibers, endomysial and perimysial fibrosis, internalized nuclei, as well as fiber splitting in conjunction

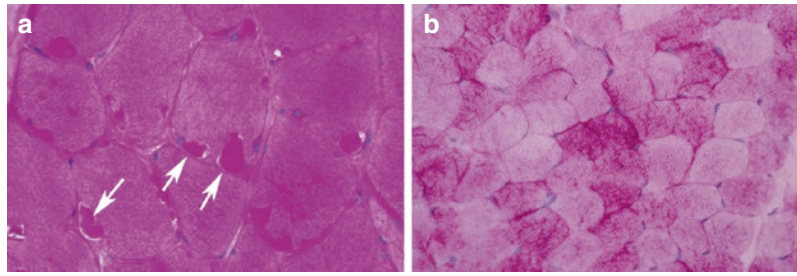

Fig. 13.20 McArdle disease. (**a**) PAS-stained section reveals a diffusely increased amount of glycogen as well as several subsarcolemmal glycogen deposits/blebs *(see arrows).* (**b**) Control PAS stain (frozen sections)

with features of myofiber degeneration and regeneration. However, some muscular dystrophies have milder histopathologic changes. In most cases, diagnoses are made with either an immunohistochemical stain specific for the missing protein or genetic testing. Keep in mind that IBM is the biggest PM mimic histologically if rimmed vacuoles and other inclusions of IBM are not present in the pathology specimen.

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14 Making the Diagnosis of Myositis: Skin Biopsy and Interpretation

Inbal Sander

Key Points to Remember

- Cutaneous dermatomyositis (DM) is characterized by typically subtle basilar vacuolar change.
- The histologic findings are relatively nonspecific and overlap significantly with those of lupus erythematosus, among other entities.
- Thus, clinical-pathologic correlation remains the gold standard in the diagnosis of cutaneous dermatomyositis.
- Skin biopsy can especially be useful in patients with clinical suspicion of DM without pathognomic clinical findings of DM (heliotrope, Gottron's sign, and Gottron's papules).

Introduction

Skin biopsy is a valuable tool in the assessment of the cutaneous lesions of dermatomyositis and serves to distinguish it from other skin diseases that mimic dermatomyositis. This chapter will review the characteristic histologic findings in cutaneous lesions of dermatomyositis, including regional variations. The chapter will review the histologic differential diagnosis and how skin histopathology and ancillary studies can aid in diagnosis.

Histologic Findings in Cutaneous Dermatomyositis

Cutaneous Dermatomyositis is a Vacuolar/Interface Dermatitis

Biopsies taken from active areas of dermatomyositis (DM) skin disease demonstrate changes very similar to those seen in lupus erythematosus and fall into the reaction pattern characterized as a vacuolar/interface dermatitis. The main findings include vacuolization of basilar keratinocytes with a sparse T-cell infiltrate (Fig. 14.1). The location of this change at the interface between the epidermis and superficial dermis has led to the descriptive term, "interface dermatitis."

On routine sections (hematoxylin and eosin [H&E], stained formalin-fixed paraffin-embedded tissue sections), one observes vacuolar changes in the cytoplasm of basal epidermal keratinocytes with a

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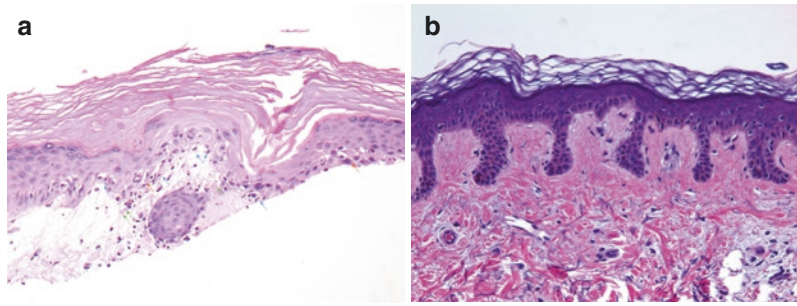

Fig. 14.1 (**a**) 200×, H&E, vacuolar interface change with basilar vacuolization of keratinocytes (blue arrows) and dyskeratosis (orange arrows) in the basilar epidermis. The papillary dermis demonstrates colloid bodies (green arrows) and a sparse lymphocytic infiltrate. (**b**) 200×, H&E, normal skin for comparison

lymphocytic infiltrate extending from the superficial dermis into the basal keratinocyte layer. In DM skin, the vacuolar change can be subtle, and the lymphocytic infiltrate, sparse. The cytoplasm of affected basilar keratinocytes will typically appear pinker than the surrounding keratinocytes, termed "dyskeratosis," which represents the sequelae of the lymphocyte-induced injury to the keratinocyte. The superficial dermis that abuts the undersurface of the epidermis often contains cytoid bodies (amorphous pink globules composed of degraded keratinocyte-derived keratin), which are sequalae of the basilar vacuolopathic change. Likewise, melanophages (histiocytes that have ingested keratin-derived melanin pigment) are found in the papillary dermis, indicative of recent damage to the basilar keratinocyte layer (see Fig. 14.1).

Other characteristic histologic findings include basement membrane thickening, increased ground substance/mucin in the dermis, and ectatic superficial blood vessels correlating with clinical poikilodermatous (dyspigmentation, telangiectases, and atrophy) changes [1–3]. While eosinophils can be seen in the infiltrate of a wide range of inflammatory myopathies, they should be sparse in cutaneous DM [4, 5], but their presence distinguishes DM from other vacuolar/interface processes such as erythema multiforme and viral exanthems. Nevertheless, cutaneous lupus erythematosus and several other interface dermatoses remain diagnostic considerations [4]. Table 14.1 summarizes the common histopathologic features seen in cutaneous DM.

Table 14.1 Characteristic histologic findings in cutaneous lesions of dermatomyositis

Subtle vacuolar/interface change to basilar keratinocytes
Sparse T-cell infiltrate
Basilar keratinocyte dyskeratosis
Colloid bodies and melanophages in the papillary dermis
Thickened basement membrane zone
Rare to absent eosinophils
Ectatic blood vessels
Increased interstitial mucin
Thickening of the basement membrane zone

Where to Biopsy and When to Biopsy?

Active lesional skin should be biopsied as nonlesional skin demonstrates no characteristic findings [2]. Coordination with a dermatologist, ideally one experienced in assessing DM, is invaluable in selecting an optimal biopsy site and in excluding other clinical mimickers of cutaneous DM. Punch biopsy and shave biopsy are both routinely submitted. While punch biopsy offers the advantage of evaluating deeper dermis and subcutaneous tissue, most clinical presentations of dermatomyositis have histologic changes that predominantly involve the upper dermis and epidermis, making shave

biopsy a very reasonable approach in the correct clinical setting. Punch biopsy is a preferred biopsy method for palmar/plantar, ulcerative, and panniculitic lesions to allow visualization of deeper vasculature and subcutaneous fat. As skin biopsy is a relatively inexpensive, safe, and rapid procedure, it should be strongly considered in the evaluation of patients with possible cutaneous DM.

Additional Stains Used in the Workup of Suspected Cutaneous Dermatomyositis

While not routinely used in clinical practice, immunophenotypic studies provide additional insight in characterizing the lymphocytic infiltrate in cutaneous dermatomyositis. Much like other vacuolar/interface dermatoses, the lymphocytic infiltrate includes predominantly CD4+ helper T cells with HLA-DR+ macrophages, rare to absent B cells [3], and small numbers of neutrophils in rare instances [5, 6].

Plasmacytoid dendritic cells (PDCs) are present in DM and have been noted to be more sparse and superficially located in DM skin as compared to lesions of cutaneous lupus. PDCs are involved in production of type I interferons [7].

Increased mucin or glycosaminoglycans (GAGs) in the dermis can be identified with special stains. GAGs have been show to be able to stimulate fibroblasts, raising possibility of a pathogenic role in DM skin lesions. Investigators studying the location and type of GAGs noted distinct patterns of GAG staining in the dermis of DM patients [8]. Periodic acid-Schiff (PAS) staining can be used to highlight basement membrane thickening seen on routine hematoxylin- and eosin-stained sections.

Regional/Anatomic and Clinical Variations in Histologic Findings in Cutaneous Dermatomyositis

Although the features of cutaneous DM are relatively nonspecific, site-specific features can be appreciated. For example, biopsy of Gottron papules often shows hyperkeratosis along with basal layer vacuolopathy and dermal lymphocytic inflammation [2, 9].

While the specificity of mechanic's hands is yet to be established due to significant overlap with common forms of hand dermatitis, the histologic features reflect findings of cutaneous connective tissue disease, namely, hyperkeratosis, vacuolar interface change, and dermal mucin deposition [10]. A small subset of biopsies may show a characteristic "pseudocheckerboard" pattern; however, this pattern may also appear in biopsies of eczematous forms of dermatitis, limiting its utility [11].

The ovoid palatal patch is a recently described clinical finding, occurring in the setting of anti-TIF1-gamma autoantibodies (TRIM33, p155/140). This upper palate lesion has a characteristic lichenoid or dense band-like lymphocytic infiltrate at the dermal-epidermal junction [12].

A vesiculobullous pattern of DM has also been reported and demonstrates a classic vacuolar interface adjacent to areas of marked subepidermal edema [13–16] (Fig. 14.2).

Most DM changes are superficial, but a deeper medium-vessel lymphocytic vasculitis has been reported which correlates with the clinical phenotype of palmoplantar nodules and cutaneous ulcerations [17, 18].

Panniculitis, a less frequent clinical feature of dermatomyositis, is histologically identical to lupus panniculitis and is characterized by a lobular predominantly lymphocytic panniculitis with scattered plasma cells. Interstitial dermal mucin

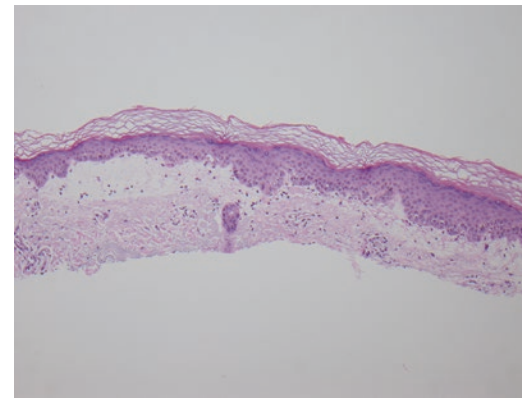

Fig. 14.2 100×, H&E, subepidermal clefting and edema with adjacent area of vacuolar dermatitis

with a lymphocytic vasculitis in deeper vessels can also be seen. Interestingly, plasmacytoid dendritic cells were noted in the involved fat lobules, with later-stage lesions showing hyaline necrosis of the fat lobule and calcification [19].

Cutaneous dermatomyositis commonly affects the scalp and can overlap clinically with the presentation of psoriasis or seborrheic dermatitis. On histology, DM of the scalp demonstrates preserved follicular architecture with changes of a chronic telogen effluvium. Ectatic blood vessels, interstitial mucin, vacuolar change, and thickening of the basement membrane are also observed [20]. These histologic features are distinct from the psoriasiform epidermal hyperplasia, hyperkeratosis, hypogranulosis, and neutrophilic infiltrate seen in lesions of well-developed psoriasis.

There are numerous other nonspecific cutaneous findings in DM, including calcinosis cutis in areas of active or inactive skin disease. The histopathologic features may occur in areas of inactive skin disease and cannot be distinguished from calcinosis cutis occurring in other settings.

Histologic Differential Diagnosis

The constellation of histologic findings remains nonspecific in cutaneous DM highlighting the critical importance of clinical-pathological correlation. Thus, the diagnostic report should reflect the nonspecificity of the histopathologic findings and may include terms such as "vacuolar interface dermatitis" with a note commenting on the histologic differential diagnosis and possible compatibility with dermatomyositis, connective tissue diseases, and other interface dermatoses in the appropriate clinical setting.

The main differential diagnostic consideration is cutaneous lupus erythematosus. While the histologic findings in DM may be more subtle, these entities are indistinguishable on histology alone [21]. Discoid lupus lesions can have a dense inflammatory infiltrate with associated follicular plugging. However, the distinction between early, partially treated, and subacute forms of cutaneous lupus remains difficult to differentiate from DM.

The histologic pattern of a vacuolar interface dermatitis also includes drug eruptions including those on the erythema multiforme spectrum and a variety of lichenoid dermatoses (such as erythema dyschromican perstans/ashy dermatosis and lichen planus pigmentosus), which each present in a clinically distinct fashion. Psoriasis can be difficult to distinguish on clinical grounds; however, there are distinct histologic findings in well-developed lesions of psoriasis. Some areas of histologic overlap exist between psoriasis and DM, namely, biopsy of mechanic's hands and elbow, knee, and scalp lesions. These locations can demonstrate psoriasiform epidermal hyperplasia and hyperkeratosis thus raising some diagnostic uncertainty [22]; however, the presence of interface vacuolar change, even if subtle or sparse, would point to the correct diagnosis. One case report utilized gene expression patterns to distinguish DM from psoriasis where the histologic and clinical findings showed significant overlap with psoriasis [22].

An exceedingly uncommon clinical mimicker of DM is multicentric reticulohistiocytosis. Fortunately, biopsy would quickly resolve this clinical question [23].

Ancillary Techniques

Direct immunofluorescence (DIF), a technique whereby antibodies conjugated to a fluorophore are applied to samples of patient tissue obtained from skin biopsy, is falling out of favor in the diagnosis of dermatomyositis, due to a lack of specificity and sensitivity. DIF biopsies must be preserved and transferred to the lab in a special media, Michel's media, and not placed in formalin for fixation as the sensitivity and specificity of this already limited test are further mitigated when performed on formalin-fixed paraffin-embedded tissue [24, 25]. As seen in cutaneous lupus, DM lesions show granular deposition of multiple immunoreactants (C3, IgG, IgA, and IgM) at the dermal-epidermal junction. However,

the frequency of this finding depends on numerous variables, including recent topical treatment and the age and photodistribution of the lesion making DIF a suboptimal ancillary tool in the diagnosis of dermatomyositis.

Early studies showed perivascular deposition of complement factors using DIF, suggesting more evidence of endothelial injury in DM compared to cutaneous lupus erythematosus [26].

Special stains (e.g., colloidal Fe to evaluate for interstitial mucin and PAS to evaluate for basement membrane thickening) and immunohistochemistry (to distinguish GAG subtypes or stain for plasmacytoid dendritic cells) are areas requiring additional study.

Conclusion

Skin biopsy should be used in patients with DM cutaneous rashes to confirm the clinical suspicion and can be especially useful in cases which lack pathognomonic clinical findings of DM (heliotrope, Gottron sign, and Gottron papules). Until more specific diagnostic criteria are identified, one must employ meticulous clinicopathologic correlation with careful attention to optimal sampling of active, clinically characteristic cutaneous lesions in DM.

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Making the Diagnosis of Myositis: Lung Biopsy and Interpretation

15

Frank Schneider and Patty Chen

Key Points to Remember

- Myositis-associated interstitial lung disease can precede myositis symptoms.
- Biopsy findings are often nonspecific and require multidisciplinary discussion.
- Lung biopsy should be considered to (a) confirm a diagnosis, (b) exclude a differential diagnosis, or (c) when the choice of therapy depends on certain histopathologic features.
- Myositis patients have a worse prognosis with interstitial lung disease than without, but myositis-related usual interstitial pneumonia has a better prognosis than idiopathic pulmonary fibrosis.
- Small biopsies (bronchoscopic biopsies, needle aspirates, core biopsies) often suffice for focal lesions, while surgical biopsies (or generous cryobiopsies) are usually needed for diffuse lung disease.

Introduction

Lung involvement occurs in up to 80% of patients with idiopathic inflammatory myopathies (IIM), depending on the subtype and the presence of associated myositis autoantibodies [1]. The onset may be acute and fulminant or insidious and chronic with variable rates of progression. The main questions practitioners face are: (a) Does the lung disease in a myositis patient represent lung involvement by myositis, or is it an independent disease process? (b) Should it be biopsied, and, if so, which biopsy method is optimal? (c) Do the histopathologic features offer any guidance for treatment, further workup, or prognosis? In this chapter, we will provide a practical discussion of the above questions to help rheumatologists, pulmonologists, and other caregivers make a more informed decision whether or not a lung biopsy should be part of their diagnostic workup and how it can best help in management and prognosis.

Histopathologic Patterns of Myositis-Associated Lung Disease

Lung disease in myositis patients is either (a) intrinsic to the lung and presumed to be part of the patient's autoimmune disease or (b) a secondary complication related to the underlying systemic

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disease or its treatment. The latter includes aspiration pneumonia (possibly related to esophageal dysfunction), opportunistic infections (secondary to immunosuppression), and drug toxicities (e.g., methotrexate, anti-TNF therapy, or biologic agents) [2–4]. This chapter focuses on the lung disease that is thought to be a feature of IIM. Various histopathologic patterns of lung disease have been described in patients with IIM [5–13]. These range from acute lung injury patterns resembling diffuse alveolar damage (DAD) or organizing pneumonia (OP) to chronic lung injury patterns characterized by interstitial lung disease (ILD) showing fibrosis patterns resembling usual interstitial pneumonia (UIP) or nonspecific interstitial pneumonia (NSIP) (Fig. 15.1). Capillaritis and vasculopathy resembling that seen in pulmonary hypertension have been described but are rare compared to the aforementioned forms of lung involvement [5, 14].

Acute lung injury patterns are characterized primarily by airspace fibrin exudates. In DAD, such fibrin exudates form hyaline membranes lining alveolar walls. The term DAD does not imply diffuse lung involvement but instead that the alveolus is diffusely involved at the microscopic level. In fact, DAD is commonly patchy or even focal in a small area in the lung. The diffuse damage involves the alveolar septal capillary (capillary leak result in fibrinous airspace exudates), the alveolar septal interstitium (edema and immature fibroblast proliferation), and alveolar lining epithelium (reactive type 2 pneumocyte hyperplasia). Over time, the airspace fibrin is either absorbed or organized into the loose mucopolysaccharide-rich plugs seen in OP. Acute lung injury patterns are theoretically reversible as long as fibrosis does not ensue. One can find patchy scarring in lung biopsies presumed to reflect previous acute or organizing lung injuries, but such scarring does not appear to be progressive or physiologically limiting unless widespread. Chronic lung injuries are characterized by varying degrees of fibrosis that initially involve the interstitium and later lead to lobular collapse with architectural distortion and more significant fibrosis. Pulmonary pathologists use the American Thoracic Society/European Respiratory Society terminology for the classification for idiopathic interstitial pneumonias [15]. While this nomenclature is intended for idiopathic ILD, most pathologists will use it to describe a histopathologic pattern regardless of the underlying etiology. The treating physician must then determine whether, for example, the UIP represents idiopathic pulmonary fibrosis or lung involvement related to a systemic autoimmune rheumatic disease such as myositis. The pathologist may not be aware of the serology of the patient or how to incorporate such data into the pathologic description.

The UIP pattern is characterized by fibrotic remodeling and marked architectural distortion with honeycomb changes [15]. The fibrosis is accentuated in the periphery of pulmonary lobules with fibroblast foci at the interface of fibrosis and less involved lung. UIP is also characterized by markedly abnormal lung juxtaposed to (often very small) areas of relatively normal alveolar tissue (i.e., a heterogeneous appearance).

The NSIP pattern involves the alveolar septa of the pulmonary lobule in a more diffuse or homogeneous fashion with less architectural remodeling [15]. Honeycombing and fibroblast foci are rare or absent in this pattern. Both UIP and NSIP usually have less involved or spared areas in a biopsy, so the presence of such areas cannot be taken as evidence of a UIP pattern. The homogeneous involvement by NSIP refers first and foremost to (a) diffuse involvement of the individual microscopic lung lobule and (b) not having the variegated appearance typical for UIP with completely remodeled lung juxtaposed to essentially normal alveolar septa.

The lymphoid interstitial pneumonia (LIP) pattern is characterized by extensive infiltration of alveolar septa by lymphocytes [15]. Idiopathic LIP is rarely diagnosed, as most cases are either placed into the cellular NSIP category or represent lymphoproliferative disease. Therefore, histopathologic features of LIP should prompt additional testing to exclude lymphoma. Desquamative interstitial pneumonia (DIP) or respiratory bronchiolitis-associated interstitial pneumonia in a myositis patient first and foremost raises the possibility of smoking-related ILD [15].

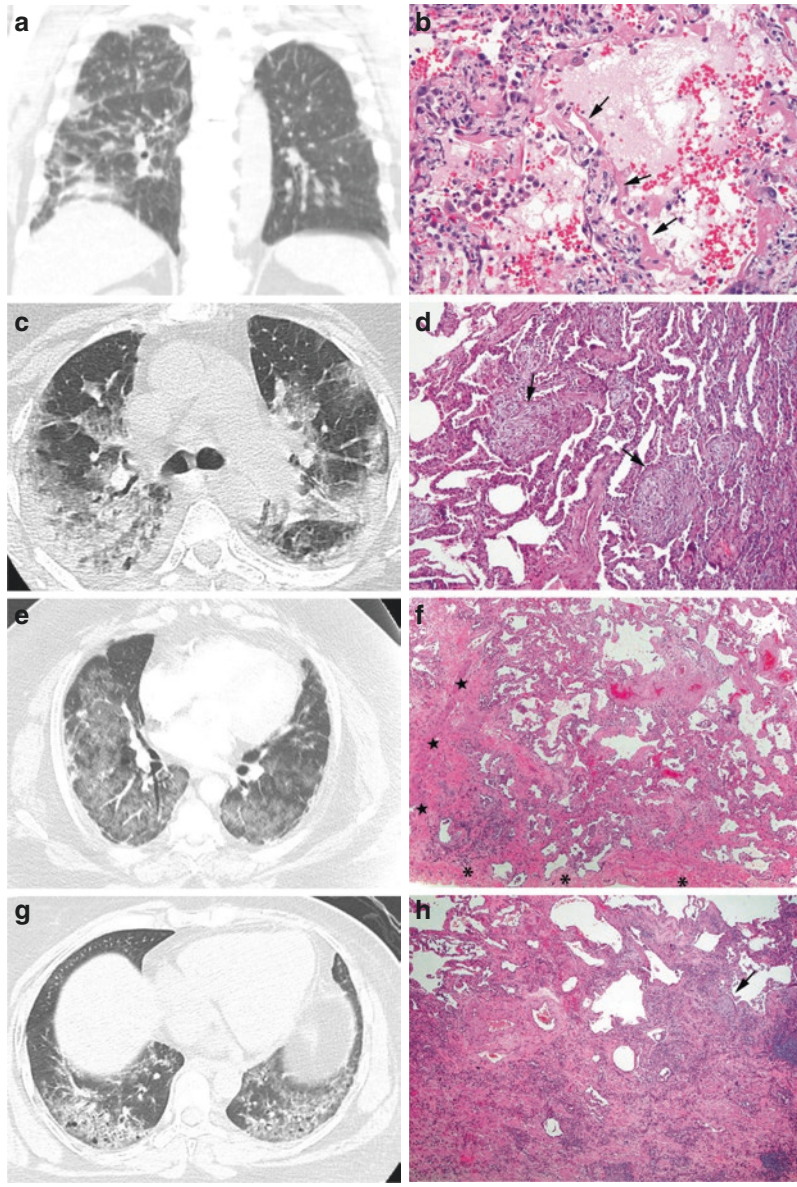

Fig. 15.1 Examples of the most common histopathologic patterns of myositis-related lung disease with corresponding chest computed tomography findings. (**a** and **b**) Diffuse alveolar damage in a patient with anti-glycyl(EJ)-tRNA synthetase syndrome; (**c** and **d**) Organizing pneumonia in a patient with dermatomyositis; (**e** and **f**) Nonspecific interstitial pneumonia (NSIP) pattern fibrosis in a patient with anti-histidyl(Jo1)-tRNA anti-synthetase syndrome; (**g** and **h**) Usual interstitial pneumonia (UIP) pattern fibrosis in a patient with anti-alanyl(PL12)-tRNA synthetase syndrome. Hallmark features of acute lung injuries are hyaline membranes (**b**, arrows) and fibroblastic plugs in airspace (**d**, arrows). Alveolar septal scarring in NSIP is diffusely and homogeneously involving the pulmonary lobule bordered by interlobular septa (**f**, stars) and pleura (**f**, asterisks). UIP pattern fibrosis is accentuated in the subpleural and paraseptal areas (**h**, lower portion) with relative sparing of the centrilobular areas (**h**, upper portion). Fibroblast foci are often found at the interface between scarring and uninvolved lung (**h**, arrow). The radiologist's impression for **g** was "possible UIP pattern." (Hematoxylin and Eosin, original magnification ×100 (**b**), ×40 (**d**, **f**, **h**)

Types of Lung Disease in Myositis

- Intrinsic to the autoimmune disease
  - Acute lung injury
    - Diffuse alveolar damage
    - Organizing pneumonia
  - Chronic lung disease
    - Usual interstitial pneumonia (UIP)
    - Nonspecific interstitial pneumonia (NSIP)
    - *Uncommonly*—lymphoid interstitial pneumonia (LIP) or desquamative interstitial pneumonia (DIP) or respiratory bronchiolitis-associated interstitial pneumonia (RB-ILD)
- Secondary causes
  - Aspiration pneumonia
  - Opportunistic infections
  - Pulmonary edema
  - Pulmonary arterial hypertension
  - Drug toxicities
    - Methotrexate, anti-TNF drugs

Distinguishing Myositis-Associated Lung Disease from Other Lung Diseases

Distinguishing myositis as the causative factor from other etiologies or idiopathic lung disease is difficult. First, there are no pathognomonic histopathologic features that allow unequivocal classification of lung disease as myositis-related or for that matter as autoimmune in etiology. Second, in 20–30% of patients, lung involvement is the initial manifestation of IIM, preceding the onset of myositis symptoms by months to years [16–18]. The latter can be especially problematic in older patients, since the likelihood to suffer from a primary lung disease such as idiopathic pulmonary fibrosis (IPF) increases with age, making the distinction between idiopathic ILD and myositis-associated ILD in an amyopathic patient even more challenging.

In comparison with idiopathic ILD, biopsies from patients with autoimmune ILD including myositis are more likely to show one or more of the following features: fewer fibroblast foci, smaller honeycomb cysts, more inflammatory cells, plasma cells and germinal centers, more T cells, follicular bronchiolitis, and pleuritis [19–24]. Other features that may prompt the pathologist to raise the possibility of autoimmune disease include increased numbers of eosinophils and non-necrotizing granulomas [21, 25]. None of these features are specific for autoimmune- or myositis-related lung disease, and there are no specific quantitative cutoffs for any of these features in any particular patient. When a pathologist identifies isolated or several of these features, the pathologist's interpretation depends not only on the clinical history available to them but also on their comfort level as to how such findings are reported [26]. When faced with a broad differential diagnosis, the pathologist must decide how to report their findings weighing the possibility of additional expensive testing vs. the risk of missing an uncommon condition. Thus, the most efficient discussion often utilizes a multidisciplinary team of rheumatologists, pulmonologists, radiologists, and pathologists [27, 28].

Table 15.1 lists the histopathologic patterns one might see in a lung biopsy from a myositis patient, together with the differential diagnoses to be considered and excluded. Many differential diagnostic considerations can be readily ruled out based on the patient's medical history, presentation, or clinical course.

Histopathological Features of ILD Suggestive of CTD-ILD Including Myositis-Associated ILD

- Fewer fibroblast foci
- Smaller honeycomb cysts
- More inflammatory cells, plasma cells, and T cells
- Lymphoid aggregates with and without germinal centers
- Follicular bronchiolitis
- Pleuritis
- Eosinophils
- Non-necrotizing granulomas

Table 15.1 Histopathologic patterns in lung biopsies and their associated differential diagnoses

Histopathologic finding	Differential diagnoses to consider	Conversation starters when meeting your pathologist…
UIP pattern fibrosis	Idiopathic pulmonary fibrosis (IPF)	Superimposed DAD/OP present? Inflammation prominent (especially in areas spared by fibrosis)? Lymphoid aggregates/follicles present? Bronchocentric component to the lung injury? Signs of aspiration? Granulomas? Pleuritis? Large number of eosinophils or plasma cells? Vasculitis/capillaritis?
	Connective tissue disease	
	Chronic hypersensitivity pneumonitis	
	Drug toxicity, chemotherapy, radiation therapy	
	Asbestosis, other exposures	
	IgG4-related disease	
	Inflammatory bowel disease	
	Focal scarring mimicking UIP but not representing diffuse fibrosing lung disease (e.g., organized pneumonia, old infarct, middle lobe syndrome)	
NSIP pattern; fibrosing and/or cellular interstitial pneumonia	Connective tissue disease	Presence or predominance of lymphocytes, plasma cells, eosinophils, neutrophils, necrosis, granulomas? Viral cytopathic effect? Underlying fibrosis (extent, what pattern)? Vasculitis/capillaritis? Association with drugs?
	Drug toxicity	
	Hypersensitivity pneumonitis	
	Idiopathic NSIP	
	Infection	
	Undersampled UIP	
	Inflammatory bowel disease	
DAD, OP	Infection	Necrosis? Presence or predominance of lymphocytes, plasma cells, eosinophils, neutrophils, granulomas? Foreign material (with or without giant cells)? Viral cytopathic effect? Vasculitis/capillaritis? Alveolar hemorrhage? Relative abundance of hyaline membranes Underlying fibrosis (extent, what pattern; often obscured by the acute changes)?
	Connective tissue disease	
	Drug toxicity	
	Hypersensitivity	
	Undersampled NSIP or UIP with patchy OP	
	Eosinophilic lung disease (eosinophils reduced by steroid treatment prior to biopsy)	
	Inflammatory bowel disease	
	Toxic exposure, sepsis	
	Granulomatosis with polyangiitis (“BOOP” variant)	
	Trauma, shock	
Non-necrotizing granulomas	Infection	Bug stains (consider stains for fungal and acid-fast stains on multiple blocks) Airway-centric disease? Geographic necrosis? Vasculitis (especially granulomatous)? Capillaritis? Eosinophils? Too many lymphocytes (consider immuno-phenotyping or B-cell gene rearrangement studies) Presence of necrotizing granulomas Polarizable, exogenous material Extent of fibrosis if any
	Sarcoidosis	
	Hypersensitivity pneumonitis	
	Drug toxicity (including chemotherapy)	
	Aspiration	
	“Hot tub” lung	
	Connective tissue disease (especially Sjögren syndrome and rheumatoid arthritis)	
	Inflammatory bowel disease	
	Lymphoma/LIP	
	Sarcoid-like reactions to lymphoma elsewhere in the body	
	Beryllium exposure	
	Granulomatosis with polyangiitis (Wegener)	
	Eosinophilic granulomatosis and polyangiitis (Churg Strauss)	
	Talc granulomas	

(continued)

Table 15.1 (continued)

Histopathologic finding	Differential diagnoses to consider	Conversation starters when meeting your pathologist…
Eosinophilia	Infection	Number and distribution of eosinophils Prior steroids (can decrease eosinophils in biopsy)? Necrosis Granulomatous inflammation? Vasculitis/capillaritis (features of EGPA)?
	Aspiration	
	Connective tissue disease	
	Eosinophilic lung disease	
Vascular changes	Age-related changes	Reviewed with elastic stains? Recanalizing thrombi? Eccentric or concentric vascular scarring? Vascular changes in area of fibrosis or in areas uninvolved by fibrosis?
	Fibrosis-related	
	Chronic embolic disease	
	Vasculitis (incl. healed)	
	Pulmonary hypertension	
Essentially normal biopsy	Sampling error	Biopsy taken from area of radiologic abnormality? Reviewed with elastic stains? Constrictive bronchiolitis can be patchy
	Small airways disease	
	Vasculopathy	

The right column lists specific features evaluated by pathologists that may support one diagnosis over another
UIP usual interstitial pneumonia, *NSIP* nonspecific interstitial pneumonia, *DAD* diffuse alveolar damage, *OP* organizing pneumonia, *BOOP* bronchiolitis obliterans-organizing pneumonia (an obsolete term, the recommended terminology is *organizing pneumonia*), *LIP* lymphoid interstitial pneumonia, *EGPA* eosinophilic granulomatosis and polyangiitis (Churg Strauss)

Association of Myositis Subtypes and Autoantibodies with Histopathologic Features

Lung involvement is more common in certain cohorts of myositis patients, especially those with polymyositis/dermatomyositis (PM/DM including clinically amyopathic dermatomyositis), anti-tRNA-synthetase syndromes, and anti-MDA5, anti-NXP2, or PM/Scl autoantibodies [29–32]. Table 15.2 shows the approximate frequencies of ILD in various cohorts of myositis patients and the associated histopathologic patterns [33–37].

Interstitial fibrosis showing an NSIP pattern is more common than a UIP pattern of fibrosis in PM/DM patients (60% vs. 20%) [38]. On the other hand, the most common pattern found in antisynthetase syndrome patients is UIP. DAD is common in patients with Jo-1 antibodies, but DAD and organizing lung injuries can also affect patients with non-Jo-1 antisynthetase antibodies including EJ, OJ, PL7, and PL-12 [17, 39–42].

Prognosis of Myositis-Related Lung Disease

Lung involvement in myositis increases morbidity and mortality [43]. ILD is the second major contributor to morbidity in PM/DM patients after muscular disease, and respiratory failure is responsible for death in up to 50% of patients with myositis-associated lung disease [10, 44]. Long-term radiographic follow-up of antisynthetase syndrome patients showed progression to fibrosis in more than one-third of cases [45].

Since most patients do not undergo lung biopsy, predicting the outcome of an individual patient based on the biopsy result requires some generalization. Correlations of histopathologic features with clinical outcomes are available for a relatively small number of patients, while correlations of radiographic features with clinical outcome are available for a relatively large number of patients. If certain radiographic features correlate with specific histopathologic patterns, more outcome data become available for predicting clinical course based on biopsy results.

Table 15.2 Frequency of interstitial lung disease in various cohorts of myositis patients and associated histopathologic patterns

Frequency of interstitial lung disease in patients with myositis-specific or myositis-associated autoantibodies [32–34, 37]											
	Dermatomyositis-specific autoantibodies				Other myositis-specific autoantibodies			Myositis-associated autoantibodies			
Antibody	Mi-2	NXP2	MDA5	TIF1γ	SRP	HMGCR	SAE	Ro/SSA	U1RNP	PM/Scl	Ku
Frequency of ILD (%)	0–4	0–25	60–90	3–<10	0–15	37	18–71	ND	7	38	27
Frequency of interstitial lung disease in patients with anti-tRNA-synthetase syndromes [32–34, 37]											
Antibody	Jo-1	PL-7	PL-12	KS	OJ	EJ	SC	YRS	Zo	JS	
Frequency of ILD (%)	84	84	95	100	55	100	ND	ND	100	ND	

Histopathologic patterns of lung disease in dermatomyositis/polymyositis [37]						
Pattern of ILD	UIP	NSIP	OP	DAD	LIP	Unclassifiable
Relative frequency[a] (%)	19	61	11	7	1	1
Histopathologic patterns of lung disease in anti-tRNA-synthetase syndromes [35, 36, 38–41]						
Pattern of ILD	UIP	NSIP	OP	DAD	LIP	Other
Relative frequency[b] (%)	54	16	12	16	1	1[c]

Case numbers in the literatures are low. Relative frequencies are best interpreted as approximate because phenotypes overlap and not every case report is considered in this table

ILD interstitial lung disease, *UIP* usual interstitial pneumonia, *NSIP* nonspecific interstitial pneumonia, *OP* organizing pneumonia, *LIP* lymphoid interstitial pneumonia, *DAD* diffuse alveolar damage, *DM* dermatomyositis, *PM* polymyositis

[a]Based on 85 patients [38]

[b]Based on 51 patients [36, 37, 39–42]

[c]Fibrosing interstitial pneumonia and vasculopathy, acute fibrinous, and organizing pneumonitis

Of course, imaging features are not entirely specific for a particular histopathologic finding. If that were the case, obtaining biopsies would offer no additional value.

Patients with myositis-associated lung disease either present with rapidly progressive disease or slowly progressive disease or are asymptomatic with imaging abnormalities alone.

Acute lung disease in myositis patients can be rapidly progressive, treatment-resistant, and fatal. Patients with anti-MDA5 antibodies fall into this group as well as other patients with amyopathic dermatomyositis [6, 46, 47]. The radiographic findings in this cohort are characterized by the presence of ground-glass opacities and the absence of reticulation unless there is an underlying fibrosing lung disease [48]. The histopathologic pattern found in these patients is typically DAD, although cases of NSIP have been described [7, 11, 49–51]. Care should be taken not to equate the radiographic features with a histologic pattern despite the good correlation in many patients. The chest CT may suggest organizing pneumonia, but the corresponding biopsy could still show DAD [13]. Patients may also have underlying chronic diffuse fibrosing disease and develop superimposed acute lung injury that could obscure the fibrotic changes on the chest CT. Acute exacerbations of chronic lung disease are often associated with more rapid progression and deterioration, and they are more commonly associated with UIP than NSIP [52].

At the other end of the spectrum are patients with subacute and chronic lung disease, often with insidious onset, and with variable rates of progression. Biopsies in these patients show OP, NSIP, and UIP. Patients with OP have a better prognosis than those with UIP [7]. UIP should still be considered an unwelcome finding as immunosuppressive treatment increases the risk of infection and other complications. In addition, two-thirds of patients with myositis-associated

UIP show deterioration of their ILD, while OP and NSIP patterns were more commonly found in patients without improvement or even resolution of lung disease [52]. Patients with antisynthetase syndrome-associated UIP can demonstrate long-term survival for many years [53].

Idiopathic UIP (i.e., IPF) still has a worse prognosis than any chronic fibrosing ILD related to IIM [20]. The study by Park et al. suggests that this is not solely due to an unrecognized higher number of NSIP patterns among the IIM patients [54]. Myositis-related UIP specifically has been shown to carry a better prognosis than IPF [55]. In this study, the cumulative and event-free survival was significantly worse in a comparator IPF group (hazards ratio 2.9 vs. 5.0) even after controlling for age at ILD diagnosis, gender, ethnicity, and baseline forced vital capacity. Respiratory failure was still the most common cause of death in both groups. Improved survival has also been shown independently for antisynthetase syndrome-related lung disease when compared to IPF [56].

Pulmonary vasculopathy can be an ominous sign in lung biopsies from IIM patients. One pitfall in lung biopsies is the presence of often striking vascular remodeling and fibrosis in areas of scarred lung. Such changes do not correlate well with hemodynamic parameters [57]. When such findings are noted in a biopsy, pulmonary vascular pressures should be estimated by echocardiography or measured by right heart catheterization before rendering a diagnosis of, or even treating, pulmonary arterial hypertension. Recognizing pulmonary hypertension is important because mean pulmonary arterial pressures of >25 mmHg are associated with a poor prognosis [58].

Histopathologic patterns of myositis-associated lung disease correlate with radiographic features and outcomes [52, 59, 60].

Histopathologic pattern	Radiographic pattern with the histopathologic pattern	Clinical course/prognosis
Diffuse alveolar damage	Bilateral consolidations with airspace and ground-glass opacities	Rapidly progressive/poor prognosis
Organizing pneumonia	Consolidations, linear opacities	Subacute disease/good prognosis
Nonspecific interstitial pneumonia	Ground-glass opacities and irregular linear opacities	Chronic disease/good prognosis when cellular, variable prognosis when fibrotic
Usual interstitial pneumonia	Honeycombing, traction bronchiectasis	Chronic disease/variable prognosis with risk of deterioration

Should I Obtain a Lung Biopsy?

High-resolution computed tomography (HRCT) of the chest is necessary prior to lung biopsy attempt. Chest imaging, in conjunction with consideration of the prebiopsy clinical differential diagnosis, should dictate the need and type of biopsy to consider (Table 15.1). A lung biopsy should be done when (a) confirmation of a diagnosis is required, (b) exclusion of a differential diagnostic consideration is necessary, or (c) the clinical differential diagnosis includes conditions where histology will contribute to the choice of therapy [61]. A biopsy is most impactful when it changes the pretest probability, but assessing the resulting post-test probability can be difficult. Since biopsy findings are often nonspecific, practitioners will frequently receive pathology reports stating terms such as "consistent with," "in favor of," or "arguing against" a certain hypothesis or condition. Further, there is a clear lack of standardization of pathology reports and inherent variability that pathologists express regarding uncertainty in most biopsies [62]. The key to optimal utilization of lung biopsy in ILD is having realistic expectations and considering whether a biopsy can provide the expected information. This is best determined with a multidisciplinary approach. The pathologist can provide information as to what features to expect with each differential diagnostic possibility and the likelihood of being able to distinguish those differential diagnostic considerations based on tissue examination. For example, a surgical biopsy

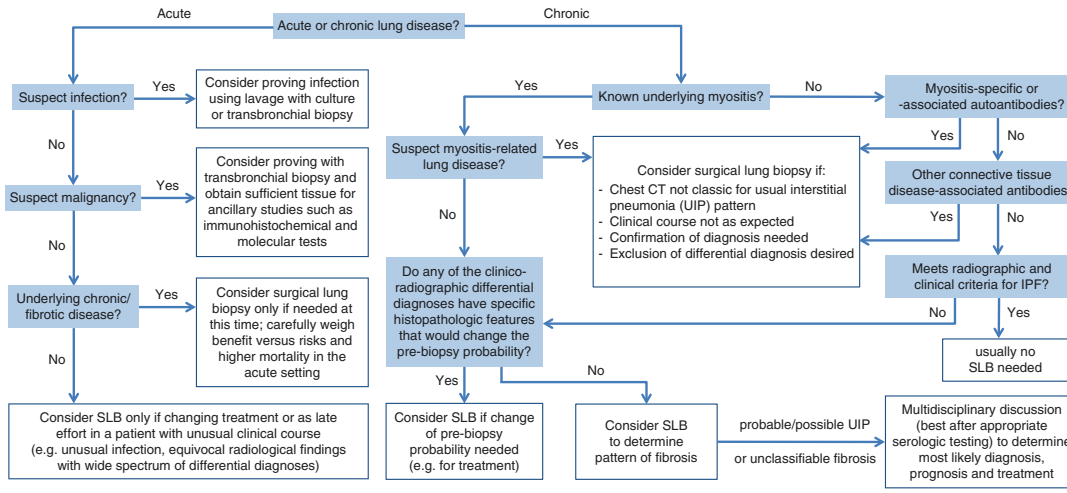

Fig. 15.2 Algorithmic approach to deciding whether a lung biopsy should be obtained. This should serve only as an example of the thought process; actual clinical decision-making requires consideration of all circumstances. *SLB* surgical lung biopsy, *UIP* usual interstitial pneumonia, *IPF* idiopathic pulmonary fibrosis

in the setting of an HRCT chest showing a definite UIP pattern will almost certainly demonstrate UIP histopathologically [27]. If the UIP pathology is consistent with clinical findings and no major concerns for other differential diagnoses such as infection or malignancy exist, one can avoid lung biopsy. This is especially true if one has consistent myositis (such as antisynthetase antibodies) or other CTD-associated antibodies. On the other hand, lung biopsy in patients with radiographic NSIP will more likely not show a UIP pattern histologically [27]. Therefore, a non-UIP pattern of ILD or a UIP pattern with atypical features on chest HRCT often dictates the need for lung tissue. An algorithmic approach to this process is suggested in Fig. 15.2.

What Kind of Biopsy Should I Ask for?

Masses and focal lesions can often be biopsied with a targeted technique [63]. These include transthoracic needle aspirations or core biopsies (usually CT-guided, rarely US-guided) and bronchoscopic needle aspirates, brushes, washes, and biopsies (either without imaging or targeted using fluoroscopy or navigational bronchoscopy). Occasionally, surgical resection of a focal lesion is needed, usually in cases where neoplasia is being considered. Neoplasms typically enter the differential diagnosis in patients with fibrosing lung disease (incidental metastatic or primary lung carcinoma), those with PET-avid nodules (which can occasionally occur in immune-mediated lung disease including sarcoidosis, rheumatoid arthritis, and vasculitis but usually have lower FDG uptake than carcinomas), and patients with autoimmune ILD previously treated with immunosuppressive therapy and increased risk of treatment-related malignancy (e.g., lymphoma) [64]. Specimen triage is important and should be guided by the differential diagnosis. Samples obtained for carcinoma should acquire sufficient material to separate primary lung from metastatic disease with immunohistochemical stains allowing for molecular testing if malignancy is confirmed. Samples of possible lymphoma may benefit from flow cytometric immunophenotyping in addition to microscopic examination [65].

Infection is often included in the differential diagnoses based on the histopathologic features even in patients for whom the pretest probability of infection is low. Generally, bronchoalveolar lavage or transbronchial biopsy can rule out infection. Although routine cultures have limited

cost-effectiveness, the threshold to culture these specimens should be low [66]. Since the majority of this patient cohort is eventually subjected to immunosuppression, culture results can offer important reassurance before initiating such therapy in patients with negative Grocott and AFB stains for fungal and acid-fast organisms, respectively.

Ground-glass opacities are commonly biopsied to distinguish airspace from interstitial and inflammatory from neoplastic disease [67]. In fine-needle aspirates (FNAs), architectural relationships within the tissue are typically lost. Therefore, they often have limited value in distinguishing non-neoplastic airspace from interstitial disease. Although FNAs are often sufficient to detect adenocarcinomas and other epithelial neoplasms, a negative result may have low negative predictive value depending on the cancer prevalence [68]. Transbronchial and core biopsies can be useful, minimally invasive techniques to derive useful information. Both methods show intact architecture that usually allows separation of airspace from interstitial disease. It is also important to note that congestive heart failure, pulmonary edema, or general volume overload can lead to a diffuse ground-glass pattern and should be diagnosed without the need for a lung biopsy. Computed tomography-guided FNAs or core biopsies are overall low-risk procedures. A recent meta-analysis found a pneumothorax rate of 25% following core biopsies, with about one quarter of those requiring intervention [69]. The complication rates for FNAs were much lower, and risk factors include smaller nodule diameter, larger needle diameter, and increased traversed lung parenchyma.

Cellular interstitial pneumonias are more difficult to assess because inflammatory cell infiltrates into alveolar septa are quite common and may not represent a diffuse lung disease. In small biopsies, the pathologist must decide whether the finding is an insignificant incidental finding or representative of the ground-glass opacity. Abnormal interstitial constituents, such as an unusually high number of eosinophils, capillaritis, or granulomas, can be detected in small biopsies (as long as they were sampled) [70]. Mild fibrosis of alveolar septa is frequently seen in biopsies, especially from individuals with cigarette smoke exposure but also in the vicinity of small airways disease or in subpleural locations. Unless such alveolar septal scarring uniformly affects the majority or all of a small biopsy, one must be careful not to overcall such findings as diffuse fibrosing interstitial lung disease, especially in the absence of a radiological correlate. Organizing pneumonia is a common finding in small biopsies from ground-glass areas of the lung. Typically, pathologists will offer a differential diagnosis in this situation that includes infection and other conditions ranging from hypersensitivity pneumonitis to myositis-related lung disease to idiopathic organizing pneumonia, depending on the features besides airspace organization [71]. Transbronchial biopsies offer the advantage (over CT-guided transthoracic biopsies) that the bronchial tree can be directly visualized, thus enhancing sampling of airway abnormalities such as granulomas.

Diffuse fibrosing lung disease is difficult to classify in most small (i.e., nonsurgical) biopsies because there is not enough tissue to recognize the pattern of distribution within the pulmonary lobule or the distribution of disease across many lobules. While some transbronchial biopsies show certain features of UIP, one should not rely on a transbronchial biopsy to deliver diagnostic certainty regarding the distribution of fibrosis or etiology in diffusely involved lung [72, 73]. The recent advent of transbronchial cryobiopsies offers a promising method to obtain larger samples of lung tissue without having to resort to a surgical lung biopsy [74]. The diagnosis rate of diffuse parenchymal lung disease with cyrobiopsies is higher than that with traditional forceps biopsies. At the same time, the mortality from cryobiopsy has been reported to be less than 10% of that from surgical lung biopsies [75]. Surgical lung biopsies are commonly performed using video-assisted thoracoscopic surgery (VATS biopsy). Sampling of diffuse fibrosing lung disease should include more than one site because of the variability of histologic features within the lung and the coexistence of different patterns in the same patient [76, 77]. Ideally, a biopsy

includes not only areas of end-stage fibrosis but also the interface between fibrosis and less involved lung as well as seemingly uninvolved lung remote to the area of fibrosis. End-stage fibrosis is merely the final common pathway for several chronic lung diseases (e.g., occupational lung disease, sarcoidosis, IPF, autoimmune ILD including different patterns such as UIP, NSIP, OP, etc.), and larger tissue samples increase the chance of finding features that may suggest a certain etiology. Care should be taken not to overinterpret biopsies from right middle lobe or the lingua since these sites can show nonspecific changes including scarring [78]. The risk of a surgical lung biopsy may be small in many patients, but it is not negligible. The average in-hospital mortality after elective surgical lung biopsies in the USA was 1.7% between 2000 and 2011 [79]. However, this average risk may significantly under- or overestimate the risk for any given patient based on his or her individual risk factors such as respiratory failure, admission to the intensive care unit, immunosuppressed state, multiple organ failure, pulmonary arterial hypertension, or underlying solid or hematologic malignancy [80, 81]. Therefore, the need for a surgical lung biopsy should be considered carefully and sampling only pursued if the benefit of refining the differential diagnosis or altering treatment outweighs the risks.

HRCT features	Preferred procedure for lung biopsy in most cases[a]	Purpose
Nodules or masses	Transthoracic needle aspirations or core biopsies (usually CT-guided)	Exclude neoplasm, infection, IgG4 disease, or granulomatous disease such as sarcoidosis
Consolidation (possible infection)	Transbronchial or CT-guided core biopsies Consider culture from tissue or lavage/wash	Exclude bacterial, viral, or fungal infection
Ground-glass opacities	Transbronchial or CT-guided core biopsies Surgical lung biopsy	Exclude lepidic adenocarcinoma, distinguishing airspace from interstitial disease
Interstitial pneumonias	Transbronchial biopsy Cryobiopsy Surgical lung biopsy	Distinguish infection from noninfectious disease
Diffuse fibrosing lung disease	Surgical lung biopsy Possibly cryobiopsy	Determine histopathologic pattern of ILD

[a]Surgical lung biopsy usually performed using video-assisted thoracoscopic surgery (VATS)

Conclusion

Lung disease in a myositis patient can be myositis-related, secondary to infection, or represent an unrelated idiopathic condition. Since treatments and outcomes differ in these scenarios, lung biopsy should be considered if the biopsy findings could alter patient management. Histopathologic features in lung biopsies from myositis patients are seldom specific or pathognomonic. Therefore, close communication with the pathologist interpreting the biopsy is recommended to arrive at the best possible conclusion for each patient.

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Making the Diagnosis of Myositis: Muscle MRI

16

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Introduction

Myositis patients present with acute or subacute muscle weakness, typically affecting the proximal muscles of the upper extremity, lower extremity, and spine in a symmetric distribution. Five main clinicopathological subtypes are distinguished among adult patients, including dermatomyositis (DM), cancer-associated myositis (CAM), polymyositis (PM), immune-mediated necrotizing myopathy (IMNM), sporadic inclusion-body myositis (sIBM), and overlap myositis (or myositis associated with other systemic autoimmune rheumatic diseases) [1].

The diagnosis of a myositis patient includes the typical presentation of symmetric proximal muscle weakness, elevated muscle enzymes (e.g., creatine kinase or CK), a myopathic electromyographic (EMG) pattern, characteristic pathological changes in skeletal muscle biopsy, and the presence of myositis-specific autoantibodies. A critical step in the diagnosis of myositis is to exclude myositis mimics, especially in the setting of "polymyositis" where the pathognomonic rash of DM is lacking and the observation that many mimics such as metabolic myopathies and muscular dystrophies [2] may present with the aforementioned features. MRI could aid in recognizing patterns of muscle involvement among various mimics and myositis subtypes. Although EMG is used as a guide to muscle biopsy, MRI may provide an improved and noninvasive tool for selecting the site of muscle biopsy. Despite advancement in the outcome measures of myositis, we currently lack an objective imaging measure to gauge the response to therapy. Moreover, differentiating disease activity vs. damage, both of which lead to muscle weakness, poses a significant clinical challenge which may be addressed by muscle MRI. An early and accurate monitoring of disease activity is of great importance in the tailoring of treatment intensity. In this chapter, we review the different roles of MRI and other imaging tools assisting in the diagnosis and management of idiopathic inflammatory myopathies (IIM) (Table 16.1).

Table 16.1 Potential roles of muscle imaging in IIM

Sensitive detection of muscle pathology
Exclusion of IIM mimics
Differentiation of IIM subsets
Guiding muscle biopsy
Disease activity vs. damage
Response to therapy

MRI Protocols in IIM

MRI provides an excellent soft-tissue contrast at high resolution. Further, general advantages

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of MRI are its noninvasiveness, broad availability, and lack of ionizing radiation. In contrast to ultrasound, MRI provides better resolution of the soft tissue and bone. Muscle abnormalities found by MRI in IIM include muscle edema, fatty replacement, and muscle atrophy. The sequences most commonly used (Table 16.2) in musculoskeletal MRI are T1-weighted (T1w),

Table 16.2 MRI sequences in myositis imaging. Examples are shown in Fig. 16.1

MRI sequences	Useful key features	Potential application
T1w	High anatomical resolution	Damage evaluation (atrophy, fibrosis, and fatty replacement)
Fat-suppressed T2w	Detection of muscle edema Resolution superior to fluid-sensitive sequences	Disease activity, target muscle biopsy, therapeutic response
Fluid-sensitive Sequences (STIR, TIRM, SPAIR)	Detection of muscle edema	Disease activity, target muscle biopsy, therapeutic response
Gadolinium	Contrast enhancement not superior to muscle edema seen on fluid-sensitive sequences	Not commonly used

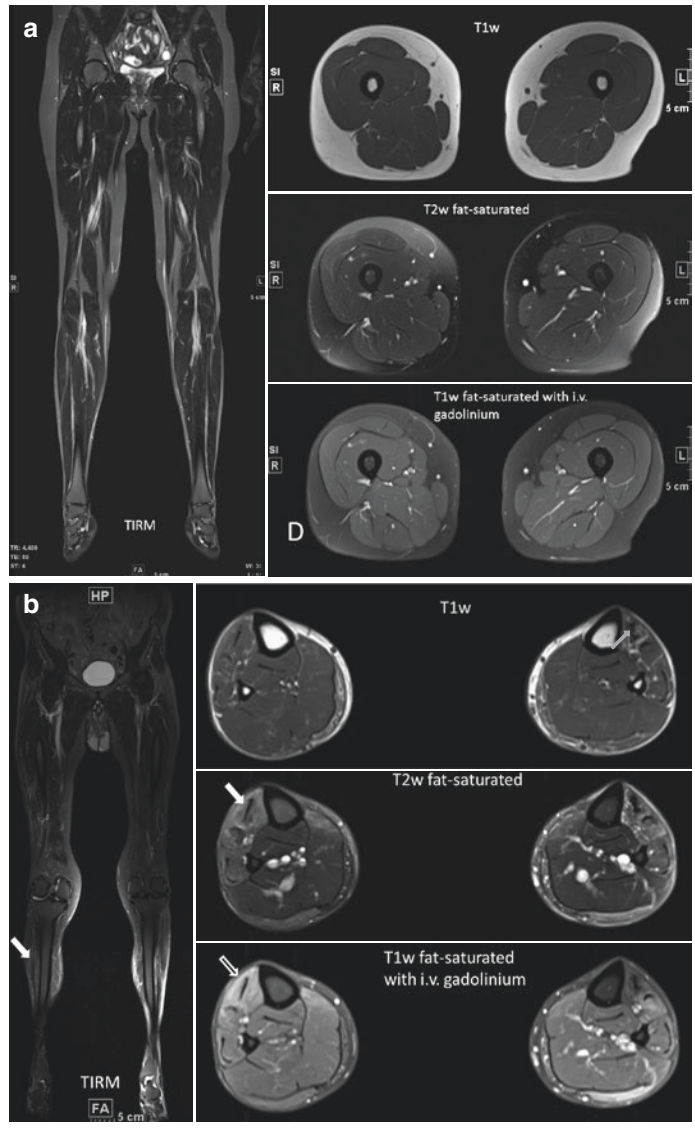

Fig. 16.1 (**a**) MR sequences used in diagnosing myositis of a healthy patient. (**b**) Identical MR sequences in a 71-year-old male patient with sIBM. The TIRM and T2w fat-saturated images reveal muscle edema in the right tibial anterior muscle as hyperintensities (white arrow) and enhancement (black arrow with white edge). Fatty infiltration of the left tibial anterior muscle is revealed as hyperintensity in T1w images (gray arrow)

T2-weighted (T2w), both with and/or without fat signal suppression, and fluid-sensitive sequences (e.g., short tau inversion recovery (STIR), turbo inversion recovery magnitude (TIRM), spectral attenuated inversion recovery (SPAIR)) [3]. T1w images provide high anatomical resolution and are sensitive in detecting fat but insensitive with regard to water detection. The signal intensity of healthy muscle in T1w sequences is below water and above fat. T1w sequences are used to depict fatty atrophy and to discriminate between acute and chronic diseases.

In T2w sequences both water and fat appear hyperintense, and the signal intensity of normal muscle is lower than water and fat. Muscle edema reflects an increased amount of intracellular or extracellular free water [4] and thus appears hyperintense in the fluid-sensitive T2w sequences. Since fat also appears hyperintense in T2w sequences, fat-suppressed T2w sequences have been developed, facilitating the specific detection of edema.

STIR, TIRM, and SPAIR sequences are fluid-sensitive sequences that use different techniques to better detect water. In muscle protocols they are used to sensitively reveal muscle edema.

In the more acute phases of IIM, the signal intensity of such fluid-sensitive sequences correlates with disease activity [5].

Gadolinium contrast does not enhance the detection of muscle edema by fluid-sensitive sequences and is also not superior to T2w fat-suppressed sequences. Since the application of gadolinium also requires longer scan times, muscle MRI is usually performed without contrast agents [3, 6].

Types of Muscle Magnetic Resonance Imagings

(a) *Thigh Muscle MRI:* For practical reasons, the thighs are often selected for MRI, as proximal leg muscles are frequently involved in myositis and a convenient target for biopsy [7]. The scan time of such regional MRI is relatively short, but at the same time muscle involvement in other body regions remains undetected (Fig. 16.2).

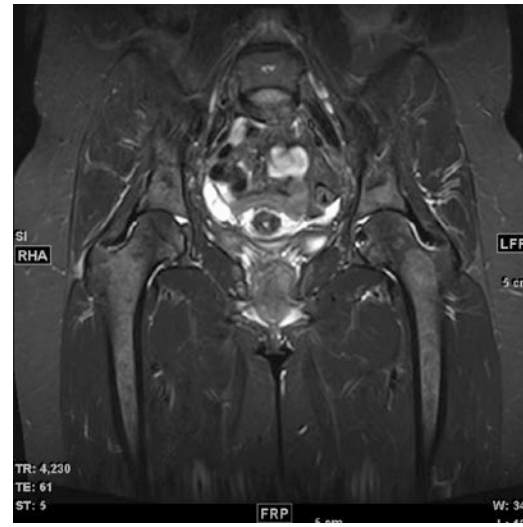

Fig. 16.2 Thigh muscle MRI—coronal TIRM image in a healthy female person

(b) *Whole-Body Magnetic Resonance Imaging:* Whole-body MRI (wb-MRI) allows a comprehensive visualization of all large muscle groups, rendering it especially useful in early disease stages when some muscles may only be involved subclinically [8, 9]. Furthermore, wb-MRI may reveal characteristic distribution patterns of muscle inflammation assisting in the differential diagnoses. In the case of paraneoplastic IIM, wb-MRI also offers the possibility of detecting the underlying malignancy. The duration of the standard wb-MRI protocol is 45 minutes, which may be challenging for the patient and clinical centers in terms of time and cost-effectiveness (Fig. 16.3).

(c) *Short Whole-Body Magnetic Resonance Imaging:* A shortened wb-MRI protocol with omission of the trunk has recently been reported. The diagnostic accuracy of this shortened protocol was similar to the regular wb-MRI protocol with a 30% time-saving [10].

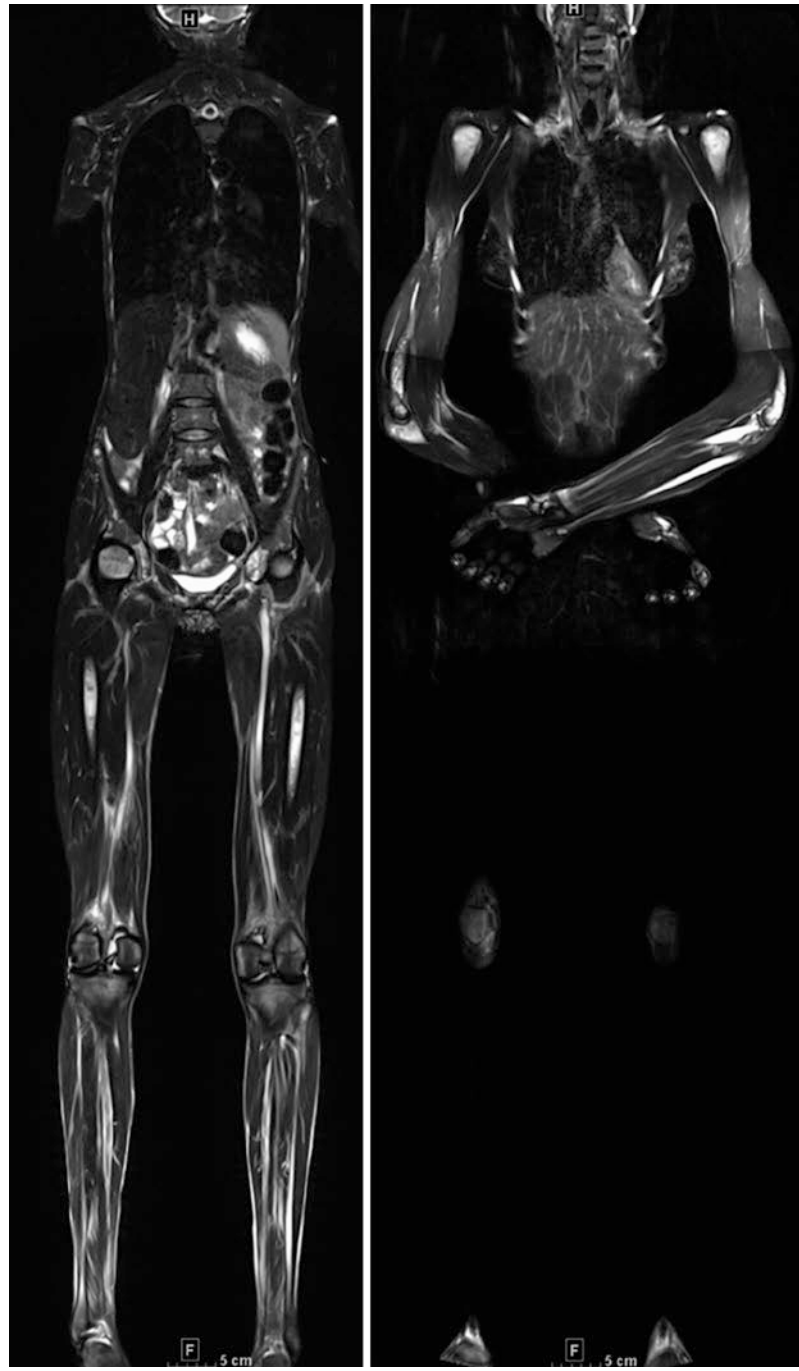

Fig. 16.3 Coronal TIRM image of a whole-body MRI in a healthy female

Diagnostic Yield of Magnetic Resonance Imaging

In some centers muscle MRI of the proximal extremities is routinely performed in the diagnostic workup of IIM. In the vast majority of patients with acute IIM (76–97%), MRI shows muscle edema, consistent with inflammation [11]. This finding is significantly associated with muscle weakness and elevated serum CK values [5, 12],

Table 16.3 Diagnostic yield of thigh MRI [15]

Type of myositis	Sensitivity	Specificity
PM	63.1%	59.0%
DM	82.6%	64.2%
IMNM	62.4%	90.8%
IBM	83.7%	87.7

while fatty infiltration and muscle atrophy represent chronic myositis.

A retrospective study evaluated the diagnostic yield of MRI in comparison with the clinical diagnosis of myositis in 51 IIM patients (29 PM/22 DM) [12]. In this study, MRI had a sensitivity of 92.3% and a specificity of 83.3% for PM/DM. A similar sensitivity of 91% was reported in a prospective study of 48 patients with suspected IIM (DM, PM, IMNM, nonspecific myositis), but a lower specificity of 61%, when biopsy-proven myositis was the gold standard [13]. There was no subgroup analysis done to differentiate sensitivity and specificity for PM, DM, or IMNM or nonspecific myositis. In a retrospective evaluation of 17 patients with sIBM, a characteristic pattern of muscle involvement was defined [14]. Compared to MRI findings of 118 patients with other myopathies, the authors reported a sensitivity and specificity, both exceeding 95%. The pattern of muscle involvement characteristic for sIBM is described in more detail below. One study [15] examined the specificity and sensitivity of thigh MRI in the detection of IIM subtypes (Table 16.3).

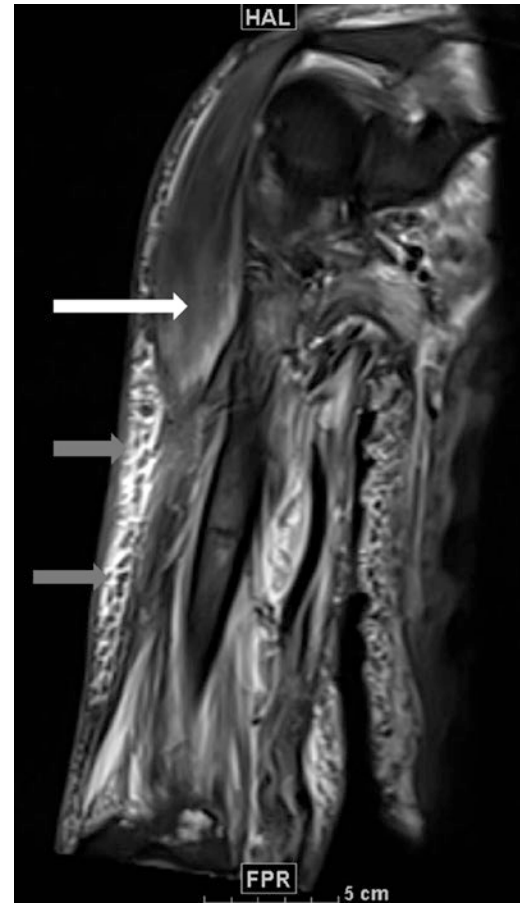

Fig. 16.4 TIRM sequence of a 63-year-old male patient with extensive intramuscular (white arrow) and subcutaneous edema (gray arrow)

Distribution of Magnetic Resonance Imaging Involvement in IIM Subtypes

Several studies have demonstrated that the IIM subtypes tend to affect particular muscle groups. The recognition of such different patterns may help to narrow the differential diagnosis.

In the early course of PM, for example, the muscle edema is distributed symmetrically in the proximal muscles of all extremities. Muscle involvement of the upper extremities may include the deltoid, trapezius, biceps, and triceps muscle [8, 16]. In the lower extremities, the quadriceps muscles (vastus medialis, intermedius, and lateralis) and the tibialis anterior are preferentially involved [17]. In progressive disease, an involvement of pharyngeal muscles and neck flexors has also been observed [18].

In DM, the MRI pattern is similar to PM in its symmetry and involvement of proximal muscle groups (Fig. 16.4). However, edematous inflammation of muscle fasciae (50–100%) [19] and subcutaneous fatty tissue (85%) [20] are also common (Figs. 16.4 and 16.5). Five of 26 prospectively studied juvenile DM patients with subcutaneous edema on the initial thigh MRI developed clinically apparent calcinosis at the same location within 9 months [20]. Patients with a more diffuse or homogenous distribution of

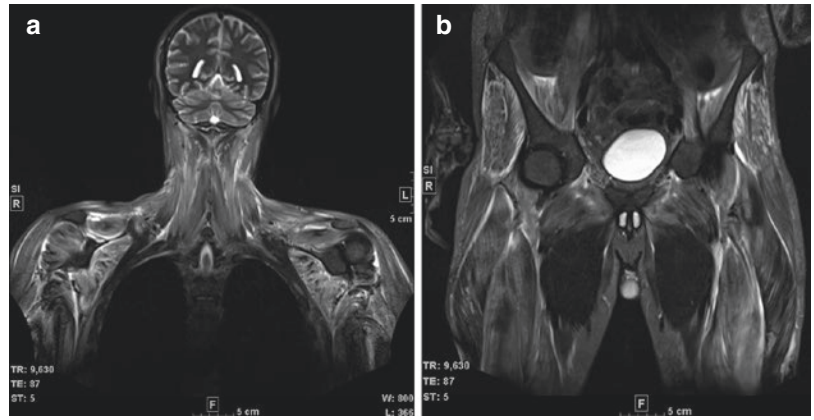

Fig. 16.5 Coronal TIRM image of the shoulder girdle (**a**) and thighs (**b**) in a 66-year-old male patient with DM demonstrating extensive edema in all proximal muscles

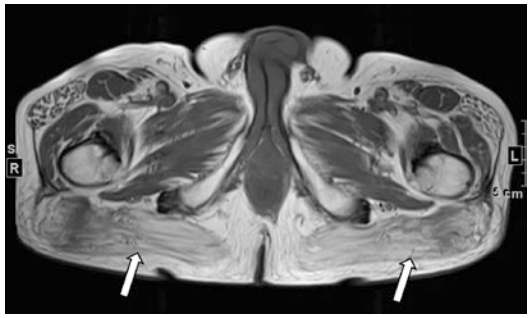

Fig. 16.6 T1-weighted axial image of the pelvis of an 80-year-old male patient with IMNM. The arrows show the greater gluteal muscles with excessive fat degeneration

muscle inflammation had a more severe disease course compared to patients with a more patchy distribution [21].

In IMNM, MRI revealed characteristic edematous and atrophic changes of the hip rotators and glutei (Fig. 16.6) [15]. Muscle abnormalities in IMNN [associated with antibodies directed against signal recognition particle (SRP) or HMG-CoA reductase (HMGCR); see Chap. 24] appeared to be more severe compared to patients with DM or PM [15]. On thigh MRI, patients with anti-SRP antibodies had more atrophy and fatty replacement than patients with anti-HMGCR antibodies [15]. However, there are no studies to differentiate IMNM from PM findings on MRI.

In sIBM, fatty infiltration and atrophy are more common than inflammatory changes. In comparison to PM, the lesions of sIBM tend to be more asymmetric and distal in location [6]. In the thigh muscles, a predominant involvement of the quadriceps with relative sparing of the rectus femoris is reported [22, 23]. Some authors describe a "melted" appearance of the distal quadriceps and involvement of the sartorius muscle [14]. In the calves, the medial gastrocnemius is most frequently infiltrated with fat, whereas the soleus muscle is relatively spared (Fig. 16.7). Corresponding to the weakness of finger flexors, MRI may reveal an intramuscular fat accumulation in the flexor digitorum profundus muscles [22, 23].

Magnetic Resonance Imaging in Guiding Muscle Biopsies

MRI represents a sensitive tool to detect muscle involvement in suspected IIM, but the detection of muscle edema and fatty atrophy by MRI is not specific for inflammation. Thus, the diagnosis of IIM should never be based on MRI alone and a muscle biopsy is often required for confirmation [2].

The regional distribution of muscle involvement in IIM may range from a few muscles to several muscle groups, but the disease process may be patchy (Fig. 16.8). Although EMG-guided biopsy has a high yield, it is invasive and painful, suggesting the need for an imaging-guided approach. Moreover, the "blind" acquisition of a muscle biopsy is error-prone, as indicated by a retrospective study of 153 PM/DM patients in which 25% of blind

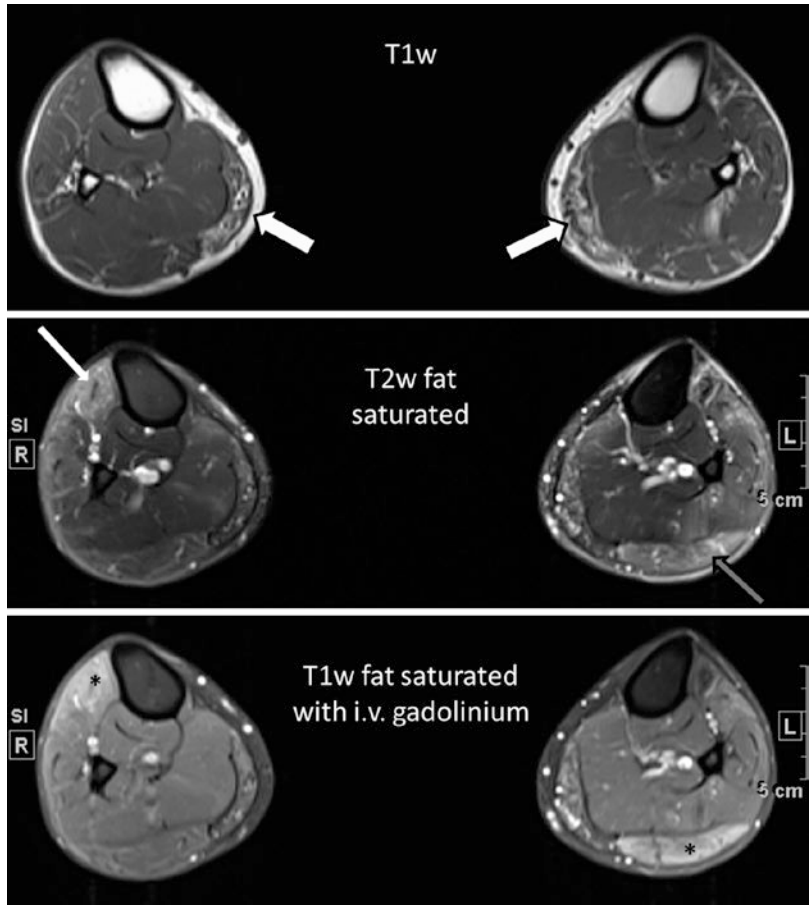

Fig. 16.7 Seventy-one-year-old male patient with sIBM. Axial T1w, fat-saturated T2w, and fat-saturated T1w images after contrast administration at identical levels demonstrating symmetric fatty infiltration of the medial head of the gastrocnemius (broad white arrow). There is some edema and gadolinium enhancement (asterisks) in the right tibialis anterior muscle (thin white arrow) and in the lateral head of the left gastrocnemius (thin gray arrow)

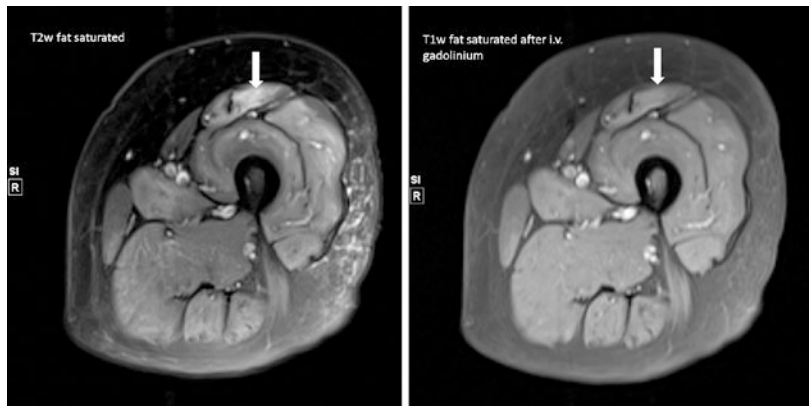

Fig. 16.8 Eighty-year-old female patient with edema and contrast enhancement restricted to the rectus femoris muscle and almost complete sparing of the vastus lateralis and medialis muscles. The rectus femoris was chosen for biopsy, yielding IMNM

biopsies lacked inflammatory infiltrates [24]. Muscle biopsies from sites that featured signal hyperintensity in T2w fat-suppressed and STIR images contained significantly more inflammatory cells than those obtained from sites with a normal MRI [5]. In a prospective study of 48 patients with suspected IIM, the overall false-negative rate of muscle biopsy was 23% [13]. Biopsies, which were performed at sites of high signal intensity in T2w fat-suppressed or

STIR images revealed a false-negative rate of 19%, compared with 67% of biopsies at MRI-negative sites [13]. Additional work suggests that a pre-biopsy MRI is cost-effective due to lower re-biopsy rates [25]. Thus, the use of MRI in guiding muscle biopsy increases the diagnostic accuracy and MRI may replace an EMG-guided approach in the future regarding the workup of myositis.

MRI Pattern in Myositis Mimics

Although muscle edema and fatty atrophy are not observed in normal muscle and can be detected sensitively by MRI, they are not specific for IIM (Fig. 16.9a, b). The differential diagnosis of IIM is wide and includes inherited myopathies (muscle dystrophies and metabolic myopathies), as well as myopathies due to medications, infections, or endocrine disorders. The MRI presentation of the IIM mimics can be similar to the involvement seen in true idiopathic inflammation, although a few IIM mimics have more specific radiographic features (Table 16.4).

Muscle edema can also be seen in numerous other conditions such as after radiation therapy and muscle injury [26], rhabdomyolysis [27], and even after physical exercise [28]. Fatty atrophy is also observed after muscle denervation [29] and in chronic disuse states [30].

Magnetic Resonance Imaging for Disease Activity Versus Damage

The noninvasive nature and lack of ionizing radiation render muscle MRI suitable for serial use in the longitudinal monitoring of disease activity and damage. It may be clinically difficult to differentiate ongoing myositis activity in patients with persistent or recurrent muscle weakness from irreversible damage or glucocorticoid myopathy. Similarly, the determination of serum muscle enzymes may be of limited value in patients (where the CK can be normal in the presence of active disease) as well as in long-standing myopathies. In this situation, the detection of muscle edema by MRI may help to distinguish between acute inflammation and chronic muscle damage (Fig. 16.10 top row) [31], providing an important clue for therapeutic decision-making.

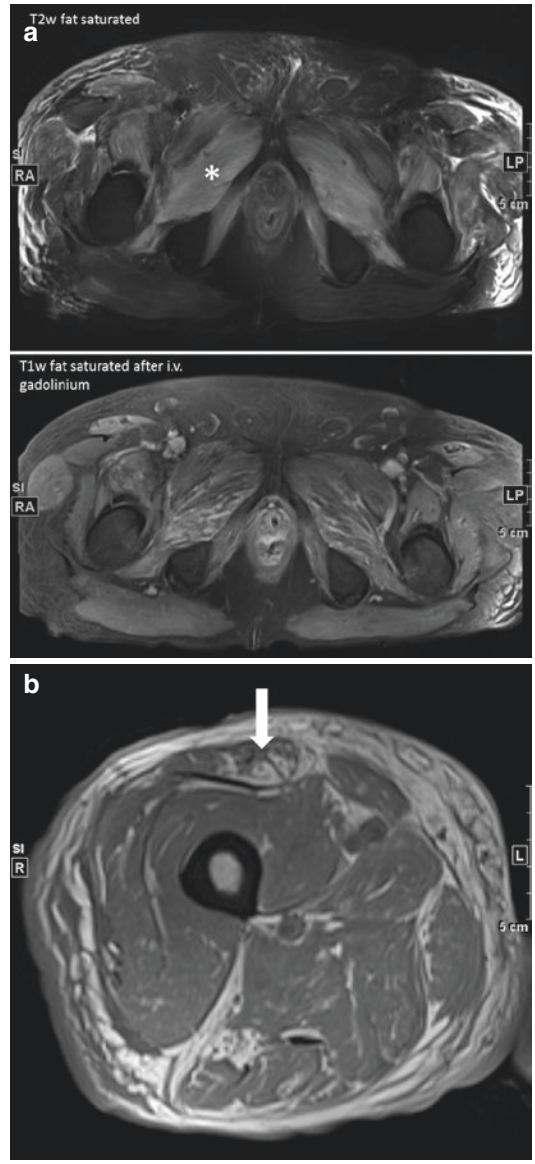

Fig. 16.9 (**a**) Muscle edema in a 75-year-old male with limb-girdle muscle dystrophy type 2a (calpainopathy). Extensive edema in most pelvic muscles, predominantly in the external obturator muscle (asterisk) with slight linear and not patchy contrast enhancement. (**b**) Fatty infiltration of the right rectus femoris muscle (arrow) in the same patient

Table 16.4 Clinical presentation and MRI findings of select IIM mimics

IIM mimic	Clinical presentation	MRI findings	Ref
Limb girdle dystrophy (LGMD) 2A	Onset up to eighth decade. Slowly progressive weakness and atrophy of proximal muscles due to mutations in *dysferlin* gene. Autosomal recessive inheritance. Endomysial or perivascular T lymphocytes possible	Predominant atrophy of posterior thigh muscles (semimembranosus, semitendinosus, biceps femoris, and adductors). At calf levels, soleus muscle and the medial head of the gastrocnemius involved, sparing of the lateral gastrocnemius	[64]
Becker's muscular dystrophy	X-chromosomal recessively inherited mutations in the *dystrophin* gene. Progressive weakness of legs and pelvic muscles. Calf hypertrophy. Cardiomyopathy	Prominent involvement of the gluteus maximus (80% of patients), atrophy of gluteus medius, adductor magnus, long head of biceps femoris, and semimembranosus (70% each)	[65]
Statin-induced myopathy	Can range from myalgia to rhabdomyolysis	Fatty atrophy in T1w sequences (29% of patients). Edema in 62% of T2w STIR images, mainly in dorsal thigh muscles (biceps femoris, semimembranosus, semitendinosus) and superficial calf muscles (soleus and gastrocnemius). Muscle edema associated with elevated serum CK and weakness	[66]
Infectious myositis	Viral, bacterial, fungal or parasitic. Bacterial and fungal myositis tends to present as a localized myositis, and viral and parasitic muscle infections tend to present as diffuse myositis Pyomyositis due to *staphylococcus aureus*, predominantly in the tropics Polymyositis in early HIV infection, possibly T-cell-mediated. Bilateral proximal muscle weakness and CK elevation	In pyomyositis abscess formations are hypointense in T1w and hyperintense in T2w and STIR sequences with a hyperintense rim on unenhanced T1w images and peripheral enhancement after contrast medium application In myositis due to *Candida tropicalis*, MRI showed numerous microabscesses and diffuse muscle edema Pork tapeworm causes cystic lesions with low signal in T1w and high signal in T2w images. MRI may depict scolices HIV-associated polymyositis may show abnormal signal intensity in T2w and STIR sequences	[67–74]
Diabetic muscle infarction	Rare complication of poorly controlled insulin-dependent diabetes. Pain and swelling, mainly of thighs and calves	Diffuse edematous enlargement of involved muscles and increased signal intensity on T2w, STIR, and gadolinium-enhanced images	[75, 76].
Rhabdomyolysis	Life-threatening from a large variety of causes, including drug abuse, excessive muscle exercise, ischemic injury, infections, or direct muscle injury	Widespread muscle edema. Affected muscles hyperintense in T2w and STIR sequences and hypointense in T1w	[77, 78]
Sarcoidosis	Four types of muscle involvement Acute myositis: painful swelling of muscles Chronic myopathy: muscle weakness and atrophy Nodular type: palpable intramuscular masses Asymptomatic type: Incidental detection of granulomas in biopsy	Acute sarcoid myositis: diffusely increased signal in T2w sequences Asymptomatic and chronic myopathy: The granulomas along muscle fibers cannot be detected by MRI, only by histology Nodular sarcoidosis: more specific with a star-shaped central decrease of signal intensity in axial T1w and T2w sequences, surrounded by increased intensity ("dark-star" sign). Axial or sagittal images, in which muscle fibers run parallel, show three stripes: The inner stripe with decreased signal intensity and two outer stripes with increased signal intensity ("three stripes"-sign). On histology the central area with decreased signal intensity is fibrotic, and the surrounding hyperintensity represents granulomatous inflammation	[79–83]

(continued)

Table 16.4 (continued)

IIM mimic	Clinical presentation	MRI findings	Ref
Hypothyroid myopathy	Muscle stiffness and hypertrophy in untreated hypothyroidism	Distal legs predominantly affected. Hypertrophic muscles on T1w, increased signal intensity on T2w and STIR images	[84–86]
Metabolic myopathies	Exercise intolerance and recurrent rhabdomyolysis	Lower body MRI of 20 patients with long-chain fatty acid oxidation disorders demonstrated distinct patterns of increased signal intensity in T1W and STIR sequences. In very long-chain acyl-CoA dehydrogenase deficiency (VLCADD), increased T1W signals in proximal muscles. In long-chain hydroxyacyl-CoA dehydrogenase deficiency (LCHADD), mainly distal involvement. STIR hyperintensity in VLCADD and LCHADD associated with increased serum CK T1w changes reflect fatty infiltration, STIR hyperintensity edema	[87]

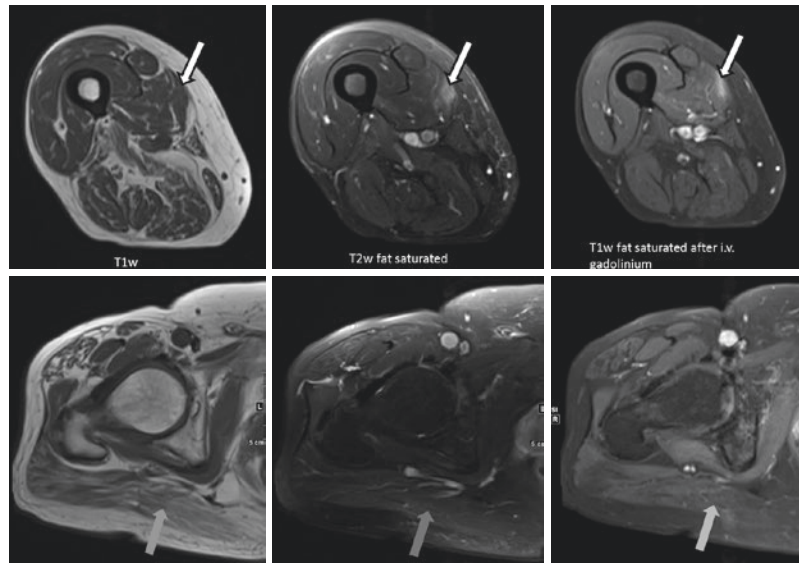

Fig. 16.10 Focal active inflammation in the vastus medialis muscle of a 79-year-old male with IMNM (upper row, white arrows). Extensive fatty infiltration of greater gluteal muscle (lower row, gray arrows)

Muscle weakness in the setting of MRI findings of extensive replacement by fatty tissue (Fig. 16.9 bottom row) has been correlated with a lack of improvement with immunosuppressive therapy [32].

Magnetic Resonance Imaging for Treatment Response

Several studies have shown that muscle edema on MRI decreases during therapy (Fig. 16.11) [5, 21, 33, 34]. Muscle MRI may even better reflect clinical improvement than muscle biopsy [5]. The presence of muscle edema on MRI is also significantly associated with the presence of muscle weakness and elevated serum CK values [5, 12]. In a study of 41 juvenile DM patients, 18 patients underwent a follow-up wb-MRI [21]. Eleven of these patients had lower MRI scores in response to treatment. Moreover, nine patients showed total resolution of inflammation in wb-MRI, whereas in the clinical assessment, only five patients met the criteria for remission. The authors suggest that loss of muscle strength may result from muscle damage rather than from

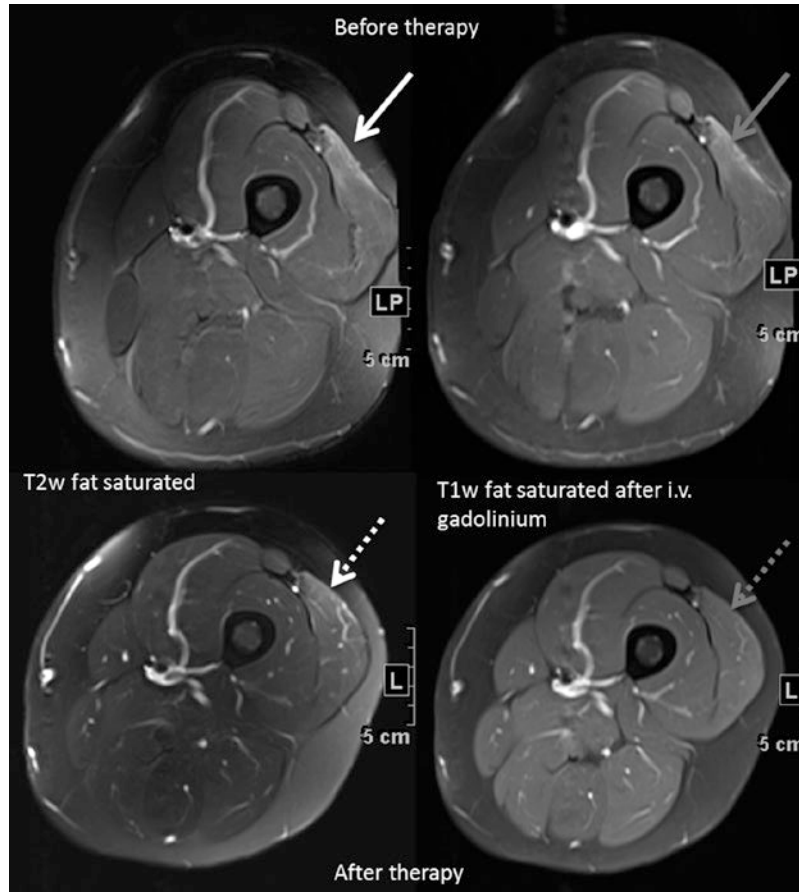

Fig. 16.11 Sequential images of a 22-year-old male with PM demonstrating regressing muscle edema (white arrows) and contrast enhancement (gray arrows) in the left lateral vastus muscle 5 months after the initiation of therapy

myositis activity, and that the clinical assessment has overestimated disease activity.

Taken together, these observations suggest that MRI provides valuable information regarding disease activity and treatment response. MRI may therefore complement the purely clinical assessment and serve as a myositis outcome measure. The IMACS group has now adopted the finding of muscle atrophy assessed by radiographic methods in its myositis damage index [35].

Other Advantages of Magnetic Resonance Imaging in Myositis

MRI can also be used to screen for cardiac involvement [36, 37] as heart-specific sequences (late contrast-enhanced T1w sequences) are added to the wb-MRI protocol. According to the Lake Louise consensus criteria, MRI findings are consistent with myocarditis if they meet at least two of the following three criteria: (1) increased signal intensity in T2w images representing edema, (2) increased early myocardial gadolinium enhancement reflecting hyperemia or capillary leakage, and (3) increased late gadolinium enhancement in a non-ischemic distribution representing irreversible cellular injury [38]. Left ventricular dysfunction and pericardial effusion may provide additional evidence for myocardial involvement. However, the performance of the myocarditis criteria has not been validated in IIM.

Finally, MRI may also detect intramuscular calcifications in IIM where fluid collections represent "milk of calcium." The latter have a variable signal amplitude on T2w images, depending on the calcium content of the collections [39].

Functional Magnetic Resonance Imaging Techniques

Blood oxygenation level-dependent MRI (BOLD MRI) is a functional MRI technique quantitating muscle microcirculation by measuring changes between diamagnetic oxy-hemoglobin and paramagnetic deoxy-hemoglobin. As the BOLD MRI signal depends mainly on blood oxygenation, blood flow can be derived under standardized conditions. In systemic sclerosis, BOLD MRI has revealed impaired skeletal muscle microcirculation [40]. BOLD MRI studies have not yet been carried out in IIM, but the technique has the capacity to noninvasively quantify vascular involvement in IIM, especially DM, where vasculopathy may be a key factor in pathogenesis.

Magnetic resonance spectroscopy (MRS) noninvasively quantifies pH and energy metabolites within tissues. In IIM, this technique has revealed impaired energy supply [41, 42] but is not part of the routine diagnostic armamentarium.

Diffusion-weighted (DWI) MRI is a functional MRI technique that measures the random motion of protons within water and calculates the extent of fluid motion in terms of diffusion and perfusion. IIM patients had increased diffusion values in inflamed muscles, whereas fatty-infiltrated muscles had decreased values [43].

T2 mapping is a different imaging method, which relies on proton transverse relaxation time (T2). T2 signals increase with augmented muscular water content, such as with edema or after exercise [44, 45]. The advantage of T2 mapping is that the technique provides a quantifiable measure of water content (and inflammation in myositis).

Muscle Ultrasound

The advantage of muscle ultrasound (US) over MRI consists of its broad availability, ease in handling, and lower cost. In the pediatric population, the use of muscle US is even more attractive as MRI often requires sedation in young children. A large study suggested that substitution of MRI for US in musculoskeletal diseases, when appropriate, could lead to several billion dollars of savings [46]. In this respect the use of US in diagnostic workup appears attractive.

In standard B-mode, normal muscle tissue has low echogenicity [47]. On longitudinal scans, the perimysium appears as oblique, parallel, echogenic striae against the hypoechoic background representing the muscle fibers [48]. On transverse scans, the perimysium appears as finely dotted echoes.

Conventional US has been evaluated in 61 patients with PM, DM, or sIBM. In acute DM/PM, capillary leakage blurs the normal muscle architecture and decreases echogenicity. The resulting edema can augment muscle volume. In chronic myositis, muscles become atrophic and infiltrated with fat and therefore have reduced volume and increased echogenicity [49]. Granulomatous myositis is characterized by the highest echo intensities and a tendency toward muscle hypertrophy [50].

The sensitivity of US in detecting muscle abnormalities of adult IIM patients was 83%, although statistically not superior to electromyography (92% sensitivity) and serum CK values (69% sensitivity) [50]. US offers the possibility to detect tissue calcifications as large hyperechoic foci with acoustic shadowing and fluid collections as “milk of calcium” [51, 52].

Contrast-enhanced power Doppler US was compared with MRI in a prospective study of 35 patients suspected to have DM or PM. The sensitivity of contrast-enhanced US was 73%, while the specificity was 91%. MRI however had nominally better figures (77% and 100%, respectively) [53]. Despite the inferiority compared to MRI, contrast-enhanced US may be an accessible and feasible alternative to MRI, especially in resource-poor settings. One of the major disadvantages of musculoskeletal US is that its performance is highly dependent on the experience of the examiner.

FDG-PET

Positron emission tomography (PET) uses short-lived positron-emitting radioisotopes as tracers. The uptake and storage of fluorine-18-labeled deoxyglucose (FDG) is routinely used for the

sensitive detection of lymphomas and other malignancies. Since inflammation increases the glucose demands of tissues, the diagnostic utility of FDG-PET is used in a variety of immune-mediated inflammatory conditions, such as sarcoidosis [54] and large-vessel vasculitis [55].

The role of FDG-PET in the diagnosis of IIM remains controversial. One study revealed an increased FDG-uptake in only 33% of IIM patients (13 PM/11 DM) [56], while a 12-patient (2 PM/10 DM) study showed a significantly increased FDG uptake in proximal muscles, but no significant correlations between uptake and disease duration, muscle strength, and CK levels [57]. A third study (5 PM/15 DM) noted a significant correlation between increased FDG uptake in proximal muscles and elevated CK values, decreased muscle strength, and inflammatory cell infiltrates in biopsy [58].

Since some IIM are associated with an increased risk of malignancy [59], FDG-PET may also provide a sensitive screening tool for neoplasm detection [60]. FDG-PET may also offer the added possibility to detect interstitial lung disease as an extramuscular complication [56, 58], but it is not yet part of the routine diagnostic workup of IIM.

^{99m}Technetium Pyrophosphate Scintigraphy

An increased uptake of ^{99m}technetium pyrophosphate (^{99m}Tc-PYP) in muscles affected by IIM has been described in case reports [61, 62]. A retrospective analysis of 166 patients with suspected myopathy assessed the diagnostic value of ^{99m}Tc-PYP scintigraphy [63]. The scan was positive in 60% of patients with the final diagnosis of IIM. ^{99m}Tc-PYP scintigraphy was however not able to discriminate between inflammatory and non-inflammatory myopathies. In individuals with biopsy-proven IIM, the diagnostic sensitivity was 43%, and its specificity was 60%. The low-positive and high-negative likelihood ratios of ^{99m}Tc-PYP muscle scintigraphy (5.0 and 0.65, respectively) suggest a limited value in the routine diagnostic workup of patients with suspected IIM.

Conclusion

MRI is perhaps the most valuable imaging technique in the diagnostic workup of IIM as it is sensitive, provides good spatial resolution, and resolves different muscle pathologies such as edema, fatty infiltration, atrophy, and concomitant fasciitis. Wb-MRI not only provides an overview of the extent of muscle involvement but may also reveal further organ pathology (heart involvement) and underlying malignancies.

IIM subgroups and IIM mimics may manifest with characteristic patterns of muscle involvement. Although MRI examination may therefore assist in narrowing down the differential diagnosis of a given myopathy, muscle biopsy still remains the gold standard for most myopathies. In this setting, MRI assists in the selection of a suitable biopsy site and lowers false-negative results compared with blind muscle biopsies.

Last but not least, muscle MRI can assist in the discrimination of active myositis and muscle damage and therefore may be a useful in assessing treatment response.

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Making the Diagnosis of Myositis: Laboratory Testing in Myositis

17

Olivier Benveniste and Lucile Musset

Key Points to Remember

- There are five muscle enzymes and all or some of them could be elevated in myositis: CK, aldolase, LDH, AST, and ALT.
- Evaluate all muscle enzymes at baseline and follow up the one most elevated longitudinally for disease activity.
- CRP and ferritin are rarely elevated except in the subgroups of myositis associated with a cancer or interstitial lung disease.
- ANA can be negative even in the presence of a positive MSA, which should be specifically tested in case of strong IIM suspicion.

Introduction

Muscle Enzymes: CK, Aldolase, LDH, AST, and ALT

There are five muscle enzymes including creatine kinase (CK), the transaminases aspartate aminotransferase (AST) and alanine aminotransferase (ALT), lactate dehydrogenase (LDH), and aldolase, which leak into the circulation from damaged muscle leading to serum elevation. Moderate to high correlations were observed among them [1]. All of them have been used as indirect markers of any condition inducing myolysis including the idiopathic inflammatory myopathies (IIM). Some of these enzymes are more specific for muscle tissue (CK, aldolase), while others are present in nearly all living cells (LDH) or in hepatocytes (transaminases).

Serum Transaminases There is a strong correlation between CK and the serum transaminases (AST, ALT). Serum transaminases were elevated in 80% of patients with IIM at the time of presentation and normalized in 85% of the patients at the time of CK normalization [2]. Nevertheless, the AST and ALT are less sensitive and specific than CK in most disease subsets of IIM. However, in some patients, especially juvenile dermatomyositis (JDM), AST and ALT elevations are more frequent than CK elevations and correlate well with disease activity. Therefore, an elevated AST

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and ALT could simply be a marker of disease activity in IIM or the result of liver damage induced by the treatment of IIM. It is generally easy to differentiate between the two using other muscle enzymes, including the alkaline phosphatase and gamma glutamyl-transpeptidases (γGT) as concomitant markers of muscle and liver disease, respectively.

- AST (SGOT) or ALT (SGPT) elevations are common in myositis due to disease activity.
- AST or ALT are often better markers of disease activity than the CK in juvenile dermatomyositis.

Lactate Dehydrogenase (LDH) LDH is far less specific for muscle damage than the CK or aldolase as it may be elevated with malignancy [3] which can be seen with myositis.

Aldolase In the case of normal CK levels, aldolase is the best muscle-specific laboratory test in most cases.

Creatine Kinase (CK) Given the limitation of other muscle enzymes, CK should always be done in the workup of muscle diseases in general and IIM in particular. It is advisable to measure all muscle enzymes at initial evaluation, and then follow up those that are abnormal longitudinally to assess treatment response and disease activity. Serum CK levels are generally good markers of disease activity in IIM. However, for certain dermatomyositis [4] and inclusion body myositis [5] patients, CK levels can be slightly elevated or normal even in the setting of active disease. Hence, they may not be good markers of disease activity in these IIM subsets. In some DM patients, notably those with anti-Mi-2 antibodies, CK levels are markedly elevated (often >5000 IU/L) at onset and normalize with treatment [6], so following the CK is reasonable in these cases. Finally, with the anti-synthetase syndrome with anti-Jo-1 antibodies [7], and immune-mediated necrotizing myopathies with anti-SRP [8] or anti-HMGCR [9] antibodies, CK levels clearly correlate with disease activity and should be used in the follow-up of these patients. On the other hand, with interstitial lung disease-predominant anti-synthetase syndrome, CK levels do not correlate well with disease activity and aldolase may be more appropriate to monitor in such patients.

- Serum CK levels could be normal in many active (juvenile) dermatomyostis and inclusion body myositis.
- However, serum CK levels are always high in active polymyositis or necrotizing myopathies.

Creatine Kinase Elevations in Other Conditions One of the most common causes for CK elevation is eccentric exercise. Serum levels depend on gender, muscle mass, exercise intensity, and duration in addition to the individual training state, and there is a remarkable inter-individual variability in the degree to which serum enzyme activities increase with exercise [10]. Thus, one must first retest these enzymes at rest, at least 5–7 days after strenuous activity or any eccentric exercise, as the peak CK elevation often occurs at 4 days post exercise [11]. With intense exercise, muscle enzyme release cannot be used to predict the magnitude of the muscle function impairment caused by muscle damage [12]. That is, CK levels up to 100,000 IU/L can be perfectly asymptomatic or reveal an exertional heat illness with rhabdomyolysis. Similar muscle enzyme leakage in the blood can be observed in all muscle diseases from rhabdomyolysis (toxic, genetic, heat illness) to inherited dystrophies or metabolic myopathies or IIM, as well as during mechanical [13] or electrical [14] injuries.

Using receiver-operating characteristic (ROC) curve analysis, victims of catastrophic earthquakes [13] demonstrated that crush injuries, when compared to other injuries with no muscle damage, showed the highest specificity (100%) and positive predictive value (100%) for serum

CK. Similarly, sensitivity was high (99.4%) along with the negative predictive value (99.0%) in distinguishing crush from non-crush injuries. The muscle enzymes were measured in the blood of more than 500 victims clearly demonstrating that the serum CK level was the best marker of muscle injury.

Inflammatory Markers: Ferritin, ESR, CRP, etc

Generally speaking, inflammation within muscle tissue (i.e., the inflammatory infiltrate) is the hallmark of IIM. Nevertheless, systemic inflammation is rarely observed during IIM as the levels of ferritin, ESR, or CRP remain nearly normal, even in treatment-naïve active disease patients. As expected, high CRP levels in the setting of IIM are more predictive of bacterial infection [15]. Notable exceptions include disease not solely confined to muscle as in overlap syndromes where arthritis and ILD are present. This is typically seen with the anti-synthetase syndrome. In a series of anti-synthetase (+) patients, fever, weight loss and elevated inflammatory markers are frequently observed [16, 17]. Furthermore, ILD is associated with elevated serum levels of CRP as well as the interferon-gamma-inducible chemokines CXCL9 and CXCL10 [18]. Similarly, with JDM and adult MDA5 positivity, high serum CRP and ferritin levels are seen with ILD [19, 20]. In the same vein, mean ESR was significantly higher in idiopathic inflammatory myopathies with ILD (compared to those with no ILD) [21].

Inflammatory markers may also be elevated in cancer-associated myositis. A recent meta-analysis noted that the following factors are all associated with an increased risk of malignancy: age greater than 45, male sex, dysphagia, cutaneous necrosis, cutaneous vasculitis, rapid onset of myositis (<4 weeks), elevated CK, but also higher ESR, and higher CRP levels [22].

For all these reasons, it is recommended to check at least the CRP in the workup of myositis patients especially in those with high risk for ILD and/or cancer.

- Elevated ESR and CRP are associated with arthritis, ILD, and cancer in myositis.
- Elevated ferritin is associated with a worse prognosis of ILD in some myositis subsets including those with the anti-MDA-5 antibody.

Anti-nuclear Antibodies and Anti-cytoplasmic Pattern in Myositis

The detection of autoantibodies against nuclear and/or cytoplasmic antigens (so-called anti-nuclear antibodies (ANA)) is the initial test for the laboratory diagnosis of systemic autoimmune rheumatic diseases (SARD) including myositis. The gold standard for ANA testing is the indirect immunofluorescence (IIF) test on human epidermoid carcinoma cells (Hep-2

Table 17.1 Localization of the fluorescence on HEp-2 cells for the main myositis-specific and myositis-associated antibodies using indirect immunofluorescence assays

Myositis-specific antibodies	**HEp-2 cell patterns**
Anti-aminoacyl-tRNA synthetases: anti-Jo-1, PL-7, PL-12	Cytoplasmic
Others: anti-OJ, -EJ, -KS, -HA, -Zo	Cytoplasmic (but rarely observed in routine practice)
Miscellaneous:	
Anti-SRP	Cytoplasmic
Anti-Mi-2	Nuclear
Anti-HMGCoA-R	Cytoplasmic
Anti-TIF1-γ	Nuclear
Anti-MDA5	Cytoplasmic/negative
Anti-SAE	Nuclear
Anti-NXP-2	Nuclear
Myositis-associated antibodies	
Anti-Ro-52/TRIM21	Nuclear/cytoplasmic/negative
Anti-Ro-60 (SSA)	Nuclear/cytoplasmic
Anti-La (SSB)	Nuclear
Anti-Ku	Nuclear
Anti-U1RNP	Nuclear
Anti-PM-Scl	Nuclear

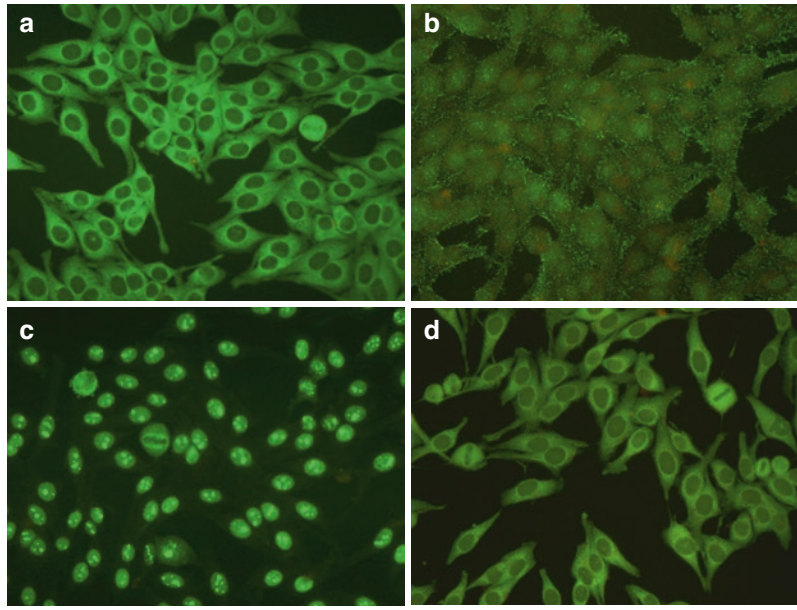

Fig. 17.1 Indirect immunofluorescence assay on HEp-2 cells. Serum dilution: 1/80; magnification ×40. (**a**) Serum with anti-aminoacyl-tRNA synthetase antibodies (anti-PL7), showing typically cytoplasmic speckled pattern with no nuclear or nucleolar fluorescence. (**b**) Serum with anti-histidyl-tRNA synthetase antibodies (anti-Jo1), with speckled cytoplasm, without nuclear fluorescence. (**c**) Serum with anti-PM-Scl antibodies. Mixed pattern on HEp-2 cells, showing homogeneous staining of nucleoli with speckled pattern of the nucleoplasm in interphase cells. The mitotic chromatin show no staining. (**d**) Serum with anti-signal recognition particle (SRP) antibodies, with fine speckled cytoplasm, without nuclear fluorescence. (Courtesy of Dr. J-L Charuel)

cells). ANA IIF is intended for diagnostic purposes, not for monitoring disease progression or for prognosis. The lack of inter-laboratory standardization and other problems in ANA testing (analytical variability due to the preparation of substrates, globulins, microscope reading, and the subjectivity of interpretation) are particularly relevant for the detection of myositis-associated and myositis-specific antibodies. Different patterns of fluorescence are reported according to antigen-antibody reactivity and identifiable patterns could be nuclear and/or cytoplasmic (Fig. 17.1, Table 17.1). A standardized classification pattern was recently proposed [23, 24], but inter-laboratory discrepancies remain. Thus, if there is a clinical suspicion of myositis (e.g., anti-Jo-1, or anti- HMGCR antibodies), the recommendation is for the detection of myositis antibodies irrespective of the ANA result. Moreover, in routine practice, tests based on a (restricted) mixture of defined extractable nuclear antigens, i.e., ANA testing by ELISA or techniques other than IIF, should not be referred to as ANA detection [23]. In such a mixture, the main antigens recognized by myositis antibodies are not present leading to false-negative results.

Anti-cytoplasmic Pattern in Anti-synthetase Syndrome

It is now clear that cytoplasmic fluorescence observed on HEp-2 cells must be systematically reported regardless of the nuclear fluorescent pattern, since anti-synthetase autoantibodies target cytoplasmic antigens. Cytoplasmic fluorescence used as an initial screening test in patients potentially having antisynthetase syndrome, has diagnostic utility in terms of sensitivity and specificity [25].

Myositis Autoantibodies: When to Order and How to Interpret

The detection of MSA and MAA by western blot, immunoprecipitation using radio-labeled antigens or immunodiffusion are not universally available. Further, these are labor-intensive and technician-dependent techniques with no accepted standardization. Despite these limitations, they remain the gold standard and any newer methodology must be validated against them. Current commercially available tests including ELISA, chemiluminescence (CLIA), dot-blot or line-immunoassays (ALBIA) are not standardized and have variable false-positive and -negative rates depending on the assay characteristics. However, these assays are cheaper with less operator-dependent error and are helpful for diagnosing many myositis patients around the world. Nevertheless, a reliable and validated myositis panel is clearly necessary and eagerly awaited.

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Role of ANA and Myositis Autoantibodies in Diagnosis

18

Neil J. McHugh and Ira N. Targoff

Key Points to Remember

- The discovery of several new myositis autoantibodies is a major advance in working towards early diagnosis especially when more reliable and standardised assays become available.
- Myositis-specific autoantibodies help identify distinct patterns of disease within the myositis spectrum of disease.
- A negative ANA screening test does not rule out the presence of a myositis autoantibody, and further testing may be necessary.
- Knowledge of the full repertoire of myositis autoantibodies is important across specialties as some myositis autoantibodies are more closely associated with skin and lung disease than with myositis itself.

Introduction

In recent years, the discovery and addition of newly defined autoantibody specificities to those more traditionally associated with inflammatory myopathy has changed the landscape in terms of diagnostic utility and potential approach to management of idiopathic inflammatory myopathies (IIM). The concept of serologically defined subsets of disease that redefines the long-standing broader concepts of polymyositis versus dermatomyositis, and possibly even inclusion body myositis, has gained increased recognition. In addition, the terminology of myositis-specific and myositis-associated autoantibodies may come under question when one considers the full spectrum of end-organ involvement in that some autoantibody specificities are closely associated with accompanying lung or skin disease, sometimes even in the absence of myositis itself. In this chapter, we will illustrate how myositis-related autoantibodies are detected, how their presence may impact on the ability to form a diagnosis, identify more closely defined patterns of disease, and influence a personalised medicine approach towards disease management.

Autoantibody Detection

ANA Testing in Myositis The conventional screen for the presence of an autoantibody is an

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antinuclear antibody (ANA) test. An ANA is usually performed by indirect immunofluorescence (IIF) using rodent tissue or a human cell line (usually HEp-2 cells) as the substrate. The results of a HEp-2 test should give the titre of ANA detected and the pattern of staining. Whilst an ANA test remains a useful screen for many autoimmune rheumatic diseases such as lupus and scleroderma (high sensitivity >95%), it is not very useful in myositis for two main reasons. First, most myositis antibodies are not present at high titre nor do they provide a distinctive pattern on IIF that may otherwise help confirm the autoantibody identity. The frequency of ANA positivity may be as low as 50% in some myositis cohorts [1]. Second, many myositis antibodies yield a cytoplasmic rather than a nuclear staining pattern on IIF (e.g. anti-synthetase antibodies [anti-ARS]), and often the ANA result is reported as a negative test even in the presence of these cytoplasmic staining patterns (Fig 18.1). An ANA negative result may therefore be misleading resulting in a delayed diagnosis and an incorrect assumption of 'autoantibody negativity' in myositis. Thus, a reflex strategy of doing specific autoantibody testing only if the ANA test is positive may fail to detect some myositis autoantibodies. Therefore, the clinician must specifically request that myositis autoantibody testing be undertaken in addition to an ANA screen.

A negative ANA by IF may be misleading in myositis and specific myositis autoantibody testing should be done.

Staining Pattern of Myositis Autoantibodies on IIF As noted above, some of the important myositis autoantibodies react with antigens located in the cytoplasm of the cell, which leads to anti-cytoplasmic rather than antinuclear reactivity on ANA tests based on IIF. Although some laboratories will report the cytoplasmic reaction and consider this a positive result for the IIF (ANA test), most laboratories report a negative ANA even if prominent cytoplasmic reactivity is present.

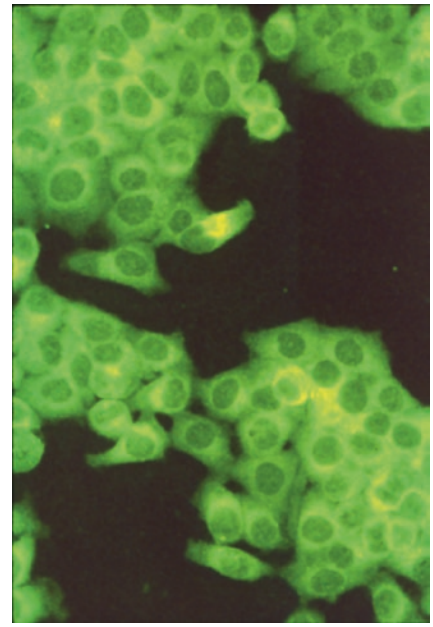

Fig. 18.1 Indirect immunofluorescence with anti-Jo-1 antibodies demonstrating strongly positive cytoplasmic staining and negative nuclear staining

Antinuclear patterns are seen with some of the traditional or newer myositis autoantibodies, including anti-Mi-2 and anti-p155/140, which give fine speckled nuclear patterns, with anti-Ku and anti-RNP (associated with overlap disorders) also demonstrating nuclear patterns. Patients seropositive for anti-PM-Scl autoantibodies demonstrate both nuclear and nucleolar staining patterns, and patients may have scleroderma or myositis alone or an overlap of these two diseases. Patients with anti-U3RNP or anti-Th/To typically give a pure nucleolar pattern. Nuclear patterns are also seen with sera from some myositis patients when no clinically identifiable autoantibody is detected, suggesting the presence of an unidentified autoantibody.

In contrast, anti-synthetase and anti-SRP autoantibodies usually show cytoplasmic patterns by IIF. The aminoacyl-tRNA synthetases are predominantly located in the cytoplasm of the cell, where they play a crucial role in protein synthesis by binding amino acids to their corresponding transfer RNAs. The signal recognition particle is also in the cytoplasm and plays an important role in the process of translocation,

directing newly synthesised polypeptides to the endoplasmic reticulum. Specifically ordering an ANA by IIF and anti-Jo-1 testing (usually by ELISA) may be more sensitive for detecting all anti-synthetase autoantibodies if the reading of the ANA by IIF is reliable as the availability, reliability and standardisation of detecting the non-Jo-1 antisynthetase antibodies is unpredictable. Anti-SRP typically gives a low to moderate titre of fine-speckled cytoplasmic fluorescence. Sera from other myositis patients may show cytoplasmic patterns, suggesting that other autoantibodies to cytoplasmic proteins occur in myositis. Important anticytoplasmic autoantibodies can occur in other conditions, such as patients with anti-ribosomal P protein autoantibodies associated with lupus or autoantibodies to other distinctive cytoplasmic structures or proteins such as anti-mitochondrial autoantibodies. However, a cytoplasmic pattern without nuclear staining is relatively more common in myositis. Thus, while seeing a cytoplasmic pattern by IIF can provide an important clue to the possible presence of an anti-synthetase or other myositis autoantibody, this should be followed by additional testing for more specific identification of the autoantibody in order to properly assess its clinical significance. While cytoplasmic patterns and staining may be very important in alerting the clinician to the possible presence of an anti-synthetase or anti-SRP, the absence of such a pattern does not exclude the presence of any of these autoantibodies.

Even with IIF ANA screening and the assessment of cytoplasmic staining along with myositis antibody panel testing, some PM or DM patients will not demonstrate autoantibody positivity. However, an increasing number of autoantibodies in myositis are being recognised and new autoantibodies continue to be identified as described below. Some unidentified autoantibodies may be found to have an association with myositis in the future.

Commercial Myositis Assays There are several other assay systems for detecting myositis antibodies that include enzyme-linked immunosorbent assays (ELISA), chemiluminescent immunoassay, immune-diffusion, addressable laser bead immunoassay (ALBIA), immunoblotting techniques (line blot, dot blot), and RNA or protein radio-immunoprecipitation (IP). The assay may be for the detection of single autoantibody specificity (e.g. single test ELISA) or to screen for a range of specificities (e.g. ANA ELISA) or for multiplex testing of a panel of autoantibodies in the one assay system (e.g. bead assay, line blot, protein IP). There is no one single reliable assay although RNA or protein IP is often used as the reference assay as it can more reliably detect most myositis-related autoantibodies according to molecular weight (Fig. 18.2). However, protein IP is costly, time-consuming, and not widely available, and thus many commercial assays are becoming available for the increased repertoire of known myositis autoantibodies. The assays available show variable results in terms of performance, and there is currently no standardised approach to myositis autoantibody testing. In addition, the positive predictive value (PPV) of a positive result will be determined by the prevalence of myositis in the

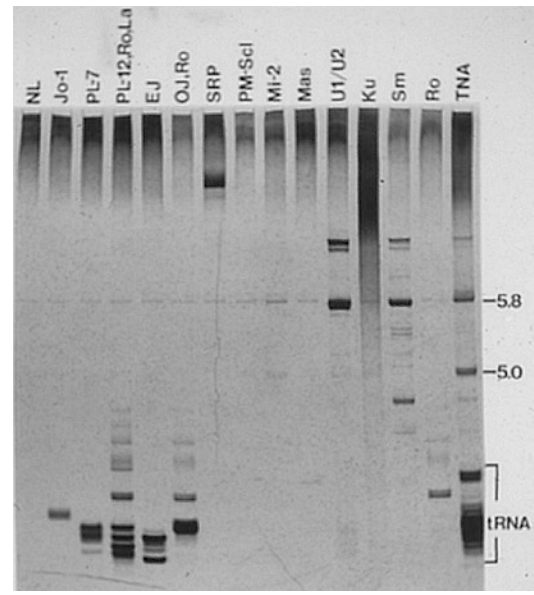

Fig. 18.2 RNA-immunoprecipitation with myositis autoantibodies

population being tested (e.g. high PPV of anti-HMGCR in suspected statin-induced myotoxicity versus low PPV for anti-HMGCR in a community setting). At present, until more data is available comparing the performance of newer assays, it is advisable to confirm that a positive myositis antibody result is consistent with findings from the ANA IIF screen (including cytoplasmic patterns). If the clinical pattern of disease is discordant with the laboratory result, then a separate assay or system of detection should be considered.

Several commercial myositis panels are available, but there is a lack of standardisation.

Clinicians should corroborate a positive myositis antibody test result with the clinical pattern of disease.

Diagnosis

Myositis-Specific Autoantibodies (MSA) and Myositis-Associated Autoantibodies (MAA) Autoantibodies present in myositis are conventionally described as myositis-specific autoantibodies (MSA) and myositis-associated autoantibodies (MAA) and are highly specific for the spectrum of myositis diseases, often representing a unique clinical phenotype. However, the term MSA remains somewhat misleading as some MSAs are more closely associated with skin or lung involvement with no obvious muscle inflammation [2]. For instance, anti-tRNA synthetase antibodies are associated with a syndrome in which patients may never exhibit muscle disease (see Chap. 20). On the other hand, MAA describes a group of autoantibodies that may be found in other autoimmune conditions that occur in overlap with myositis such as lupus and scleroderma. For example, as noted above, anti-PM-Scl is an MAA often associated with an overlap of myositis and scleroderma which may also identify a pattern of disease similar to the anti-synthetase syndrome [3]. There may be a case in the future for combining MSA and MAA under one descriptor such as myositis-related autoantibodies or myositis-spectrum autoantibodies.

MSA and MAA are highly specific and represent unique clinical phenotypes.

MSA and MAA represent a myositis spectrum of disorders but may not have overt myositis.

Since the early description of the classic MSAs, including anti-Mi-2 [4], -Jo-1 [5], and -SRP [6], there has been a growing list of more recently discovered MSAs leading to an identifiable autoantibody in about 70% of adult IIM or juvenile dermatomyositis (JDM) cases [2]. Furthermore, the percentage of cases where an MSA or an MAA is not present has diminished significantly and is likely to continue as novel autoantibodies are discovered. The full list of currently known MSAs is shown in Table 18.1. Remarkably, the presence of more than one MSA in any one patient is extremely rare, likely pointing to a close association between MSA generation and disease pathogenesis. Indeed, there is abundant evidence that each MSA is associated with a homogeneous pattern of disease within the myositis spectrum of conditions (Table. 18.1) (Fig. 18.3).

The sensitivity of a collective myositis panel is increasing as more autoantibodies are discovered and as better assays become available.

Dating from the original Bohan and Peter criteria for dermatomyositis and polymyositis in 1975 [7, 8] when MSAs were not recognised, there have been several attempts to modify or develop new criteria [9]. In addition, the concept of pure polymyositis has largely been subsumed by the separately defined entities inclusion body

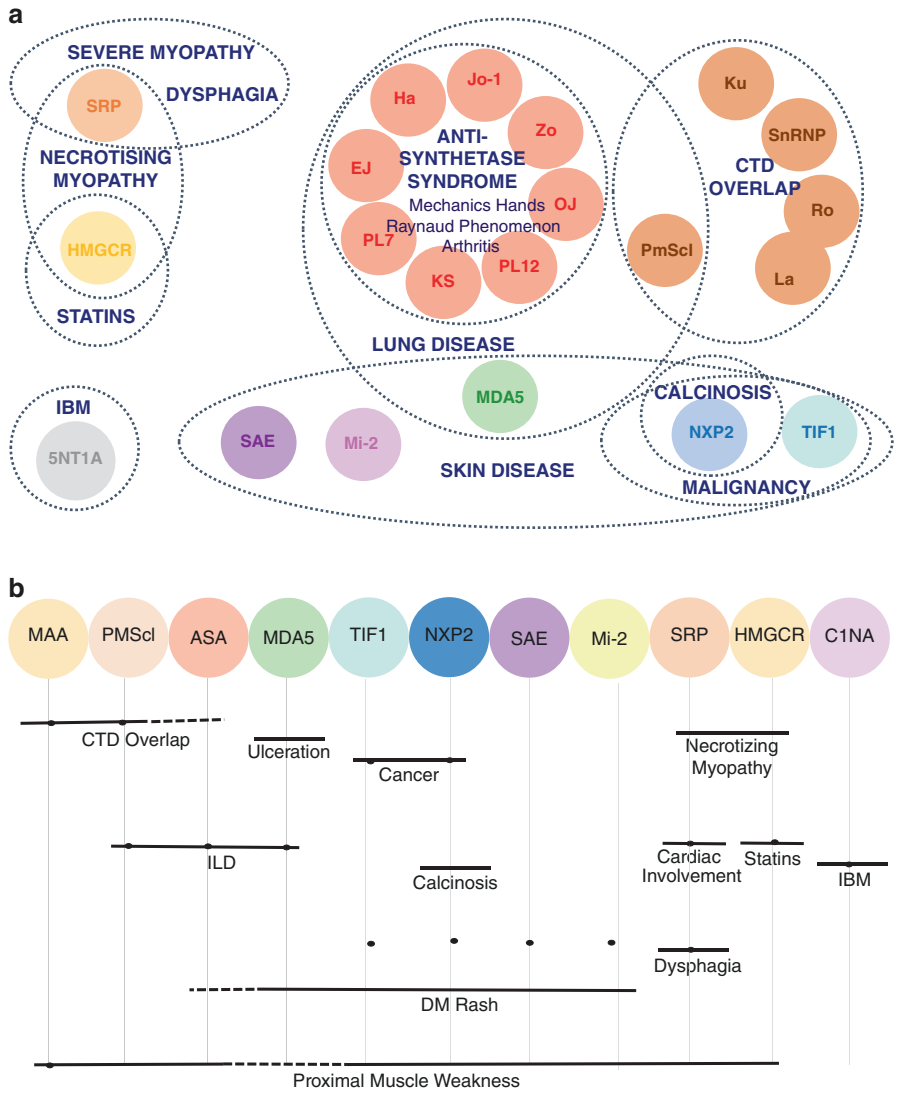

Fig. 18.3 (**a**, **b**) Provides an illustration of the association of various organ and clinical features with different myositis specific autoantibodies

myositis (IBM), immune-mediated necrotising myositis (IMNM), and overlap myositis syndromes. There has also been recognition of a group of patients presenting with cutaneous features of dermatomyositis who may never exhibit clinical myositis, and referred to as clinically amyopathic dermatomyositis (CADM) [10]. The concept of the anti-synthetase syndrome is well established with its own proposed criteria [11]. Moreover, there is growing awareness that there are patients with idiopathic interstitial pneumonia who may not fulfil any of these connective tissue disease criteria yet may have clinical or serological evidence of an autoimmune disorder that has led to the proposed criteria for interstitial pneumonia with autoimmune features (IPAF) [12]. Most of these proposed criteria are classification criteria that need further investigation of their performance as diagnostic criteria at a much earlier stage of the disease course.

Table 18.1 Myositis-specific autoantibodies, autoantigens, and clinical associations

Autoantibody	Autoantigen	Autoantigen function	Clinical phenotype
Anti-ARS Anti-Jo-1 Anti-PL-7 Anti-PL-12 Anti-EJ Anti-OJ Anti-KS Anti-Zo Anti-YRS	tRNA synthetase Histidyl Threonyl Alanyl Glycyl Isoleucyl Asparaginyl Phenylalanyl Tyrosyl	Intracytoplasmic protein synthesis Binding between an amino acid and its cognate tRNA	Anti-syn syndrome Myositis Interstitial pneumonia Mechanics hands Arthritis Fever Raynaud phenomenon
Anti-Mi-2	Helicase protein part of the NuRD complex	Nuclear transcription	Adult and juvenile DM Hallmark cutaneous disease
Anti-SRP	Signal recognition particle 6 polypeptides and ribonucleoprotein 7SLRNA	Intracytoplasmic protein translocation (endoplasmic reticulum)	Severe necrotising myopathy
Anti-HMGCR	3-Hydroxy-3-methylglutaryl-coenzyme A reductase	Biosynthesis of cholesterol	Necrotising myopathy associated with statin use
Anti-TIF-1γ	Transcription intermediary factor 1 gamma subunit	Nuclear transcription Cellular differentiation	Severe cutaneous disease in juvenile DM and cancer in adults
Anti-NXP-2	Nuclear matrix factor 2	Nuclear transcription (tumour suppressor gene p53)	Juvenile and adult DM Calcinosis and malignancy in adults
Anti-SAE	Small ubiquitin-like modifier activating enzyme	Post-translational modification – targets include nuclear transcription factors	Adult DM May present with CADM first
Anti-MDA5	Melanoma differentiation-associated protein 5	Viral RNA recognition	CADM Rapidly progressive interstitial lung disease
Anti-CN1A	Cytosolic 5'nucleotidase 1A	Hydrolysis of AMP	Inclusion body myositis (Sjogren syndrome)

So it is of considerable interest that the more strictly defined subsets of disease described earlier also segregate with different profiles of MSA [2]. IBM has, perhaps, come more within the fold of an autoimmune disorder with the discovery of autoantibodies to cytosolic 5′-nucleotidase 1A (cN-1A) present in somewhere between 30% and 70% of cases [13, 14]. IMNM has two main profiles of MSA, anti-HMGCR associated although not exclusively so with statin use [15], and anti-SRP with patients who often have severe refractory muscle disease [16]. CADM may embrace several MSA profiles including what was initially described as anti-CADM-140 [17], now known as anti-MDA5 [18]. Other MSAs over-represented in CADM include anti-TIF1-γ and anti-SAE [2]. Within the anti-synthetase syndrome there appears to be even closer-defined patterns of disease associated with individual aminoacyl-tRNA synthetases, such as more frequent arthritis with anti-Jo-1 [19] and lung disease with non-Jo-1 anti-synthetase specificities [20].

> Myositis autoantibodies define clinical subsets of myositis and serve to predict organ involvement and clinical features which can aid the clinician in management.

Therefore, it is not surprising that there have been attempts to include serological findings into the proposed classification criteria for IIM. Tannimoto et al. added four new criteria to the Bohan and Peter criteria one of which was the presence of anti-Jo-1 [21]. A more substantial addition was proposed in the Targoff criteria by which time the concept of myositis-specific and

myositis-related autoantibodies had been established [22]. The latter criteria proposed the inclusion of an MSA such as anti-synthetase, anti-Mi-2, or anti-SRP autoantibodies along with the traditional Bohan and Peter criteria. To qualify for the diagnosis of definite IIM, the patient needed to have at least one of the following three main criteria: a compatible biopsy, cutaneous DM features, or an MSA. More recently, there has been an effort within the International Myositis Assessment and Clinical Studies (IMACS) group called the International Myositis Classification Criteria Project (IMCCP) that has analysed data collected prospectively including serological testing available at the time, resulting in newly developed and validated EULAR/ACR classification criteria for myositis which includes anti-Jo-1 [23]. However, it will be important in future endeavours to include the full repertoire of MSAs in order to further refine classification criteria for myositis.

More than One Myositis Autoantibody As summarised above an important feature of myositis autoantibodies is mutual exclusion. However, certain myositis-associated autoantibodies may occur in association with MSAs and may in fact be more likely to occur. In particular, anti-Ro60, anti-Ro52 and anti-U1RNP can occur in association with MSAs, and anti-Ro52 is more likely to occur with anti-synthetases or anti-PM-Scl than in those without MSAs. On the other hand, some MAAs (e.g. anti-PM-Scl or anti-Ku) rarely occur in association with each other or with MSAs. Anti-U1RNP gives a classic coarse speckled pattern, and when it occurs in association with an anti-synthetase (e.g. anti-EJ or anti-PL-12), the cytoplasmic pattern of the myositis autoantibody may be less evident, missed, or absent.

> Myositis-specific autoantibodies are generally mutually exclusive.

Autoantibodies Associated with Juvenile Dermatomyositis JDM is worthy of separate mention as it is one of the more common autoimmune rheumatic disorders of childhood. The classic or traditional MSAs such as anti-Mi-2, anti-SRP, and the anti-synthetases are less common in JDM than in adult myositis but when present seem to associate with similar patterns of disease as seen in adults [24]. Collectively, the newer MSAs, anti-NXP2, anti-TIF1-γ and, less commonly, anti-MDA5 make up about 50% of JDM cases and have considerable potential impact on the diagnostic utility of MSA testing in JDM with earlier detection of cases [24]. Similar to adults, each MSA associates with sub-phenotypes of disease, e.g. anti-NXP2 with calcinosis. However, unlike adult-onset myositis the presence of anti-TIF1-γ in JDM does not appear to be associated with cancer, although longer-term studies into late adulthood would be of interest.

> Myositis autoantibodies are being increasingly used for diagnostic confirmation and are being incorporated into classification criteria for myositis.

Conclusion

Myositis specific autoantibodies are being increasingly used in the day to day practice to confirm the clinical diagnosis in many forms of myositis. The combined sensitivity of all myositis autoantibodies approaches 70%. Therefore a negative myositis autoantibody panel does not rule out the possibility of IIM. Each myositis specific autoantibody is highly associated with a unique clinical phenotype serving to direct clinicians in the management and prognosis of myositis patients.

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Role of Myositis Autoantibodies in Management and Prognosis

19

Takahisa Gono and Masataka Kuwana

Key Points to Remember

- Anti-TIF1-γ, anti-NXP2, and the absence of MSA/MAA are predictive of concomitant malignancy in adults.
- Anti-synthetase and anti-MDA5 antibodies are associated with a high risk for ILD. Anti-MDA5-associated ILD tends to be treatment-refractory requiring intensive immunosuppression, while anti-ARS-associated ILD may be more responsive to immunosuppression including glucocorticoids and rituximab.
- Immune-mediated necrotizing myopathy, particularly in anti-SRP-positive patients, is associated with treatment-refractory disease and warrants aggressive therapy, while anti-Jo-1 and anti-Mi-2 antibodies are associated with a favorable response to rituximab.

Introduction

The muscular and extramuscular manifestations of the various subsets of idiopathic inflammatory myopathy (IIM) include cutaneous, gastrointestinal, pulmonary, cardiac, musculoskeletal, and vascular features. Therefore, disease subsetting or phenotyping is of vital importance for the appropriate management of myositis, particularly interstitial lung disease (ILD) and malignancy, as these complications are the leading causes of death in myositis patients [1]. Myositis-specific autoantibodies (MSAs) and myositis-associated autoantibodies (MAAs) are powerful predictive and prognostic tools regarding future clinical manifestations, treatment response, and prognosis when assessing patients and developing a management plan. Figure 19.1 incorporates autoantibody assessment in a proposed algorithm for the diagnosis and treatment of polymyositis (PM) and dermatomyositis (DM) patients.

Malignancy Survey

There is a well-known association of cancer with DM (and to a lesser extent PM) in up to 20% of cases [2, 3] with the diagnosis frequently being made within 1 year before or after the diagnosis of myositis [4]. Therefore, malignancy screening is essential at the time of a myositis diagnosis and

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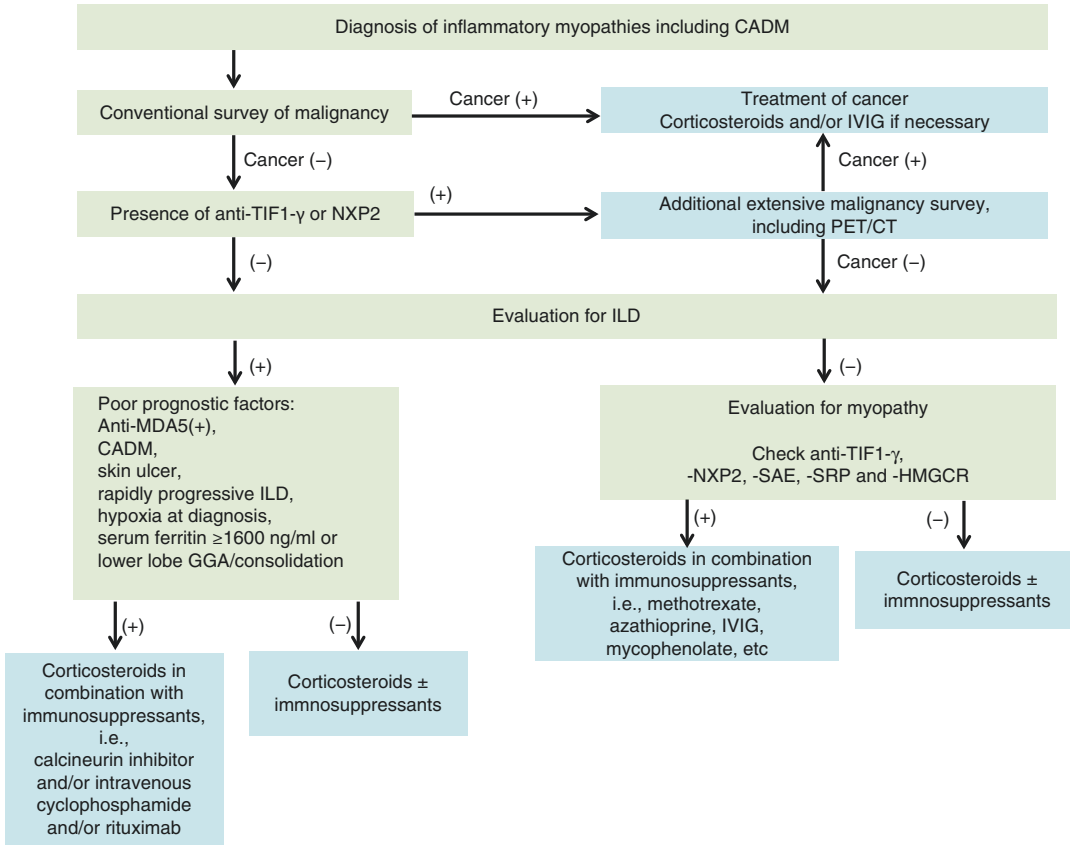

Fig. 19.1 A proposed algorithm for the management of PM/DM patients considering the MSA profile. MSAs myositis-specific autoantibodies, CADM clinically amyopathic DM, PET positron emission tomography, CT computed tomography, ILD interstitial lung disease, GGA ground-glass attenuation

the contribution of autoantibody testing is critical in stratifying the malignancy risk. In this regard, the presence of anti-TIF1-γ autoantibody or the absence of other MSAs/MAAs, including anti-Jo-1, anti-PM-Scl, anti-U1RNP, anti-U3RNP, and anti-Ku, at the time of myositis diagnosis indicates a high risk of cancer-associated myositis (CAM) [5]. In fact, this combination had a 94% sensitivity and 99% negative predictive value for the diagnosis of CAM, although the specificity and positive predictive value were only 45% and 9%, respectively for a CAM diagnosis. A meta-analysis of 312 patients with DM revealed that the sensitivity and specificity of anti-TIF1-γ antibody for the diagnosis of concomitant cancer were 78% and 89%, respectively [6], while other MSAs, most importantly anti-NXP2, and perhaps anti-SAE and anti-HMGCR positivity were also associated (to a much lesser degree) with malignancy in adult PM and DM patients [3, 5, 7–10] (Fig. 19.2). Even with anti-TIF1-γ positivity, patients over age 45 are most at risk for malignancy, as juvenile and younger adult DM patients may not be at risk for cancer. Nevertheless, clinicians should conduct an extensive malignancy survey with a diagnosis of DM and anti-TIF1-γ antibody or anti-NXP2 positivity, but the degree of cancer screening in DM patients negative for these autoantibodies remains a matter of debate. An extensive malignancy screen should include age-appropriate cancer screening; comprehensive blood tests including cancer markers; CT scans of the chest, abdomen, and pelvis; and, perhaps, a whole-body PET-CT scan in selected cases. Screening for malignancies in low-risk patients (without these high-risk antibodies) should be

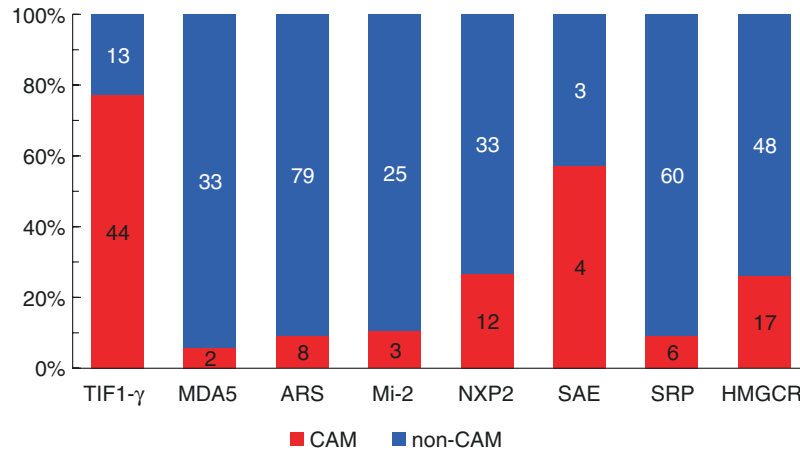

Fig. 19.2 Prevalence of concomitant malignancy in patients with PM/DM, stratified by MSAs [3, 5, 7–10]. MSA myositis-specific autoantibody, CAM cancer-associated myositis

guided by clinical suspicion and the prevalence of individual cancers in specific ethnic groups or the country of origin. Age-appropriate screening and noninvasive tests (e.g., fecal occult blood, gynecological evaluation, prostatic-specific antigen) should be considered in all patients.

High risk for malignancy: anti-TIF1-γ, anti-NXP2, absence of an MSA/MAA.

High-risk patients should undergo extensive cancer screening and close follow-up.

Risk Stratification and Treatment of Interstitial Lung Disease

The frequency of ILD in patients with IIM is highly variable, ranging from 10% to 90%, depending on the autoantibody spectrum [11]. Moreover, the clinical course and treatment response of ILD are variable as some patients may have mild ILD responsive to glucocorticoids alone, while others may have rapidly progressive ILD (RP-ILD) resistant to intensive immunosuppressive regimens, leading to death due to respiratory failure. Clinical diagnoses are somewhat useful in predicting 5-year overall survival rates in patients with ILD: 82% in patients with PM, 71% in those with classic DM, and 59% in those with CADM [12]. However, MSAs provide much more useful information regarding frequency, severity, and treatment response in ILD. Figure 19.3 summarizes the frequency of ILD in patients with individual MSAs [8, 10, 13–15]. Anti-synthetase autoantibodies and anti-MDA5 are strongly linked to the presence of ILD, with a frequency approaching 90% and 50%, respectively, in the western literature. Anti-MDA5 is associated with an even higher risk in Asian countries. Although Caucasian patients with anti-SAE have a lower risk of ILD than Asian populations, the number of patients examined are too small to be confident of this association [10, 16]. The 5-year overall survival rates in patients with anti-synthetase antibodies were much better than those with anti-MDA5 (96% versus 67%) [12], as anti-MDA5 is strongly associated with RP-ILD, as shown in Fig. 19.4 [17–19]. Even though anti-MDA5 is clearly associated with CADM, its presence has a worse prognosis due to RP-ILD rather than the CADM clinical subset itself [20, 21]. Other risk factors for poor ILD outcomes in patients with PM/DM include skin ulcers, rapidly progressive deterioration of pulmonary function, hypoxia at diagnosis, hyperferritinemia, and ground-glass attenuation/consolidation in the lower lobe of the lung by high-resolution computed tomography (HRCT)

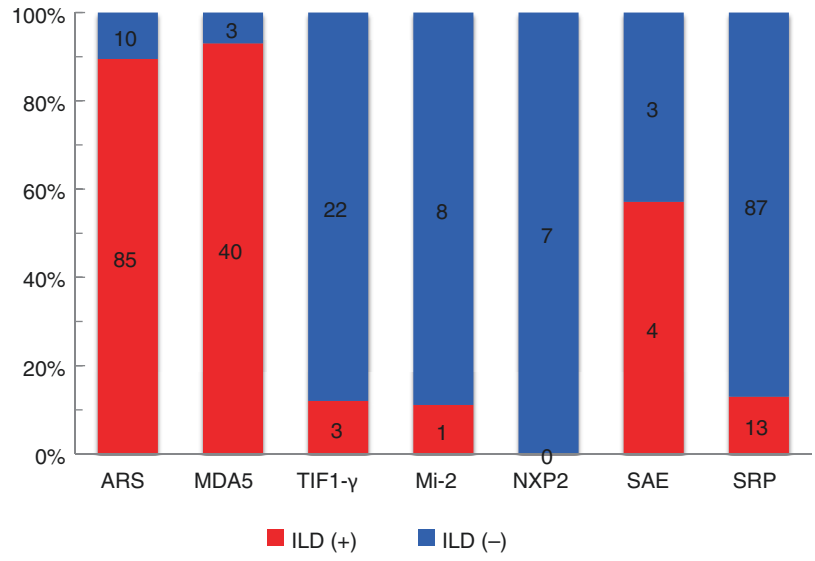

Fig. 19.3 Prevalence of ILD in patients with PM/DM stratified by MSAs [8, 10, 13–15]. ILD interstitial lung disease, MSA myositis-specific autoantibody

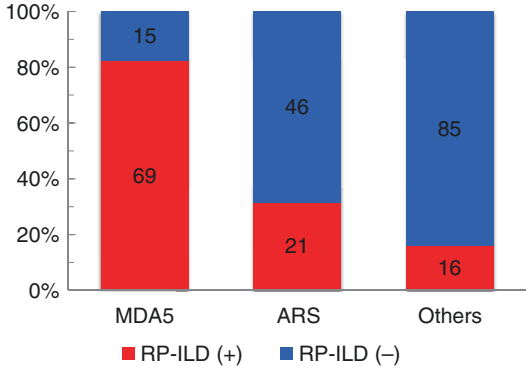

Fig. 19.4 Prevalence of RP-ILD in patients with PM/DM stratified by MSAs [17–19]. RP-ILD rapidly progressive interstitial lung disease, MSA myositis-specific autoantibody

[12, 22, 23]. Patients with an MSA associated with a high risk of ILD should undergo high-resolution CT scanning of the chest even in the absence of overt pulmonary symptoms and should be monitored for future development of ILD. In patients with an established diagnosis of ILD, one should initiate early and aggressive immunosuppressive treatment in the setting of

Anti-synthetase and anti-MDA5 autoantibodies have the highest risk of ILD.

Anti-MDA5-associated ILD is most often rapidly progressive.

anti-MDA5 positivity or other risk factors for ILD progression.

Although most studies demonstrate the need for intensive immunosuppressive treatment, there is no clear evidence that one particular regimen is superior to another. High-dose glucocorticoids, in combination with immunosuppressive agents including calcineurin inhibitors, intravenous cyclophosphamide pulse therapy, and rituximab, are used in anti-MDA5-positive patients with a high risk for developing RP-ILD [24, 25]. For such patients, it is important to initiate intensive immunosuppressive regimens as early as possible. On the other hand, the short-term response to treatment with high-dose glucocorticoids is often favorable in patients with anti-synthetase autoantibodies, although ILD recurrence frequently occurs during steroid tapering necessitating additional immunosuppressive agents. In synthetase-positive patients, the choice of an immunosuppressive agent depends on severity, but rituximab is emerging as a frequently used agent [26, 27].

Anti-synthetase-associated ILD may be more responsive to immunosuppression including glucocorticoids and rituximab.

Anti-MDA5-associated ILD tends to be treatment refractory requiring intensive immunosuppression.

Refractory Myopathy

The severity of skeletal muscle involvement is quite variable, ranging from no apparent clinical myopathy (i.e., CADM) to severe disability. In some studies, DM patients with anti-TIF1-γ, anti-NXP2, and anti-SAE antibodies have more extensive myopathy (including dysphagia and severe muscle weakness) compared with subjects with an anti-synthetase, anti-MDA5, or anti-Mi-2 antibody [28–30]. Anti-SRP and anti-HMGCR are associated with immune-mediated necrotizing myopathy, which is often resistant to conventional immunosuppressive treatment [31]. In contrast, anti-synthetase, anti-U1RNP, anti-PM/Scl, or anti-Ku antibodies predict favorable responses to the treatment of myositis. Patients positive for MSAs linked to treatment resistance should receive glucocorticoids combined with any one of several immunosuppressive drugs, such as azathioprine, methotrexate, intravenous immunoglobulin, and rituximab (Fig. 19.1) [32–35]. Reports show that the therapeutic response to rituximab is more favorable in patients who are autoantibody positive, particularly those with anti-Jo-1 or anti-Mi-2, than in those with no MAA [26].

Immune-mediated necrotizing myopathy (particularly anti-SRP) is associated with treatment-refractory disease and should be managed aggressively, while anti-Jo-1 and anti-Mi-2 autoantibodies are associated with a favorable response to rituximab.

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20 Traditional Myositis Autoantibodies: Synthetase, Mi-2, SRP, Ku, PM-Scl, Ro, U1RNP

Samera Vaseer and Ira N. Targoff

Key Points to Remember

- Autoantibodies to aminoacyl-tRNA synthetases (ARS) with the presence of one or more associated clinical features including myositis, interstitial lung disease (ILD), inflammatory arthritis, or mechanic's hands has been referred to as the antisynthetase syndrome. ILD can be more common than myositis and often clinically significant.
- Eight ARS autoantibodies have been described. Anti Jo-1 is the most common. The titer of anti-Jo-1 may vary with disease activity. Antibodies to different ARS may differ in the relative frequency of the features of the antisynthetase syndrome.
- Anti-Mi-2 is associated with dermatomyositis. Myositis in patients with anti-Mi-2 tends to be mild and glucocorticoid-responsive with a relatively good prognosis.
- Anti-SRP is most commonly associated with immune-mediated necrotizing myopathy, without inflammation. Myositis is often rapid in onset, with very high CK levels, early muscle damage, severe weakness, treatment refractoriness, and multiple flares. Anti-SRP patients are more likely to require multiple immunosuppressive agents.
- Anti-PM-Scl is most commonly associated with an overlap syndrome of polymyositis or dermatomyositis with scleroderma, often including polyarthritis. Anti-Ku is also associated with overlap syndromes involving myositis, as well as scleroderma and lupus.
- Anti-Ro52 may occur in the absence of anti-Ro60 in myositis more often than in most other conditions and frequently occurs in association with other myositis autoantibodies, including anti-ARS, anti-PM-Scl, or anti-SRP. It may be a marker of more severe disease and a worse prognosis.

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Introduction

Since the 1980s, the existence of certain autoantibodies strongly associated with myositis has been known [1–3]. Although no single autoantibody is present in a majority of myositis patients (low sensitivity), these "myositis-specific autoantibodies (MSA)" were distinctive in that most antibody-positive patients have myositis as their primary autoimmune disease (high specificity) despite other clinical features often being present. This was in contrast to autoantibodies such as anti-Ro/SSA or anti-U1RNP that could occur in patients with myositis, with potentially significant implications and potential diagnostic utility, but their primary association was typically with other autoimmune rheumatic diseases. Hence, these autoantibodies were termed "myositis-associated autoantibodies (MAA)" [4]. Thus, antisynthetase antibodies (anti-aminoacyl-tRNA synthetase or anti-ARS), anti-Mi-2, and anti-SRP have long been considered established MSAs [5]. Increasingly, anti-ARSs are more closely associated with unique features termed the "antisynthetase syndrome," with or without clinical features of myositis [6]. Anti-PM-Scl and anti-Ku are usually considered to be MAAs but are commonly associated with overlap syndromes involving myositis [2, 7, 8].

Later, additional autoantibodies of importance were identified, particularly in association with dermatomyositis (DM) and necrotizing myopathy (NM). This increased the proportion of patients with myositis demonstrating an identifiable specific autoantibody (i.e., MSA) and increased the combined sensitivity of MSA testing in DM, NM, and polymyositis (PM). Together with newer myositis autoantibodies, the proportion of patients with PM, DM, or NM who have an identifiable autoantibody is now considerably higher, often >80% if comprehensive testing is done [9]. Although the traditional autoantibodies have been known for a long time, their value and importance in diagnosis and management has recently increased with better availability of testing and as collaborative studies involving larger patient groups have better defined the clinical and treatment considerations of autoantibody-defined groups. It is important to note, however, that differences in testing methods could affect the sensitivity, specificity, and clinical associations of these autoantibodies [9].

Myositis-Specific Autoantibodies (MSA): Autoantibodies that are highly specific for myositis and are associated with myositis as the primary autoimmune disease.

Myositis-Associated Autoantibodies (MAA): Autoantibodies associated with other autoimmune rheumatic diseases that could occur in patients with myositis or have myositis as a clinical feature.

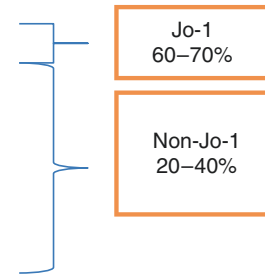
MSA and MAA can be seen in >80% of PM, NM, DM, and their associated phenotypes.

Antisynthetase Antibodies (Anti-ARS)

The aminoacyl-transfer RNA synthetase enzymes catalyze the formation of aminoacyl-transfer RNA, in which an amino acid is bound to a transfer RNA for that amino acid [1]. The transfer RNA can then contribute this amino acid to a growing polypeptide chain forming at the ribosome, at the proper position as defined by the messenger RNA. It is crucial to the accuracy of this process that each amino acid is attached to a transfer RNA specific for that amino acid. Thus, it is not surprising that there is a separate synthetase enzyme for each amino acid that is immunologically distinct from others. Autoantibodies to these enzymes do not cross-react with each other. Most patients have autoantibodies to only one of these enzymes (with the exception of those who have autoantibodies to isoleucyl-tRNA synthetase (OJ), which is part of a multienzyme complex of synthetases; although isoleucyl-tRNA synthetase

Table 20.1 Frequency of all antisynthetase antibodies. Boxes to the right show proportion of the antibodies among antisynthetase patients

Anti-Synthetase Autoantibodies	Aminoacyl t-RNA synthetase target	Frequency among all myositis
Anti-Jo-1	*anti-histidyl*	20-30%
Anti-PL-7	*anti-threonyl*	5%
Anti-PL-12	*anti-alanyl*	5%
Anti-OJ	*anti-isoleucyl*	< 5%
Anti-EJ	*anti-glycyl*	< 5%
Anti-KS	*anti-asparaginyl*	< 5%
Anti-ZO	*anti-phenylalanyl*	< 1%
Anti-Ha	*anti-tyrosyl*	< 1%



is usually the primary target, they may also react with other enzymes in the complex [10]). That is, the anti-ARS is generally mutually exclusive. These enzymes localize to the cytoplasm where protein synthesis usually takes place [2, 11, 12].

Autoantibodies have been described reacting with at least eight of these enzymes: *anti-Jo-1 (anti-histidyl); anti-PL-7 (anti-threonyl); anti-PL-12 (anti-alanyl); anti-OJ (anti-isoleucyl); anti-EJ (anti-glycyl); anti-KS (anti-asparaginyl); anti-ZO (anti-phenylalanyl); and anti-Ha (anti-tyrosyl).* Patients with autoantibodies to any of the aminoacyl-tRNA synthetases have a generally similar set of clinical features including myositis, interstitial lung disease (ILD), inflammatory arthritis, Raynaud phenomenon, a hyperkeratotic rash on the fingers referred to as mechanic's hands, and fever [5, 13]. The occurrence of one or more of these clinical features in the presence of anti-ARS is defined as the antisynthetase syndrome. Although myositis is often a major component, it may not be present. ILD can be more common than myositis and often clinically significant [14]. However, the frequency of these features may differ with different anti-ARS [13, 15, 16]. For example, there is generally a higher frequency of myositis with anti-Jo-1 (anti-histidyl-tRNA synthetase) than with anti-PL-12 (anti-alanyl-tRNA synthetase) or anti-PL-7 (anti-threonyl), where ILD is more common than myositis [15–17]. The frequency of different anti-ARS differs widely, with anti-Jo-1 the most frequent anti-ARS and the most common myositis autoantibody in most populations (20–30% of adult myositis patients). Each other anti-ARS (non-Jo-1 anti-ARS) is much less frequent (<5%), particularly among those with prominent myositis, but collectively non-Jo-1 anti-ARS constitutes up to 20–40% of any antisynthetase cohort. Autoantibodies to certain others such as tyrosyl-tRNA synthetase are very rare (<1%) and autoantibodies to some ARS have not been described. There may also be differences in the frequency of different anti-ARS in different ethnic or geographic populations [18] (Table 20.1).

Antisynthetase syndrome

One or more clinical features given below with one of the anti-ARS

- Myositis
- Interstitial lung disease
- Polyarthritis
- Mechanic's hands
- Raynaud phenomenon
- Fever

Laboratory Testing: Although anti-Jo-1 testing is widely available using enzyme immunoassay methodology and immunodiffusion, specific testing for other ARSs requires more specialized methodology, which is not only less available and reliable but requires more time to accurately complete. Protein and RNA immunoprecipitation (IP) have traditionally been used for this purpose (Figs. 20.1 and 20.2). Most ARSs show both a distinctive protein and a distinctive set of transfer RNAs by IP, which was an important factor leading to the identification of the enzymes as the antigenic targets [1, 19, 20]. Direct methods are becoming available allowing more rapid clinical

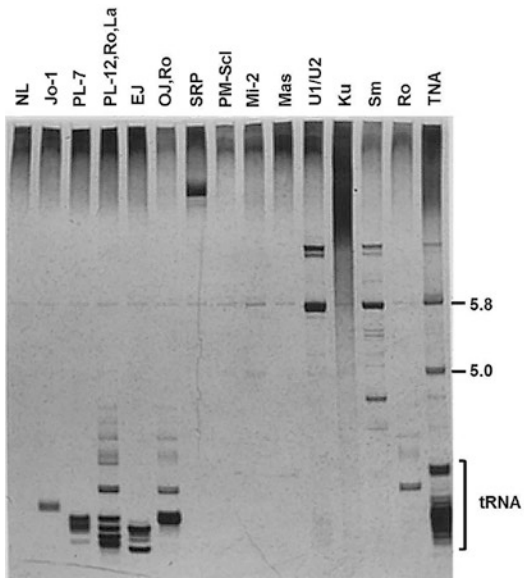


Fig. 20.1 RNA immunoprecipitation: Results of polyacrylamide gel electrophoresis (PAGE) for the detection of RNAs of immunoprecipitates using antisynthetase antibodies, anti-SRP, and others. Anti-SRP serum immunoprecipitates a strong band in the 7S region representing the 7SL RNA of the SRP, not seen with other myositis autoantibodies. The distinctive transfer RNAs associated with different aminoacyl-tRNA synthetase antigens are seen, which are distinguishable from each other. The anti-PL-12 serum shown also contains anti-Ro/SSA and anti-La/SSB and immunoprecipitates the characteristic associated RNAs. Anti-PM-Scl and anti-Mi-2 do not immunoprecipitate nucleic acids. Serum with anti-U1RNP and anti-U2RNP precipitates these small nuclear RNAs, while anti-Sm precipitates those along with U4, U5, and U6 RNAs. Anti-Ku has affinity for DNA and precipitates a heterogeneous DNA smear. Anti-Ro immunoprecipitates the hY1 (highest) through hY5 (lowest) RNAs. *NL* normal serum, *TNA* total nucleic acid. The position of the 5.8S and 5.0S RNAs, as well as the transfer RNAs (tRNAs), is shown. Mas serum precipitates a very weak unidentified RNA. (This figure was published as Figure 1, page 863, in Targoff IN. Immune manifestations of inflammatory muscle disease. Rheu Dis Clin N Am. 20(4):857–80, Copyright Elsevier 1994)

identification of these antibodies [9, 21–27]. However, most of these panels do not include all the ARSs that can occur and must be validated against the gold standard of IP. The presence of cytoplasmic staining in a consistent clinical setting would be a clue to pursue further testing (Fig. 20.3).

Serum Levels of Anti-ARS: Quantitative measurements of the antibody have suggested that the titer of anti-Jo-1 may vary with disease activity and decrease with improvement in disease status over time [23, 24]. Although detectable antibody typically persists in most patients after treatment, the occasional disappearance of the antibody has been associated with remission [28]. These results suggest that MSA, especially anti-Jo-1, could serve as potential biomarkers [23, 29].

Serum levels of anti-Jo1 may be associated with disease activity in myositis.

The myositis in patients with anti-ARSs is generally similar to that seen with other polymyositis or dermatomyositis patients, although recurrences may be more likely. Histologically, a distinctive pattern of involvement was noted in patients with anti-Jo-1, with perimysial inflammation similar to that seen with dermatomyositis, but without the concomitant capillary loss [30]. There was also evidence of fasciitis with perimysial connective tissue fragmentation in muscle from patients with anti-Jo-1 [30, 31]. In another study of myositis histological findings among 50 patients with anti-ARSs, myofiber necrosis in the perifascicular region was observed in about 50% of patients [32]. Necrosis, not restricted to the perifascicular area, seen most commonly with anti-OJ antibodies, was associated with more severe muscle involvement. The myositis may also be more responsive to rituximab treatment than for those without the antibodies [29].

Antisynthetase patients have distinct muscle histopathology: perimysial inflammation and perifascicular myofiber pathology, without the vascular changes of dermatomyositis.

There may be a delay in making a diagnosis in patients with non-Jo-1 ARSs compared to those with anti-Jo-1, which may relate in part to wider availability of testing for anti-Jo-1 [13, 33]. This may be a factor in decreased survival. For nearly half of non-Jo-1 anti-ARS patients, the initial diagnosis is an overlap syndrome or undifferentiated connective tissue disease, while those with anti-Jo-1 are more likely to have an initial diagnosis of myositis (83%) [16, 33].

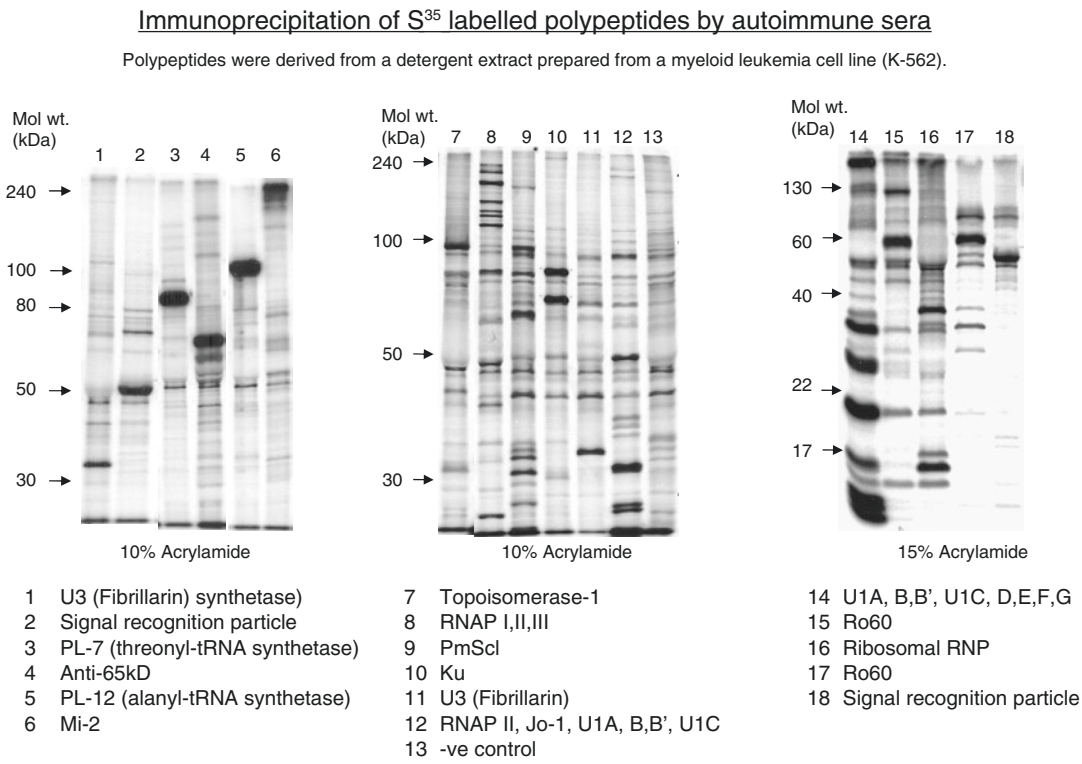


Fig. 20.2 Protein immunoprecipitation**:** The figure shows immunoprecipitation with S35-labeled HeLa cells using sera from patients with various different myositis-specific and myositis-associated autoantibodies. Anti-Mi-2 precipitates the 240 kDa main antigenic protein, which is part of a complex of proteins (the NuRD complex) (lane 6). Several other components of that complex can also be seen (at molecular weights of 150, 75, 65, and 63 kDa). In contrast, the anti-SRP serum immunoprecipitates a strong band at 54 kD and a weaker band at 72 kDa (lanes 2 and 18). The signal recognition particle (SRP) is a complex containing a unique RNA ("7SL") and specific proteins. The combination of RNA-immunoprecipitation (see Fig. 20.1) and S35-immunoprecipitation results consistent with anti-SRP results provides very specific identification of the presence of these autoantibodies. The presence of anti-Mi-2 can be sensitively detected and specifically identified by this method and can be clearly distinguished from other myositis autoantibodies (lane 6). The antisynthetases precipitate characteristic proteins and, along with RNA immunoprecipitation (Fig. 20.1), can be distinguished from other autoantibodies. In lane 3, anti-PL-7 (anti-threonyl-tRNA synthetase) shows a strong protein of approximately 80 kDa, and in lane 5, anti-PL-12 (anti-alanyl-tRNA synthetase) shows a strong protein of approximately 110 kDa. A protein of approximately 50kDa is precipitated by anti-Jo-1 in lane 12. Results for anti-PM-Scl are shown in lane 9. This antibody immunoprecipitates the multiple proteins of the exosome, including the major antigens of approximately 100 and 75 kDa. In lane 10, anti-Ku shows the typical strong proteins of 72 and 86 kDa. (Images Courtesy: Alpini Claudia, Angela Ceribelli and Lorenzo Cavagna, University of Pavia, Italy)

Antisynthetase syndrome with non-Jo-1 anti-ARS has a worse prognosis than that with anti-Jo-1 partly due to delay in diagnosis and partly to a higher frequency of ILD.

Although dermatomyositis skin involvement (such as Gottron changes or a heliotrope rash) may occur in patients with anti-ARSs, some studies have found that clinical polymyositis is more common with anti-Jo-1 [34, 35]. Dermatomyositis may be more common with non-Jo-1 anti-ARSs than with anti-Jo-1 [35]. Patients with antisynthetase syndrome may have "mechanic's hands," a hyperkeratotic rash with splitting or cracking on the edges of the fingers [5, 36]. Antisynthetase syndrome may occur in children [37, 38], where a syndrome similar to that in adults may be seen [38], but anti-ARSs are less common in children, while DM-related autoantibodies such as

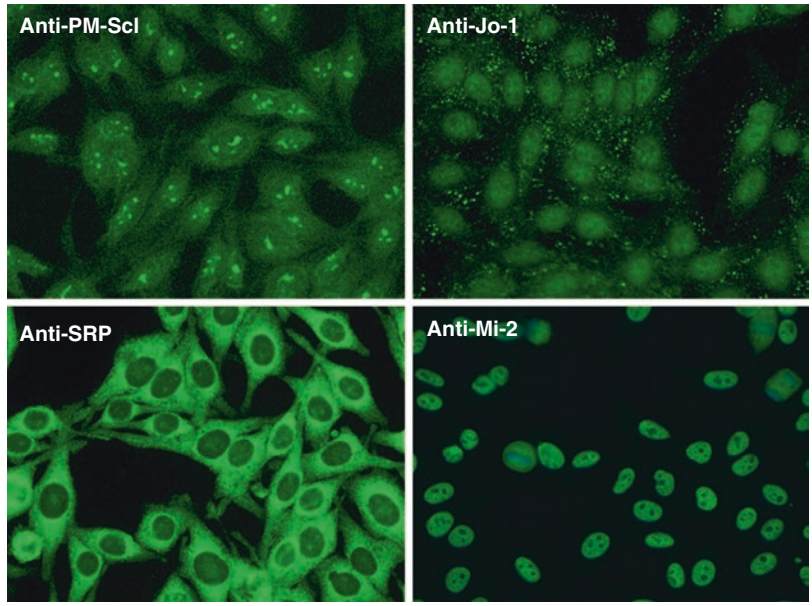


Fig. 20.3 Indirect immunofluorescence with anti-Jo-1, anti-SRP, anti-Mi-2, and anti-PM-Scl antibodies: An antinuclear antibody (ANA) test was done using indirect immunofluorescence testing on Hep-2 cell substrate with a serum that contained anti-Jo-1 (top right), anti-PM-Scl (top left), anti-SRP (bottom left), and anti-Mi-2 (bottom right) autoantibodies, respectively. Anti-PM-Scl shows a nucleolar pattern with additional nucleoplasmic staining. With anti-Jo-1, cytoplasmic fluorescence is seen. Anti-SRP autoantibodies give a characteristic cytoplasmic pattern, consistent with the known location of the SRP in the cytoplasm of the cell. Anti-Mi-2 shows a pure nuclear pattern that spares the nucleolus. (Images Courtesy: Alpini Claudia, Angela Ceribelli and Lorenzo Cavagna, University of Pavia, Italy)

anti-MJ/NXP2 and anti-p155/140 are more common [38, 39]. Patients with cancer-associated myositis usually do not have anti-ARSs [40], although occasional cases have been described.

Antisynthetase syndrome patients can have clinical dermatomyositis (including amyopathic forms) or polymyositis.

ILD is an important and common feature of antisynthetase syndrome in view of its clinical implications and impact on survival and prognosis [41–45]. The severity and progression can be variable [46]. It may be the presenting feature, while some patients have ILD without clinical myositis [6, 15, 47, 48]. Non-Jo-1 anti-ARS may be associated with a higher frequency and more severe lung disease, and certain anti-ARSs, including anti-PL-12, anti-PL-7, anti OJ, and anti-KS, appear to be more likely to present with ILD rather than myositis [16, 17, 49].

ILD is the most common and important clinical feature of the antisynthetase syndrome.

Non-Jo-1 anti-ARS has a higher frequency (80–100%) and severity of ILD than anti-Jo-1 (70–80%).

CT scan features at the time of diagnosis include nonspecific interstitial pneumonia with organizing pneumonia, either isolated or in combination [6, 47, 48, 50]. In one study of 14 antisynthetase patients, CT scans revealed ground-glass opacities with peribronchovascular interstitial thickening and traction bronchiectasis and consolidation. Honeycombing is less frequent. NSIP and predominantly organizing pneumonia with focal NSIP are common histopathological patterns [51, 52]. Consolidations decrease or dis-

appear in most cases, but the disease may progress to fibrosis in more than one third of patients. The main cause of death among patients with anti-ARS is pulmonary fibrosis followed by pulmonary hypertension. The extent of lung inflammation on high-resolution CT scanning and forced vital capacity can be factors in predicting survival in antisynthetase syndrome patients [53].

Anti-Ro52 is more likely to be present in patients with anti-ARSs than in other myositis patients [54, 55] and tends to be associated with more severe disease [56, 57]. The presence of anti-Ro52 predicts rapidly progressive ILD. Other prognostic indicators for poor outcomes of patients with the antisynthetase syndrome include malignancy and hyperferritinemia.

Anti-Ro52 is commonly seen with anti-ARS and is associated with worse prognosis.

The arthritis in association with anti-ARS can also be significant and similar to rheumatoid arthritis (symmetric polyarthritis of the small joints of the hand) [58] and may be the presenting feature. It can sometimes be deforming and may be more likely in patients with rheumatoid factor and/or anti-CCP antibody positivity, which can make the diagnosis of the antisynthetase syndrome versus rheumatoid arthritis very challenging [32].

Anti-Mi-2

Anti-Mi-2 was described using immunodiffusion [59] but later found to immunoprecipitate a multiprotein complex [60, 61] that was identified as the nucleosome remodeling deacetylase (NuRD) complex [62, 63] (Fig. 20.2), which is involved in transcriptional regulation by chromatin remodeling and histone deacetylation. There are two forms of the major antigen of the Mi-2 complex, a 240 kD and 200 kD protein, which are DNA-helicases [64]. They include Mi-2α [CHD (chromatin organization modifier, helicase, and DNA binding) 3 and Mi-2ß (CHD4)]. Most Mi-2-positive patient sera react with both proteins.

The sera usually show a fine-speckled nuclear pattern by ANA testing (Fig. 20.3) [2]. Interestingly, sera with anti-Mi-2 will sometimes react with TIF-1 proteins targeted by other patients with DM [2, 65]. Immunoprecipitation blotting may show precipitation of TIF1α, and there may be low-level cross-reaction with TIF1g by ELISA [65]. It is usually clear which antibody predominates in a patient serum.

Anti-Mi-2 was the first autoantibody to be strongly associated with myositis, particularly dermatomyositis, using immunoprecipitation or immunodiffusion [59]. These methods appear to identify binding to a particular conformational epitope, and immunoblotting assays may give results that are less specific for dermatomyositis [9]. Although found in both adult and juvenile myositis, it may be more common in adults. Malignancy has been reported, but it does not appear to have the increased frequency in cancer-associated myositis as seen with anti-TIF1g. Cutaneous involvement is typically that of classic DM with Gottron changes, heliotrope, and the "V sign" (involvement of the portion of the upper chest around the neck) and "shawl" sign (involvement of the upper back in the area covered by a shawl) [5].

Myositis in patients with anti-Mi-2 tends to be mild and glucocorticoid responsive with a relatively good prognosis despite the CK being high initially [5]. In contrast to anti-MDA5 or anti-TIF1g, anti-Mi-2 patients are less likely to have amyopathic dermatomyositis. Further, there are less associated connective tissue disease features.

Anti-Mi-2 is associated with a steroid-responsive milder phenotype of DM including classic DM with Gottron changes, heliotrope, the V sign, and shawl sign.

It was observed that the frequency of anti-Mi-2 (and of DM itself) varied greatly in different populations, from 60% in Guatemala to 3.2% in Montreal [66]. The frequency of involvement appeared to correlate with greater exposure to UV light. A high frequency was observed in Mexico and Central America in particular, which

could relate to a combination of genetic factors and environmental exposures.

Anti-Signal Recognition Particle Antibodies (Anti-SRP)

The signal recognition particle is a complex of an RNA (7SL) and six proteins involved in translocation, the process through which newly forming proteins are targeted to the endoplasmic reticulum for secretion or membrane expression. Patient antibodies usually react with the 54 and/or the 72 kD proteins [67, 68]. The antibody is easily, specifically, and sensitively identified by immunoprecipitation, which can show the RNA and the protein complex (Figs. 20.1 and 20.2) [68]. Other methods have been used, which may be less specific with resulting differences in observed clinical associations. Anti-SRP autoantibodies give a characteristic cytoplasmic pattern on ANA testing (indirect immunofluorescence) (Fig. 20.3). Most patients with this antibody previously had a diagnosis of PM [5, 68], but the more common recent association is with immune-mediated necrotizing myopathy [2, 69, 70]. In typical cases, the distinctive feature is severe muscle weakness, often greater than with typical polymyositis [69]. It can be relatively acute, or rapid in onset, with very high CK levels compared to usual PM, leading to early muscle damage, treatment refractoriness, and multiple flares [5]. Often the myositis responds incompletely and is more likely to require multiple immunosuppressive agents. However, this distinctive presentation is not uniformly seen, as some patients have better responses [71]. Increased cardiac involvement noted in early reports [68] has not consistently been observed in subsequent reports.

Anti-SRP is associated with necrotizing myopathy presenting with acute onset of severe weakness, very high CPK, and refractory disease.

Histologically, the typical picture with this antibody is a necrotizing myopathy without inflammation. One study found vasculopathy with capillary loss and deposition of membrane attack complex as seen in DM, but without perifascicular atrophy [69].

Patients with this antibody may be less likely to show connective tissue disease overlap features such as interstitial lung disease, arthritis, or Raynaud phenomenon compared with antisynthetase-positive patients [68], but overlap features can certainly occur (and are more common than in patients with anti-HMGCR antibody-positive NM).

Anti-PM-Scl and Anti-Ku

Anti-PM-Scl is an MAA originally identified using immunodiffusion, as a clarification of the originally reported specificity of anti-PM-1 [7]. It was named for the clinical association of the antibody with an overlap syndrome with features of myositis and scleroderma. The antibody was found to show a series of at least 11 proteins by immunoprecipitation that are easily recognized and identified (Fig. 20.1), although there is no associated RNA [72–74]. It shows a combination of nucleolar and nuclear staining by IIF (Fig. 20.3). The proteins with apparent molecular weights of 100 and 75 kD are the major antigens. The PM-Scl complex was identified as the exosome, which is involved in RNA processing.

Although many patients with this antibody have the typical overlap syndrome of myositis and scleroderma, some patients show only myositis or only scleroderma [72]. The myositis is often associated with typical DM cutaneous involvement, and mechanic's hands can occur. The scleroderma is most commonly limited in cutaneous involvement. However, there have been occasional reports of renal crisis [75]. There is often a significant associated inflammatory polyarthritis. The myositis tends to be responsive to treatment, often responding to lower doses of glucocorticoids than other forms of myositis, with scleroderma features remaining unchanged.

This overlap syndrome has been referred to as "scleromyositis" [76]. In some populations, anti-PM-Scl may account for a substantial proportion of myositis-scleroderma overlap patients. However, there is a strong association with HLA DR3, which varies considerably among different ethnic populations, being infrequent in Japanese patients. The antibody tends to be mutually exclusive with MSAs or scleroderma antibodies, with occasional exceptions.

Anti-PM-Scl and anti-Ku are MAA associated with scleroderma-myositis overlap syndrome.

Anti-Ku autoantibodies were first described using immunodiffusion and can be seen by immunoprecipitation with two strong proteins of 72 and 86 kD, with associated heterogeneous nucleic acid [77]. There is an additional, high-molecular-weight DNA protein kinase component. The antigen is involved in DNA repair.

Anti-Ku is an MAA that has been associated with scleroderma-myositis overlap syndrome in Japanese patients [8] and is relatively frequent in patients with that condition. In the United States, it is more common in African-American than Caucasian patients [78] and is often associated with myositis or systemic lupus or overlap syndromes [77].

Anti-Ro/SSA, Anti-U1RNP

Although the primary clinical associations of anti-Ro/SSA are Sjogren syndrome and lupus, it can be found in some patients with myositis and thus would satisfy the definition of an MAA. Of interest is that anti-Ro52, which typically occurs in association with anti-Ro60 in most conditions, is more likely to occur in the absence of Ro60 in myositis than in other situations [55]. This could possibly have diagnostic implications. When occurring in myositis, it most often is seen in association with other autoantibodies, including anti-ARS, anti-PM-Scl, or anti-SRP [54]. In those patients, it may be a marker of more severe disease and a worse prognosis.

Anti-U1RNP is commonly seen in patients with lupus who have myositis as a component of their disease and thus would satisfy the definition of an MAA [79]. It can be seen by itself or with other myositis autoantibodies. Myositis may occur in patients with anti-U1RNP as part of the MCTD spectrum. The myositis in this situation may be milder or more responsive, but can be severe in some patients. Anti-U1RNP can occur in some patients with other MSAs.

Anti-U1RNP reacts with proteins of the U1 small nuclear ribonucleoprotein, which is involved in messenger RNA splicing. Patients may have autoantibodies that are specific for proteins that are unique to this particle, or patients with anti-Sm may have autoantibodies to proteins that are shared with other U small nuclear ribonucleoproteins involved in the splicing process. Of interest in myositis patients is the occasional occurrence of autoantibodies that react with proteins that are unique to U small nuclear RNPs other than the U1 particle. Anti-U2RNP [80, 81], anti-U5RNP [82], and anti-U4/6RNP [82, 83] have been observed. Usually, these patients have overlap connective tissue disease syndromes that may involve myositis.

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21

Dermatomyositis-Associated Autoantibodies: TIF1-γ, NXP2, and MDA5

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Key Points to Remember

- Anti-TIF1-γ, anti-NXP2, and anti-MDA5 antibodies are detected principally in patients with juvenile dermatomyositis (JDM) or adult DM or clinically amyopathic dermatomyositis (CADM).
- Juvenile and adult patients with anti-TIF1-γ antibody often present with severe cutaneous features and may have prominent muscle weakness. In patients over the age of 45 years, malignancy within 1 year before or after onset of DM may be present.
- Anti-NXP2 is associated with severe systemic features including myalgias, dysphagia, and subcutaneous calcinosis in adult as well as juvenile patients. Anti-NXP2 is also reported in adult DM patients with concomitant malignancy.
- Anti-MDA5 is highly associated with ILD, especially, rapidly progressive ILD in juvenile and adult patients. Patients with anti-MDA5 often present with severe cutaneous disease including palmar papules and cutaneous ulcerations.

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Introduction

Recently, several newer myositis-specific autoantibodies (MSAs) have been identified and well characterized in patients with idiopathic inflammatory myopathies (IIM). These include anti-transcription intermediary factor 1γ (TIF1-γ), anti-nuclear matrix protein 2 (NXP2), and anti-melanoma differentiation-associated gene 5 (MDA5) antibodies. Accumulating lines of evidence indicate that measurement of these MSAs is useful to predict future clinical manifestations, response to treatment, and outcomes.

Transcription Intermediary Factor 1-γ (TIF1-γ)

A novel myositis-specific autoantibody (MSA), anti-p155, was identified by protein immunoprecipitation assay in 20% of adult DM patients [1] and shown to be more frequently detected in patients with cancer-associated myositis (CAM). This was extended to the detection of anti-155/140 antibodies in a subsequent report also noting an association with CAM [2]. Later, anti-p155 and anti-155/140 antibodies were confirmed to be principally identical and commonly recognizing a 155-kDa protein termed transcription intermediary factor 1γ (TIF1-γ). TIF1 proteins belong to the tripartite motif-containing (TRIM) protein family, involved in a broad range of biological

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processes and diverse pathological conditions, such as developmental disorders, neurodegenerative diseases, viral infections, and cancer [3]. A 140-kDa protein coprecipitated by anti-155/140 antibodies was later identified as TIF1-α, another member of TIF1 family proteins [4].

Recently, a convenient ELISA system for the measurement of anti-TIF1-γ antibody has been developed [5]. Sera positive for anti-Mi-2 antibody may give a false-positive result as there is weak cross-reactivity between Mi-2 and TIF1-γ due to amino acid homology [5]. In fact, immunoprecipitates of anti-Mi-2 antibodies always contain TIF1-γ [4]. Therefore, it is highly recommended to measure anti-Mi-2 and TIF1-γ antibodies simultaneously by ELISA. Anti-TIF1-γ is judged to be present in the case of positive anti-TIF1-γ and negative anti-Mi-2, while many anti-Mi-2-positive sera may show a low level of anti-TIF1-γ antibody.

Skin rashes, including a heliotrope rash, Gottron papules and sign, flagellate erythema, as well as malignancy, were more frequently detected in adult DM patients with anti-TIF1-γ antibody than those without [2]. Adult patients with anti-TIF1-γ antibody often present with prominent skin rashes over the joints, face, and trunk along with dysphagia and severe muscle weakness to the extent that activities of daily living are significantly impaired [6]. Such patients may have concomitant malignancy. A meta-analysis of 312 adults with DM revealed that the sensitivity and specificity of anti-TIF1-γ antibody for the diagnosis of concomitant cancer were 78% and 89%, respectively [7]. A simultaneous diagnosis of cancer and DM is frequent in anti-TIF1-γ antibody-positive patients older than 45 years of age, while cancer is rarely detected in those younger than 40 [4, 8]. On the other hand, anti-TIF1-γ antibody-positive patients are less likely to have systemic features, such as ILD, Raynaud phenomenon, and inflammatory arthritis [9, 10].

Anti-TIF1-γ antibody is detected in patients with juvenile dermatomyositis (JDM) in about 25–30% of cases [1] with no malignancy association. These JDM patients are more frequently males and have more severe cutaneous involvement, including Gottron papules, ulceration, and edema as well as more severe muscle weakness [11]. The distribution of skin lesions is more extensive, particularly periorbitally and over the small and large joints, while subcutaneous calcinosis is rare. Unlike malignancy, severe skin and skeletal muscle manifestations are consistent in adults and children with anti-TIF1-γ antibody, and a chronic or polycyclic disease is more often observed in JDM [12].

Anti-TIF1-γ antibody should be measured in any adult or child with DM and, when positive, significant cutaneous features are common. Further, in adult patients with anti-TIF1-γ antibody, particularly those over 45 years of age, an extensive malignancy evaluation is necessary irrespective of any other clinical suspicion of malignancy. Further recommendations on malignancy screening are noted in Chapter 25.

Key clinical features of anti-TIF1-γ antibody

- Exclusively DM
- Predominantly classic DM, but CADM can occur
- Adult (20%) and juvenile (30%)
- Highly associated with malignancy in adults (especially age > 45 years)
- Intensive cancer screening is required in middle-aged and elderly patients.
- Severe cutaneous and muscular disease in adult DM and JDM
- Low risk of ILD

Nuclear Matrix Protein 2 (NXP2)

Oddis and colleagues first reported a novel autoantibody to a 140-kDa protein (anti-MJ) by protein immunoprecipitation assay in sera from children with JDM in 1997 [13]. The MJ antigen was later identified as NXP2 [14], which localizes to the nuclear matrix and forms nuclear bodies via an ATP-dependent mechanism. The function of NXP2 is small ubiquitin-related modifier-mediated transcriptional repression [15].

Anti-NXP2 antibody is one of the two commonly detected myositis autoantibodies in JDM

[16], as demonstrated in a British study noting that anti-TIF1-γ and anti-NXP2 autoantibodies were found in 11 (28%) and 13 (33%) of 40 JDM patients, respectively. Subcutaneous calcinosis was reported in 54% of JDM patients with anti-NXP2 compared to 15% of those without this antibody marker [14]. In contrast, skin ulceration and cutaneous edema were less frequent in JDM patients with anti-NXP2 antibody than in those with anti-TIF1-γ antibody [14], while fatal bowel vasculitis sometimes occurs with anti-NXP2 positivity [13]. Anti-NXP2 antibody positivity is associated with chronic, persistent disease activity and physical dysfunction [16].

Anti-NXP2 antibody is also reported in adult DM patients at a much lower frequency than JDM. A Japanese study reported only 1–2% of all adult IIM patients with anti-NXP2 [17], while studies from Western countries demonstrated anti-NXP2 frequencies ranging from 11% to 30% of adult DM patients [18–20], suggesting ethnic difference in prevalence. The clinical profiles of adult patients with anti-NXP2 antibody are somewhat consistent with those of JDM patients including myalgia, dysphagia, high serum CK levels, and subcutaneous calcinosis [20]. ILD is less frequent, but concomitant malignancy was fairly common in adults, ranging from 9% to 38% [17, 18, 20, 21]. Thus, an extensive malignancy survey should be considered in adults, although additional studies are required to fully understand the association with cancer and the appropriate surveillance.

Key clinical features of anti-NXP-2

- Exclusively DM
- Classic DM
- Adult (10%) and juvenile (30%)
- Higher risk of malignancy in adults but less than anti-TIF1-γ
- Severe systemic features including myalgia, dysphagia, high CK levels, and subcutaneous calcinosis
- Low risk of ILD

Melanoma Differentiation-Associated Gene 5 Protein (MDA5)

Sato et al. first reported an autoantibody reactive with a 140-kD protein by protein immunoprecipitation assay in 2005, and they termed this antibody specificity anti-CADM-140 since the majority of patients with this autoantibody lacked clinically apparent myositis and were diagnosed as having clinically amyopathic dermatomyositis (CADM) [22]. Rapidly progressive ILD (RP-ILD) developed significantly more frequently in patients with this antibody than in those without (50% vs. 6%). Later, an RNA helicase encoded by melanoma differentiation-associated gene 5 (MDA5) was identified as a target antigen recognized by anti-CADM-140 antibody, and therefore the antibody is now designated as anti-MDA5 antibody [23]. This finding was confirmed by other investigators [24]. MDA5 recognizes double-stranded RNA viruses, such as picornavirus, and triggers the production of type 1 interferon and pro-inflammatory cytokines [25]. The measurement of anti-MDA5 antibody requires a protein immunoprecipitation assay, but ELISA-based assays are now validated and commercially available [26].

Anti-MDA5 autoantibody was found in 26 (24%) of 108 DM/CADM patients [27]. A Japanese report demonstrated that RP-ILD occurred in 82% of adult patients with anti-MDA5 antibody [23]. The close association between anti-MDA5 antibody and RP-ILD has been confirmed in many studies reported from Eastern Asia, including Japan, China, and Korea. Although a similar association with RP-ILD has been reported in the USA, the frequency is much lower at 40–50%, likely representing ethnic differences in clinical phenotypes [28–32]. Nevertheless, the presence of anti-MDA5 antibody should trigger an evaluation of underlying ILD, and if detected, aggressive therapy (perhaps even combination immunosuppressive medications) should be considered given the risk for RP-ILD [33].

The distribution of classic DM and CADM in patients with anti-MDA5 antibody is variable among ethnic groups with CADM found in 75%

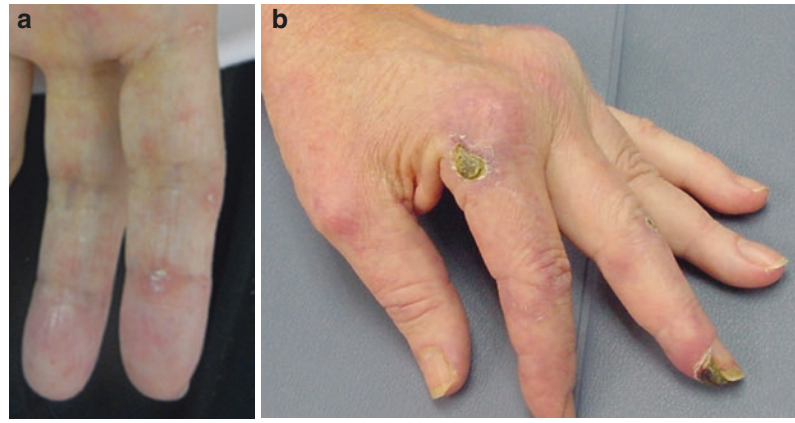

Fig. 21.1 Characteristic cutaneous manifestations in anti-MDA5 antibody-positive patients. Palmar papules (**a**) and skin ulcerations on the fingertip and dorsum of metacarpophalangeal joint (**b**)

of anti-MDA5 antibody-positive Japanese adult patients which was significantly higher than 39% in non-Japanese patients with this antibody [32].

The characteristic cutaneous manifestations include palmar papules (Fig. 21.1a), skin ulcerations on the fingertips (Fig. 21.1b), lateral nailfolds, and Gottron changes on the elbows and knees, all of which suggest an underlying severe vasculopathy [34, 35]. The palmar papules are designated as inverse Gottron papules and are felt to be associated with a poor prognosis driven by the RP-ILD. Joint symptoms are frequent, similar to those seen with the antisynthetase syndrome [24, 34]. Concomitant malignancy is uncommon, but may be detected in up to 10% of adult patients in some series [8, 36].

Anti-MDA5 antibody is also found in 10% of JDM patients [37, 38]. Clinical correlations of anti-MDA5 antibody in children are similar to adults, including a high prevalence of ILD, skin and oral ulcerations, and arthritis, with a lack of subcutaneous calcinosis or bowel vasculitis. Muscle involvement is milder in JDM patients with anti-MDA5 antibody than in those without, which is consistent with the high frequency of CADM seen in adults with anti-MDA5 antibody. Japanese studies suggest a high frequency of RP-ILD, whereas a British report noted ILD (not RP-ILD) in about 20% JDM patients [38, 39].

Therefore, anti-MDA5 antibody should be assessed in patients with severe DM rashes particularly those with palmar papules or cutaneous ulcerations and/or ILD irrespective of age. The presence of skin ulcers, severely impaired pulmonary function, and serum biomarkers including a high ferritin and elevated anti-MAD5 autoantibody titers predict a poor prognosis in adult and juvenile patients with anti-MDA5 antibody [40]. Serum hyperferritinemia (≥1600 ng/ml) is a risk factor for excess mortality in anti-MDA5 antibody-positive patients [41], while another study showed that sustained high levels of anti-MDA5 antibody titer, ferritin, and IL-18 were similarly associated with a poor response to treatment and greater mortality [36, 42]. Prospective studies to assess biomarkers useful for monitoring disease activity are necessary.

Key clinical features of anti-MDA5

- Exclusively DM, either classic DM and CADM
- Adult (24%) and juvenile (10%)
- Highly associated with ILD, especially RP-ILD
- Severe cutaneous disease—palmar papules and cutaneous ulcerations
- No or minimal muscle weakness (CADM) frequently found in Asian populations
- Arthritis
- Poor prognosis
- Lower risk of malignancy

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22 Newly Described Myositis Autoantibodies: HMGCR, NT5C1A, SAE, PUF60

Zoe Betteridge and Neil J. McHugh

Key Points to Remember

- Recent advances have led to the identification of a number of novel myositis autoantibodies, with most patients now having a detectable autoantibody.
- Anti-HMGCR autoantibodies are associated with severe proximal weakness and statin-induced myositis and can also be found in statin-naïve patients, including children.
- Anti-SAE autoantibodies are a marker for DM and are more common in Caucasian populations.
- Whilst anti-CN1A autoantibodies have been detected in a range of autoimmune diseases, their prevalence in IBM may help in the differential diagnosis from PM. Emerging autoantibodies such as anti-PUF60, anti-SMN, anti-cortactin, anti-NPC and anti-FHL1 have currently only been described in a limited number of studies, but may have a future role in the diagnosis and serological classification of myositis.

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Introduction

Myositis autoantibodies define a clinicopathological phenotype, providing prognostic and potential treatment considerations in the idiopathic inflammatory myopathies. Since the discovery of the early myositis autoantibodies (e.g. anti-Jo-1), there has been a keen interest and an ongoing quest for newly discovered autoantibodies in myositis. In the last decade, there have been several new emerging autoantibodies in myositis: anti-3-hydoxy-3-methylglutaryl-coenzyme A reductase (anti-HMGCR), anti-cytosolic 5′-nucleotidase 1A (anti-CN1A), anti-poly(u)-binding-splicing factor (anti-PUF60) and anti-small ubiquitin-like modifier (SUMO) activating enzyme (anti-SAE). In this chapter, we will discuss the role of these autoantibodies in the assessment and management of myositis as well as other emerging autoantibodies.

Anti-HMGCR

Autoantibodies, which are immunoprecipitating 100 kDa and 200 kDa proteins, were first described by Christopher-Stine et al. in a cohort of necrotizing myopathy patients [1]. The 100 kDa autoantigen target was later identified as 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR), a key enzyme involved in the

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cholesterol synthesis pathway [2]. Screening of 750 myositis patients by HMGCR ELISA found anti-HMGCR autoantibodies in 6% of adult myositis cases, with other cohorts reporting similar frequencies (5–9%) [3–6].

Clinically, anti-HMGCR-positive patients typically have severe proximal muscle weakness with a markedly elevated creatine kinase (CK) level, irritable myopathy on electromyography, evidence of muscle oedema on MRI and prominent degenerating, regenerating and/or necrotic fibres with a scant inflammatory infiltrate on muscle biopsy [1]. These findings have been validated in additional cohorts of European, Australian, Japanese and Chinese patients [3–6]. Furthermore, the development of quantitative anti-HMGCR ELISAs has shown autoantibody titres at disease onset to correlate with both CK levels and proximal muscle weakness [7, 8], suggesting that anti-HMGCR titres may help predict disease course. This autoantibody was originally identified using immunoprecipitation; however, other assays have been developed including the detection of a finely granular cytoplasmic staining pattern on immunofluorescence, an HMGCR-specific ALBIA assay, and a commercially available quantitative ELISA [18, 19].

Anti-HMGCR is seen in patients with necrotizing myopathy on muscle biopsy and accounts for 5–10% of all adult myositis cases.

Additionally, other reported clinical features of anti-HMGCR-positive patients include a high incidence of myalgia, arthralgia and dysphagia and the absence of DM-specific cutaneous manifestations [1, 5]. Whilst the initial report also described a low incidence of malignancy in anti-HMGCR-positive patients [1], recent reports have shown a cancer association with anti-HMGCR-positive myositis [9, 10]. Studies have also shown that patients with anti-HMGCR autoantibodies have a modest response to prednisone and generally require combined therapy with additional immunosuppressive drugs or intravenous immunoglobulin therapy (IVIG) [1, 8, 11].

Anti-HMGCR antibody-positive patients often require combination immunosuppression and/or IVIG.

More notably, the initial report demonstrated 63% of anti-HMGCR-positive patients to have had a prior statin exposure; and after adjusting for age, this was found to be significantly increased compared to other myositis patient groups [1]. An extended study by Mammen et al. demonstrated a similar frequency of statin exposure (67%), with 92.3% of anti-HMGCR-positive patients over the age of 50 years having used statins [2]. In contrast, a separate study on 763 currently statin-exposed, 322 formerly statin-exposed and 881 statin-naïve non-myositis cases found anti-HMGCR autoantibodies to occur in only 0.7% of cases, leading to the conclusion that anti-HMGCR autoantibodies are highly associated with statin-induced autoimmune myositis, which is different from the generally self-limited muscular manifestations associated with statin use [12]. However, whilst this statin association has been confirmed in numerous additional cohorts [2–4, 6], there remains a significant number of anti-HMGCR-positive patients who are statin-naïve, meaning that anti-HMGCR autoantibodies should be broadly regarded as a marker of necrotizing myopathy [5, 7, 8].

Statin is associated with 60–70% of all cases of anti-HMGCR antibody-positive patients and >90% of anti-HMGCR antibody patients over 50 years of age.

Recently, anti-HMGCR autoantibodies have been reported in approximately 1% of juvenile myositis patients. These statin-naïve children have severe proximal muscle weakness, distal weakness, muscle atrophy, joint contractures, arthralgia and prolonged elevated CK levels. Interestingly, juvenile anti-HMGCR-positive patients were found to require high-dose glucocorticoid treatment along with additional immunosuppression including the use of biologics [13–15]. Additional

studies in adult cohorts have reported younger anti-HMGCR-positive adults to be more likely to be statin-naïve, have more severe muscle weakness and increased CK levels at disease onset and be more refractory to treatment than older anti-HMGCR-positive patients [2, 8, 11].

Regarding pathogenesis, statins are known to upregulate the expression of HMGCR. The finding of increased levels of HMGCR expression in regenerating muscle fibres on muscle biopsies from anti-HMGCR-positive patients provides a potential link between an environmental trigger (statin exposure) and disease pathogenesis [2]. This finding further explains the 'perpetuation' of myositis in the setting of statin discontinuation since regenerating fibres provide an antigenic target for the already present anti-HMGCR autoantibody. Additionally, the finding of a DRB1*11:01 haplotype association in adult anti-HMGCR-positive patients demonstrates a further genetic predisposition [16]. However, since a minority of anti-HMGCR-positive patients are statin-naïve, and juvenile patients have been shown to have a separate HLA association (DRB1*07:01), a separate mechanism must exist for the statin-naïve anti-HMGCR-positive patients [15, 17], supporting the hypothesis that younger statin-naïve patients represent a distinct subset of anti-HMGCR-positive patients.

Whilst anti-HMGCR autoantibodies are not as prevalent as some of the other myositis specificities, the ability to clinically define a further subgroup of myositis patients, differentiate juvenile myositis patients from the muscular dystrophies and identify statin-induced myositis patients from non-autoimmune cases demonstrates the diagnostic utility of this autoantibody.

Anti-NT5C1A (Anti-CN1A)

Autoantibodies targeting a 43 kDa protein were initially reported in inclusion body myositis (IBM) cases, but not in patients with other forms of myositis or healthy controls [20]. Subsequent contemporaneous studies involving mass spectrometry and screening of a phage display library identified the target autoantigen as cytosolic 5′-nucleotidase 1A (cN1A) [21, 22], an enzyme that catalyses nucleotide hydrolysis, regulating nucleotide metabolism and DNA repair [23, 24].

Anti-cN1A autoantibody tested by a cN1A peptide dot blot assay demonstrated highly reactive anti-cN1A autoantibodies in 34% of IBM patients and 1.7% of disease controls, with 70% of IBM patients and 8% of controls having weakly reactive anti-cN1A autoantibodies, demonstrating high specificity and modest sensitivity of the autoantibody [21]. These findings were confirmed in a parallel study by Pluk et al., who demonstrated highly reactive anti-cN1A autoantibodies in 33% of 94 IBM patients and 2.9% of 140 disease controls [22].

Additional studies have challenged the specificity of this autoantibody. Whilst Herbert et al. found similar frequencies of IBM and PM/DM patients to be anti-cN1A positive by ELISA (37% and 4%, respectively), they also reported 20% of SLE patients and 36% of Sjogren syndrome (SS) cases to be anti-CN1A positive [25]. These findings were confirmed by Lloyd et al., who demonstrated anti-C1NA to be present by immunoblotting in 13.5% of SLE and 22.7% of SS cases without muscle involvement [26]. Whilst these results show that anti-CN1A autoantibodies are not specific for IBM, these biomarkers are still useful for an IBM diagnosis. Currently, patients with IBM have a high initial misdiagnosis rate (30–53%) and a mean delay to diagnosis of 4.9–8 years [23]. Since one of the more challenging differential diagnostic considerations is with PM, the finding of an autoantibody that is present in 33–76% of IBM cases, but less than 5% of PM cases, may have a significant impact on the timely diagnosis of IBM [23]. Furthermore, since the calculated diagnostic accuracy of CN1A autoantibodies for IBM in patients with muscle diseases is equivalent to the diagnostic accuracy of muscle biopsy in IBM (85%), the use of anti-CN1A for IBM diagnosis provides patients and physicians a less invasive diagnostic technique [21]. Nevertheless, the gold standard for diagnosing IBM remains a muscle biopsy.

Anti-cN1A is not specific for IBM, but could be helpful in the diagnosis of IBM.

Anti-cN1A is found in 30–40% cases of IBM and only 5% of PM cases.

Anti-cN1A is also seen in 10–20% of SLE and 20–40% of SS cases without muscle involvement.

Clinically, the initial study by Salajegheh et al. found no difference in age, disease duration, gender, race, treatment status or ANA positivity between anti-CN1A-positive and anti-CN1A-negative IBM subsets [20]. These findings have been confirmed in numerous other cohorts, who also note no association between finger flexor strength, wrist flexors or knee extensors, age at disease onset, proximal weakness, cancer, smoking history, anti-Ro/La positivity and maximum CK levels with anti-CN1A autoantibodies in IBM cases [21, 22, 25–28]. In contrast, a study by Goyal et al. found anti-C1NA-positive IBM patients to have more severe motor weakness (MRC sum score), more proximal lower limb muscle weakness (timed get up and go) and an increased odds of requiring a wheelchair or walking aid in comparison to the anti-C1NA-negative cohort. Additionally, anti-CN1A-positive patients were found to have increased levels of dysphagia and respiratory involvement (decreased FVC) and greater odds of facial weakness and raised CK levels than the anti-CN1A-negative cohort [24]. This association with facial weakness was confirmed by Lilleker et al., who also reported anti-CN1A-positive patients to have a higher adjusted mortality risk and lesser proximal upper limb weakness at disease onset. Since upper limb weakness is not a typical feature of IBM pathology, the authors suggested this negative association infers anti-CN1A autoantibodies to be a marker of more classical IBM [27]. Whilst these reports therefore suggest that anti-CN1A autoantibodies in IBM maybe a marker of more severe disease, it remains to be seen whether there is a difference in inflammatory responses or rates of disease progression in the seropositive and seronegative groups in other larger prospective studies [21].

Whilst the anti-CN1A autoantibody was originally detected by immunoblotting and has been studied using immunoprecipitation with in vitro generated protein [20, 22], ELISA assays have been developed for the screening of multiple samples [21, 25]. However, given the low concordance between CN1A peptide ELISAs and more established techniques for anti-CN1A autoantibody detection, we recommend a commercially available ELISA using full-length recombinant cN1A for autoantibody screening [23, 25]. Whilst this ELISA requires external validation, it provides routine laboratories the ability to report anti-CN1A positivity.

Whilst IBM is characterised by the degenerative features of rimmed vacuoles and abnormal protein accumulation, muscle-specific features of cytotoxic T-cell infiltrates, the clonal expansion of lymphocytes on muscle biopsy, an association with the HLA-DR3 (HLA-DRB1*0301) haplotype and the recent finding of anti-CN1A autoantibodies also infer an autoimmune component to IBM pathogenesis [25, 29]. Since CN1A proteins are known to be abundant in skeletal muscle [25] and have been demonstrated to be abnormally distributed in IBM muscle, the aberrant accumulation of CN1A in areas of microfibre degeneration may contribute to the pathogenesis of IBM [21].

Anti-PUF60

One of the most recently identified autoantibodies in myositis is anti-PUF60. This 60 kDa autoantigen was initially identified by Fiorentino et al. through routine immunoprecipitation and immunoblotting and fully characterised as poly(u)-binding-splicing factor (PUF60), through the use of a human protein array and mass spectrometry. This autoantigen has a range of functions and is known to interact with several autoantigens, including the Ro60, U1RNP, U2RNP and La [30].

Through the development of a recombinant full-length PUF60 ELISA, anti-PUF60 autoantibodies have been detected in 29% of SS, 18% of DM, 9% of SLE, 9% of IBM and 11% of PM patients, as well as 5% of healthy controls. The prevalence of anti-PUF60 autoantibodies in SS was found to be significantly higher than that in healthy controls, with a similar trend for patients with DM. However, whilst the overall prevalence of anti-PUF60 autoantibodies in DM was lower than that of SS, a greater proportion of DM patients had high-titre autoantibodies [30].

In terms of clinical associations of anti-PUF60, there was no difference in age of disease onset, gender, incidence of dysphagia, Raynaud phenomenon or arthritis, peak CK levels or cutaneous manifestations in DM patients with or without anti-PUF60 autoantibodies. However, anti-PUF60 was negatively associated with ILD and was found to be more common in Caucasian DM patients and absent in Asians. Furthermore, whilst anti-PUF60 was associated with Ro60, Ro52 and La in patients with SS, there was no association between anti-PUF60 and anti-Ro/La in the DM cohort [30].

Interestingly, whilst anti-PUF60 autoantibodies were not associated with malignancy in the DM cohort, anti-PUF60 autoantibodies have recently been significantly associated with early-stage colon cancer, where they have a positive predictive value of 87% [31]. This link to anti-PUF60 is intriguing, since Fiorentino et al. also demonstrated a strong association between anti-PUF60 and the cancer-associated myositis autoantibody TIF1 gamma present in 71% of anti-PUF60-positive DM cases [30]. Further work in additional cohorts is now required to validate these preliminary findings and ascertain any clinical differences in anti-PUF60-positive DM patients who are TIF1 gamma positive and negative.

Anti-PUF60 autoantibodies are most commonly seen in Sjogren syndrome (30%) followed by dermatomyositis (20%); however, DM patients have higher titres.

Anti-PUF60 autoantibodies are negatively associated with ILD and are associated with anti-TIF1 gamma antibody, but further studies are necessary to determine clinical associations.

Anti-SAE

Autoantibodies to the small ubiquitin-like modifier (SUMO) activating enzyme (anti-SAE) were initially described by Betteridge et al. in two DM patients [32]. A subsequent report investigating the prevalence in a predominantly Caucasian UK cohort demonstrated anti-SAE autoantibodies to occur in 4% of IIM patients and more specifically in 8% of DM patients [33]. Whilst this prevalence was validated in an additional European DM cohort (7%) [34], two studies investigating Japanese myositis cohorts found a significantly reduced prevalence of anti-SAE autoantibodies in Asian patients (1.5–1.8%) [35, 36]. Since Betteridge et al. also reported an association with HLA-DRB1*04-DQA1*03-DQB1*03 haplotype, it is feasible that the difference in anti-SAE prevalence is in part due to the frequency of this genetic risk factor in different populations [33]. Additionally, the reporting of three cases of anti-SAE in juvenile DM patients (approximately 0.5% of JDM) demonstrates that this autoantibody is present across a wide age range [36, 37].

Clinically, anti-SAE autoantibodies are strongly associated with dermatomyositis, with anti-SAE-positive patients having a high incidence of heliotrope, Gottron rashes and periungual involvement [33, 36]. These findings have been verified in all subsequent cohort studies, with anti-SAE autoantibodies only being detected in patients with classic DM rashes and patients typically presenting with rashes months before the onset of muscle weakness [33, 36].

Anti-SAE-positive patients have an increased incidence of fever, weight loss, raised inflammatory markers and dysphagia [33]. Whilst Fujimoto et al. also found high levels of systemic involvement in their anti-SAE-positive patients, the inci-

dence of dysphagia was much lower [36]. Interestingly, both European studies found a low incidence of ILD in their anti-SAE-positive patients (0–18%) [33, 34], but the majority of anti-SAE-positive patients in the Asian cohorts were reported to have ILD (50–71%), which was generally mild and responded well to treatment [35, 36]. This significant difference in the frequency of ILD in anti-SAE-positive patients in the different populations may simply reflect the generally increased levels of ILD in Asian myositis patients compared with Caucasians.

Anti-SAE autoantibodies were originally detected by immunoprecipitation and produced a positive ANA pattern on indirect immunofluorescence (fine-speckled nucleolar sparing with a fine cytoplasmic speckle, or a homogeneous pattern) [33]. More recently, other methods to detect anti-SAE autoantibodies include the use of a non-radioactive immunoprecipitation assay, a SAE1 protein ELISA and commercial immunoblots (including the EuroImmun Myositis LineBlot and the Alphadia BlueDot Polymyositis IgG assay) [32, 34, 35, 38, 39].

Anti-SAE is specific for DM and is seen in 7–8% of DM in non-Asian populations.

Anti-SAE antibody patients have a high frequency of heliotrope, Gottron rashes and periungual erythema.

Other Emerging MSA/MAAs

Whilst the majority of myositis patients have a known autoantibody, there remains a subset of cases that are negative for the established autoantibody specificities. Studies are ongoing to identify and characterise novel autoantibody biomarkers with a number of new specificities recently emerging.

Firstly, whilst autoantibodies to anti-U1 RNP are well known to be associated with SLE and other autoimmune disorders, autoantibodies to the D, E, F and G subunits without the other snRNP proteins have been recently described. This protein complex has been identified as the survival of motor neuron (SMN) complex, which plays a critical role in snRNP assembly. The anti-SMN autoantibodies were detected in three Caucasian patients with PM as confirmed by muscle biopsy and EMG, demonstrating a prevalence of 3% in IIM and 5% in PM. Clinically, two of the anti-SMN complex-positive patients had SSc overlap features with mild skin involvement, and all three cases were treated with glucocorticoids and immunosuppressive agents, but responded well to treatment. Anti-SMN autoantibodies may therefore be a marker for PM-SSc overlap patients [40].

Autoantibodies to the DNA mismatch repair enzyme, PMS1, were first reported in a US myositis cohort, where they were found to be present in 7.5% of cases and specific for myositis [41]. A subsequent study on a Japanese myositis cohort found similar findings with anti-PMS1 autoantibodies present in 6.7% of cases and no autoimmune disease controls [42]. Furthermore, a small number of cases had autoantibodies to additional mismatch repair enzymes: PMS2, MLH1 and MSH2 [41, 42]. More recently, autoantibodies to the DNA mismatch repair enzyme family (PMS1, PMS2, MLH1 and MSH2) have been detected in 6.3% of Japanese IIM patients and 7.5% of SLE cases [43]. Since Okada et al. also reported anti-PMS1 to be present in 13.5% of pancreatic cancer patients [42], anti-DNA mismatch repair enzyme autoantibodies may not be myositis specific but are best regarded as myositis-associated. These autoantibodies also clinically confer a favourable prognosis, with no positive patients having internal malignancy and cases having an improved survival rates compared with anti-MDA5 and anti-TIF1-gamma-positive patients [43].

Autoantibodies to cortactin, an actin-binding protein, have also recently been reported in IIM. Anti-cortactin was found in 20% PM, 7.6% DM and 26% necrotizing myopathy patients, but less than 5.0% of healthy or systemic autoimmune disease controls. In terms of clinical associations, only male gender was found to be significantly associated with anti-cortactin positivity, whilst

there was also a strong trend regarding the absence of DM rash. However, since the majority of anti-cortactin-positive patients had an additional MSA/MAA, the clinical associations of this novel autoantibody may have been masked by the presence of additional autoantibodies [44]. Interestingly, a separate study has also described anti-cortactin autoantibodies in 20% of myasthenia gravis patients and 12.5% of cases of other autoimmune disorders [45]. Further work is therefore required to fully determine the diagnostic utility of this novel autoantibody in the spectrum of myositis.

A study on 100 French Canadian myositis patients identified the presence of anti-nuclear pore enzyme (anti-NPC) autoantibodies in 4% of cases. This autoantibody was not detected in 393 autoimmune, non-autoimmune and healthy controls, demonstrating it to be specific for myositis or myositis overlap patients. Whilst the number of positive cases was limited, the provisional data demonstrated an increased likelihood of prominent myositis, rheumatoid arthritis overlap, mild ILD and Raynaud phenomenon, with no life-threatening systemic complications such as cancer. Whilst anti-NPC-positive patients required immunosuppression with additional immunomodulatory agents, all patients eventually responded to treatment. The data therefore infer that anti-NPC-positive patients have a favourable outcome, although additional longitudinal studies are required to verify this finding [46].

Finally, one of the most recent findings is the identification of autoantibodies to FHL1 (four-and-a-half LIM domain 1) in 25% of IIM patients and less than 6% of other autoimmune cases. Since anti-FHL1-positive patients had an increased incidence of muscle atrophy, dysphagia, pronounced muscle fibre damage and vasculitis, anti-FHL1 may serve as a biomarker of severe disease; however, additional studies are required to validate this [47].

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Myositis Mimics: The Differential Diagnosis of Myositis

23

Harlan Michelle and Andrew L. Mammen

Key Points to Remember

- Metabolic myopathies, mitochondrial myopathies, muscular dystrophies, inclusion body myositis, endocrine myopathies, and toxic myopathies have features in common with autoimmune myopathy and may be misdiagnosed as such.
- Facial weakness, scapular winging, asymmetric weakness, distal greater than proximal weakness, and extraocular muscle weakness are rare in patients with autoimmune myopathy; their presence should raise the suspicion for inherited muscle diseases or inclusion body myositis.
- As some of the most common inherited forms of myopathy are autosomal recessive, the family history is often negative.
- A careful review of the medication list and social history can help to exclude toxic myopathies such as those caused by drugs and alcohol.
- Since most autoimmune myopathy patients have extramuscular involvement, alternative diagnoses should be strongly considered in those with isolated myopathy.

Introduction

Despite the well-recognized status of the autoimmune myopathies, they remain relatively rare causes of muscle disease. Annual incidence and prevalence of autoimmune myopathies in the United States are 4.2–7.9 cases per 100,000 person-years and 14–25.3 per 100,000 individuals, respectively. By comparison, the prevalence for inherited muscular dystrophies ranges from 19.8 to 25.1 per 100,000 person-years [1–5]. Many other causes of myopathy share similar clinical and/or histopathological features of autoimmune myopathy and are frequently misdiagnosed as autoimmune conditions. These include metabolic, genetic, endocrine, and drug-related myopathies, among others (Table 23.2). Recognition of these dis-

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orders is important, as immunosuppressive therapy is generally not effective and, in some cases, may actually be harmful. This chapter focuses on the clinical and pathological identification of those myopathies most commonly misdiagnosed as autoimmune myopathies.

Table 23.1 Clinical features suggestive of a noninflammatory myopathy

Positive family history of muscle weakness
Slowly progressive evolution of weakness over years
Episodic weakness and fatigability
Facial or extraocular muscle weakness
Scapular winging
Distal > proximal weakness
Asymmetric weakness
Muscle fasciculations or cramping
Lack of myositis autoantibodies
Lack of systemic manifestations of autoimmunity such as rash, arthritis, Raynaud phenomenon, pulmonary fibrosis (ILD), sicca, etc.
Lack of response to immunosuppressive medications

Myositis Mimics: The Differential Diagnosis of Myositis

Autoimmune myopathies are a heterogeneous family of diseases characterized by muscle weakness, elevated serum muscle enzymes, and muscle biopsies revealing inflammation and/or necrosis. Since patients with inherited muscle disease, inclusion body myositis, endocrine myopathies, and toxic myopathies can present with similar clinical features, they may be misdiagnosed with autoimmune myopathy and unnecessarily treated with immunosuppressive agents. Here, we review those entities most likely to be misdiagnosed as an autoimmune myopathy,

Table 23.2 Common myositis mimics

Metabolic myopathies	
McArdle disease	
Acid maltase deficiency	
Muscular dystrophies	
Facioscapulohumeral muscular dystrophy	
Dysferlinopathies (LGMD 2B, Miyoshi myopathy)	
Inclusion body myositis	
Drug-related myopathies	**Infectious myopathies**
Statins	*Viral myositis*
Corticosteroids	*Staphylococcus aureus*
Chloroquine/hydroxychloroquine	*Streptococcus*
Amiodarone	*Toxoplasma gondii*
Procainamide	*Borrelia*
Doxorubicin	*Erhlichia*
Colchicine	*Taenia solium*
Vincristine	*Trichinella spiralis*
Zidovudine	
Alcohol	
Mitochondrial myopathies	**Myopathies related to systemic disease**
Mitochondrial encephalomyopathy, lactic acidosis and stroke-like syndrome (MELAS)	*Hypothyroidism*
Myoclonic epilepsy with ragged-red fibers (MERRF)	*Hyperthyroidism*
	Hyperparathyroidism
	Cushing syndrome
	Sarcoidosis
	Amyloidosis
	Porphyria
	Diabetes (amyotrophy)

highlighting features that distinguish them and providing guidance about how to properly diagnose them (Table 23.1).

Identifying and Diagnosing the Metabolic Myopathies

The metabolic myopathies are a heterogeneous group of inherited disorders characterized by defects in muscle metabolic utilization of carbohydrates, fats, and protein (purine). This leads to a decreased energy supply to the muscle, manifesting as episodic exercise-induced crises of myalgias, muscle cramping, and weakness often associated with myoglobinuria. Several of these disorders can also manifest with chronic proximal muscle weakness and may be mistaken for autoimmune myopathies, especially if a history of chronicity, fatigability, and myoglobinuria is not elicited. The most notable of these are McArdle disease (myophosphorylase deficiency) and Pompe disease (acid maltase deficiency), which can clinically mimic idiopathic inflammatory myopathies, especially polymyositis. There are several other metabolic myopathies including lipid storage disorders (carnitine palmitoyltransferase, CPT II deficiency) and disorders of purine metabolism (myoadenylate deaminase deficiency) that rarely can mimic polymyositis (Fig. 23.1) but are not discussed in detail due to being less common. Overall, the metabolic myopathies remain rare conditions; however, growing awareness and improved diagnostic testing have resulted in an increased number of diagnoses. Data on prevalence remains limited; estimates range from 1:283,000 in Europe for Pompe disease to 1:140,000 for McArdle disease in Spain, although this may be an underestimation [6–8]. Clinicians should recognize that apart from Pompe disease, there is no therapy for these disorders, and patients are advised to avoid strenuous exercise or physical activity, especially during stress including fasting and infection.

- Anti-c5N1A (positive in IBM)
- GAA enzyme activity assay (positive in Pompe disease)
- Thyroid function tests (TSH, free T4, free T3)
- Parathyroid hormone
- Cortisol level
- Genetic testing
- Muscle biopsy

Fig. 23.1 Algorithm for workup of myositis mimics

McArdle Disease

McArdle disease is an autosomal recessive metabolic myopathy caused by mutations in the PYGM gene. More than 100 different pathogenic mutations have been described to date [9]. These mutations result in a deficiency of myophosphorylase, a muscle-specific glycogen phosphorylase, which renders the muscle unable to utilize glycogen stores for energy and leads to accumulation of glycogen deposits within myofibers. Because cardiac and hepatic isoforms of the enzyme are not affected, McArdle disease is a "pure" myopathy without other direct organ involvement [10].

Most patients present within the first decade of life with exercise-induced muscle cramping, contractures, and excessive fatigue although the disease is rarely diagnosed before early adulthood. No definite gender or ethnic predilections have been identified.

A unique clinical feature of McArdle disease is the "second wind" phenomenon, which is characterized by sudden, significant improvement in exercise tolerance following a brief period of sustained aerobic activity [10]. About one-third of patients in the later stages of disease—typically those over the age of 40 years—will develop chronic, progressive proximal muscle weakness which may be misconstrued with an autoimmune myopathy if an earlier history of exercise intolerance and episodic weakness is not elicited [11].

Resting CK is markedly elevated (>1000 U/L) in the majority of patients, and episodic rhabdomyolysis (CK > 100,000 in crisis) may develop [11]. Myoglobinuria is also common and may lead to acute renal failure if severe. Electromyography (EMG) may reveal proximal myopathic changes. As many patients may present in adulthood with proximal muscle weakness, elevated CK levels, and myopathic EMG abnormalities, they may fulfill Bohan and Peter

classification criteria leading to a misdiagnosis of polymyositis. However, these patients will not respond to immunosuppression and continue to progress slowly.

There is limited data regarding the utility of muscle MRI in McArdle disease. One study showed increased fatty replacement in calf and thigh muscles compared to healthy controls; however, this is a relatively nonspecific finding [12]. Others have shown smaller changes in muscle T2 signal hyperintensity after exercise in patients with McArdle disease compared to healthy controls; however, this did not help distinguish McArdle disease from other metabolic myopathies [13, 14].

Prior to the widespread availability of genetic testing, muscle biopsy was the definitive means of diagnosing McArdle disease. The cardinal pathologic features are the absence of myophosphorylase activity on immunohistochemical staining, and the presence of subsarcolemmal or intermyofibrillar glycogen deposits, best appreciated with PAS staining [10]. These stains are typically performed on snap frozen tissue. In at least two large cohorts, myophosphorylase activity was absent in 100% of muscle biopsies from individuals with genetically confirmed disease [11, 24]. It should be noted, however, that the enzyme is very labile, false negatives can occur, and care should always be taken to interpret specimens alongside a normal control. In the absence of immunohistochemical staining or in the event of a false-negative result, confusion with polymyositis can arise due to the frequent presence of other typical myopathic features, such as internalized nuclei, fiber size variation, and, in some cases, nonspecific inflammation.

Due to these potential confounders, the gold standard for diagnosis is now identification of a pathogenic mutation in the PYGM gene. Sequencing and deletion/duplication analysis of this gene is commercially available through several companies and can be performed on either whole blood or saliva samples. No enzyme replacement therapy is yet available for McArdle disease; however, recognition and distinction from autoimmune myopathies remain imperative to avoid inappropriate treatment with potentially toxic immunosuppressive agents. Lifestyle modifications can also prove beneficial for quality of life in these individuals. Moderate aerobic exercise may improve exercise tolerance, although intense isometric or maximal aerobic exercise should be avoided as this may trigger myoglobinuria. Although no significant benefit has been shown from any pharmacologic or nutritional treatment, some patients have experienced modest improvement with creatine monohydrate and carbohydrate-rich diets, especially when ingested shortly before planned exercise [25].

Acid Maltase Deficiency

Acid maltase deficiency, also known as Pompe disease, is an autosomal recessive disorder caused by mutations in the GAA gene, which encodes the lysosomal enzyme acid alpha-glucosidase. Deficiency of this enzyme results in abnormal accumulation of glycogen within myofibers which disrupts muscle tissue architecture [15]. There are two primary phenotypic manifestations: a severe, infantile form with generalized hypotonia and prominent cardiorespiratory involvement and a milder, more heterogeneous late-onset form with slowly progressive proximal limb-girdle and diaphragmatic weakness. The age of presentation in late-onset disease is quite variable, ranging from early childhood to the seventh decade. In one cohort of 54 Dutch patients, the mean age of onset was 28 years with a range from 14 to 42 years [16].

Early respiratory muscle involvement is a characteristic feature of both forms. However, cardiac abnormalities are rare with late-onset disease. No definite gender or ethnic predilections have been identified.

Serum CK levels are often mildly elevated, and the EMG may be normal or show a mild, nonirritable myopathy [15–17]; myotonic discharges may also be present. Whole-body MRI studies in adult-onset disease have shown predominant involvement of axial muscles, including the paraspinal muscles, abdominal muscles, and the tongue. Mild degrees of fatty replacement in the paraspinal muscles may even be

detected in presymptomatic individuals [18]. In symptomatic individuals, MRI changes appear to correlate well with clinical weakness; however, further work remains to be done to determine whether MRI can be used to follow response to enzyme therapy [19, 20].

As with McArdle disease, muscle biopsy was previously required for definitive diagnosis. In the infantile form, the histopathologic hallmark is the presence of periodic acid-Schiff (PAS)-positive vacuoles. These are rare in the adult form, although acid phosphatase-positive globular inclusions are sometimes seen in adult cases. Electron microscopy, if available, may demonstrate cytoplasmic membrane-bound glycogen [21]. Many muscle biopsies in late-onset forms may show nonspecific dystrophic changes such as rounded atrophy, split fibers, and fibrosis or may even exhibit completely normal histology [22, 23]. Inflammatory infiltrates are not a reported feature of muscle biopsy in these individuals. Given the limitations of muscle biopsy, especially in late-onset disease, assessment of acid alpha-glucosidase enzyme activity is now considered the current gold standard for diagnosis.

The blood-based acid alpha-glucosidase enzyme activity assay screens for enzyme deficiency with confirmation made using GAA gene sequencing. A correct diagnosis is important for this condition, as acid maltase deficiency is one of the only metabolic myopathies for which enzyme replacement therapy has been FDA-approved. Myozyme and Lumizyme (both contain alglucosidase alfa) are approved for infantile Pompe's and late-onset Pompe's, respectively, as an IV infusion given every 2 weeks. Thus far, clinical experience has shown greater efficacy for children and for cardiac dysfunction, than for adults and skeletal muscle impairment. However, further work is necessary to determine the optimal delivery of therapy, especially given the very high cost associated with enzyme replacement therapy (average cost $300,000 a year) [15]. Early diagnosis and initiation of therapy may lead to better outcomes even in late-onset Pompe's making it imperative for clinicians to recognize these disorders.

Mitochondrial Myopathies

Mitochondria play a crucial role in oxidative phosphorylation and energy production. Mitochondrial dysfunction can therefore affect multiple tissues, with muscle being preferentially affected due to high-energy demands. Mitochondrial myopathy is a well-recognized and relatively common symptom of mitochondrial dysfunction, typically characterized as exercise intolerance with premature fatigue and varying degrees of muscle weakness. Although proximal muscle weakness can be seen, mitochondrial myopathies also commonly involve the extraocular muscles, which are virtually never affected in patients with autoimmune myopathy. Compared to metabolic myopathies, mitochondrial myopathies are less commonly associated with rhabdomyolysis, myoglobinuria, and exercise-induced contractures. CK levels may be normal to mildly elevated. Muscle biopsy reveals the presence of ragged-red fibers with Gomori trichrome staining, ragged blue fibers on succinate dehydrogenase stain, and the presence of cytochrome C oxidase-negative fibers. It should be noted, however, that while these findings are indicative of mitochondrial dysfunction, they can be seen with many disorders and are not specific for an inherited mitochondrial myopathy. For example, patients with DM and IBM may also have muscle biopsies showing evidence of mitochondrial dysfunction. However, patients with mitochondrial myopathy almost always lack the inflammatory infiltrates seen in patients with DM and PM.

The presence of certain extramuscular manifestations may also suggest the possibility of a primary mitochondrial disorder. For example, patients with mitochondrial encephalomyopathy, lactic acidosis, and stroke-like syndrome (MELAS) and myoclonic epilepsy with ragged-red fibers (MERRF) syndrome present with varying degrees of cognitive impairment, hearing loss, seizures, and neuropathy [99, 100].

Identifying and Diagnosing the Muscular Dystrophies

The muscular dystrophies comprise a wide variety of inherited muscle disorders tied together by the common characteristics of progressive muscle damage, muscle weakness, and causative genetic abnormalities. Abnormal genetic mutations interfere with production or quality of various sarcolemmal proteins required for normal muscle function. While the presence of a positive family history may suggest the diagnosis in some cases, it is important to remember that recessive inheritance and de novo mutations mean that many patients with a muscular dystrophy will not have other affected family members. Several types of muscular dystrophy are often confused with the autoimmune myopathies due to their presentation with proximal muscle weakness, elevated CK levels, and the presence of inflammatory infiltrates on muscle biopsy. The most common of these include facioscapulohumeral muscular dystrophy (FSHD), dysferlinopathy, and calpainopathy.

Facioscapulohumeral Muscular Dystrophy

Facioscapulohumeral muscular dystrophy (FSHD) is the third most common muscular dystrophy with a prevalence of 1:20,000. There are two types of FSHD, both of which are caused by hypomethylation of the D4Z4 region near the end of chromosome 4. In FSHD1, hypomethylation occurs because the D4Z4 region, which normally has 11–100 repeats, is contracted to 10 repeats or less. In 80% of those with FSHD2, *SMCHD1* gene mutations are responsible for hypomethylation of the D4Z4 region; in the remaining 20% of those with FSDH2, hypomethylation occurs for unclear reasons [26, 27].

Patients with FSHD typically present in the second decade of life with weakness of the shoulder girdle muscles, which may be strikingly asymmetric. Scapular winging is common and may be prominent. Relative sparing of the deltoid is also a distinctive feature; this is seen in few other myopathies and should raise suspicion for FSHD, if present. Facial weakness may be prominent on examination but is often unnoticed by the patient. Progression is variable but usually slow. Up to 80% of patients maintain independent ambulation throughout their lifetime. Dysphagia, respiratory insufficiency, and extramuscular manifestations are rare, although sensorineural hearing loss and cardiomyopathy have been reported. Life expectancy is not altered. Additional supportive features of FSHD include a mild elevation of CK (<1500 U/L) and myopathic EMG features [26, 28]. Thigh MRI may reveal acute and chronic changes predominantly in the posterior compartment, but these changes are nonspecific. Interestingly, nearly 30% of females but only 5% of males with genetically confirmed FSHD may be asymptomatic.

Although definitive diagnosis can be made via commercially available genetic testing, many patients undergo muscle biopsy prior to this. Muscle biopsy typically reveals nonspecific myopathic changes, including fiber size variability, large numbers of internalized nuclei, and fibrosis. Unlike some other dystrophies, immunohistochemistry is not helpful in making a diagnosis of FSHD. Approximately one-third of patients have a chronic endomysial inflammatory infiltrate, which is composed primarily of CD4+ and CD8+ T-cells [29, 30]. This may be confused with polymyositis or inclusion body myositis and may even fulfill classification criteria for polymyositis; however, no invasion of non-necrotic fibers is seen. The relationship of this inflammatory infiltrate to pathogenicity in FSHD is not clear. Trials of steroids in FSHD have failed to show therapeutic efficacy, and treatment is primarily supportive care [28].

Dysferlinopathy

Dysferlinopathy is an autosomal recessive limb-girdle muscular dystrophy caused by mutations in the dysferlin gene on chromosome 2. Dysferlin is thought to play a role in membrane trafficking and stability, and loss of this protein increases

myofiber susceptibility to injury and hinders repair [31].

The prevalence of dysferlinopathy is not known but may vary considerably in different populations. For example, in Libyan Jews, the prevalence is approximately 1 in 1300. The two most common dysferlinopathy phenotypes are limb-girdle muscular dystrophy type 2B (LGMD 2B) and Miyoshi myopathy. LGMD 2B manifests in late adolescence or early adulthood with slowly progressive proximal weakness. Subclinical distal weakness may also be present on examination. In Miyoshi myopathy, distal weakness is predominant with marked calf muscle involvement; onset is slightly earlier than LGMD 2B. Proximal leg and distal hand weakness may become more evident in later stages. Additional, less common, phenotypes due to dysferlin deficiency include scapuloperoneal syndrome, distal myopathy with anterior tibial onset, and asymptomatic hyperCKemia. On MRI, the pattern of muscle involvement varies dramatically according to the individual's phenotype (e.g., LGMD2B vs. Miyoshi patterns of weakness). In all of these phenotypes, the CK is often dramatically elevated up to 20–150 times normal [32].

Similar to FSHD, muscle biopsy in dysferlinopathy most commonly demonstrates nonspecific myopathic features, with one-third also exhibiting a chronic endomysial inflammatory infiltrate. In dysferlinopathy, the infiltrate is composed primarily of T-cells and macrophages [33]. This can easily be confused for polymyositis, especially in patients with predominant proximal muscle weakness. However, unlike those with autoimmune myopathy, patients with dysferlinopathy do not benefit from immunosuppressive agents. The gold standard for diagnosis is immunohistochemical staining or immunoblotting that reveals severely reduced or absent levels of dysferlin in muscle [31, 34]. Alternatively, absent dysferlin in blood monocytes can also be useful in diagnosing dysferlinopathy. Genetic testing can verify the diagnosis and aid in genetic counseling of family members.

Calpainopathy

Calpainopathy is considered to be the most common autosomal recessive muscular dystrophy, with prevalences ranging from 1 per 100,000 in Italy to 1300 per 100,000 among the Amish of Indiana. Mutations in the calpain-3 gene lead to disruptions in a calcium protease involved in sarcomere remodeling. Onset is typically in childhood with hip girdle weakness. Shoulder girdle and distal extremity weakness may become more evident in later stages. Scapular winging may be prominent; however, facial muscles are usually spared, which helps distinguish calpainopathy from FSHD. Weakness is gradual but progressive, and most patients lose independent ambulation by early adulthood. There are no clear sex differences in the clinical presentation. CK is mildly to moderately elevated. Muscle biopsy typically shows nonspecific myopathic changes with type I fiber predominance in later stages. Immunohistochemical staining for calpain-3 is reduced or absent [35]. A small number of patients may have an eosinophilic infiltrate, although this feature is neither sensitive nor specific for calpainopathy [36]. Currently, there are no treatments for this disorder.

Identifying the Inclusion Body Myositis Patient

Inclusion body myositis (IBM) is probably the muscle disorder most frequently mistaken for autoimmune inflammatory myopathy. Indeed, as many as 50% of IBM patients are initially misdiagnosed as having polymyositis [37–39]. Although an inflammatory infiltrate is a key histological feature in muscle biopsies from these patients, there is also a profound degenerative element, and the relative contribution of each to muscle damage is the subject of active debate [40].

IBM is most common in men over the age of 50, although women may also be affected [37–39]. This contrasts to the younger age and female predominance seen in autoimmune myopathies. The onset of symptoms is insidi-

ous and chronic. Patients typically report frequent falls, difficulty climbing stairs and weak grip. IBM has a distinctive pattern of muscle involvement with predominant weakness and wasting of the quadriceps and distal forearm finger flexors. Asymmetry is common. Foot drop, facial weakness, and dysphagia may be seen at early or late stages; a small percentage of patients may have dysphagia as the sole presenting symptom [37–39, 41, 42]. Malignancy and other extramuscular manifestations are rare, although a relatively high prevalence of autoimmune diseases (e.g., rheumatoid arthritis and Sjogren syndrome) is reported in the IBM population [39, 43]. Despite this association, IBM shows little response to immunosuppressive therapy [38, 44–48]. Although exercise programs have demonstrated some modest benefit, progression is generally inexorable [37, 49, 50]. Mortality is not increased despite this significant morbidity [41].

Although recognition of the characteristic clinical features can usually suggest the diagnosis, many patients may require muscle biopsy. The cardinal histopathologic features include an autoaggressive inflammatory infiltrate composed primarily of CD8+ T-cells, which often invade non-necrotic myofibers. Rimmed vacuoles are common but may be absent in up to 25% of biopsies, especially at initial presentation [51]. Electron microscopy may reveal tubulofilamentous inclusions, but is not widely available [42]. Recent studies have also identified abnormal protein aggregates in IBM muscle, including beta-amyloid, tau, TDP-43, LC3, and p62; however, their diagnostic potential is not fully understood, and their use is largely limited to research settings or specialized neuromuscular centers [52–54].

Additional supportive features of IBM include moderately elevated serum CK levels and irritable myopathy on EMG, although mixed myopathic and neurogenic potentials can be seen as well. Nerve conduction studies demonstrate a concomitant mild, length-dependent, sensory, axonal polyneuropathy in about one-third of patients [42, 55]. Muscle MRI shows a pattern of inflammation, atrophy, and fatty infiltration involving the quadriceps, medial gastrocnemius, and tibialis anterior [56, 57]. Finally, a recently discovered antibody to cytosolic 5′-nucleotidase 1a (c5N1A), an enzyme involved in muscle contraction, is more specific for IBM (92–98%) compared to polymyositis; however, the sensitivity is relatively low (30–70%), and it may be positive in up to 20% of patients with dermatomyositis, lupus, and Sjögren syndrome [58–61].

Endocrinopathies and Muscle Symptoms

Hypothyroidism is the most common endocrinologic cause of muscle dysfunction. Although subjective symptoms of muscle impairment, such as weakness, fatigability, muscle pain, and cramps, are common, the actual rate of true hypothyroid myopathy is likely relatively low. Objective proximal muscle weakness is detected on examination in less than 40% of patients, and myopathic findings on EMG are seen in less than one-third [62, 63]. True hypothyroid myopathy is characterized by subjective muscle discomfort with mild to moderate proximal muscle weakness and delayed contraction and relaxation of deep tendon reflexes. The serum CK may be mildly to markedly elevated [64]. There is no clear correlation between the degree of hypothyroidism and the severity of weakness, although cases of necrotizing myopathy in the setting of severe hypothyroidism have been reported [64, 65]. Muscle biopsy may demonstrate type II fiber atrophy with occasional type I fiber hypertrophy [66]. Diagnosis is made by the identification of hypothyroidism in the setting of proximal muscle weakness with improvement seen over 6–8 months following thyroid hormone replacement. Testing for thyroid-stimulating hormone is sufficient in most cases; however, cases of myopathy associated with central hypothyroidism have been reported; thus, testing for free T4 is also recommended [65].

Hyperthyroidism is also associated with myopathy, although to a lesser extent. While 62% of newly diagnosed hyperthyroid patients had clinical evidence of proximal muscle weak-

ness on examination, only about 10% also had myopathic findings on EMG. Along with the lack of CK elevation, the rapidity of onset and resolution, and the positive correlation between severity of hyperthyroidism and degree of weakness, these findings suggest that the weakness associated with hyperthyroidism may be more consistent with functional muscle impairment than a true myopathy [64].

Other endocrinopathies can rarely lead to myopathy. Hyperadrenocorticism in Cushing syndrome causes a steroid-induced myopathy characterized by proximal muscle weakness and wasting. Other features of Cushing syndrome, such as abdominal stria, moon facies, and abnormal body fat distribution, are usually present. Hyperparathyroidism can occasionally cause a syndrome of proximal muscle weakness and wasting with brisk reflexes. Testing patients for parathyroid hormone and calcium levels is usually sufficient for diagnosis. Of note, diabetics may also develop diabetic amyotrophy, a syndrome of pain, weakness, and wasting of the proximal thigh muscles due to a lumbosacral radiculoplexopathy [67, 68].

Toxic Myopathies

Drugs or other toxins can damage myofibers either directly, causing necrosis, or indirectly, through disruptions in electrolyte balance, lysosomal activity, mitochondrial function, cytoskeletal networks, or immune mechanisms, among others. Many toxic myopathies present with subacute proximal weakness, elevated CK, and irritability on EMG and can easily be mistaken for myositis. In most cases, careful review of the history and medication list, as well as a muscle biopsy, will clarify the clinical picture. Most toxic myopathies occur within weeks to months of drug initiation, and symptoms typically improve or even resolve within weeks of lowering the dosage or stopping the drug completely. Failure to demonstrate some improvement in this time frame should prompt re-evaluation of the diagnosis. Among the most common toxic myopathies are those related to amphiphilic drugs, colchicine, antiretroviral agents, and alcohol, which will be reviewed in this section. Statin myopathy and steroid myopathy are two other important drug-related muscle disorders which will be reviewed separately.

Amphiphilic Drugs

This category includes (a) the antimalarial agents chloroquine and hydroxychloroquine, (b) the antiarrhythmic agents amiodarone and procainamide, and (c) the chemotherapeutic agent doxorubicin. These drugs are large cationic amphiphiles, which allow them to interact with and disrupt both the myofiber cell membrane and intracellular lysosomes. The pathological hallmark of muscle biopsy is a combination of necrosis, vacuolization of non-necrotic fibers, and accumulation of cytoplasmic curvilinear or myeloid bodies. The vacuoles are derived from lysosomes and stain positively on both acid phosphatase and lipid stains. Electron microscopic studies may reveal vacuoles containing autophagic degradation products and curvilinear lipid inclusions [69].

Patients present with slowly progressive proximal muscle weakness, usually after months to years of medication usage, even at relatively low doses. CK is often modestly elevated, and EMG shows irritable myopathic changes. Other systemic features of toxicity may also be present. For example, chloroquine may also be associated with axonal polyneuropathy, cardiomyopathy, and retinopathy. Amiodarone commonly causes hypothyroidism and peripheral neuropathy among other organ system toxicities. Excretion of these drugs is slow even after cessation, and symptoms typically require months for full recovery [70–73].

Antimicrotubular Myopathy

The primary drug in this category is colchicine, although vincristine can rarely cause myopathy as well. Colchicine disrupts microtubular

networks by binding to tubulin, leading to impaired lysosomal trafficking and the marked vacuolization seen on biopsy. Patients tend to be older men who have used the drug for months to years, usually for gout. Lower renal or hepatic function increases the risk of toxicity as well as the dose and duration of the drug exposure. Patients present with subacute proximal muscle weakness, elevated CK, and irritable myopathic changes on EMG. Concomitant sensorimotor axonal polyneuropathy is common. Biopsy reveals large, spindle-shaped vacuoles that stain positively for acid phosphatase and lipids. If performed, electron microscopy may also show disoriented and fragmented myofibrils. Recovery generally occurs within 4–6 weeks of drug cessation [70, 74, 75].

Antiretroviral Agents

The first FDA-approved therapy for HIV infection in 1986, zidovudine, has now largely fallen out of favor in the United States due to its prevalent side effects and the proliferation of newer, better-tolerated antiretroviral medications. Nonetheless, it is still commonly used in the developing world due to its relatively low cost. Myopathy is a known side effect of this medication, although toxic myopathy can be difficult to diagnose in this patient population due to potentially overlapping conditions, including HIV-associated inflammatory myopathy, wasting syndrome, and polyneuropathy. Total doses of >250 grams and treatment course >9 months increase the risk of myopathy [70].

Zidovudine-related toxic myopathy can present with a spectrum of symptoms ranging from mild myalgia with elevated CK to frank proximal muscle weakness. CK is often normal to mildly elevated, and EMG demonstrates irritable myopathic changes [70, 76, 77]. The likely mechanism is mitochondrial dysfunction given the findings on muscle biopsy of ragged red fibers and numerous COX-negative fibers. Necrosis, degeneration, and lysosomal proliferation are also common features [76, 78]. While most patients do demonstrate improvement following drug cessation, unfortunately, not all will demonstrate complete recovery [70].

Alcohol

Alcoholic myopathy can manifest in both acute and chronic forms. The acute form may present as a necrotizing myopathy in which muscle swelling, cramps, and pain are common. In about half of patients, the CK is elevated to 2–10 times the upper limit of the normal range. Myoglobinuria may also be present. Treatment involves cessation of alcohol consumption with improvement of pain and strength generally seen within 1–2 weeks. An acute hypokalemic alcoholic myopathy may also be seen, usually during the withdrawal period. Muscle pain is uncommon, although CK may be elevated by 2–20 times the upper limit of normal. Key to the diagnosis is a low serum potassium (<2.5 mEq/L). Marked vacuolar changes on muscle biopsy would support the diagnosis as well. Improvement of muscle strength is usually evident within days of potassium repletion, and complete recovery is usually achieved within 2–3 weeks [70].

Chronic alcoholic myopathy affects up to two-thirds of chronic alcohol abusers [79], manifesting as proximal weakness with CK elevations of 2 to 5 times the upper limit of normal in about half of these patients. Muscle biopsy demonstrates nonspecific changes, including type II fiber atrophy, fiber size variation, and occasional necrosis and a myopathic EMG [70, 80]. Cessation of alcohol consumption is the mainstay of therapy. Patients who are able to successfully abstain from alcohol demonstrate improvement both functionally and histologically, although strength may not completely recover [80].

Self-Limited Statin-Associated Myopathic Symptoms

With more than 39 million adults in the United States taking statin medications [81], it is imperative for the physician to recognize and manage the spectrum of statin-associated muscle dis-

orders. Muscle symptoms affect up to 10% of patients on statins and are a common reason for statin discontinuation [82, 83]. Patients may develop symptoms at any point during statin therapy, although onset is most common in the first month after initiation [82]. Risk factors for statin-associated muscle disorders include female gender, low BMI, hypothyroidism, renal or hepatic dysfunction, and the use of other medications that interfere with statin metabolism [84]. Genetic factors, including a single nucleotide polymorphism in the SLCO1B1 gene on chromosome 12, are also associated with an increased risk of statin-associated myopathy [85]. Of note, higher statin dosages have been associated with increased rates of toxicity [86].

The most common statin-associated symptom is myalgia, which affects 11–29% of patients on statins. Patients report muscle pain, stiffness, or cramps, which may be generalized or localized to the thighs and calves. In patients with myalgia alone, strength is intact and CK is normal [82, 87]. Of note, some patients may present with asymptomatic hyperCKemia on statins. The diagnosis of statin-related myopathy is less common and requires objective weakness in addition to muscle discomfort. The CK level may be mildly to moderately elevated [87, 88]. Rhabdomyolysis is the rarest and most severe form of statin-associated muscle toxicity. In this condition, weakness and markedly elevated CK levels (>10,000 IU/L) are accompanied by myoglobinuria, renal impairment, and electrolyte abnormalities [88, 89].

All patients with weakness, significantly elevated CK level (>3–5 times the upper limit of normal), and/or intolerable symptoms should stop statin therapy. If improvement is seen after several weeks, re-challenge could be considered at a lower dose or the use of a non-CYP 3A4-metabolized statin such as pravastatin or fluvastatin, with careful clinical and CK monitoring. While the majority of patients are able to tolerate re-initiation [90], recurrence of symptoms supports a diagnosis of statin-associated muscle disorder and alternative lipid-lowering therapy should be considered. If symptoms continue despite statin cessation, muscle biopsy can be considered to rule out other causes of myopathy. It should be noted, however, that muscle symptoms can persist up to 14 months following statin cessation and CK tends to lag behind clinical improvement [91, 92]. Muscle biopsies are usually not indicated in patients with suspected statin-related myopathy. If performed, the biopsy may be normal or may exhibit nonspecific abnormalities (e.g., COX-negative fibers, increased lipid stores, and cytoplasmic vacuoles [92, 93]) or myofiber necrosis (in the case of acute statin-triggered rhabdomyolysis).

Steroid Myopathies

Steroid myopathy is one of the most common types of drug-induced myopathy and may be mistaken for an exacerbation of autoimmune myopathy or polymyositis due to the distribution of weakness. Patients typically present with slowly progressive, painless, proximal muscle weakness affecting the pelvic girdle more than the upper extremities. Other features of Cushing syndrome are often present, including obesity, moon facies, buffalo hump, striae, and osteoporosis. CK is normal to slightly elevated. Although normal in early stages, EMG may show a nonirritable myopathy later in the disease. The most striking feature on muscle biopsy is type II myofiber atrophy, although other nonspecific myopathic features can also be seen [70, 94].

Steroids exert a direct catabolic effect on skeletal muscle, leading to myofiber atrophy rather than degeneration. While any individual can develop steroid-induced myopathy, older age, concomitant malignancy, and physical inactivity increase the risk [95–97]. Fluorinated glucocorticoids, such as dexamethasone, betamethasone, and triamcinolone, are also associated with greater risk of myopathy compared to nonfluorinated prednisone and prednisolone [95, 98]. Dose-effect is variable with some patients developing myopathy soon after initiation of low-dose glucocorticoids while others remaining unaffected even after months of therapy with high doses. Generally, however, doses equivalent to 10 mg/day or less of prednisone are rarely associated with myopathy, whereas doses equivalent to 30 mg/day or more of prednisone increase the risk of myopathy [95, 96].

Treatment involves cessation or reduction of steroid therapy if possible. Some improvement should be noticeable within 3–4 weeks, although months may be required for complete recovery. If the patient is unable to completely stop steroid therapy, then the lowest possible dose should be utilized, and therapy should be switched to a non-fluorinated preparation if applicable [70, 95].

Other Myositis Mimics

Infectious myopathies include viral myositis, bacterial pyomyositis, protozoan infection (e.g., *Toxoplasma gondii*, *Borrelia*, *Ehrlichia*), and helminthic infection (e.g., trichinosis, cysticercosis). These are more common in immunocompromised individuals and are generally accompanied by other infectious symptoms. Some systemic metabolic diseases may also be accompanied by myopathy, including sarcoidosis, amyloidosis, and porphyria [101].

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24 Immune-Mediated Necrotizing Myopathy (IMNM)

Brittany Adler and Lisa Christopher-Stine

Introduction

Immune-mediated necrotizing myopathy (IMNM), also known as necrotizing autoimmune myopathy (NAM), is a recently recognized subgroup of myositis within the idiopathic inflammatory myopathies. Approximately 20% of idiopathic inflammatory myopathies can be subclassified as IMNM [1]. Like other idiopathic inflammatory myopathies, IMNM is thought to have an autoimmune etiology based on the presence of specific autoantibodies and a clinical response to immunosuppression. Although IMNM was not previously differentiated from polymyositis in the 1975 criteria for idiopathic inflammatory myopathy established by Bohan and Peter [2, 3], there has been an increasing recognition that IMNM is a distinct clinical entity. It was formally reclassified as its own subgroup at the 119th Muscle Study Group/European Neuro-Muscular Centre (MSG/ENMC) in 2003 [4].

Key Clinical Features of IMNM Patients with IMNM present with similar clinical symptoms as polymyositis, mainly proximal muscle weakness without dermatomyositis rashes. Compared to the other idiopathic inflammatory myopathies, patients with IMNM tend to have higher CK levels, more prominent myalgias [5], and more extensive muscle atrophy and functional disability [6]. Because the presentation in IMNM can be indistinguishable from that of other inflammatory myopathies, the muscle biopsy in IMNM is often important in making the diagnosis. Histologically, patients with IMNM have prominent myocyte necrosis and muscle fiber regeneration and a relative paucity of lymphocytic infiltration [7]. The extensive muscle necrosis may explain why CK levels are higher in IMNM compared to the other myopathies.

Key clinical features of IMNM	
Age and gender	Males and females, although females and younger age more common with anti-SRP; older age (>50) more common with anti-HMGCR
Presentation	Similar to PM: Severe proximal muscle weakness with myalgia
Onset	Acute to subacute in anti-SRP, subacute to insidious in anti-HMGCR mostly after exposure to statins
Other	No rash and rare extramuscular features with anti-HMGCR
Muscle enzymes	Very high CK levels
Muscle biopsy	Muscle fiber necrosis with little or no endomysial inflammation
EMG/MRI	Irritable myopathy pattern/muscle edema
Prognosis	Refractory to therapy, early muscle atrophy, and early loss of function
Treatment	Aggressive immunosuppression for anti-SRP; early IVIg for anti-HMGCR

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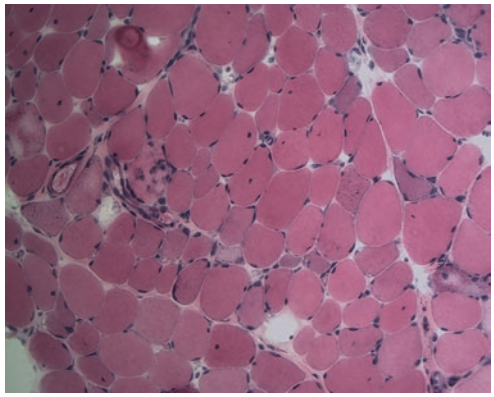

Necrotizing Myopathy Muscle Biopsy Frozen H&E stain shows rounded atrophy, myofiber degeneration and regeneration, necrosis, myophagocytosis, and internalized nuclei.

Differential Diagnosis of IMNM Although muscle fiber necrosis is a characteristic feature of IMNM, necrosis is a nonspecific finding, and therefore, a diagnosis of IMNM cannot be made based on histology alone. Genetic, toxic, or endocrinologic myopathies [8] can also induce muscle fiber necrosis, as well as some viral infections including HIV [9] and hepatitis C [10]. The limb-girdle dystrophies, dysferlinopathy, and fascioscapulohumeral muscular dystrophy can be challenging to distinguish from IMNM as they can have a similar necrotizing histopathology and a subacute presentation with proximal muscle weakness and elevated CK [11, 12]. Drugs such as zidovudine (AZT) [13, 14], amiodarone [15], telbivudine [16], vincristine [17], as well as statins and fibrates cause a self-limited necrotizing myopathy. Lastly, endocrinopathies such as hypothyroidism can cause a necrotizing myopathy [18], so IMNM should prompt a thorough medical history including the determination of autoantibodies.

Differential diagnosis of IMNM	
Other idiopathic inflammatory myopathies	Polymyositis
Muscular dystrophies	Limb-girdle muscular dystrophy, dysferlinopathy and fascioscapulohumeral muscular dystrophy
Drugs	Statin myopathy, fibrates, zidovudine, amiodarone, vincristine, telbivudine, etc.
Endocrinopathies	Hypothyroidism
Infections	HIV, hepatitis C
Injury	Rhabdomyolysis

Diagnostic Criteria for IMNM The 2003 ENMC workshop established specific criteria for the diagnosis of IMNM including an elevated CK, subacute or insidious proximal muscle weakness, and the lack of a DM rash. Three laboratory criteria are necessary: (1) myopathic EMG, (2) MRI evidence of muscle edema, or (3) positive myositis-specific autoantibodies. Lastly, patients must have muscle fiber necrosis and sparse inflammatory cells on muscle biopsy [4]. The 2003 ENMC workshop-specific criteria for the diagnosis of IMNM are shown in Table 24.1.

Table 24.1 2003 Muscle Study Group/European Neuromuscular Centre (MSG/ENMC) diagnostic criteria for IMNM [4]

Diagnostic criteria	
Clinical	Inclusion criteria: Age > 18 years. Subacute or insidious onset. Symmetric proximal > distal and neck flexor > neck extensor weakness. Exclusion criteria: Clinical features of IBM. Ocular weakness, isolated dysarthria, neck extensor>flexor weakness. Toxic myopathy, active endocrinopathy, amyloidosis, family history of muscle dystrophy, or proximal motor neuropathies (SMA).
Laboratory (biochemical)	Elevated CK.
Laboratory (1 of 3)	Abnormal EMG: Fibrillation potentials, positive sharp waves, or complex repetitive discharges, short-duration, small amplitude, polyphasic MUAPs. Muscle MRI: Increased signal (edema) within muscle on STIR images. Serum myositis-specific antibodies.
Biopsy	Prominent muscle fiber necrosis. Sparse inflammatory infiltrate, no perimysial infiltrate. MAC deposition on small vessels or pipestem capillaries. Rare tubuloreticular inclusions in endothelial cells.

Types of IMNM IMNM is a heterogenous group of diseases that can occur in isolation (usually autoantibody associated) or be secondary to a connective tissue disease (CTD) or malignancy. The two known autoantibodies associated with IMNM are anti-signal recognition particle (anti-SRP) and anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase (anti-HMGCR), one of which is identified in approximately two-thirds of IMNM cases [19]. In approximately one-third of cases, no known myositis-specific autoantibody is identified. Although IMNM may occur in the absence of pathologic autoantibodies, it is more likely that additional autoantibodies have not yet been discovered. Anti-HMGCR and anti-SRP myopathy will be the focus of this chapter, but IMNM in the setting of CTD and malignancy will also be discussed.

Anti-HMGCR Autoantibody-Positive Myopathy, Also Called Statin-Associated Immune-Mediated Necrotizing Myopathy

Anti-HMGCR Ab+ myopathy accounts for approximately 6% of all idiopathic inflammatory myopathies [20] and 40% of all IMNM [19]. This syndrome is in most cases associated with statin use and is sometimes called statin-associated IMNM. It is clinically and pathologically distinct from the more common statin intolerance experienced by many patients (self-limiting statin myopathy), which typically manifests as myalgias and a mildly elevated CK and, in some cases, muscle weakness or rhabdomyolysis and resolves with statin discontinuation in weeks to months. By contrast, statin-associated IMNM is a severe autoimmune disease defined by the presence of autoantibodies against HMGCR, and it does not resolve after statin withdrawal and often requires immunosuppression.

Anti-HMGCR Ab+ myopathy presents as noted above (Table 24.1) with subacute or insidious proximal muscle weakness, markedly elevated CK levels, irritable myopathy on electromyogram, and muscle edema on MRI. The HMGCR autoantibody should only be checked when the features suspicious for this syndrome are seen. The CK level on presentation ranges from 3000 to 24,000 U/L (average 10,000 U/L) [19], with an elevated serum aldolase in about 75% of patients [21]. Patients do not present with rhabdomyolysis as muscle breakdown is generally subacute or chronic and in less than 20% of patients the CK is normal [21], typically in long-standing disease secondary to muscle atrophy. Dysphagia occurs in 25–60% of patients and 20% experience weight loss [7, 22], but extramuscular features such as interstitial lung disease (ILD), rash, sicca complex, arthritis, and Raynaud phenomenon are notably rare. Anti-HMGCR Ab+ myopathy affects males and females equally [19]. Seemingly, African-American patients are more likely to be statin-naïve and have inflammatory infiltrates on muscle biopsy [20].

Statin Association In older adult cohorts, the vast majority of patients (over 90%) with anti-HMGCR Ab+ myopathy report statin use [20], but statin exposure may be even higher as patients may be unknowingly exposed to supplements such as red yeast rice which contains statins. However, statin-induced myopathy remains an extraordinarily rare complication of statin use with an estimated incidence of only 2 per million per year [23]. Since screening of serum from hyperlipidemic subjects on a statin or patients with self-limiting statin myopathy identified no anti-HMGCR autoantibodies [24], we do not recommend that patients be tested for HMGCR autoantibodies prior to starting statin therapy or in patients with a self-limiting statin myopathy.

The onset of anti-HMGCR+ myopathy generally occurs after several years of statin use with a range between 2 months and 6 years [25], highlighting the need for vigilance even in patients who have been doing well on a statin for years. It rarely develops after cessation of a statin and is seen with multiple statins, including atorvastatin (Lipitor), simvastatin (Zocor), fluvastatin (Lescol), and rosuvastatin (Crestor). The risk of anti-HMGCR+ myopathy is higher with atorvastatin compared to rosuvastatin or simvastatin [26], and an association between statin dose and

risk of anti-HMGCR+ myopathy has not yet been demonstrated. Type II diabetes is a significant risk factor for unclear reasons [26].

Although statin exposure is the greatest known risk factor for anti-HMGCR Ab+ myopathy, there is increasing evidence that patients may develop this disease in the absence of statin exposure, particularly in younger patients [21]. As few as 45% of patients in a younger European cohort of anti-HMGCR Ab+ myopathy reported a history of statin use [27]. In addition to being younger, statin-naïve HMGCR+ myopathy patients have a higher CK, are less likely to be Caucasian, and do not respond well to immunosuppression compared to statin-exposed patients [18, 28]. There are also reports of children (even infants) with anti-HMGCR Ab+ myopathy, further supporting that statin exposure is not necessary for developing this disease [29]. Pediatric cases of anti-HMGCR Ab+ myopathy are mistaken for congenital muscular dystrophy [29], highlighting the importance of assessing autoantibody status and obtaining a muscle biopsy even when statin use is not suspected. Certainly, many cases of this treatable myopathy are missed because of poor disease awareness and the incorrect assumption that this is an exclusively statin-associated disease.

Genetic and Environmental Association There are strong immunogenetic risk factors that predispose to anti-HMGCR Ab+ myopathy. The major histocompatibility (MHC) type II human leukocyte antigen (HLA) allele DRB1*11:01 has been identified as a major genetic risk factor across a wide spectrum of races and ethnicities, including Caucasians, African-Americans, and Japanese [30–32].

Pathology and Pathogenesis The pathogenesis of anti-HMGCR autoantibodies in the development of myopathy remains unclear. Anti-HMGCR autoantibodies target the intracellular catalytic domain of HMGCR, an important enzyme in the cholesterol synthesis pathway that is inhibited by statins. Statins upregulate HMGCR, which is thought to contribute to the initiation of autoimmunity. Regenerating muscle fibers also upregulate HMGCR, and this may help perpetuate the immune response [20]. HMGCR antibodies correlate with CK levels and strength and decrease with treatment, although they rarely normalize even in patients who achieve remission [28]. Thus, anti-HMGCR autoantibodies are specific for autoimmune necrotizing myopathy.

Muscle biopsies from patients with anti-HMGCR Ab+ myopathy demonstrate characteristic necrotic myofibers and muscle fiber regeneration. There is a notable paucity of inflammatory infiltrate, although a minority of patients do have collections of inflammatory cells in a perivascular distribution [20]. There is also MHC Class I upregulation on non-necrotic muscle fibers. Macrophages, which are involved in muscle regeneration and phagocytosis of necrotic muscle fibers, are universally present. T-cell and B-cell infiltration are found in only a small number of muscle specimens with T cells having sparse endomysial distribution [33].

The lack of inflammatory cells suggests that mechanisms other than cellular cytotoxicity may be important in the pathogenesis of necrotizing myopathies. Abnormal capillary endomysial complement deposition [i.e., membrane attack complex (MAC) C5b9] is seen [34, 35]. A distinct morphological feature termed "pipestem capillaries" has been described in which there is increased thickness of the vascular wall with deposition of MAC [36]. However, the role of complement in the pathogenesis of IMNM remains unclear.

Anti-SRP Autoantibody-Positive Myopathy

Approximately 3–6% of all patients with idiopathic inflammatory myopathies [7, 37, 38] and 15–20% of patients with immune-mediated necrotizing myopathy [19] have antibodies that recognize signal recognition protein (SRP) leading to rapidly progressive symmetrical proximal muscle weakness, severe myalgias [34], markedly elevated CK levels, and frequently severe muscle atrophy and disability within months [39]. It is not

uncommon for patients to be bed-ridden on presentation, which is unusual in anti-HMGCR Ab+ myopathy. In severe disease, distal muscles as well as bulbar and trunk musculature can be affected [40] and dysphagia is very common [22, 38, 39]. Other autoimmune features include Raynaud phenomenon in 20–76% [7, 38, 41] and an occasional debilitating inflammatory arthritis. The rashes of DM are notably absent. Cardiopulmonary complaints are common, including dyspnea on exertion, and ILD has been reported in up to 25% of patients [39]. Patients with anti-SRP+ myopathy report more subjective palpitations than other types of myopathies [42], and there are reports of arrhythmias, conduction abnormalities on EKG [39] [38], congestive heart failure, and cardiac fibrosis. Pulmonary function tests should be obtained at baseline to monitor for both respiratory muscle involvement and ILD, and any complaints of dyspnea should be evaluated with a thorough pulmonary and cardiac workup.

Anti-SRP Ab+ myopathy most often presents in young- to middle-age [39] patients, but it can also be seen in the pediatric or elderly population [29, 43]. It disproportionately affects females compared to males in a 3:1 ratio [39] and more commonly occurs from August to January [34], suggesting a viral trigger. Statin exposure is not a risk factor. The genetic risk factors for anti-SRP Ab+ myopathy are distinct from those that predispose to anti-HMGCR Ab+ myopathy. In particular, HLA-B*5001 and DQA1*0104 are found in greater frequency in patients with anti-SRP Ab+ myopathy in the United States [44].

The diagnostic evaluation for anti-SRP Ab+ myopathy is similar to that in other types of myositis including monitoring the CK (typically in the range of 3000–25,000 IU/L at onset) [34]. An irritative pattern on electrodiagnostic testing is seen due to myonecrosis. Muscle MRI can be useful to guide the optimal location for a muscle biopsy. MRI shows more prominent muscle edema compared to other types of myopathy, including statin-associated IMNM, and demonstrates more extensive muscle atrophy and early fatty replacement [45]. Fascial involvement is less common than with DM. Muscle biopsy in anti-SRP Ab+ myopathy demonstrates myopathic changes with prominent myocyte necrosis, minimal inflammation, and endomysial fibrosis that is indistinguishable from biopsies from patients with anti-HMGCR Ab+ myopathy.

The role of anti-SRP autoantibodies in the pathogenesis of anti-SRP Ab+ myopathy remains unclear, although there is some evidence that antibodies may play a pathogenic role in the disease. In particular, anti-SRP autoantibody titers correlate with CK levels [46, 47]. There is also evidence in vitro that anti-SRP autoantibodies may directly inhibit SRP-dependent protein translocation into the endoplasmic reticulum [48]. Moreover, sera from patients with anti-SRP Ab+ myopathy can induce myonecrosis of cultured myoblasts through a complement-mediated mechanism [49] (Table 24.2).

Autoantibody-Negative Immune-Mediated Necrotizing Myopathy

Little is known about the group of patients with autoantibody-negative necrotizing myopathy. Studies on this group of patients are limited by the heterogeneity of the disease. Seronegative patients generally have a similar clinical presentation and biopsy features as patients with necrotizing myopathy with anti-HMGCR and anti-SRP autoantibodies. One notable difference is that this group of patients has a higher rate of cancer-associated myositis with a frequency of approximately 25% necessitating more vigilant cancer screening especially within 3 years of the onset of myositis and in patients over the age of 50 years [50].

Immune-Mediated Necrotizing Myopathies Associated with Anti-Synthetase Syndrome and Other Connective Tissue Diseases

There are multiple reports of necrotizing myopathy occurring in association with antisynthetase syndrome [51, 52]. In one series of 38 patients with necrotizing myopathy on muscle biopsy,

Table 24.2 Key distinguishing features of anti-HMGCR Ab+ and anti-SRP Ab+ IMNM

	Anti-HMGCR Ab+ myopathy	Anti-SRP Ab+ myopathy
Prevalence	40% of IMNM, ~6% of all myositis	15–20% of IMNM, 3–6% of all myositis
Risk factors	Statin use (most [80%], but not all cases), usually months to years of exposure; no improvement with discontinuation	Unknown
Genetic risk factors	DRB1*11:01	HLA-B*5001, DQA1*0104 (United States), HLA-DRB1*08:03 (Japan)
Sex ratio (M:F)	1:1	1:3
Age	Middle-age to elderly (though can affect children and young); Younger patients tend to be less statin-associated, higher CK, more non-Caucasian, and refractory to therapy	Younger age group is more common (though can affect children or elderly)
Clinical manifestations	Subacute to chronic Mild-moderate muscle weakness Markedly elevated CK levels Dysphagia (50%)	Acute to subacute Severe muscle weakness Markedly elevated CK levels Dysphagia (66%) Prominent myalgias
Extramuscular manifestations	No ILD No arthritis or Raynaud No DM rash	ILD (25%) Arthritis and Raynaud present but mild Rare DM rash
Malignancy risk	Increased	No known cancer association
EMG	Irritable myopathic pattern	Irritable myopathic pattern
MRI	Muscle fiber edema, muscle atrophy, fatty replacement	Muscle fiber edema, muscle atrophy, fatty replacement
Histopathological features	Necrotizing myocytes and muscle fiber regeneration, mild lymphocytic infiltrate, MAC deposition	Necrotizing myocytes and muscle fiber regeneration, mild lymphocytic infiltrate, MAC deposition
Treatment	Often responds to IVIG with or without steroids Steroid plus additional immunosuppressive Mycophenolate mofetil Methotrexate Azathioprine Rituximab Tacrolimus	Need aggressive immunosuppressive approach with multiple therapies Prednisone 1 mg/kg IVIG 2 g/kg/month Mycophenolate mofetil Methotrexate Azathioprine Rituximab Tacrolimus Cyclophosphamide
Prognosis	Variable. Age >50 or statin association is a favorable feature Age <50 or non-statin association is more refractory	Usually refractory leading to early muscle atrophy and disability

42% had anti-HMGCR antibodies and 6 had anti-SRP antibodies but 2 each had anti-PL-12 or anti-PL-7 antibodies, while one was anti-Jo-1 positive [19]. Therefore, the antisynthetase autoantibodies should be ascertained in the routine evaluation of IMNM. Necrotizing myopathy can also occasionally be seen on muscle biopsy from patients with DM, so a careful skin examination should also be performed.

Necrotizing myopathy has also been described in other connective tissue diseases, most notably scleroderma [53–55] but also systemic lupus erythematosus overlap syndromes [5]. In one study of 25 patients with scleroderma-polymyositis overlap syndrome, almost all the patients (96%) had muscle fiber necrosis and 9 (37%) had minimal lymphocytic infiltrate on muscle biopsy [56]. Myositis-specific autoantibodies are often absent

in overlap syndromes except anti-SSA/B antibody which can be seen with or without clinical Sjogren overlap. Anti-PM-Scl antibody is sometimes detected in scleroderma myositis overlap patients [5]. An appropriate history and laboratory evaluation for an underlying connective tissue disease should be obtained for all patients with IMNM.

Cancer-Associated Necrotizing Myopathy

There have been numerous reported cases of cancer-associated IMNM since the first case was described in 1969 [57–59]. The most common malignancies seen with IMNM are gastrointestinal adenocarcinomas and small cell and non-small cell carcinomas of the lung, although larger-scale studies are needed to confirm these associations [53]. In our experience, patients with cancer-associated necrotizing myopathy tend to have more fulminant and refractory disease compared to patients without an associated malignancy. Although the nature of this association with cancer remains unclear, it is possible that a malignancy can induce the inflammatory myopathy as a paraneoplastic phenomenon, as has been described in other diseases [60].

Although there is an increased risk of a cancer diagnosis within the first few years of onset of IMNM [61], the risk of malignancy varies depending on the autoantibody status of the patient. The risk is highest in those patients who do not have an identifiable myositis-associated autoantibody [50]. Patients with anti-HMGCR Ab+ myopathy may also have an increased risk of cancer, although it needs to be confirmed in subsequent larger studies if the increased risk is more than the baseline risk in the elderly population it targets [62]. There is no known association between malignancy and anti-SRP Ab+ myopathy, and these patients therefore do not require more frequent cancer screening unless there is a clinical suspicion for malignancy [50].

The clinical course of paraneoplastic necrotizing myopathy is variable, and some patients have disease that is refractory to treatment, while others have a more favorable prognosis [61, 63]. Although some patients can achieve remission of their myopathy after treatment of the underlying malignancy [64, 65], severity of the myopathy does not always parallel growth of the tumor. Some patients have persistent autoimmunity even after the cancer is successfully treated, which suggests that the immune response can self-perpetuate even after the inciting trigger is removed. Patients with paraneoplastic necrotizing myopathy often require immunosuppressive and immunomodulatory therapies that are similar to those given to IMNM patients without an associated malignancy.

Selected Management Features

New-onset necrotizing myopathy requires prompt recognition and initiation of treatment to prevent fatty replacement and atrophy in the muscle and permanent disability. Although prednisone is often used initially, the response is often partial, necessitating additional disease-modifying therapy. In a Mayo Clinic cohort of IMNM patients, over 90% of patients required combination immunomodulatory therapies [66]. However, no clinical trials to date have effectively compared the efficacy of these different treatments. Intravenous immunoglobulin (IVIG), methotrexate, azathioprine, mycophenolate mofetil, rituximab, and, occasionally, tacrolimus or cyclosporine have all been used in the treatment of IMNM. In severe or refractory cases, glucocorticoid pulse therapy, cyclophosphamide or plasmapheresis can be considered [27].

Management of Anti-HMGCR Ab+ Myopathy

The management of statin-exposed and statin-naïve anti-HMGCR Ab+ myopathy is similar, although statin-naïve patients are typically less responsive to immunosuppressive therapy [18]. In our experience, patients with anti-HMGCR Ab+ myopathy generally have only a modest initial response to prednisone, and an additional immu-

nomodulatory agent is almost always necessary [19, 27]. Anecdotally, we have used IVIG with considerable success in statin-associated necrotizing myopathy, sometimes achieving disease control with IVIG monotherapy administered at a dose of 2 g/kg/month. Although patients can have an excellent clinical response to IVIG alone, many continue to have elevated CK levels and persistent HMGCR autoantibody titers, which suggests that IVIG attenuates myopathy but does not extinguish the autoimmune process [67].

For more refractory patients failing IVIG monotherapy, other immunosuppressive agents should be added. Mycophenolate mofetil, methotrexate, azathioprine, and rituximab have all been used to treat anti-HMGCR Ab+ myopathy, but no clinical trials have compared their efficacy. Prolonged treatment with multiple immunomodulatory agents is required and relapses are common. Sixty percent of patients in one cohort required two immunosuppressive agents in addition to prednisone at some point during their course [28], while five of six anti-HMGCR+ myopathy patients treated with prednisone and various immunomodulatory agents relapsed with tapering of prednisone. This highlights the importance of a gradual and prolonged steroid taper over the course of months in this patient population [68].

The safety of reintroducing statins or other cholesterol agents in statin-induced autoimmune myopathy is not yet clear and relapse can occur with re-exposure to a statin. If cholesterol-lowering therapy due to high cardiovascular risk is necessary, it is advisable to use nonstatin medications or non-CYP3A4 inhibiting statins at the lowest possible dose. No data exists on the safety of other cholesterol-lowering agents such as ezetimibe or the new class of PSK-9 inhibitors in patients with HMGCR Ab+ myopathy.

Anti-SRP+ Myopathy

Patients with anti-SRP+ myopathy generally have more severe disease on presentation compared to anti-HMGCR+ myopathy and require a long-term multimodal treatment approach with immunosuppressive agents. Over half the patients are refractory to therapy [40] and half relapse when immunosuppression is tapered [39, 66]. Many have refractory myopathy requiring at least three trials of different immunosuppressive agents and combination therapy [38]. Approximately one-third of patients have a favorable treatment response achieving adequate disease control [38]. Even among patients who respond well clinically and serologically to immunosuppression, many continue to develop significant muscle atrophy and do not return to their baseline muscle strength [39, 40].

Although IVIG can be useful in anti-SRP+ myopathy, IVIG monotherapy or combination therapy with IVIG and steroids are often insufficient and patients typically require additional immunosuppression. Similar to anti-HMGCR Ab+ myopathy and unlike other idiopathic inflammatory myopathies, patients with anti-SRP+ myopathy are frequently resistant to steroids [34]. Methotrexate, azathioprine, mycophenolate mofetil, and rituximab are reported to be beneficial in anti-SRP+ myopathy. In our experience, rituximab is more effective in anti-SRP+ myopathy than in anti-HMGCR Ab+ myopathy. Among eight patients with refractory anti-SRP Ab+ myopathy, six had improved strength and CK levels as well as decreased anti-SRP autoantibody levels after treatment with rituximab [69]. However, rituximab is not always successful, and there are several reports of rituximab failure in anti-SRP Ab+ myopathy [70]. Tacrolimus and cyclosporine can also be effective therapeutic approaches especially when interstitial lung disease is present. High-dose cyclophosphamide may be one option to achieve durable remission in patients otherwise refractory to other agents [71].

Conclusion

In summary, immune-mediated necrotizing myopathy (IMNM) is a distinct subset of the idiopathic inflammatory myopathies that is characterized histologically by necrotizing muscle fibers and a minimal inflammatory infiltrate. Compared to the other myopathies, patients tend to have very high CK levels and more severe weakness and

muscle atrophy. Anti-SRP and anti-HMGCR antibodies are the two known autoantibodies associated with IMNM. One-third of patients do not have any identifiable myositis-specific antibodies, and it is possible that some autoantibodies associated with IMNM have yet to be discovered. Statin use and malignancy are the greatest risk factors for IMNM, although the risk of malignancy varies with autoantibody status. Patients often respond well to immunosuppression and immunomodulatory agents, although many patients require a multimodal treatment approach and flare when therapy is tapered.

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Cancer-Associated Myositis

25

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Key Points to Remember

- The DM phenotype is most frequently associated with cancer.
- Risk factors for cancer include age, gender, myositis subtype, autoantibody subset, severe skin rashes, or refractory disease.
- Protective factors include anti-PM-Scl, antisynthetase antibodies, and interstitial lung disease.
- Cancer screening in patients with myositis should include an autoantibody profile, mainly anti-TIF1-γ, and anti-NXP-2 in DM.
- Screening is achieved by a comprehensive history and physical examination and basic lab tests as well as imaging including a pan-CT of chest/abdomen/pelvis or whole-body PET/CT and age- and gender-appropriate mammogram, PAP smear, PSA, and colonoscopy.
- Myositis and cancer do not always follow a parallel outcome.
- A close relationship between the myositis treating physician and oncologist is recommended for the optimal management of patients with CAM.
- IVIG and prednisone are favored therapies for CAM.

Introduction

The initial reports suggesting a relationship between dermatomyositis (DM) and cancer were published in 1916 by Stertz [1] and Kankeleit [2], who described two patients with gastric and breast cancer, respectively. Subsequently, several reports suggested a relationship between myositis and cancer [3]. In the seminal paper of Bohan and Peter [4], Cancer-associated myositis (CAM) was included as a clinical subset. In 1985, Manchul et al. [5] reported an increased risk of cancer in both DM and polymyositis (PM) patients (21%) compared with nonmyositis control groups (4%), noting that most cancer cases occurred before or at the onset of myositis. They found no increased incidence of cancer after the onset

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of myositis, leading them to propose that cancer screening was unnecessary after the diagnosis of myositis. Lakhanpal et al. [6] later compared myositis patients with an age- and sex-matched control group noting a nonsignificant increase in cancer risk (25% vs. 17%) concluding that an association between cancer and myositis was possible, but not clinically relevant. Due to more robust European cancer registries in the 1990s, epidemiologic studies clearly demonstrated an association between cancer and myositis. In 1992, Sigurgeirsson [7] showed that the relative risk of cancer at myositis onset or later was increased and was higher in DM than PM patients. Similar results were later reported by Airio et al. [8] in Finland, Chow et al. [9] in Denmark, Stockton et al. [10] in Scotland, Buchbinder et al. [11] in Australia, and Chen et al. [12] in Taiwan. Moreover, meta-analyses from Zantos et al. [13] and Hill et al. [14] confirmed these findings (Table 25.1).

Epidemiology

Epidemiological studies have reported varying rates of cancer in DM and PM with different relative risk (RR), odds ratio (OR), or standardized incidence ratio (SIR) (i.e., the reported number of cancer cases/expected number of cancer cases according to national age-specific, sex-specific, and period-specific cancer rates) (see Table 25.1). Differences are due to varying demographic and geographic issues but also relate to differences in cancer definition, detection methods, ascertainment of the data, etc. A large meta-analysis of pooled data from Sweden, Finland, and Denmark reported an SIR of 3.0 for DM and 1.4 for PM, with 30% and 14% cancer frequency in DM and PM, respectively [14]. Another meta-analysis of four different studies showed an overall combined relative risk of cancer of 4.4 (95% CI 3.0, 6.6) and 2.1 (95% CI 1.4, 3.3) in DM and PM, respectively [13].

Table 25.1 Main epidemiologic studies in cancer-associated myositis

	Type of study	Patients		Prevalence of cancer		Measure of effect	Statistic (95% CI)	
		DM	PM	DM	PM		DM	PM
Manchul et al. [5]	Case–control Cohort	31	40	26% (8)	18% (7)	OR: odds ratio	4.49 (1.4–14.2)	
Lakhanpal et al. [6]	Case–control	50	65	22% (11)	28% (18)	OR: odds ratio	1.6 (0.8–3)	
Sigurgeirsson et al. [7]	Cohort	396	392	24% (94)	15% (58)	RR:	Men: 2.4 (1.6–3.6) Women: 3.4 (2.4–4.7)	Men: 1.8 (1.1–2.7) Women: 1.7 (1–2.5)
Zantos et al. [13]	Meta-analysis	513	565	14%		OR: odds ratio	4.4 (3.0–6.6)	2.1 (1.4–3.3)
Airio et al. [8]	Cohort	175	71	36% (63)	37% (26)	SIR	6.5 (3.9–10)	1.0 (0.5–1.8)
Chow et al. [9]	Cohort	336	203	8% (26)	13% (26)	SIR	3.8 (2.6–5.4)	1.7 (1.1–2.4)
Buchbinder et al. [11]	Cohort	321	85	18% (58)	42% (36)	SIR	6.2 (3.9–10)	2 (1.4–2.7)
Hill et al. [14]	Meta-analysis	618	914	32% (198)	15% (137)	SIR	3 (2.5–3.6)	1.3 (1.0–1.6)
Stockton et al. [10]	Cohort	419	286	18% (77)	25% (71)	SIR	7.7 (5.7–10.1)	6.2 (3.9–10)
Chen et al. [12]	Cohort	1012	643	9.4% (95)	4.4% (33)	SIR	5.1 (5–5.2)	2.2 (2.1–2.2)

OR odds ratio, *RR* relative risk, *SIR* standardized incidence ratio, *PM* polymyositis, *DM* dermatomyositis

Cancer-associated myositis

- Definition: Cancer diagnosed within 3–5 years before or after myositis onset
- Dermatomyositis: 20–30% (SIR 3–4)
  - Common cancers—ovarian, lung, pancreatic, non-Hodgkin lymphoma, stomach, colorectal, and breast cancers.
- Polymyositis: 10–20% (SIR 1.5–2)
  - Common cancers—Non-Hodgkin lymphoma, lung and bladder cancer
- The highest risk is 1 year before or after myositis diagnosis.
- Male > female (slightly)
- Risk increases with age (>45 years higher risk)
- Most common type: Adenocarcinoma

Apart from the increased risk of cancer in myositis patients compared with the general population, and in DM versus PM, all studies agree that cancer appears more often 1 year before and 1 year after myositis onset, with a progressive decrease thereafter [7–10]. Nonetheless, authors differ regarding the period of time myositis patients are at a higher risk of cancer compared with the general population, citing time frames ranging from 3 to 5 years before and after the onset of the disease [7, 9–11]. The role attributed to gender as a modifier of the cancer risk in myositis patients also varies, but most studies suggest a slightly higher risk for men compared to women (3.3 vs. 2.8 for DM and 1.4 vs. 1.2 for PM) [14]. In addition, an older age at myositis onset increases the risk of cancer. It has been estimated that cancer risk triples in DM patients >age 45 years [9, 10, 12] and the mean age of CAM is 50–60 years with a wide range.

The risk of cancer in myositis groups other than DM and PM, such as clinically amyopathic dermatomyositis (CADM), sporadic inlusion body myositis (sIBM), juvenile dermatomyositis (JDM), and immune-mediated necrotizing myopathy (IMNM), has been less extensively investigated. CADM seems to be associated with a risk of cancer similar to that of classic DM where 14% of a cohort developed internal malignancies [15]. Other population-based studies report an increased risk for malignancy in sIBM, myositis associated with another rheumatic disease, childhood myositis, and IMNM [11, 16]. However, these associations require further confirmation.

As in the general population, adenocarcinomas are the most commonly reported CAM, although all histological types are noted. Hill et al. [14] reported that ovarian, lung, pancreatic, non-Hodgkin lymphoma, stomach, colorectal, and breast cancers were the malignancies most often associated with DM, whereas non-Hodgkin lymphoma, lung cancer, and bladder cancer, all with an SIR>2, were more common in PM. It is important to note that tumor distribution varies with the patients' geographical location. For example, nasopharyngeal cancers are common in Korea, Singapore, Hong Kong, Taiwan, and southeastern China [12, 17–19]. The contribution of specific autoantibodies will be discussed later.

Risk Factors

Certain clinical, biological, or personal risk factors should guide clinicians to pursue an occult malignancy [20] in myositis, whereas some factors are protective (Table 25.2).

DM (including amyopathic DM) has a sixfold higher CAM risk than sIBM, which has a risk similar (or slightly higher) as that of the general population, while PM has an intermediate risk. Male sex and older age are consistent CAM risk factors, while meta-analyses have cited skin necrosis, refractory myositis, and dysphagia as features suggesting CAM [21, 22]. The immunosuppressive drugs used to treat myositis patients do not seem to increase the risk for developing cancer. There is a negative association between interstitial lung disease with or without antisynthetase autoantibodies and cancer, although smaller series have reported a relationship [23].

This can be practically relevant as exemplified in two scenarios. For example, in a 67-year-old male with DM presenting with skin necrosis and refractory disease, the suspicion of CAM is high, whereas in a 43-year-old woman with PM and

Table 25.2 Risk and protective factors for patients with myositis to harbor a cancer

Risk factors for CAM	*Protective factors*
Older age	Interstitial lung disease
Male sex	Antisynthetase antibodies (Jo-1)
Dysphagia	Anti-Ro antibodies
Skin necrosis	Anti-PM/Scl antibodies
Myositis refractory to therapy	
Type of myositis (DM, CADM >PM)	Myositis overlap syndromes, sIBM, JDM
Low level of complement (C4)	Raynaud phenomenon
High levels of muscle enzymes (i.e., CK)	Lymphocytopenia
Characteristic capillaroscopy pattern[a]	

CAM cancer-associated myositis, *CK* creatine kinase, *DM* dermatomyositis, *PM* polymyositis, *sIBM* sporadic inclusion body myositis, *CADM* clinically amyopathic dermatomyositis

[a]Severe structural derangement of the microvasculature with disorganization of normal capillary distribution

Raynaud phenomenon with a positive anti-PM-Scl or anti-synthetase autoantibody and interstitial lung disease (ILD), the probability of an occult neoplasm is low. Moreover, newly recognized autoantibodies now provide a better risk assessment in addition to the aforementioned factors.

Autoantibody Associations

Recently, several autoantibodies have been associated with CAM including anti-transcription intermediary factor 1 gamma (anti-TIF1-γ; formerly referred to as anti-p155/140), anti-nuclear matrix protein-2 (anti-NXP-2), and anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase (anti-HMGCR).

Anti-TIF1-γ antibodies are the most widely studied autoantibody marker in cancer. One meta-analysis [24] reported a 27-fold higher risk of developing cancer in TIF1-γ (+) DM patients with a sensitivity and specificity of 78% and 89%, respectively. Moreover, the high negative predictive value of TIF1-γ (95%) provides clinicians with the confidence that negative testing makes an occult malignancy very unlikely. One drawback is that TIF1-γ is only detected in DM. Currently, anti-TIF1-γ determination is recommended in all recently diagnosed DM patients and should be included in the screening algorithm for cancer in this population. Furthermore, its availability is increasing and its detection is becoming more standardized.

Anti-NXP-2 [25, 26], another DM-specific autoantibody, is accompanied by only a 3.7-fold increased risk of CAM, considerably lower than that of anti-TIF1-γ. In addition, certain clinical manifestations such as severe muscle disease and calcinosis are more commonly seen in anti-NXP-2-positive myositis patients.

In 2011, anti-HMGCR antibodies were described as markers of a statin-associated myopathy [27], which along with anti-SRP antibody represents two-thirds of IMNM patients. In a comparison of patients with anti-SRP or anti-HMGCR, IMNM patients without autoantibody had a higher associated risk of CAM [16]. There is some suggestion of an increased risk of CAM in anti-HMGCR antibody (+) patients, but further studies are needed to establish a clear relationship between anti-HMGCR positivity and CAM [16, 28].

Before the descriptions of these new autoantibodies, cancer was noted to be more frequent in DM, PM, and IMNM patients *without* any of the myositis-specific or myositis-associated antibodies that were routinely tested (i.e., anti-Jo-1, anti-U1-RNP, anti-U3-RNP, anti-Ku, and anti-PM-Scl). Indeed, in one of the first papers published on anti-p155, Chinoy et al. [29] reported that cancer risk was higher not only in anti-p155 (+) myositis patients but also in patients who had no myositis-specific or myositis-associated autoantibodies. Stratifying the risk of cancer in a large population-based cohort taking into account autoantibody status (particularly anti-TIF1-γ and anti-NXP-2), as well as other clinical and demographic parameters would be interesting.

High-risk autoantibodies in cancer-associated myositis

- Anti-TIF1-γ antibodies
  - Highest risk
  - Only in DM

  - OR = 27
  - Sensitivity 78% and specificity 89%
- Anti-NXP-2
  - Second highest risk
  - Mostly in DM
  - OR = 3.7
  - Sensitivity 26% and specificity 76%
- Anti-HMGCR
  - Unconfirmed risk
  - IMNM
  - SIR = 2.8
  - Sensitivity and specificity unknown
- Myositis-specific antibody-negative
  - Confirmed risk
  - PM, DM, OR = 5.8
  - Sensitivity 93.8% and specificity 44.7%
  - IMNM, SIR = 8.4
  - Sensitivity and specificity unknown

Cancer Screening

Although no studies show that the early diagnosis of cancer translates into a better outcome in CAM, cancer screening is broadly accepted as a standard practice at myositis onset. It is reasonable to screen myositis subsets that have a clear increased risk of neoplasm including DM and amyopathic DM patients where up to one-third of such patients have malignancy. Despite controversial data, cancer screening is also recommended in PM and IMNM patients, particularly those with anti-HMGCR antibodies and those possessing no specific myositis antibodies. Current evidence does not support cancer screening in sIBM or juvenile myositis, even though anti-TIF1-γ and anti-NXP-2 autoantibodies are common in JDM.

Myositis patients should be evaluated for cancer at least at the time of the myositis diagnosis. The presence of clinical risk or protective factors (Table 25.2) should not be used as a basis to indicate or exclude initial cancer screening in individual DM, amyopathic DM, PM, or IMNM patients as none of these epidemiological features is a reliable cancer predictor in an individual patient.

Cancer screening begins with a comprehensive clinical history (including the family history of cancer), a thorough physical examination, chest radiography, a complete blood count, and extensive biochemical testing (Table 25.3). Any abnormalities should be thoroughly investigated with appropriate follow-up testing. For example, the presence of iron-deficiency anemia should prompt endoscopy and colonoscopy. With no identifiable abnormalities, an occult cancer screening approach should be individually tailored according to age, sex, and ethnicity. This should also take into account the cancer epidemiology of the geographic region (e.g., South-East Asia for nasopharyngeal carcinoma) or other factors [12].

From a practical perspective, we suggest that screening for occult cancer should systematically include chest and abdominal computed tomography (CT) scanning, urine cytology, and fecal occult blood testing (Table 25.3). In addition, female patients should undergo a thorough gynecological examination, as well as mammography

Table 25.3 Tests recommended for cancer screening in myositis

Screening should be based on individuals' age, gender, ethnicity, and cancer prevalence in geographical location
Risk stratification use risk factors, disease subtypes, autoantibodies, etc
All patients:
Comprehensive history and examination (including family history)
Chest radiograph
CBC, LFTs, serum creatinine, ESR
Pan-CT: CT chest and abdomen
Urine cytology
Fecal occult blood testing
Endoscopy and colonoscopy if age >50 years
Female patients:
Gynecological examination—PAP smear
Mammography
Gynecological ultrasound
Male patients:
Testicular ultrasound if <50 years of age
Serum PSA if >50 years of age
Controversial test for screening
Tumor markers including CA-125 and CA-19-9

CBC complete blood count, *LFTs* liver function tests

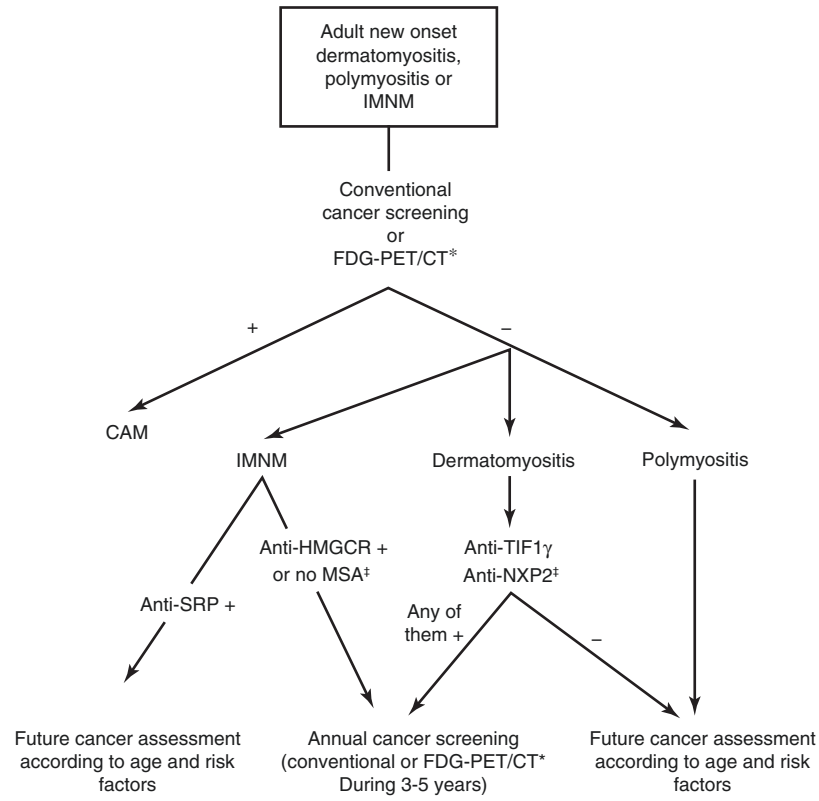

Fig. 25.1 Algorithm for cancer screening in patients with idiopathic inflammatory myopathy. IMNM: immunomediated necrotizing myopathy, FDG-PET/CT [18F]: fluorodeoxyglucose PET/computed tomography, CAM: cancer-associated myositis, MSA: myositis-specific antibody. *If available. ‡Anti-NXP2 and anti-HMGCR association with cancer needs further investigation

and pelvic ultrasound, to rule out breast, ovarian, and cervical cancer. Testicular ultrasound should be considered in men younger than 50 years and serum prostate-specific antigen (PSA) levels in men older than 50 years. We recommend gastroscopy and colonoscopy in all patients older than 50 years and in those younger than 50 years who have a positive fecal occult blood test, iron-deficiency anemia, or clinical symptoms suggesting bowel disease [30, 31]. A rational cancer-screening strategy is proposed in Fig. 25.1 along with recommended testing in Table 25.3.

Role of Tumor Markers in Cancer Screening

The use of tumor markers as screening tools for cancer remains controversial [32, 33] due to their low sensitivity in early stages of malignancy [34]. Nonetheless, some authors support their utility in myositis, under the theoretical assumption that a higher sensitivity would be achieved in patients with a higher risk of cancer than the general population. A prospective study [33] showed that an elevated CA-125 level at myositis diagnosis was associated with a markedly increased risk of developing a malignancy during the follow-up period (OR 29.7, $p < 0.0001$, 95% CI 8.2–106.6), while with CA 19–9, there was a trend toward significance ($p = 0.07$; OR, 4.5; 95% CI, 1–18.7). This suggested that certain tumor markers might be useful in predicting an occult malignancy. However, false positivity and nonspecific elevation of these markers in benign conditions raise some concerns regarding their routine usefulness. In our experience, broad, systematic analysis of tumor markers in screening strategies has a low yield and can even be misleading. Rational, individualized use of

tumor markers (e.g., CA-125 determination when ovarian cancer is suspected after a gynecologic ultrasound or prostate-specific antigen determination in older male patients) remains our recommendation.

Role of Positron Emission Tomography/Computed Tomography (PET/CT) in Cancer Screening

Positron emission tomography/computed tomography (PET/CT) using [18F] fluorodeoxyglucose (FDG) should be considered a potentially useful tool in occult cancer evaluation. PET/CT has shown higher sensitivity than CT and other imaging techniques for detecting occult malignancy in some neurologic paraneoplastic syndromes [35, 36]. The usefulness of PET/CT in myositis was compared with conventional methods of cancer screening (thoracoabdominal CT, mammography, gynecologic examination, ultrasound, and tumor markers), with equivalent results [37]. Both approaches had a high positive predictive value of 93% with equivalent sensitivity, specificity, and negative predictive value (NPV) for excluding occult malignancy. Hence, PET/CT is comparable to broad cancer screening in terms of accuracy with the advantage that a single imaging test would be more convenient for patients. Availability and economic issues are the main drawbacks for generalized use of PET/CT in these patients.

Follow-Up of Cancer-Associated Myositis

Negative cancer screening at myositis onset does not rule out the likelihood of CAM in the future, since the cancer risk remains high for years [13, 14]. Therefore, continued surveillance is required. Nevertheless, the intensity of this surveillance can vary depending on the degree of suspicion for malignancy in each case. For patients with PM or DM with no clinical or serologic risk factors for cancer or with protective factors, we suggest periodic history and physical examination assessment with basic laboratory testing along with the conventional cancer screening. In these cases, future cancer assessment should not differ from the approach used in the healthy population of similar age and sex. In contrast, in patients with a high risk of CAM (such as anti-TIF1-γ or anti-NXP-2 (+) DM patients [24, 26], or IMNM patients without myositis-associated autoantibodies or positivity to anti-HMGCR antibodies [16]), careful clinical surveillance and the yearly repetition of complete cancer screening or a PET/CT should be considered for 3–5 years around the diagnosis of myositis. However, there are no studies demonstrating the benefit of this yearly assessment. Finally, patients with refractory myositis should also undergo regular evaluations to rule out an underlying cancer. A rational cancer-screening strategy is proposed in Fig. 25.1.

Management of cancer-associated myositis

- Treatment of cancer
  - Surgery, chemotherapy, and radiation
  - Immunosuppressive drugs to control myositis
- Prednisone in tapering doses in consultation with oncologist
- IV immunoglobulin (IVIG)
- Cyclosporine
- Individualized immunosuppression based on response

Management

Patients with CAM should be managed from the perspective of both their cancer treatment and myositis management. Clinicians should recognize that the prognosis is more dependent on cancer progression than on the myositis. Nevertheless, a patient with muscle weakness or skin ulcer harbors a greater risk of complications when receiving chemotherapy treatment. Thus, aiming for

optimal improvement of the myositis and its clinical features is desirable for success in the treatment of cancer. However, cancer treatment should never be delayed due to concerns about myositis activity. Although treatment of the tumor (surgery, chemotherapy, radiotherapy) may lead to remission of the myositis [38], many patients require long-term immunosuppression to control myositis even with cancer remission. Furthermore, myositis can recur upon relapse of malignancy years after initial presentation. It is of paramount importance for myositis-treating physicians and oncologists to maintain close communication as a team to offer patients the best treatment options.

A reasonable approach to treat CAM patients is to treat myositis with prednisone (1 mg/kg/d) and/or intravenous immunoglobulin (IVIG) (2 g/kg monthly). Some centers use triple therapy with prednisone, IVIG, and cyclosporine (3–5 mg/kg/d). Other immunosuppressive agents such as azathioprine, methotrexate, mycophenolate mofetil, or even tacrolimus can be employed, even though these agents are associated with an increased cancer risk as well. We favor IVIG and cyclosporine as both these agents tend to be more immunomodulatory as opposed to immunosuppressive. Depending on the evolution of the cancer, myositis-treating physicians should adjust or change the immunosuppressive regimen, using an individualized approach in each case. Communication with oncologists is particularly important when several chemotherapy drugs are employed in an effort to mitigate harmful drug interactions.

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Myositis-Associated Interstitial Lung Disease

26

Sonye K. Danoff

Key Points to Remember

- Interstitial lung disease is a common pulmonary manifestation in autoimmune myositis.
- Interstitial lung disease may be the first, only, or dominant manifestation in myositis.
- Patients with antisynthetase antibodies and MDA5 are at the highest risk of developing ILD.
- The diagnosis of ILD in a patient with compatible symptoms (cough, dyspnea on exertion) is made using PFTs (restrictive pattern, decreased DLCo) and high-resolution chest CT scanning. Lung biopsy is usually not needed to make the diagnosis in patients with known or suspected myositis.
- The presentation of ILD can range from asymptomatic or mild to fulminant and life-threatening. The treatment is matched to the acuity of illness with some patients requiring little or no specific treatment, while others require aggressive immunosuppression.
- The prognosis of myositis-associated ILD is generally good, but a poorer prognosis is associated with clinically amyopathic disease; anti-MDA5 and non-Jo-1 antisynthetase autoantibodies; elevated CRP, ESR, or high ferritin levels; and advanced age at presentation.
- For carefully selected patients with progressive ILD despite therapy, lung transplantation can be considered.

Introduction

While lung involvement in myositis can take many forms, the focus of this chapter will be on parenchymal lung injury resulting in interstitial lung disease (ILD). Other aspects of lung involvement in myositis, including comorbid considerations, are discussed in Chap. 7. The pathogenesis of myositis-associated ILD remains poorly understood, but the potential of myositis-specific autoantibodies recognizing lung epitopes has been proposed [27]. Similarly, the anti-MDA-5 autoantibody recognizes a cytoplasmic viral RNA receptor present in the lung [21, 33]. These observations raise the question as to

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whether the lung may participate as a site of early antigen presentation contributing to it being a target of autoimmune attack [10]. Nevertheless, the full story remains to be determined, and there are ongoing efforts to unravel these enigmatic associations. What is clear is that many patients with myositis either present with or manifest ILD at some point in the course of their disease. These patients generally fall into two categories. In the first group, lung involvement is the predominant, first, or the only manifestation of myositis (as seen in some patients with the antisynthetase syndrome or clinically amyopathic anti-MDA-5-positive disease) [37]. The second group of patients have myositis and subsequently develop ILD. This group often poses more therapeutic challenges particularly if lung disease presents at a time when concomitant immunosuppression is being used for other autoimmune manifestations. An example of each scenario is illustrated below.

Case No. 1

A 55-year-old black woman who was previously well acutely developed dyspnea on exertion while shopping. She was admitted to a local hospital and a high-resolution CT (HRCT) scan (Fig. 26.1) showed diffuse ground glass opacities and traction bronchiectasis. She was treated for presumed community-acquired pneumonia but failed to improve. A surgical lung biopsy demonstrated usual interstitial pneumonia (UIP), and a diagnosis of idiopathic pulmonary fibrosis (IPF) was made. She was told there was no available therapy and advised "to get her affairs in order." When the patient presented to an outpatient ILD clinic several months later, she was not only profoundly dyspneic but had also developed significant muscle weakness. Her family history was notable for a cousin with rheumatoid arthritis. On review of systems, she noted a 2-year history of Raynaud phenomenon and complaints of difficulty lifting her feet when walking up steps. She was on no medications. Her physical examination revealed tachycardia and tachypnea. She had small lung fields on percussion and bibasilar crackles on auscultation as well as a loud P2 and lower extremity edema. Her skin examination revealed periungual hyperpigmentation and a rash over her upper eyelids. She had proximal muscle weakness with 4/5 strength of her hip flexors. Laboratory findings after hospital admission revealed a negative ANA and negative anti-Ro/La, -RNP, -topoisomerase, and -Jo-1 autoantibodies. The rheumatoid factor was mildly elevated, but the anti-CCP was negative. Her CK, aldolase, AST, and ALT were normal. Subsequent myositis autoantibody testing revealed a positive anti-PL12, and she was diagnosed with the antisynthetase syndrome and autoimmune ILD.

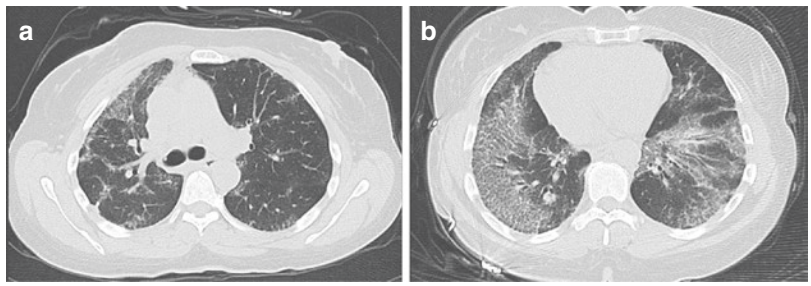

Fig. 26.1 Chest CT imaging from a patient presenting with acute-onset dyspnea. The CT shows a diffuse pattern of ground glass opacities affecting both lungs and present centrally as well as peripherally. In the context of an acute-onset dyspnea, infection must be considered. However, if infection is ruled out, ILD is a likely diagnosis. This pattern is consistent with radiographic nonspecific interstitial pneumonia (NSIP), and, therefore, an underlying connective tissue disease should be suspected

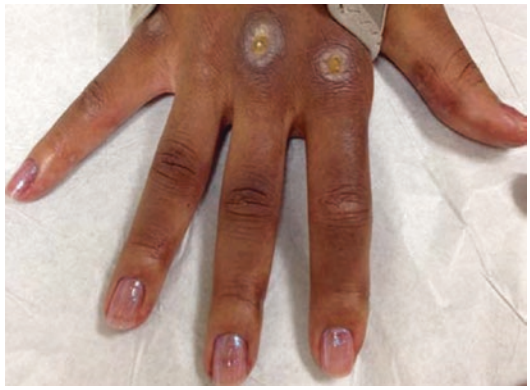

Fig. 26.2 Patient presented with ulcerative lesions over the metacarpophalageal joints

Case No. 2

A 45-year-old black woman presented to her primary care provider with a new erythematous rash affecting her hands, face, and upper chest. She rapidly developed painful, ulcerative lesions on her MCPs and elbows (Fig. 26.2). She was referred to rheumatology and diagnosed with dermatomyositis and started on oral prednisone. Within 2 weeks, she reported progressive shortness of breath leading to hospitalization, and an HRCT scan showed diffuse bilateral ground glass opacities. She required high-flow oxygen and received intravenous pulse glucocorticoids but failed to improve, so intravenous immune globulin (IVIg) was initiated. Her oxygen was slowly weaned, and she was discharged to home.

Although many patients with myositis are at risk of developing ILD, some are at greater risk than others. The first step in identifying ILD is to be vigilant for concerning symptoms of early ILD.

Symptoms

The most common initial feature of ILD is progressive dyspnea on exertion (DOE). Some patients recall a preceding upper respiratory infection leading to speculation that a viral prodrome stimulates autoimmunity. In fact, previous retrospective reports have noted a prior history of pneumonia, TB, and bronchitis [38]. The occasional patient will present to a community hospital with dyspnea and a chest X-ray showing bilateral "infiltrates" which leads to a misdiagnosis of "double pneumonia." Other features include a dry cough, typically worse during the daytime but exacerbated by exercise or deep breathing. An uncomfortable tightness in the chest or pain with breathing may also accompany lung involvement. Finally, nonexertional fatigue is a frequent symptom, with the common complaint of an inability to "just get anything done." Unfortunately, acute respiratory failure can be seen in patients with rapidly progressive ILD, whereupon a patient deteriorates within weeks leading to oxygen-dependence, hospitalization, and even intubation. Such patients may indeed encounter their first rheumatology evaluation in the intensive care unit with respiratory failure. Because the symptoms of ILD are nonspecific, a high index of suspicion for autoimmune ILD in the myositis patient is necessary. A thorough review of systems is critical to ascertain features of autoimmunity including a history of Raynaud phenomenon, rashes, mechanic's hands, inflammatory joint pain, muscle weakness, or dysphagia.

Presenting features of ILD	Clinical associations	Clinical course
Asymptomatic	On routine testing for other problems or during cancer screening	Asymptomatic ILD requires monitoring, but no therapy
Progressive dyspnea on exertion	Most common symptoms of ILD	Slowly progressive ILD
Chronic dry cough	Common and difficult to evaluate	Slowly progressive ILD
"Double pneumonia"	Misdiagnosis preceding ILD diagnosis	Slowly progressive ILD
Respiratory failure requiring O_2 and/or intubation	Uncommon but known complication; delayed diagnosis; anti-MDA5 antibody positivity	Rapidly progressive ILD

Physical Examination

Physical examination findings of ILD are variable, but the most common finding is small lung fields on percussion and auscultatory bibasilar crackles. However, the absence of these findings is not sufficient to exclude ILD. Other clinical findings include tachypnea and tachycardia with exercise desaturation on ambulation, perhaps also suggesting pulmonary artery hypertension (PAH). Patients may have clubbing. As noted above, attention should be paid to features of Raynaud phenomenon, ischemic digits or pitting ulcers, nail fold capillary abnormalities, Gottron sign or other dermatomyositis rashes, mechanic's hands, cutaneous ulcerations, calcinosis, proximal muscle weakness, or inflammatory arthropathy.

All ILD patients should be evaluated for underlying autoimmunity including an assessment for myositis and other autoimmune features on a thorough history and examination.

Signs and Symptoms of Possible Underlying Myositis

Raynaud phenomenon
Ischemic digital pits/ulcers
Nail fold capillary abnormalities
Several erythematous rashes
Mechanic's hands
Cutaneous ulcerations
Calcinosis
Muscle weakness or myalgia
Esophageal dysmotility
Arthralgia or arthritis
Elevated CK, aldolase, transaminases
Elevated ESR, CRP
Positive ANA
Positive anti-SSA, RF, anti-CCP

Autoantibodies Associated with ILD (See Chaps. 20–21)

Many myositis-specific autoantibodies have a much greater association with ILD (70%–90%), than clinical signs or symptoms [17]. The antisynthetase syndrome is characterized by autoantibodies directed against amino-acyl tRNA synthetases with ILD as a cardinal feature [28]. Many such patients have no clinically significant myositis, particularly those possessing non-Jo-1 antisynthetase antibodies (e.g., anti-PL-7, -PL-12, -EJ, -OJ, -KS, -Zo) with anti-PL-7 and -PL-12 being the most common (Table 26.1) [36]. The actual prevalence of ILD in patients with these autoantibodies is likely underestimated as many patients present with only ILD as muscle and/or skin involvement is poorly recognized.

Further, anti-MDA-5 is another autoantibody marker of ILD, and in the USA up to 50% of patients with anti-MDA5 have ILD, while this association is much stronger in Asian populations [22, 31]. Importantly, many such patients have rapidly progressive ILD which portends a much worse prognosis and must be treated aggressively and early in the disease course [31]. Anti-small ubiquitin-like modifier (SUMO)-activating enzyme (anti-SAE) antibody has also been associated with ILD (50%–70%) in Asian

Table 26.1 Association of antisynthetase and other myositis autoantibodies with ILD

Antibody	ILD (%)	Myositis (%)
Anti-Jo-1	84	78–100
Anti-PL-12	95	60
Anti-PL-7	84	84
Anti-OJ	55	100
Anti-EJ	100	100
Anti-KS	100	0
Anti-ZO	100	100
Anti-MDA5	60–90	–
Anti-SAE	0–18% Western 50–70% Asian	100
Anti-PM-Scl		
Anti-RNP		
Anti-Ku		
Anti-RNP		

References: Solomon et al. [36], Lega et al. [25], Moghadam-Kia et al. [31], Aggarwal et al. [1]

cohorts, but similar associations are not seen in other geographic areas. ILD associated with anti-SAE is generally mild with a good prognosis [5, 15, 32, 39].

Several myositis-associated autoantibodies including anti-PM-Scl, anti-Ku, anti-RNP, and anti-Ro52 have significantly higher associations with ILD, partly due to overlap with systemic sclerosis. Conversely, other myositis-specific autoantibodies are rarely associated with ILD (e.g., anti-SRP, -HMGCR, -Mi-2) [25].

Demographics and Clinical Features Associated with ILD

Apart from myositis-specific and myositis-associated autoantibodies, there are certain demographic and clinical features associated with a high risk of ILD. Recent studies in both Europe and the USA suggest that black race is associated with an increased risk of ILD as well as disease severity [9, 20]. Among the clinical subset of myositis, necrotizing myopathy, cancer-associated myositis, and inclusion body myositis are somewhat protected from ILD, whereas dermatomyositis, clinically amyopathic dermatomyositis, and overlap myositis (e.g., systemic sclerosis) have a greater risk. Younger patients (age < 18) generally have less frequent ILD except for those with the anti-Jo-1 antibody. Additional clinical factors reportedly associated with a greater ILD risk include an elevated ESR and CRP, Raynaud phenomenon, and abnormal nail fold capillaroscopy [6, 29].

Natural History of ILD

Despite the presence of common mechanisms of injury in ILD, there is variability in natural history. Hence, monitoring and reassessing disease at regular intervals is critical to patient outcome. We recommend complete PFTs (spirometry, lung volumes, and DLCo) at 3–4-month intervals in patients with symptomatic disease. This provides a dynamic measure of changes in lung function in response to therapy. Further, HRCT chest imaging is critical initially but also useful at times of pulmonary flare in combination with PFTs. However, HRCT provides no added value for stable or clinically improving patients.

The natural history of myositis-ILD can be divided broadly into three categories: (1) clinically asymptomatic, (2) slowly progressive, and (3) acute, rapidly progressive [30]. Patients with clinically asymptomatic disease require no therapy beyond that which is given for their other disease manifestations. This group of patients may be identified by HRCT imaging which often reveals minor infiltrates and a lack of clinical symptoms or significant PFT abnormalities. In slowly progressive disease, symptoms may gradually emerge over weeks to months, but functional limitation ensues with both PFT and imaging abnormalities. The most concerning scenario is the patient with rapidly progressive ILD (RP-ILD) who may progress from normal to respiratory failure in days to weeks. Notably, the initial presentation does not dictate the nature of the ongoing disease as patients with initial RP-ILD may stabilize and return to normal or near-normal function over time with aggressive therapy.

Radiographic Patterns in Myositis-Associated ILD

HRCT imaging is valuable in the diagnosis and monitoring of myositis-associated ILD [25]. While a number of radiographic ILD patterns are observed, one of the most common is nonspecific interstitial pneumonitis (NSIP). This typically involves “compression” of the lower lobes (Fig. 26.3) presumably due to an elevated diaphragm often resulting in areas of apparent consolidation immediately above the diaphragm (Fig. 26.4). The patterns can range from a more ground glass-appearing pattern to a more fibrotic picture with associated honeycombing. In addition, esophageal dilatation is common. Usual interstitial pneumonia (UIP) is also fairly common and typically leads to bilateral bibasilar findings also with significant honeycombing and traction bronchiectasis.

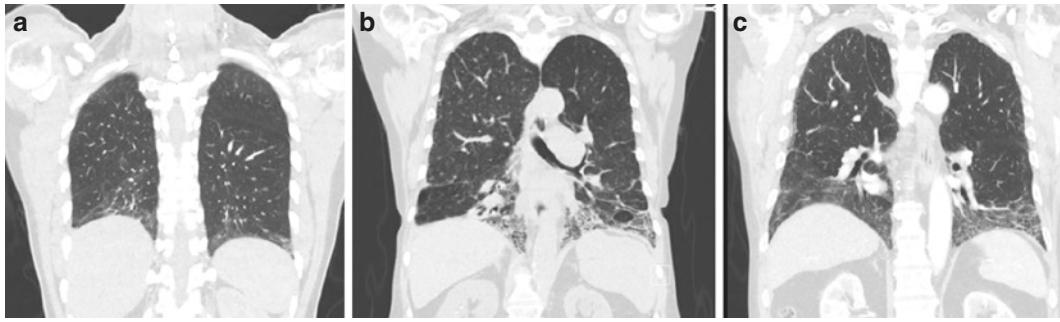

Fig. 26.3 Common CT image findings in myositis-associated ILD including basilar predominance with variable ground glass opacities and reticulation. (**a**–**c**) Coronal sections from three different patients with myositis-associated ILD

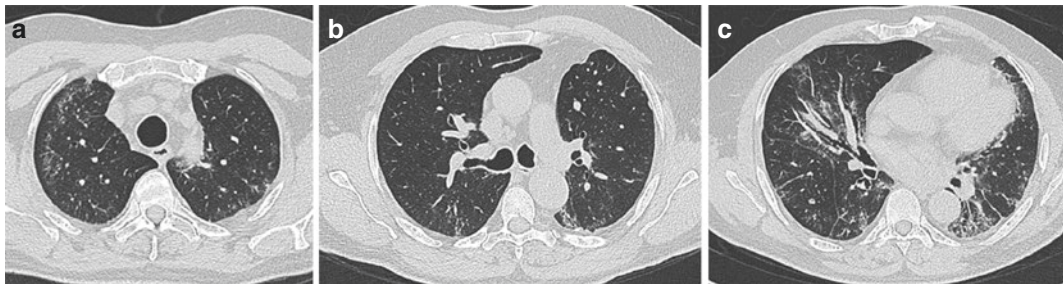

Fig. 26.4 (**a**–**c**) Sample cuts from a high-resolution chest CT scan of a myositis ILD patient with biopsy-proven UIP showing a peripheral distribution and reticulations but also notable for significant ground glass opacities. (**a**) upper lung, (**b**) mid lung, (**c**) lower lung

Strategies for Treating ILD

Pharmacologic Therapy

The treatment of myositis-associated ILD is discussed in detail in Chap. 32. Briefly, there have been no randomized clinical trials to guide therapy. However, many case series and case reports along with expert opinions do provide some guidelines. As with many manifestations of autoimmune disease, the therapy for lung involvement must be individually tailored. The choice of immunosuppressive is often driven by lung involvement, although severe muscle, skin, and/or joint manifestations must be considered. Patients with mild or asymptomatic ILD can be simply followed. For acute, severe, or rapidly progressive ILD, hospitalization is necessary with therapy including intravenous pulse glucocorticoids (typically 1 g of methylprednisolone IV daily for 3–5 days) followed by a tapering prednisone dose and a steroid-sparing agent such as azathioprine, mycophenolate mofetil (MMF), cyclosporine, cyclophosphamide, tacrolimus, or intravenous immunoglobulin [13, 18, 23]. The decision of which steroid-sparing agent to use is largely dependent on individual patient characteristics and physician familiarity with these medications. At present, there is no strong evidence supporting the use of one agent over the others. Rituximab is emerging as an agent often considered in severely ill patients [3, 12, 35] either alone or in combination with cyclophosphamide. For patients with mild or moderately progressive ILD, therapy is typically initiated in the outpatient setting and includes a combination of prednisone (0.5–1 mg/kg ideal body weight) and one of the aforementioned steroid-sparing agents (e.g., azathioprine or MMF). In patients on greater than 20 mg prednisone daily for more than a month, prophylaxis for pneumocystis is recommended. Similarly, proton pump inhibitor (PPI) therapy should be considered for patients on high-dose steroids.

Among the most challenging issue is the timing of tapering therapy for ILD after clinical improvement. Certainly, tapering glucocorticoids is essential while maintaining a secondary immunosuppressive agent. There is no definitive approach to tapering steroids, but we suggest tapering glucocorticoids after initiating a steroid-sparing agent and so long as there is stable lung function and symptom improvement. A similarly difficult decision includes the timing of the taper of the steroid-sparing immunosuppressive agent as patients generally are at risk of an ILD flare when steroids or other immunosuppressive therapy is slowed or stopped. More concerning is that an ILD recurrence may be far more difficult to control at this time. Hence, we have adopted a "go slow" approach to such tapering with careful observation for disease recurrence followed by the rapid escalation of therapy if symptoms recur. Nevertheless, in patients with severe disease and little lung reserve (e.g., FVC% < 50%), a low dose of prednisone (5–7.5 mg) and/or lower doses of a concomitant immunosuppressive agent are continued indefinitely.

Nonpharmacologic Therapy

Many patients with newly diagnosed ILD require supplemental O_2 with activity with periodic assessment for oxygen desaturation as a reasonable metric. For patients with a resting or ambulatory room air O_2 saturation < 88%, oxygen supplementation is indicated. Documentation requirements vary, but generally, it is necessary to demonstrate that desaturation is prevented at a given level (in liters per minute) of oxygen. This will provide the oxygen prescription, which should be reassessed periodically.

Pulmonary rehabilitation provides an important adjunct to therapy for ILD [11] and focuses on improving stamina through a graded exercise program. O_2 monitoring is required during the sessions, and after completion of the standard rehabilitation program, many centers will allow patients to continue in a nonmonitored extension program. For patients who elect not to continue, exercise should be continued at home to maintain the gains in endurance and strength.

Vaccination is recommended for all patients with lung disease to minimize the risk of common viral and bacterial infections, which can occur with any pre-existing lung injury. Centers for Disease Control and Prevention recommendations include yearly influenza vaccination as well as both pneumonia vaccines (Prevnar and Pneumovax) for most patients. Some patients will also need boosters for pertussis. While vaccination cannot eliminate the risk of infection, the risk is clearly mitigated.

Prognosis of Myositis-Associated ILD

The prognosis of myositis ILD is largely driven by the nature of the lung disease, with rapidly progressive ILD conferring the worst prognosis. Among patients with antisynthetase antibodies, the presence of non-Jo-1 antibodies (EJ, OJ, PL-7, PL-12) was associated with increased mortality [34]. A number of other factors have been associated with worse prognosis in myositis-associated ILD including older age, presence of MDA5 antibody, and clinically amyopathic disease associated with ILD [7, 8, 16]. Among patients with MDA5 antibody, an elevated initial serum ferritin, $P[A\text{-}a]O_2$ of ≥30 mmHg and increased ground glass opacities were associated with poorer survival [14]. Co-expression of Ro52 is also associated with increased mortality in Jo-1 patients [30].

Poor prognostic factor for myositis-associated ILD

Anti-MDA5 autoantibody
Non-Jo-1 antisynthetase autoantibodies
Anti-SSA (anti-Ro52) with antisynthetase syndrome
Older age of onset
Clinically amyopathic dermatomyositis
High ferritin levels
High ESR, CRP
Rapidly progressive ILD

Outcomes and Selection for Lung Transplantation

For a select subset of patients with myositis-associated ILD, with otherwise stable nonpulmonary features, lung transplant may be an option with progressive fibrotic disease. Recent reports suggest acceptable outcomes for patients with myositis-associated ILD undergoing lung transplantation similar to other forms of ILD [2]. There has been only one case report of possible ILD recurrence in a myositis patient who developed post-transplant lung dysfunction [4]. The major issues to consider in referring a patient with myositis-ILD for lung transplant include the degree of muscle weakness, active skin lesions, or esophageal dysmotility. The main goal in a lung transplant evaluation is ascertainment of comorbidities which would limit the benefit of lung transplantation. For example, muscle weakness might limit postsurgical rehabilitation and active skin lesions could lead to an increased susceptibility to skin infections. Esophageal dysmotility or gastroesophageal reflux disease (GERD) can increase the risk of post-transplantation lung injury resulting in chronic lung allograft dysfunction (CLAD). Nevertheless, in appropriately selected patients with myositis-associated ILD, lung transplantation is a viable option.

- Lung transplant is a viable but last option for myositis-associated ILD.
- Inactive disease in other organs is an important factor for favorable outcome of lung transplant.

Other Pulmonary Complications

In addition to primary lung involvement, other treatable disorders may complicate or mimic the symptoms of ILD such as venous thromboembolism (VTE) [24] or pulmonary artery hypertension (PAH) [19]. Thus, we routinely order echocardiography in any patient with a disproportionately low DLCo compared with their lung volumes or in the patient experiencing a drop in DLCo. Although typically less consequential, pneumomediastinum does occur more frequently in patients with dermatomyositis and can be a dramatic, if not dangerous, event [26]. Pneumomediastinum is usually treated conservatively with observation. Muscle weakness, particularly affecting the bulbar muscles, can also increase the risk of aspiration. This symptom may occur in the context of generalized muscle weakness or in a more narrow distribution just impacting swallowing. The presence of bulbar weakness is often manifested by frequent choking and coughing when the patient eats or drinks. More diffuse muscle weakness can also affect the respiratory muscles including the diaphragm and may result in reduced lung volumes as well as worsening pulmonary symptoms with bending over, lying flat, or eating large meals, all of which result in increased pressure on the diaphragm.

Conclusion

Pulmonary involvement in myositis is common and carries with it significant morbidity and mortality. ILD in particular is more common in patients with antisynthetase antibodies, MDA5 as well as myositis-scleroderma overlap syndromes. While prognosis is generally good, certain clinical and demographic features portend a poorer outcome. The mainstay of treatment is immunosuppressive medications and the intensity of treatment is matched to the severity of disease, such that patients with mild or asymptomatic disease may require no specific therapy, while those with rapidly progressive disease require aggressive treatment, often with multiple agents. Lung transplantation can be considered in carefully selected patients with progressive lung disease despite therapy.

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Pregnancy in Myositis

27

Melinda Nagy-Vincze and Katalin Dankó

Key Points to Remember

- Pregnancy outcomes for the mother are generally good in myositis during active or inactive disease.
- Pregnancy outcomes for fetus are good in myositis during inactive disease. However, high rates of abortion, late fetal loss, intrauterine retardation, and neonatal death are reported in active myositis.
- Pregnancy-induced myositis may lead to poor fetal outcome; fortunately, it is relatively rare.
- Postpartum flare up or disease onset is uncommon in myositis and has good prognosis.
- Steroids and IVIG are the mainstay of treatment for myositis from conception to delivery.

Introduction

Several systemic autoimmune rheumatic diseases (SARD) affect both fetal and maternal outcomes in pregnancy. Compared to other infants, mothers with SARD have an increased risk of complications such as spontaneous abortion, low birth weight, and a higher frequency of admission to a neonatal intensive care unit and perinatal death [1–3]. In addition to the general risk of autoimmunity to the fetus and mother, some disease-specific abnormalities including congenital heart block in Sjögren syndrome have been noted. Not only the specific SARD adversely affects both the fetus and the mother, but pregnancy may also simultaneously affect the SARD of the mother in a positive or negative manner. In systemic lupus erythematosus (SLE), an increased risk of maternal disease exacerbation is well known. Pre-eclampsia is a particular risk for women with SLE or antiphospholipid syndrome [2]. In women with rheumatoid arthritis, their disease often improves or enters remission during pregnancy but may flare during the postpartum period. Compared to the general population, women with SARD had higher rates of hypertension, antepartum hemorrhage, and severe maternal morbidity and required longer hospitalization [1–3]. These differences in pregnancy outcomes emphasize the complex interactions between hormonal changes

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and the immune system in pregnant women with SARD. In general, the only absolute contraindication for pregnancy is the presence of pulmonary hypertension, a clinical condition described more frequently in systemic sclerosis and also found among SLE, mixed connective tissue disease, rheumatoid arthritis, myositis, and Sjögren syndrome. This complication carries a disturbing mortality risk of up to 50% during gestation [4].

Very limited information is available regarding pregnancy outcomes in women with myositis. This is a rare disease with an onset often after the childbearing years, with only 12–14% occurring in the reproductive period [5, 6]. We found a few case reports and retrospective studies in the literature—altogether only 91 IIM cases with 125 pregnancies [5–42] (Table 27.1). Pinal-Fernandez et al. reported that pregnancy does not seem to carry a worse prognosis for the mother or the fetus in patients with IIM. Nearly half of the patients improved clinically when they became pregnant; on the contrary, a relapse of IIM symptoms was common afterward. Pregnancy does not appear to be a trigger for IIM [21].

Pregnancy Effect on the Disease

There are three distinct presentations of myositis that can be seen in relation to pregnancy: flare up of pre-existing disease during pregnancy, pregnancy-induced myositis (most often in the first or third trimester), and postpartum disease onset or flare. Interestingly, the occurrence or exacerbation of IIM during one pregnancy does not necessarily predict the relapse of symptoms in a subsequent pregnancy.

- *Effect of pregnancy on the pre-existing disease*: Patients with previously active disease can improve clinically when they became pregnant [21]. It is even possible to decrease the dose of corticosteroids and immunosuppressants during pregnancy, without disease flare. The reason for improvement is still unknown, but hormonal effects and the changes in T helper cell dominancy during pregnancy could play a key role [1–3].
- In some cases, one can observe an exacerbation of myositis during pregnancy in previously inactive maternal disease [6, 8, 12, 13, 34, 42]. Exacerbations mainly occurred during the second and third trimester of pregnancy [41].
- *Pregnancy-induced myositis*: In pregnancy-induced cases, myositis symptoms can develop in all three trimesters. According to case series, myositis onset occurs most frequently in the first and third trimester. Many cases reported poor fetal outcome in pregnancy-induced IIM; fortunately, this is a rare occurrence. Maternal myositis can persist for years [25], but spontaneous recovery has also been observed after delivery [14, 30].
- *Postpartum disease onset or flare*: There is no consensus as to how this is defined, but a maternal postpartum flare is uncommon. Most patients do well, with only one maternal death related to disease exacerbation [10].

Disease Effect on Pregnancy (Maternal and Fetal Outcomes)

Maternal Outcome The maternal pregnancy outcome is generally favorable whether pregnancy occurred during active or inactive disease. No myositis-specific obstetrical or general complications secondary to myositis have been identified. In myositis, uterine contractility is unaffected, although severe striated muscle weakness may necessitate assisted labor and delivery [25]. For pregnant patients with active myositis, some physicians recommend cesarean section to avoid maternal exhaustion and to decrease the risk of rhabdomyolysis and myoglobinuria. Long-term use of medium or high doses of glucocorticoids during pregnancy increases the risk of gestational diabetes, hypertension,

Table 27.1 Data of pregnancy outcome in IIM based on a review of literature

	Number of patients	Number of pregnancies	Disease activity during pregnancy						Maternal outcome		Fetal outcome							
			Active	Inactive	Pregnancy induced	Exacerbation during pregnancy	Post-partum	No data	Good	Complicated	Healthy	IUGR	Abortion	Neonatal death	Stillbirth	IU Death	Extrauterine gravidity	No data
PM	35 (38.5%)	47 (37.6%)	10 (8%)	12 (9.6%)	13 (10.4%)	5 (4%)	5 (4%)	2 (1.6%)	46 (36.8%)	1 (0.8%)	20 (16%)	9 (7.2%)	7 (5.6%)	1 (0.8%)	2 (1.6%)	6 (4.2%)	1 (0.8%)	1 (0.8%)
DM	48 (52.7%)	64 (51.2%)	4 (3.2%)	30 (24%)	17 (13.6%)	4 (3.2%)	2 (1.6%)	7 (5.6%)	61 (48.8%)	3 (2.4%)	35 (28%)	13 (10.4%)	12 (9.6%)	1 (0.8%)	0	1 (0.8%)	0	1 (0.8%)
IIM (no subset data)	8 (8.8%)	14 (11.2%)	0	0	0	2 (1.6%)	0	12 (9.6%)	14 (11.2%)	0	0	0	0	0	0	0	0	14 (11.2%)
Summary	91 (100%)	125 (100%)	14 (11.2%)	42 (33.6%)	30 (24%)	11 (8.8%)	7 (5.6%)	21 (16.8%)	121 (96.8%)	4 (3.2%)	55 (44%)	22 (17.6%)	19 (15.2%)	2 (1.6%)	2 (1.6%)	7 (5.6%)	1 (0.8%)	16 (12.8%)

infections, and premature membrane rupture [25]. The risk of other immunosuppressive drugs during pregnancy is discussed below. No data is available concerning the effect of myositis on breastfeeding.

Female myositis patients also have difficulties with conception and fertility, as seen with other SARD. Fertility rates are significantly lower in patients with myositis perhaps due to decreased sexual activity, chronic inflammation, and glucocorticoid and immunosuppressive drug use [37]. Diminished ovarian reserve has also been identified in DM patients of reproductive age [4–6, 38].

Researchers have shown that women in their reproductive years treated with cyclophosphamide (CYC) will experience a dramatic decrease in anti-Müllerian hormone (AMH), regardless of their baseline measures. AMH secretion from granulosa cells of growing ovarian follicles is a good endocrine marker for estimating the ovarian reserve [4], and the degree of this decline is directly proportional to the cumulative dose of CYC. Even a short course and a low cumulative dose can negatively influence the AMH levels. This well-described complication of CYC should cause managing physicians to consider alternative therapies for young women [4, 38].

Fetal Outcome Myositis patients with inactive disease generally have good fetal outcomes. However, significantly worse outcomes have been noted in cases of pregnancy during active disease or pregnancy-induced myositis or an exacerbation of underlying myositis during pregnancy. Abortion, late fetal loss, intrauterine retardation, preterm delivery, and neonatal death have been reported in mothers with active disease [39]. Twenty-seven to 43% of pregnancies with active disease were complicated by fetal death as compared to 6–13% in healthy mothers. In addition, 12–33% of newborns had intrauterine growth retardation in pregnancies with active disease as compared to 6–13% in healthy mothers [27, 35]. Healthy babies were born in 24–57% of cases versus 76–82% [27, 35], respectively. None of these abnormalities showed disease specificity with PM or DM. Pregnancy-induced DM with or without muscle weakness and severe PM can also be associated with intrauterine retardation or death [8, 33, 40].

Myositis is not transmitted from the mother to the fetus, but there may be an elevated serum creatine kinase (CK) level in the neonate for a few months after delivery without clinical significance [22].

Anesthetic Management for Cesarean Delivery in Myositis Patients

As previously mentioned, some physicians recommend delivery by cesarean section for myositis patients regardless of the fetal or maternal status. Potential complications from surgery or anesthesia should be considered particularly in patients with lung and cardiac problems or those on long-term glucocorticoids [42]. General anesthesia may trigger malignant hyperthermia and potentiate the effects of a muscle relaxant so these agents should be avoided in those with active myositis and a high CK. Similarly, myositis patients are sensitive to non-depolarizing muscle relaxants and antagonists to these agents may worsen muscle weakness and cause cardiac dysrhythmias [42].

Spinal-epidural anesthesia during cesarean section may be better for myositis patients as it combines the rapid, reliable, intense spinal blockade together with the flexibility of an epidural catheter. The catheter also allows supplementation of anesthesia and can be used for postoperative analgesia [42].

Clinical and Pathological Correlations

Due to limited retrospective data and ethical complexities, the pathological and immunological changes in pregnant myositis patients is poorly

described. Several hypotheses have been proposed regarding fetal complications and disease onset or flare in myositis including maternal hormonal changes, altered immune function, or a consequence of exposure of the mother to fetal antigens. Pregnancy shifts a woman's immune system toward T-helper 2 predominance, which could explain disease onset or a flare during pregnancy in myositis. Furthermore, autoantibodies such as anti-Ro and antiphospholipids may have a direct pathogenic role in pregnancy-related complications. No data has been reported regarding the role of myositis-specific auto-antibodies in fetal complications in IIM, although anti-Jo-1 positivity has been associated with high pregnancy risk for the fetus (OR 8.9, $p = 0.023$) [5, 8, 25, 33, 34].

Other hypotheses have also been proposed, such as immunologic disruption caused by viral infections including coxsackie viruses, parvoviruses, enteroviruses, and retroviruses that act as initiating factors based on the impairment of humoral immune responses of gravid women to certain viral antigens [1, 9].

Treatment of Myositis During Pregnancy

Drugs used to treat myositis may interfere with fertility or increase the risk of miscarriages and congenital abnormalities, so one must be cautious with therapy before and during pregnancy.

Glucocorticoids are generally the first treatment option as there is a very low risk to the fetus. Placental enzymes inactivate prednisolone and hence decrease the steroid concentration in the fetal blood to 10% [25]. Dexamethasone passes through the placenta, so the use of prednisone, prednisolone, or methylprednisolone is recommended. The decision to change the steroid dosage should not differ in the pregnant or nonpregnant state, except for factoring in the risk-benefit ratio of steroids during pregnancy. The potential side effects of glucocorticoids during pregnancy include adrenal insufficiency in newborn babies, a higher risk for neonatal CMV infections, stillbirth, maternal hypertension, and gestational diabetes. High doses of glucocorticoids increase the risk of side effects, so the lowest effective dose must be administered (ideally not more than 15 mg/day) [4]. Patients may require stress dose steroids at the time of delivery to prevent acute adrenal insufficiency [4, 43]. Other morbidities related to steroid use are similar to those seen in nonpregnant women including avascular necrosis of bone, weight gain, osteopenia, immunosuppression, hyperglycemia, hypertension, cataracts, and others [4].

Intravenous immunoglobulin (IVIG) remains a good treatment option during pregnancy with severe disease or steroid-resistant cases. IVIG is recommended as a second-line treatment in combination with prednisone for DM patients who have not adequately responded to corticosteroids (level B) and in combination with immunosuppressive agents as a steroid-sparing agent (level C) [43]. IVIG is also recommended for patients with PM not responding to first-line immunosuppressive treatment (level C) [43]. The complex mechanism of IVIG (e.g., binding and removing microbial toxins, targeting surface autoantigens, reducing T-cell proliferation, suppressing pro-inflammatory cytokines and B-cell differentiation, neutralizing autoantibodies, etc. [43]) as well as case reports [23, 24, 33, 35] and its use in other SARDs including antiphospholipid syndrome and SLE [44, 45], suggest that monthly administration may help conception and mitigate abortion and other complications [46, 47].

Other immunosuppressive drugs: Table 27.2 *summarizes the risk and safety of other conventional immunosuppressive drugs and biologic agents in pregnancy-associated myositis and lactation* [4, 48, 49].

Drug	Pregnancy FDA class	Safety in pregnancy	Safety in lactation	Key consideration
Azathioprine	D	Relatively safe; potential rare side effects include IUGR, bone marrow depression, and neonatal infection Maximal dose during pregnancy: 1.5–2 mg/kg/day	Relatively safe; Transfer in breast milk is minimal	Passes through the placenta, but fetus cannot convert it to its active from
Hydroxychloroquine	C	Safe	Safe	Passes through the placenta but has no known fetal adverse effects
Tacrolimus or cyclosporine	C	Relatively safe. Potential but rare side effects: Low birth weight, stillbirth	Considered as safe. Can be detected in breast milk, only in low concentration	Passes through the placenta, but the frequency of fetal adverse event is low
Sulfasalazine	B	Safe	Safe	Passes through the placenta but has no known fetal adverse effects
Methotrexate	X	Contraindicated due to teratogenic side effects. It has to be stopped at least 3 months before conception	Contraindicated	Passes through the placenta and excreted in breast milk
Leflunomide	X	Contraindicated	Unknown	Passes through the placenta and has teratogenic side effects
Cyclophosphamide	D	Contraindicated due to teratogenic side effects. It has to be stopped at least 3 months before conception	Contraindicated, it causes neutropenia and thrombocytopenia in the infant	Passes through the placenta and excreted in breast milk
Mycophenolate	D	Contraindicated	No information about the excretion in breast milk but not recommended	Passes through the placenta and has teratogenic side effects
Biological therapy		Not definite data in myositis Increasing evidence of safety in other SARDs	Not definite data in myositis Increasing evidence of safety in other SARDs	In patients with controlled disease, they should be stopped 2–6 months before conception
Infliximab	B	Relatively safe, but not recommended after the 16th gestational week	Safe	Passes through the placenta but has no known fetal adverse effects
Adalimumab	B	Relatively safe, but not recommended in the third trimester	Safe	Passes through the placenta but has no known fetal adverse effects
Certolizumab	B	Safe (preferred)	Safe (preferred)	No to minimal transfer through the placenta but has no known fetal adverse effects
Etanercept	B	Safe	Safe	Passes through the placenta but has no known fetal adverse effects
Golimumab	B	No information available	No information available	No information available

Drug	Pregnancy FDA class	Safety in pregnancy	Safety in lactation	Key consideration
Rituximab	C	Contraindicated, should be stopped 6 months before conception	Not recommended	Passes through the placenta and causes fetal B-cell depletion and also has teratogenic side effects
Tocilizumab	C	Stop 3 months before conception	Not recommended	No data available
Anakinra	B	Not recommended	Not recommended	No data available
Abatacept	C	Not recommended	Not recommended	No data available
Belimumab	B	Not recommended	Not recommended	No data available
Glucocorticoids	**C**	**Safe**	**Safe**	**Safe**

Table 27.2 Management plan for pregnancy in myositis patients

Planning pregnancy with myositis patients (based on a single center's experiences)	
General rules	Discuss risks of pregnancy to both fetus and mother during active disease or while on certain myositis drugs Give contraceptive options especially if active disease or on certain drugs
Preconception	Achieve remission/inactive disease at least 3 months before conception
	Review medications and stop MTX, CYC, MMF, and biologics 3–6 months before conception. Low-dose steroids, hydroxychloroquine, azathioprine, and IVIG are preferred
	Recommended laboratory tests at least 1–3 months before conception: Antiphospholipid antibodies and anti-SSA antibody Evaluate for cardio-pulmonary organ involvement (cardiomyopathy, ILD, PAH, etc.)
During pregnancy and after labor	Refer to high-risk obstetrician or someone with experience with autoimmune disease-related pregnancies Careful follow-up/collaboration with the obstetrician and pediatrician Monitor for intrauterine growth retardation and preterm labor
	Immediate intervention in case of worsening symptoms with steroids or IVIG Monitor steroid-related maternal and fetal side effects Consider possibility of cesarean section in severe active disease to avoid maternal exhaustion and risk of rhabdomyolysis and myoglobinuria Monitor for pregnancy-induced myositis
Postpartum and lactation	Monitor for postpartum myositis flare
	Avoid certain drugs if breast feeding

Azathioprine passes through the placenta, but the fetus cannot convert it to its active form, so this drug can be continued during pregnancy. The maximum dose is 1.5–2 mg/kg, and potential side effects include intrauterine retardation, bone marrow depression, and a high risk for neonatal infection [48]. Azathioprine transfer into breast milk is minimal, with no significant effects on the breastfeeding infant [4].

Hydroxychloroquine does pass through the placenta but has no adverse fetal effects, so it is generally considered safe during pregnancy [4, 48].

Cyclosporine A also passes through the placenta and can be detected in breast milk, but can be continued. Potential but rare side effects include stillbirth or a low birth weight [4, 48].

Recommendations regarding tacrolimus come from the transplant literature. There is no increased risk to the fetus and it is detected in low concentration in breast milk and case reports have not noted adverse effects in infants [4].

Sulfasalazine use requires folate supplementation during the preconception period and during pregnancy as this drug is a potent inhibitor

of the reduced folate carrier [4]. However, it can be continued during pregnancy.

Cyclophosphamide (CYC), methotrexate (MTX), and mycophenolate mofetil (MMF) are contraindicated due to teratogenic effects. These agents should be stopped at least 3 months before conception, and if pregnancy occurs while on these drugs, the mother should be seen by a high-risk obstetrician with a discussion on pregnancy termination. CYC and MTX are excreted in breast milk and should not be used by lactating mothers. In addition, CYC can cause neutropenia and thrombocytopenia in the infant. There is no data on the effect of MMF on lactation [4, 48].

Biological therapies (e.g., anti-TNFα, anti-CD20 antibodies, etc.) are associated with insufficient information to make definitive recommendations, so their use should be avoided during pregnancy if possible except certolizumab. The Food and Drug Administration (FDA) approved a label update for certolizumab that includes pharmacokinetic data showing negligible to low transfer of the biologic through the placenta and minimal mother-to-infant transfer from breast milk and therefore is the currently preferred anti-TNF agent during pregnancy and lactation. Although there is growing evidence that all anti-TNF alpha inhibitors (and other agents such as rituximab and abatacept) are safe both for the mother and fetus with no significantly increased risk for miscarriages or other fetal complications, the risk and benefit of biological drugs should be discussed before their administration. In patients with controlled disease, they should be stopped 2–6 months before conception [4, 48].

Concomitant Medication

For common medications such as antihypertensive drugs, antibiotics, diabetes treatment, etc., the same rules apply to the myositis patient as a healthy mother during pregnancy. Here, we will briefly present the most frequently used concomitant medication in myositis during pregnancy.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are often used for pain control. Before pregnancy, inhibition of cyclooxygenase with a classic NSAID or a selective COX-2 inhibitor can delay or even prevent ovulation during a normal menstrual cycle. During pregnancy, the lowest possible NSAID dose should be used for the shortest time. It is also recommended to be discontinued at the 32nd week of gestation due to a higher risk of fetal and maternal hemorrhage, fetal renal dysfunction, oligohydramnion, and premature closure of the ductus arteriosus. Some NSAIDs can be used during breastfeeding (i.e., ibuprofen, indomethacin, and naproxen). The use of acetaminophen should be preferred for pain control [4].

For patients with antiphospholipid antibodies or overlap myositis (especially SLE), low-dose aspirin should be considered for the prevention of thrombotic events and can be used safely before and throughout pregnancy and lactation. Clopidogrel can be used with no malformation risk during pregnancy, as an alternative to low-dose aspirin. Breastfeeding is not recommended due to the lack of data on clopidogrel. Warfarin should be switched to low-molecular-weight heparin in patients with antiphospholipid syndrome [4]. The effect or side effects of non-vitamin K antagonist oral anticoagulants (NOAC—rivaroxaban, apixaban, dabigatran) during pregnancy have not been verified, so these agents should be avoided in pregnancy and in the preconception period. There is also no data on their use during lactation or their effect on infants [4].

Conclusion

Complications during pregnancy were frequently reported in patients with active myositis. IVIG and glucocorticoids remain the best treatment options for active disease during pregnancy. Optimal pregnancy success can be expected when pregnancy is undertaken while the disease is in remission. Pregnancy must be carefully planned due to the teratogenic side effects of certain immunosuppressive drugs. Rheumatologists, neurologists, dermatologists, or other health-care

personnel managing myositis patients should counsel patients to maintain reasonable birth control measures while on certain immunosuppressive drugs. All myositis patients during pregnancy should be carefully followed up by a team composed of high-risk obstetricians and other subspecialty physicians familiar with SARD working in close collaboration with a neonatal intensive care unit. The combined efforts of this management team should result in a generally favorable pregnancy outcome.

Conflict of Interest The authors have no conflict of interest to declare.

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Pathogenesis of Myositis

28

Dana P. Ascherman

Key Points to Remember

- Both genetic (involving MHC, non-MHC loci) and environmental factors likely contribute to myositis pathogenesis.
- Myositis reflects the interplay between innate and adaptive immune responses as well as "non-immune" mechanisms encompassing endoplasmic reticulum (ER) stress and tissue hypoxia.
- Adaptive immune responses in idiopathic inflammatory myopathy involve reciprocal interactions between B and T cells that can be therapeutically targeted.
- T cells contribute to the development/perpetuation of inflammatory myopathy through cytolytic as well as cytokine-mediated pathways.
- Growing experimental evidence for the complementary role of Toll-like receptor signaling and innate immune activation in idiopathic inflammatory myopathy will likely lead to novel treatment paradigms.

Introduction

Over the past 20 years, we have made remarkable progress in elucidating the pathogenesis of idiopathic inflammatory myopathy (IIM). Investigative efforts have defined the complex interplay between different components of the adaptive and innate immune systems, reinforcing basic paradigms of autoimmunity applicable to a number of systemic rheumatic disorders. At the same time, these studies have highlighted unique aspects of IIM, most notably the role of the myocyte as an active participant in deleterious immune cascades contributing to tissue pathology. Moreover, assessment of human muscle tissue and various modeling strategies have advanced our understanding of "non-immune" mechanisms—encompassing endoplasmic reticulum (ER) stress and dysregulated autophagy—that play critical roles in the disease process. Overall, as our understanding of these intersecting pathways has increased, we have seen the emergence of more targeted therapies that ultimately hold the promise of greater efficacy and diminished side effects relative to traditional, globally immunosuppressive agents.

Genetics and Environment

Viewed broadly, IIM reflects the confluence of environmental factors and immunological "danger" signals in genetically predisposed individu-

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als. Although the precise contribution of genetic risk is difficult to gauge, HLA association studies and more recent GWAS demonstrate clear linkages of different IIM autoantibody/disease subsets with both MHC and non-MHC genes. Examples of the former include associations between the HLA-DRB1*0301/DQA1*0501/DPB1*0101 haplotype and Jo-1 antibody positive myositis [1, 2] as well as the link between HLA-DRB1*0301/0101 and IBM [3], while examples of the latter include *STAT4* (IIM), *PTPN22* (PM), *IL18RI* (PM), and *GSDMB* (DM) [4]. Intriguingly, single nucleotide polymorphisms (SNPs) in some of these non-MHC genetic loci (most of which are involved in immune function) confer protection from the development of IIM—though the precise interaction with environmental triggers such as UV exposure (Mi-2 antibody positive DM) [5], smoking (Jo-1 antibody positive PM/DM) [6], and/or viral infection (suggested by seasonal variation of disease onset in defined serological subgroups [7]) remains undefined.

Adaptive Immunity

Several pieces of evidence underscore contributions of the adaptive immune response to IIM immunopathogenesis. Beyond HLA associations that implicate antigen-specific T cells in the disease process, the close link between class-switched autoantibodies and predictable clinical phenotypes provides ample evidence of antigen-driven processes capable of shaping the immune repertoire. At the tissue level, the influx of clonally restricted T-cell populations in PM/DM [8] as well as IBM [9] is also indicative of adaptive immune responses fueled by undefined muscle-derived antigens. Selective targeting of pathogenic cell populations therefore represents an appealing therapeutic strategy, though temporal evolution of the B and T cell repertoire through processes such as epitope spreading has complicated efforts to develop B/T cell receptor-based vaccines, altered peptide ligands, or other clonally restricted treatments applicable in IIM.

Role of B and T Cells

As indicated earlier, the contribution of B cells and humorally mediated autoimmunity to the underlying pathogenesis of IIM is suggested by the link between various myositis autoantibodies, unique clinical phenotypes, and, in some cases, serum autoantibody levels showing association with disease activity. In the case of anti-Jo-1 antibodies targeting histidyl-tRNA synthetase, for example, serum titers have been detected prior to disease onset [10] and then correlate over time with specific disease manifestations, including myositis, arthritis, and interstitial lung disease [11, 12]. More detailed repertoire analysis of the Jo-1 antibody response has demonstrated sequential processes of class switching, spectratype broadening/epitope spreading, and affinity maturation—all of which are immunological hallmarks of an antigen-driven process associated with the development of the anti-synthetase syndrome [10, 13–15]. Unfortunately, despite some provocative studies linking Jo-1 and other autoantibodies targeting RNA/RNA binding proteins to enhanced IFNα/β signaling ([16]; see below), very little evidence exists for direct, antibody-mediated tissue damage. On the other hand, the (presumed) effectiveness of B cell-targeted therapies such as rituximab highlights the role of B cells as potent antigen-presenting cells (APCs) capable of supporting antigen-specific T cells that fuel underlying adaptive immune responses in IIM. The association of anti-Jo-1 seropositivity with a response to rituximab adds further support for this hypothesis [17].

Through direct cytolytic as well as indirect cytokine-mediated effector mechanisms, T cells play a key role in directing muscular as well as extra-muscular organ pathology characterizing various subsets of IIM. While early studies demonstrated that the type of APC plays a critical role in determining T cell responses targeting an immunodominant portion of Jo-1 [18], for example, more systematic exploration of TCR repertoire has revealed close overlap in clonally restricted T cells isolated from muscle and lung—potentially linking different components

of the anti-synthetase syndrome [19]. Detailed subset analyses have variably implicated TH1, TH2, and more recently, TH17 cells [20, 21], each of which are characterized by different cytokine/chemokine profiles responsible for mediating interactions with other cell types (including muscle cells that can upregulate MHC class II in the setting of active disease [22]) as well as signaling cascades contributing directly to muscle dysfunction (e.g., TNFα [23]). Of note, animal models suggest that defects in subpopulations of $CD4^+CD25^{high}FoxP3^+$ regulatory T cells (Treg) may compound the problem by allowing these pro-inflammatory/myopathic processes to proceed unchecked [24, 25]; however, immunohistochemical characterization of muscle-infiltrating lymphocytes derived from human myositis patients has not revealed any clear quantitative deficiency in this important cell type (indicating the need for corresponding functional analysis) [26].

Beyond these conventional categories of $CD4^+$ T cells that interact with $CD8^+$ T cells found in PM and IBM, unique populations of T cells isolated from involved muscle tissue in different IIM subsets include steroid/apoptosis-resistant $CD4^+$ and $CD8^+$ $CD28^{null}$ T cells [27–29] as well as more recently described IL-15-dependent $CD8^+NKG2D$ cells which have properties of NK-like T cells and are capable of driving myocytotoxicity through perforin-mediated mechanisms [30]. Although the precise role of immune-mediated mechanisms is less well defined in IBM, this subset of IIM is also characterized by the influx of $CD8^+$ T cells that include a subpopulation with cell surface markers of clonally restricted large granular lymphocytes potentially indicative of a pre-leukemic phenotype [31]. Counterbalancing these observations, the relative lack of T cell infiltration in variants of immune-mediated necrotizing myopathy [associated with anti-signal recognition particle (SRP) and anti-Hydroxy-3-Methylglutaryl-Coenzyme A Reductase (HMGCR) antibody profiles] underscores the heterogeneity of IIM subtypes as well as the need to look beyond therapies that exclusively target T lymphocytes.

Role of Innate Immunity

Despite the preponderance of data supporting the role of adaptive immune responses in different subsets of IIM, several lines of evidence emphasize an equally important role for components of the innate immune system. More specifically, animal models have separately implicated Toll-like receptor (TLR) 4 and 7 (TLR4, TLR7) signaling in the disease process [32, 33], ultimately leading to downstream activation of NF-κB and consequent upregulation of pro-inflammatory cytokine responses. Beyond the direct evidence for TLR signaling in these models of myositis, immunohistochemical analysis of human polymyositis/dermatomyositis biopsy specimens shows that autoinvasive cells (mononuclear cells including T cells) express a range of TLRs which include TLR2, TLR4, and TLR9 [34]—each of which can activate MyD88/NF-κB-dependent signaling cascades shown by RNA profiling to be operative in diseased muscle tissue [35]. TLR engagement of various endogenous/exogenous ligands [including nucleic acid (TLR3/7/9), lipoproteins (TLR2/4), or alarmins such as HMGB1 (TLR2/4)] triggers pathways that not only activate APCs and effector lymphocytes but may also promote direct, NF-κB-mediated impairment of muscle function [36, 37] (via myocyte-expressed cell surface and endosomal TLRs [38, 39]). At the same time, TLR2/4 signaling stimulates the production of pro-IL-1β [37, 40], providing a potential link to NLRP3 inflammasome activation and caspase 1-mediated conversion of cytokine precursors to pro-inflammatory mediators such as IL-1β and IL-18.

Complementing these signaling pathways, various soluble mediators contribute to the interface between innate and adaptive immune responses in IIM. One of the histopathological hallmarks of DM, for example, is the tissue deposition of C5b-9, terminal components of the complement cascade known as the membrane attack complex (MAC) [41]. Although not rigorously proven, complement activation (which may be triggered by immune complex formation) likely contributes to the microvascular pathology of

DM that is marked by morphological alterations of the capillary endothelium, capillary dropout, and perivascular infiltrates consisting of B cells and $CD4^+$ T cells [42]. Even more intriguing are data showing that putative autoantigens have direct signaling properties which are independent of B/T cell receptors and therefore extend beyond the conventional paradigms of adaptive immunity. Following Wakasugi's seminal observation that subfragments of tyrosyl-tRNA synthetase could function as biologically active cytokines [43], for example, Howard et al. demonstrated that two other known myositis autoantigens—histidyl-tRNA synthetase (HRS = Jo-1) and asparaginyl-tRNA synthetase (ARS = KS)—possessed chemokine-like properties capable of stimulating lymphocytes, activated monocytes, and immature dendritic cells [44]. Collectively, these findings provide additional supportive evidence for the direct role of known autoantigens such as HRS in the pathogenesis of the antisynthetase syndrome.

With the advent of increasingly refined immunohistochemical and RNA profiling techniques, a more complete view of the complex signaling network mediated by other, more traditional, cytokines and chemokines (elaborated by mononuclear cells as well as myocytes) has emerged. Collectively, these molecules representing components of the innate and adaptive immune systems directly impact key process ranging from intercellular communication and chemotaxis to cellular activation. While a complete discussion of the cytokines and chemokines thought to be involved in the pathogenesis of IIM is beyond the scope of this review, at least two cytokine families are worthy of discussion—namely, TNF-associated cytokines (TNFα, BAFF) and type I interferons (consisting of IFNα and IFNβ). TNFα, in particular, is clearly dysregulated in IIM and has the capacity to directly impair myocyte function [23, 45, 46]; unfortunately, however, attempts to treat IIM with TNFα blockade have been largely unsuccessful (and potentially harmful) in adult myositis [47]. BAFF is another TNF superfamily member with pleiotropic functions promoting B cell activation, differentiation, and proliferation. This cytokine is intimately linked with type I interferon signaling, as IFNα/β produced by plasmacytoid dendritic cells stimulates myeloid dendritic cells to secrete BAFF in the vicinity of developing B cells [48, 49]—again demonstrating the potential interface between innate and adaptive immune responses. Further supporting this connection between innate and adaptive immunity in IIM, results from *in vitro* experimental systems as well as autoantibody-cytokine association studies suggest that immune complexes containing RNA/RNA binding proteins contribute to stimulation of endosomal TLR3/7 and subsequent upregulation of IFNα/β [16, 50]. Coupled with evidence of a type I interferon gene signature profile in the peripheral blood and muscle tissue of DM patients, the correlations between clinical improvement and suppression of IFN-mediated gene expression in early phase trials of sifalimumab [51] provide proof of principle that IFNα/β plays an integral role in disease pathogenesis—at least for DM.

Non-immune Mechanisms

Beyond these collective data implicating both adaptive and innate immune responses in the pathogenesis of IIM, several pieces of evidence underscore an equally important role for "non-immune" mechanisms that contribute to muscle dysfunction in these disorders. From a clinical/epidemiologic perspective, the lack of complete clinical response to immunomodulatory therapy in certain disease subsets as well as the frequent discordance between degree of tissue inflammation and muscle weakness highlight the potential involvement of nonimmune factors ranging from tissue hypoxia to endoplasmic reticulum (ER) stress [52]. In a murine model of myositis based on conditional upregulation of class I MHC molecules, for example, Nagaraju et al. have shown that mice clearly develop weakness prior to the influx of inflammatory cells [53]. Although mononuclear cell (predominantly macrophagic) infiltrates likely play a key role in perpetuating the disease process, augmented MHC I expression independently triggers various components of the ER stress response—including ER overload that

culminates in NF-κB activation, expression of pro-inflammatory cytokines, and further upregulation of MHC I [54]. Coupled with immunohistochemical studies demonstrating intracellular co-localization of MHC I with calnexin (a marker of ER stress) in diseased muscle tissue from humans and mice, muscle-associated gene expression profiles showing upregulation of NF-κB-dependent transcripts as well as Grp78 and other genes linked to ER stress pathways provide compelling evidence that these mechanisms are operative in human disease [54]. Additional signaling cascades involving TLR4 and TRAIL also lead to NF-κB activation and induction of autophagy, a stress-induced salvage pathway that is linked to mitochondrial pathology, the unfolded protein response (UPR, a component of the ER stress response), and non-apoptotic cell death in certain subsets of inflammatory myopathy [55].

While the relative contribution of these non-immune pathways to PM/DM remains undefined, it is clear that non-immune mechanisms play a significant, if not predominant, role in IBM where defects in activity of sirtuin I lead to abnormal accumulation of membrane-bound amyloid β-precursor protein (AβPP). AβPP not only promotes aberrant myostatin signaling but also interferes with proteasome processing—ultimately leading to accumulation of misfolded proteins that include tau and amyloid β (Aβ) [56]. In turn, aggregates of misfolded Aβ can directly disrupt muscle cells through generation of reactive oxygen species, amplifying damage mediated through the UPR component of ER stress (in conjunction with other misfolded proteins) [56].

Vascular Pathology and the Role of Ischemia

In both PM and DM, abnormalities in the microvasculature point to a role for tissue ischemia as an additional "non-immune" factor contributing to tissue pathology. Although more pronounced in DM, muscle tissue in both PM and DM is characterized by a reduction in capillary density, thickened capillary endothelium, and increased expression of molecules linked to tissue hypoxia [such as vascular endothelial cell growth factor (VEGF), intercellular adhesion molecule 1 (ICAM-1), and vascular cell adhesion molecule 1 (VCAM-1)] [57]. Moreover, the development of frank vasculitis in JDM [58] and vasculitic ulcers as well as ischemic digits in seropositive MDA-5 patients [59] provides an even more direct example of vascular targeting leading to tissue hypoxia and associated metabolic derangements that, in muscle, can synergize with inflammatory pathways to compound muscle weakness. While the distribution of vascular abnormalities in DM muscle tissue does not necessarily explain the characteristic perifascicular atrophy (since diminished vascular supply might be expected to have a greater impact on the interior of muscle fascicles), the composite data provide at least indirect evidence that vascular pathology and associated tissue hypoxia represent important co-factors promoting muscle dysfunction in some subsets of IIM.

Conclusions

As demonstrated by the schematic in Fig. 28.1, the idiopathic inflammatory myopathies result from the confluence of immune as well as nonimmune pathways that culminate in both muscular and extra-muscular organ pathologies. While various environmental insults such as infection, UV exposure, and smoking are likely responsible for initiating disease in genetically predisposed individuals, disease progression ultimately hinges on complex networks linking antigen-specific B and T cells with cellular and humoral components of the innate immune system. Additional contributions from ER stress, dysregulated autophagy, and microvascular pathology amplify the disease process, potentially explaining the discordance that can be seen between degree of tissue inflammation/necrosis and severity of organ dysfunction. Determining the relative balance of these pathways in different subsets of IIM is critically important and will depend, in part, on the development of more refined *in vitro* and *in vivo* models—with the ultimate goal of defining novel molecular targets and expanding the therapeutic repertoire for this potentially devastating group of diseases.

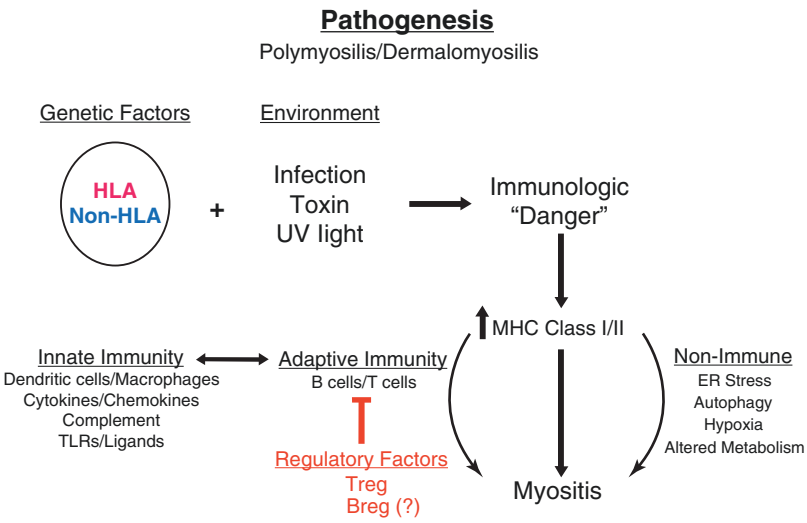

Fig. 28.1 Pathogenesis of polymyositis/dermatomyositis. This schematic illustrates the collective contributions of genetic predisposition, environmental triggers, and immunologic danger to the initiation of immune as well as nonimmune cascades that culminate in myositis/muscle dysfunction

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29 Management Considerations: Pharmacologic Intervention

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Key Points to Remember

- Most moderate to severe myositis requires long-term immunosuppression over years.
- Glucocorticoids are the first-line therapy for myositis; however, they have significant long-term side effects as well as lack of long-term response in most patients.
- Methotrexate and azathioprine are first-line nonsteroidal immunosuppressive agents for myositis.
- Mycophenolate mofetil and tacrolimus are typically used for refractory interstitial lung disease (ILD).
- Rituximab has shown promising results in patients with antisynthetase syndrome and is commonly used for refractory ILD associated with this syndrome.
- Intravenous Immunoglobulin (IVIG) is preferred in the setting of malignancy, infection, dysphagia, refractory dermatomyositis, and statin-associated necrotizing myopathy.

Introduction

Managing myositis is challenging even for experienced clinicians who commonly assess and evaluate these patients. Many chapters in this book support that observation. The disease is quite variable in its presentation, with the potential for multiorgan involvement, and in some patients, many organs are concomitantly affected. That is, treating this disease and its subsets involves much more than simply managing muscle weakness related to muscle inflammation. Certainly, glucocorticoids are necessary, and some myositis patients respond well to steroids alone. However, in most cases, other immunosuppressive agents are required, and introducing them early in the course of management can mitigate steroid toxicity and facilitate more rapid resolution of disease features. Combination therapy with different immunosuppressive agents should also be considered and the use of IVIg, an immunomodulatory agent, has shown particular efficacy in many clinical scenarios. Finally, the more frequent use of biologics has emerged, and the future of myositis management certainly includes this class of agents that are increasingly being tested in clinical trials. One notable factor is the rarity of myositis – even though there are many clinical subsets of myositis that manifest quite differently. Thus, investigators have encouraged international collaborations as essential in the development of novel therapies for this enig-

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matic group of autoimmune diseases [1]. Outcome measures to gauge treatment response have only been available for a few years, and myositis treatment response criteria continue to develop.

Immunosuppressive Medications

Glucocorticoids Even though there are no controlled clinical trials, glucocorticoids remain the first treatment option in myositis. Due to their known side effects, the dose and duration should be carefully considered. The starting dose is generally 1 mg/kg/day, which often translates to 60–80 mg/day for most patients (often initially divided into twice daily dosing). Patients with severe myositis or major extramuscular complications such as interstitial lung disease (ILD) often receive intravenous pulse therapy with 1 gram of methylprednisolone for 3 consecutive days followed by the initial dose noted above. The duration of the initial dosing will vary, but one should generally not continue high doses for longer than 1–2 months at which time it is reasonable to drop the dose by 20–25% of the existing dose monthly. This often results in a prednisone dose of about 5–10 mg/day within 6 months. A low dose of prednisone may be necessary for an extended period depending on side effects, clinical response, and the concomitant administration of other immunosuppressive agents. Adrenocorticotropic hormone (ACTH) gel or repository corticotropin injection (RCI) was approved for myositis in 1952 and later in 2010. The efficacy of RCI was reported retrospectively [2, 3] and, most recently, in an open-label trial [4]. In patients failing to respond to glucocorticoids, diagnosis verification must occur (perhaps even a repeat muscle biopsy) along with consideration for the development of steroid myopathy or the presence of malignancy.

Methotrexate Due to adverse effects and the potential for relapse, glucocorticoids are rarely used alone. Methotrexate is often the first immunosuppressive agent used in myositis unless there are obvious contraindications such as severe ILD or liver problems, and it may be started concomitantly with glucocorticoids. Retrospective studies [5, 6] support its use, and the administration is flexible as methotrexate can be given orally or subcutaneously usually at a starting dose of 10–15 mg/week with dose titration up to 25 mg/week (or higher in some cases). In fact, in an open-label placebo-controlled randomized trial in treatment-naïve juvenile DM patients, the combination of glucocorticoids and methotrexate showed a better response compared to steroids alone [7]. However, in adult polymyositis and dermatomyositis, a European open-label randomized placebo-controlled multicenter trial studying the efficacy and safety of combined methotrexate/glucocorticoid therapy vs. glucocorticoids alone (Prometheus Trial) was not as favorable as the primary endpoint was not reached. Monitoring for methotrexate toxicity includes periodic assessment of a complete blood count, liver enzymes, creatinine, and albumin given the potential for hematologic side effects and other organ toxicity.

Azathioprine Azathioprine is a preferred initial immunosuppressive agent by some and is felt to have similar efficacy to methotrexate [8]. It can be given in patients with liver disease or concomitant ILD and initiated at a dose of 50–100 mg/day with a progressive increase to 2–3 mg/kg/day. A double-blind, longer duration controlled trial completed many years ago comparing azathioprine in combination with prednisone versus prednisone alone showed the superiority of azathioprine when functional status and steroid dose were studied [9]. A later randomized, crossover study of 30 patients with a suboptimal response to methotrexate or azathioprine alone experienced an improvement with a combination of oral methotrexate and azathioprine, which was also noted to be more effective than intravenous methotrexate [10]. Thus, the combination of methotrexate and azathioprine should always be considered even when a favorable response is lacking to either agent alone. One should screen for thiopurine methyltransferase (TPMT) deficiency before beginning azathioprine and toxicity monitoring includes periodic assessment for

bone marrow suppression and liver enzyme abnormalities.

Mycophenolate Mofetil (MMF) MMF exerts its immunosuppressive effects by inhibiting purine synthesis and impairing B and T lymphocyte proliferation. Most reports of MMF's efficacy in myositis including cutaneous responses come from case reports or case series [11–14]. However, complete remission was seen in seven refractory polymyositis and dermatomyositis patients when MMF was combined with intravenous immune globulin [15]. The efficacy of MMF has been reported both in autoimmune ILD in general and in myositis-associated ILD [16–19]. In a study of 125 patients with autoimmune ILD, 32 had polymyositis or dermatomyositis and were treated with MMF for a median of 897 days. The forced vital capacity (FVC) improved significantly at 52, 104, and 156 weeks and the DLCO at 52 and 104 weeks including a trend toward statistical improvement in FVC% and DLCO% in the myositis subset at the 1-, 2-, and 3-year time points [16]. MMF is administered orally at starting doses of 250–500 mg twice daily with daily doses eventually ranging between 2000 and 3000 mg daily. The complete blood count and platelets are monitored along with liver and kidney studies.

Cyclosporine and Tacrolimus Cyclosporine and tacrolimus are both calcineurin inhibitors with different mechanisms of action. Cyclosporine inhibits the production and release of IL-2 and IL-2-induced activation of T lymphocytes, while tacrolimus binds to an intracellular protein, FKBP-12 that inhibits T-cell activation. The initial report of tacrolimus effectiveness was a case series of eight refractory myositis patients, six of whom were anti-Jo-1 autoantibody positive, while two patients had severe muscle weakness and the anti-SRP autoantibody [20]. An observational study from Japan reported 16 polymyositis and 15 dermatomyositis patients treated with tacrolimus with significant lowering of the serum creatine kinase and improvement in muscle strength after 2–4 months [21]. T cells are implicated in both myositis and ILD as activated CD8+ T cells have been found in the lung tissue of myositis-associated ILD [22], while regulatory T cells are decreased in autoimmune interstitial pneumonitis [23]. Thus, both cyclosporine and tacrolimus have a therapeutic rationale in treating myositis-associated ILD. Fourteen dermatomyositis patients with ILD were given cyclosporine (4 mg/kg/day) combined with glucocorticoids within 12 days from diagnosis, and imaging (lung HRCT) and functional studies (PFTs) both improved [24]. Thirteen patients with anti-synthetase autoantibodies and ILD (12 Jo-1/1PL-12) received tacrolimus for an average of 51 months and showed significant improvement in muscle strength, CK, and all PFT parameters [25]. Although normally reserved for use in refractory ILD patients, tacrolimus was used as a first-line glucocorticoid-sparing agent in a cohort of antisynthetase-associated ILD patients with reasonable efficacy [26]. Toxicity does limit the use of both cyclosporine and tacrolimus mainly related to kidney problems, and monitoring blood levels are necessary with tacrolimus administration.

Cyclophosphamide Cyclophosphamide is an alkylating agent that can be given orally or intravenously, but due to concerns regarding the development of a secondary malignancy, its use is reserved for severe myositis manifestations. This would include refractory myositis, rapidly progressive ILD, systemic vasculitis or patients failing to respond to many of the aforementioned immunosuppressive agents. Eleven of seventeen myositis-associated ILD patients received monthly IV cyclophosphamide for at least 6 months, and dyspnea not only improved, but six of seven requiring supplemental oxygen were able to discontinue its use [27]. Vital capacity was better in 12 subjects by at least 10% along with improved HRCT imaging. Cyclophosphamide can also be used in combination with rituximab as reported in a cohort of patients with synthetase autoantibody positivity and severe ILD [28]. Oral cyclophosphamide dosing is initiated at approximately 50 mg daily, and the dose is progressively increased to 100–150 mg/day with careful hematologic monitoring and particular attention to bladder toxicity. Intravenous monthly is considered safer with a starting dose of 500–750 mg/m^2.

Intravenous Immunoglobulin (IVIg)

IVIg is an immunomodulatory agent with an imprecise mechanism of action but acts to suppress inflammatory and immune-mediated processes in myositis without direct immunosuppressive actions. Many years ago, its effectiveness was reported in a double-blind, crossover, controlled trial of 15 refractory dermatomyositis patients [29], and in an open-label trial of 35 polymyositis patients, sustained improvement was reported in 70% [30]. Three years later, efficacy was maintained in 50% of the subjects even after drug discontinuation. However, 26 (16 polymyositis and 10 dermatomyositis) refractory patients enrolled in a randomized, double-blind, placebo-controlled Japanese trial failed to improve their muscle strength [31]. An important randomized, placebo-controlled phase 3 study hopes to confirm the efficacy and safety of IVIg in refractory dermatomyositis (ClinicalTrials.gov identifier: NCT02728752). A subcutaneous form of gamma globulin administered through a programmable pump improved four dermatomyositis and three polymyositis patients and was steroid-sparing allowing a drop in concurrent immunosuppressive medication [32]. In 2013, the American Academy of Neurology endorsed the use of IVIg in refractory DM but due to a lack of evidence, neither supported nor refuted its use in polymyositis [33]. IVIg is initially administered at a dose of 2 g/kg monthly (given over two consecutive days), and if there is a therapeutic effect, this dose is often continued for 3–6 months. Subsequently, the dose or interval of administration can be changed dependent on the response of the patient. The obvious advantage of IVIg is that it can be given with other immunosuppressive agents or in the setting of infection or malignancy. Conversely, it is very expensive and sometimes in short supply, which certainly limits its long-term use.

Biologic Agents

Biologic agents afford a more direct effect (than standard immunosuppressive agents) assuming that the target of the biologic agent is implicated in either the pathogenesis of myositis or its many secondary extramuscular manifestations. Potential biomarkers have been explored using a variety of experimental techniques including cytokine/chemokine analyses, advanced immunohistochemistry, flow cytometry, microarrays, and RNA sequencing analysis.

B Cell Depletion (Rituximab) Rituximab depletes CD20-positive B cells that are known to be involved in the pathogenesis of myositis. Several case reports and case series [34–36] initially noted improvement with rituximab. A group of necrotizing myopathy patients with the anti-SRP autoantibody, a known poor prognostic marker of disease activity, nicely responded to rituximab with an improvement in muscle strength and CK levels as early as 2 months after initiating rituximab in six of the eight patients. Three subjects had a sustained response for 12–18 months [37]. Although a small open-label trial of four patients with refractory polymyositis regained full muscle strength with a marked drop in the serum CK [38], another open-label trial only demonstrated three of eight dermatomyositis patients with a modest improvement in muscle strength and no cutaneous response [39]. In the largest randomized, double-blind, controlled clinical trial ever completed in myositis [Rituximab in Myositis (RIM) Trial], 75 polymyositis, 72 dermatomyositis, and 48 juvenile dermatomyositis subjects received 2 1-gram rituximab infusions 2 weeks apart [40]. Patients were refractory to glucocorticoids and at least one immunosuppressive agent and the primary endpoint incorporated a newly studied definition of improvement (DOI). Although the primary endpoint was not achieved, 83% of these refractory subjects met the predetermined DOI with a significant steroid-sparing effect of rituximab and a lack of significant adverse events. Subsequently, studies from the RIM Trial demonstrated that the presence of an antisynthetase autoantibody, especially anti-Jo-1, as well as anti-Mi-2 autoantibodies, and a lower disease damage score at trial entry predicted a beneficial response to B cell depletion [41]. Juvenile dermatomyositis subjects also seemed to respond to rituximab better than their adult counterparts.

The efficacy of rituximab in autoimmune and myositis-associated ILD has been studied in several retrospective uncontrolled studies. In 50 patients with severe, progressive ILD (10 with myositis), rituximab therapy was associated with significant improvements in the FVC with stabilization of the DLCO after 6–12 months [42]. A large Norwegian antisynthetase cohort with severe ILD was retrospectively assessed (median follow-up 52 months) after rituximab, and an improvement in the FVC, FEV-1, and DLCO was reported along with a 34% reduction in an imaging metric on HRCT testing [28]. Although the muscle strength and CK both improved, a confounding variable was the concomitant use of cyclophosphamide in 10 of the 12 patients with acute disease. Further, there were 7 deaths among the 34 rituximab-treated patients, and three subjects had *P. jirovecii* pneumonia. In another retrospective study, 17 anti-Jo-1-positive patients received rituximab and myositis, and ILD outcomes were compared to 30 conventionally treated patients, with 16 of the former patients showing a more rapid and marked response [43]. Finally, 25 antisynthetase-positive subjects from 2 centers received rituximab (84% for progressive ILD), and stability or improvement in pulmonary function or severity of ILD on HRCT was observed in most patients [44]. The most common imaging pattern in this cohort was nonspecific interstitial pneumonia (NSIP).

Anti-TNF Agents Although tumor necrosis factor has been implicated in the pathogenesis of myositis [45], the effect of anti-TNF agents has been variable. For example, five DM patients treated with etanercept had worsening muscle weakness and no rash or CK improvement [46]. However, a randomized, double-blind, placebo-controlled trial of etanercept for 1 year in 16 DM patients led to a significantly lower prednisone at week 24 and a longer time to treatment failure [47]. Case reports have similarly suggested efficacy with infliximab, another anti-TNF agent [48–51], but in an open-label, pilot trial of 13 patients with refractory IIM, infliximab was ineffective [52]. Further, another double-blind placebo-controlled crossover trial studying infliximab in 12 polymyositis and dermatomyositis had a response rate of less than 33% after 14 weeks of therapy [53]. Thus, it is likely inadvisable to recommend anti-TNF therapy for myositis especially when reports demonstrate that these agents may cause myositis [54–56]. However, these biologics should still be considered in patients with a prominent inflammatory arthropathy, and the calcinosis of JDM has responded to anti-TNFs [57]. Doses are similar to those used in rheumatoid arthritis.

Abatacept Abatacept acts to inhibit co-stimulation of T cells that are known to be involved in both the pathogenesis of myositis and myositis-associated ILD (see above). Case reports have reported some benefit with abatacept in myositis [58–61], and a recent randomized open-label "delayed-start" treatment trial of this biologic agent in 11 polymyositis and 9 dermatomyositis patients assessed disease activity as well as changes in muscle biopsy [62]. In this refractory group of patients, a significant response was detected in nearly half the cohort, and an increase in T regulatory cells in those with repeat muscle biopsy also supported a beneficial effect. Abatacept was administered in a similar regimen as dosed in RA and was well tolerated with no concerning safety signals. This agent is now being assessed in a Phase 3 clinical trial in myositis (ClinicalTrials.gov identifier: NCT02971683).

Other Biologic Agents Tocilizumab, an interleukin-6 receptor antagonist, approved in the treatment of RA, was used in two refractory polymyositis patients with an improvement in the serum CK as well as MR imaging of the thigh musculature [63]. A dermatomyositis/systemic sclerosis overlap patient given tocilizumab similarly demonstrated resolution of rash with gradual CK and myositis improvement [64]. An investigator-initiated, multicenter, randomized, double-blind, controlled trial assessing the efficacy of tocilizumab in myositis is in progress (ClinicalTrials.gov identifier NCT02043548). Evidence that type I interferon is implicated in the pathogenesis of IIM [65] led to a preliminary trial that assessed sifalimumab, an anti-IFN-

alpha monoclonal antibody, in polymyositis and dermatomyositis [66]. Suppression of the IFN signature in peripheral blood and muscle tissue (66% and 47%, respectively) was noted, which correlated with clinical improvement and subjects with ≥15% improvement in the MMT had greater neutralization of the blood and tissue IFN signature compared to those with <15% improvement. Anakinra, a recombinant IL-1 receptor antagonist administered subcutaneously (100 mg daily) in 15 refractory myositis patients for 12 months, led to a clinical response in 7 patients [67].

Other Treatment Considerations

Necrotizing Myopathy Necrotizing myopathy (NM) is associated with markedly elevated muscle enzymes with severe muscle weakness, often in the setting of anti-hydroxymethylglutaryl-Co-A reductase (anti-HMGCR) [68] and anti-SRP (signal recognition particle) autoantibodies. Treatment should be aggressive including a combination of high-dose or pulse intravenous glucocorticoids combined with another immunosuppressive agent. IVIg should be considered early in statin-associated NM [69], and rituximab was effective in anti-SRP-associated NM [37].

Antisynthetase Syndrome The clinical manifestations of patients with any one of the known antisynthetase autoantibodies frequently cluster together in the setting of the "antisynthetase syndrome." In addition to myositis, patients manifest fever, Raynaud phenomenon, mechanic's hands, polyarthritis, and interstitial lung disease (ILD). The treatment of the antisynthetase syndrome is problem-oriented and driven by the most troublesome clinical features. Fever and polyarthritis usually respond to low- or moderate-dose glucocorticoids, while Raynaud phenomenon is treated as it is in other systemic autoimmune disorders. Mechanic's hands can be a stubborn manifestation that may flare when the syndrome is active or independent of the other antisynthetase syndrome features. Topical agents including steroid creams and a variety of emollients or inhibitors of T-lymphocyte activation such as tacrolimus or pimecrolimus ointment may also be effective. Occlusive dressings can be considered intermittently in severe cases. As described earlier in this chapter, the arthritis of the antisynthetase syndrome can be very similar to that seen with RA leading to similar treatment regimens employed for the RA patient. Thus, methotrexate is an acceptable immunosuppressive agent to administer for arthritis as long as the ILD is not a dominant feature and anti-TNF agents are effective as well. As noted earlier in this chapter, ILD is a major cause of morbidity and mortality in myositis patients; particularly those with the antisynthetase syndrome and the use of MMF, cyclophosphamide, calcineurin inhibition and B cell depletion have been discussed. In the RIM Trial, the presence of an antisynthetase autoantibody (primarily anti-Jo-1) strongly predicted clinical improvement in myositis [41]. A randomized pilot trial of abatacept in the treatment of synthetase-positive patients is currently enrolling patients with the primary goal of assessing its effect on ILD (ClinicalTrials.gov Identifier: NCT03215927).

Interstitial Lung Disease Beyond the medications discussed earlier in this chapter for myositis-ILD, azathioprine has led to some improvement in retrospective case series as well as a cohort of 70 patients where 25 improved [70, 71]. Another prospective open-label study demonstrated stabilization and functional improvement after a median of 35 months in progressive ILD [72]. IVIg use in ILD is limited to case reports where a polymyositis patient and an amyopathic dermatomyositis patient refractory to high-dose glucocorticoids and cyclosporine A both responded to IVIg therapy [73, 74]. Additional data on calcineurin inhibitor use in ILD notes 48 Asian patients with DM-ILD demonstrating significantly better survival after early cyclosporine treatment compared to those receiving delayed cyclosporine [75]. Similarly, a retrospective study of 49 previously untreated myositis-associated ILD patients receiving tacrolimus plus conventional therapy or conventional therapy alone showed a significantly longer event-free

survival with the combination of tacrolimus [76]. Further, tacrolimus improves lung disease when cyclosporine was previously ineffective [77, 78].

Dysphagia Involvement of the oropharyngeal musculature can be profound and very difficult to treat in myositis patients leading to prominent proximal dysphagia and a risk for aspiration and pneumonia. Patients may respond to glucocorticoids and other immunosuppressive agents, but IVIg must be considered early in the course of such patients. In a retrospective study of 73 PM-DM patients with steroid-refractory life-threatening dysphagia, IVIg was very beneficial when combined early on with high-dose glucocorticoids [79]. Sixty patients had resolution of esophageal manifestations that led to a return of normal oral feeding and discontinuation of feeding tubes. IVIg is generally administered at a dose of 2 g/kg monthly either on 2 consecutive days or over a 5-day period if there is a concern for an excessive volume with a shorter duration.

Conclusion

The future of myositis treatment includes many immunosuppressive therapies and an emerging number of potential biologic agents along with combination therapy. Investigators will certainly employ advanced technological diagnostics to identify logical cytokines or other immunopathogenic targets as the treatment of myositis and other autoimmune disorders evolves.

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Management Considerations: Juvenile Dermatomyositis

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Key Points to Remember

- Rarity and heterogeneity of juvenile dermatomyositis (JDM) as well as a lack of randomized controlled clinical trials make treatment recommendations challenging, and currently, recommendations are based mainly on expert experience and consensus through CARRA and PRINTO.
- Glucocorticoids remain the mainstay of treatment of JDM; however, due to long-term side effects as well as morbidities, alternative immunosuppressive therapies need to be considered.
- In a large European randomized controlled trial, methotrexate or cyclosporine in combination with prednisone was shown to lead to shorter time to inactive disease than prednisone alone.
- IVIG is used most frequently for the initial treatment of severe, refractory disease and for prominent skin disease.
- There is ample evidence for the role of cytokines and other immune pathways in the pathogenesis of JDM making them attractive targets for treatment; therefore, specific biological agents need to be evaluated in clinical studies.

Introduction

Juvenile myositis, which predominantly includes juvenile dermatomyositis (JDM) and, less commonly, juvenile polymyositis (JPM), is a subset of idiopathic inflammatory myopathies (IIM).

Treating physicians rely on the collective experience of adult rheumatologists, neurologists, and pediatric rheumatologists, clinical trials in adult DM, and regional experiences given the lack of randomized clinical trials and treatment strategies. With current therapies, the prognosis and course of JDM have improved dramatically, now with a 5-year survival rate >95%. Despite these advances, it remains a disease with significant morbidity including calcinosis, lipodystrophy, and persistent muscle weakness, with many patients on chronic immunosuppression years after diagnosis [1–3]. As

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there is no cure for JDM, the goals of treatment include remission and limitation of morbidities including those associated with medications. Aggressive therapy is warranted given the potential for development of calcinosis and visceral vasculopathy as well as ongoing damage affecting muscle [1, 4, 5].

General Approach

Published approaches to the assessment and treatment of JDM have been generated by collaborative research groups including the International Myositis Assessment and Clinical Studies Group (IMACS), the Paediatric Rheumatology International Trials Organization (PRINTO), and Childhood Arthritis and Rheumatology Research Alliance (CARRA) [6–9].

Currently, the mainstay of JDM treatment is the combination of high-dose oral and/or IV glucocorticoids in addition to other immunosuppressive agents. The first-line, nonsteroid immunosuppressive therapies include methotrexate, intravenous immunoglobulins (IVIG), and cyclosporine [10]. The second- or third-line therapies for refractory disease include the nonbiologic medications, mycophenolate mofetil [11, 12], azathioprine [13], tacrolimus [14], and cyclophosphamide [15], as well as biologic therapies, including anti-TNFs [16–18], abatacept [19], and rituximab [20–23].

An incomplete understanding of the etiopathogenesis of JDM limits therapy. Cellular (B and T cells, natural killer cells, and plasmacytoid dendritic cells) and soluble elements (type I interferons; IL-I, IL-6, and IL-17; and chemokines) of the innate and adaptive immune systems are implicated in initiating and maintaining an aberrant immune response that leads to the development of an autoimmune vasculopathy, resulting in chronic inflammation. With an increased knowledge of the contribution of these constituents to disease pathogenesis, avenues for using targeted therapies that affect the proinflammatory milieu are being investigated.

Disease heterogeneity is another complicating factor, but the identification of myositis-specific antibodies (MSA) and their concomitant phenotype opens the door to tailored therapies, which include addressing problems such as calcinosis with aggressive therapy [24, 25].

JDM is rare, so a collective approach utilizing the aforementioned collaborative groups is important, and consensus treatment plans (CTPs) have been developed to provide variation in treatment approaches [26]. Prospective data collection will also contribute to comparative research [27]. To date, CARRA has published four CTPs including one for the initial treatment of moderate JDM, a second for ongoing treatment of moderate JDM, a third for persistent skin disease in the context of quiescent muscle disease, and a fourth for skin disease in patients without muscle involvement at diagnosis [8, 26–28].

Pharmacologic Therapy

Glucocorticoids

Glucocorticoids remain the cornerstone therapy in JDM as summarized by Stringer's survey of 167 North American pediatric rheumatologists regarding initial treatment practices [29]. Clinical cases provided either typical presentations, atypical presentations, or refractory presentations; typical presentations included mild, moderate, severe, and ulcerative disease. In all four typical presentations, oral and/or IV glucocorticoids are first-line therapies. The method of administration varies from high-dose oral (2 mg/kg/day) in mild cases (>50% of respondents) to IV methylprednisolone (IVMP) 30 mg/kg/dose for three to five doses followed by high-dose oral glucocorticoids in moderate, severe, and ulcerative disease. Gastrointestinal vasculopathy may limit the absorption of oral medication, and IV administration of steroids is preferable in this situation. The more immediate anti-inflammatory response of high-dose IV corticosteroids as well as the potential for overall steroid-sparing makes this an attractive initial approach to treatment of potentially morbid and chronic inflammatory diseases such as JDM [30, 31]. Subsequently, JDM experts from CARRA developed three consensus treatment plans (CTPs) reflecting initial treatment of moderately severe

JDM [8]. All three protocols propose treatment with corticosteroids at doses of 2 mg/kg/day orally with methotrexate at a dose of 15 mg/m^2/week or 1 mg/kg/week. In addition, IVMP, 30 mg/kg/dose IV up to 1 g for three consecutive days and then optionally one dose/week, and/or IVMP plus intravenous immunoglobulin (2 g/kg every 2 weeks for three doses, then monthly, thereafter) are additional therapies that may be added based on disease severity in an effort to spare steroid exposure and limit morbidity. Subsequently, glucocorticoid tapering every 2–4 weeks should follow driven by the clinical response, with a goal of discontinuation 10–12 months from initial diagnosis [8]. These treatment plans are currently being used by members of CARRA as part of routine clinical care with the goal of prospectively collecting data to be analyzed to identify the treatments with the best outcomes with the least ill effects for children with JDM. Milder cases are treated with lower doses and shorter courses of glucocorticoids. There is evidence that very mild presentations may be successfully treated without systemic glucocorticoids [32].

Hydroxychloroquine (Plaquenil)

Hydroxychloroquine is used as adjunctive therapy for the treatment of cutaneous manifestations in JDM as well as for its purported steroid-sparing effects. In a multivariate analysis of 65 patients with active JDM from the CARRA JDM Legacy Registry, hydroxychloroquine use ($p = 0.045$) was found to be a significant predictor of improvement in the patient/parent global health score [33]. It is administered at a dose of 5–6 mg/kg/day to a maximum dose of 400 mg/day. Rare adverse effects include skin hyperpigmentation and retinal toxicity.

Methotrexate

Methotrexate (MTX) acts as an antimetabolite that modulates the function of many of the cells involved in inflammation and affects the production of various cytokines including reducing the production of TNF-α, interferon-γ, and IL-1 [34]. MTX was initially used as therapy in JDM patients who did not have complete or sustained response to corticosteroids [35–38]. Currently, MTX is the most common first-line agent used, alone or in combination with other agents, in up to 84% of cases [29]. Moreover, MTX, in combination with corticosteroids, is the most common combined therapy at disease onset (range 30–44% depending on severity).

Ramanan et al. investigated MTX as a steroid-sparing agent in a retrospective cohort study of 31 patients with JDM [30]. Patients received 10–20 mg/m^2/week of MTX orally or subcutaneously depending on initial response to oral MTX along with prednisolone 2 mg/kg/day. Prednisolone was weaned according to the protocol but only if disease was well controlled. There was a significant reduction in mean duration of corticosteroid use from 27 to 10 months as compared with historical controls.

In a recently published international PRINTO study, Ruperto et al. compared the efficacy and safety of prednisone alone, prednisone with methotrexate, and prednisone with cyclosporine in 139 children with newly diagnosed JDM in the only randomized clinical trial of pharmacologic treatment in JDM to date [39]. Median time to clinical remission, time to treatment failure, and total steroid exposure were superior to therapy with prednisone alone. Comparing combination therapies, there were fewer adverse effects reported with prednisone plus methotrexate versus prednisone plus cyclosporine.

Typical dosing of MTX for children with JDM is 15 mg/m^2 or 1 mg/kg with weekly oral or subcutaneous administration [8]. Initial improvement usually begins 4–6 weeks after initiating therapy. Most side effects associated with MTX are mild and reversible. Abdominal discomfort and nausea are the most commonly noted adverse effects. Monitoring liver transaminases secondary to liver toxicity is performed every 1–3 months. The risk of opportunistic infection is as low as the risk of malignancy. MTX is a teratogen, and women of childbearing age should be counseled regarding this risk and the need for effective contraception during treatment.

Cyclosporine

Cyclosporine affects T-cell mediated immunity by inhibiting transcription of the IL-2 gene, resulting in reduced IL-2 and other cytokines with consequent block of cytotoxic T-cell development and proliferation of T helper cells [31]. Case reports and series describe experience with cyclosporine therapy in JDM including refractory disease, disease associated with steroid toxicity, and interstitial lung disease (ILD) [40–43]. In Europe, it is often used over MTX as adjunctive therapy in combination with glucocorticoids [44]. Cyclosporine is an option in the CARRA CTP developed to address persistent skin disease in JDM patients with quiescent muscle disease at a dose of at least 3 mg/kg [26]. Based on current experience and the results of the PRINTO study, cyclosporine is a reasonable alternative to MTX for first-line therapy with glucocorticoids. It also has a role as adjunctive therapy in cases of refractory disease or those patients with interstitial lung disease (ILD). Cyclosporine dosing in JDM falls in the range of 2.5–7.5 mg/kg/day divided into two doses [36, 39]. Adverse effects of cyclosporine include hypertension, reversible decreases in renal function, and hypertrichosis.

Mycophenolate Mofetil (MMF)

Mycophenolate mofetil (MMF) is a nonbiologic DMARD that selectively inhibits the proliferation of B and T cells by inhibiting inosine monophosphate dehydrogenase, the rate-limiting enzyme in the synthesis of guanosine nucleotides [45]. Retrospective chart reviews describe MMF efficacy in treating recalcitrant skin and muscle disease with a steroid-sparing effect [11, 12]. Given its beneficial effect in treating severe skin disease in adult dermatomyositis as well as experience in improving skin of children with JDM, MMF was included in the CARRA CTP developed to address persistent skin disease in JDM patients with quiescent muscle disease [14, 28, 46].

Standard dosing for MMF is 600 mg/m^2/day divided into two doses. Gastrointestinal tolerability is the most common side effect. Adverse effects include cytopenias and opportunistic infections. The **R**isk **E**valuation and **M**itigation **S**trategy (REMS) program informs patients of childbearing age and their parents about the higher risk of birth defects and miscarriages with the use of mycophenolate. Drug monitoring labs should include a CBC with differential and platelets every 1–2 weeks until a stable dose is reached, then every 4–12 weeks.

Azathioprine (Imuran)

Azathioprine is not considered a first-line agent in the treatment of JDM due to the lack of evidence supporting its efficacy relative to other therapies and is used primarily in treating refractory disease. Dosing is 1–3 mg/kg/day. The most common side effects are gastrointestinal (abdominal pain, nausea, and diarrhea). There is risk for bone marrow toxicity based on the level of thiopurine-S-methyltransferase (TPMT), which is involved in the metabolism of azathioprine. The level of activity of this enzyme should be measured prior to initiation of therapy to assess risk. Drug monitoring labs should include CBC with differential and platelets every 1–2 weeks until a stable dose is reached and then every 4–12 weeks. Liver function tests (AST and ALT) and creatinine should be monitored every 12 weeks.

Cyclophosphamide (Cytoxan)

Cyclophosphamide is generally reserved for treating severe disease manifestations of JDM such as skin or gastrointestinal ulceration, severe weakness, or calcinosis incompletely or not responsive to other therapies. Monthly intravenous pulses of cyclophosphamide resulted in significant improvement in 10 of 12 patients after 6 months in an open-label study [47]. Dosing ranges from 500 to 1250 mg/m^2/dose once monthly IV have been reported. Side effects may include anorexia, nausea, and vomiting. Leucopenia and thrombocytopenia occur although they are rarely clinically significant. A

major risk of cyclophosphamide is bladder toxicity, including hemorrhagic cystitis, secondary to prolonged contact of the bladder wall mucosa with the metabolite acrolein. To prevent cystitis, adequate hydration before, during, and following administration of cyclophosphamide is crucial. Mesna administration should be considered when administering cyclophosphamide intravenously. Cyclophosphamide can affect fertility, and consideration of cumulative dosing as well as use of gonadotropin-releasing hormone agonists (GnRH-a) such as leuprolide acetate in preserving ovarian function in young women should be considered. In male patients, sperm cryopreservation may be considered.

Intravenous Immunoglobulin (IVIG, Gamunex, Gammagard)

Intravenous immunoglobulin (IVIG) has demonstrated efficacy in JDM with wide-ranging effects including, but not limited to, modulation of cell migration; generation of anti-idiotype antibodies thereby reducing pathogenic autoantibodies; effects on activation, differentiation, and effector functions of B cells, T cells, and dendritic cells; and inhibition of the complement system by preventing the formation of the membrane attack complex (MAC) and subsequent tissue damage [48, 49].

IVIG has been used as adjunctive therapy in refractory skin and muscle disease and is steroid-sparing. The efficacy and safety have been reported in open-label studies, both retrospective and prospective [50–54]. In a retrospective controlled study, 30 of 78 children receiving IVIG after failing initial therapy with prednisone, IVMP, and MTX (refractory disease) were compared to 48 controls who had responded to first-line therapy. IVIG-treated patients maintained similar or lower disease activity (with no severe adverse effects) than controls from 30 days to 4 years post diagnosis having higher disease activity at baseline [55]. The improvement was most marked in steroid-resistant cases. In patients who experience systemic reactions to IVIG, subcutaneous administration of Ig (SCIG) has been reported as a viable option [56, 57].

In the 2010 CARRA treatment utilization report, IVIG was used most frequently for initial treatment of severe disease, treatment of refractory disease, and for pronounced skin disease [29]. Subsequent to this report, IVIG is included as a recommended treatment in two of the three published CARRA JDM CTPs [26, 27]. The recommended treatment dose for IVIG is 2 g/kg/dose as frequent as every 2 weeks depending on disease severity [27]. Infusion-related reactions are common especially in patients receiving their first dose of IVIG. These are rarely serious and include headache, flushing, chills, myalgia, nausea, and hypertension. These can be ameliorated or prevented by decreasing the infusion rate, pretreating with acetaminophen, diphenhydramine, and/or methylprednisolone or by changing to a different formulation. Other possible adverse effects include aseptic meningitis, thromboembolic events, and anaphylaxis.

Biological Therapies

As more is learned about the basic mechanisms of pathogenesis involved in IIM including the cellular and soluble mediators of inflammation, the possibility of modulating the immune system with better directed therapies has opened the door to the development and use of specific biological agents.

In a recently published report, CARRA investigators published the findings from three surveys regarding biologic use for the treatment of JDM by North American pediatric rheumatologists from 2011 to 2016 [58]. The majority of rheumatologists (51.1%) initiated treatment with a biologic due to lack of response to methotrexate, steroids, IVIG, or another immunosuppressant (azathioprine, mycophenolate, or cyclosporine). At the 2016 CARRA meeting, the 31 physicians attending the JDM work groups ranked the biologics they would use in treating JDM refractory to first- and second-line therapies. They ranked in order: rituximab, abatacept, tocilizumab, and anti-TNF (infliximab and adalimumab). It was concluded that the next step would be to study comparative effectiveness of these medications in refractory JDM.

B-Cell Depletion

Despite the predominance of T cells in inflammatory infiltrates of IIM, there is much evidence to support the role of B cells in the pathogenesis of these diseases. In DM and JDM, the mononuclear infiltrates demonstrate an increased percentage of B cells at all sites relative to IBM as well as the ratio of CD4+ to total T-cell number being significantly greater in DM than in PM and IBM [59]. The frequent identification of serum autoantibodies, particularly in JDM, DM, and PM, and the correlation of these with distinct clinical phenotypes (i.e., antisynthetase syndrome) and molecular pathways (type I IFN activation) strengthen this evidence [60–62]. Additionally, both adult and childhood disease demonstrates that local maturation of B cells occurs in affected muscle tissue with organization of B cells, T cells, dendritic cells (DCs), and plasma cells into a secondary lymphoid organ strengthening the rationale of B-cell-depleting therapy [63–65].

Rituximab (Rituxan)

Rituximab is a monoclonal antibody that facilitates depletion of B cells for 6–8 months by targeting CD 20, a B-cell-specific surface receptor expressed at the early stages of B-cell development [66].

To evaluate the efficacy and safety of rituximab in refractory myositis including JDM, a large prospective, randomized controlled study, the Rituximab in Myositis (RIM) trial was conceived [22]. Patients were randomized either to a rituximab early or rituximab late group. There was no significant difference in time to improvement between treatment groups at 44 weeks; however, 83% of the patients met the definition of improvement. Of importance, the addition of rituximab was noted to have a significant steroid-sparing effect. In the post hoc analyses of JDM patients in the RIM trial, autoantibody positivity, interferon gene expression signatures and interferon chemokine scores, less disease damage, and the clinical group of JDM have all been identified as predictors of response to rituximab [67–69]. Significant improvements in skin disease activity as measured by a physician visual analog scale (VAS) were noted in JDM patients enrolled in the RIM trial following rituximab therapy [70]. Rituximab is often administered at 750 mg/m^2/dose for two doses given 2 weeks apart with a maximum dose of 1000 mg. There is a risk of infusion reaction with rituximab with symptoms including fever, chills, bronchospasm, hypertension, and rash. These are rarely serious and can be managed or prevented by decreasing the infusion rate, pretreating with acetaminophen, diphenhydramine, and/or methylprednisolone. More rare adverse effects include infection, hypogammaglobulinemia, and immunogenicity.

Anti-T Cell

The lymphomonocytic inflammatory cell infiltrates found in skeletal muscle biopsies from patients with IIM including JDM consist of an abundance of CD4+ and CD8+ T cells [59]. Consequently, phenotypes of T cells with potential for cytotoxicity have been identified in IIM including JDM [71–74].

Abatacept (Orencia)

Abatacept is a human fusion protein of CTLA-4 and the Fc portion of human immunoglobulin G1 and is an antagonist of the T-cell costimulatory molecule CD28 that acts by blocking the costimulatory signals needed for T-cell activation [74]. There are a limited number of case reports detailing the positive response of abatacept in various IIM including a patient with JDM with myositis complicated by calcinosis [19]. There is a phase 4 treatment study currently enrolling patients with refractory JDM for treatment with abatacept [NCT02594735].

Anti-cytokines

Proinflammatory roles of cytokines in inflammatory myopathies include, but are not limited to, cellular migration to the affected tissue (CCL20/

CCR6, chemokine/receptor complex); upregulation of MHC class I and II molecules on muscle (TNF-α, type I interferon [type I IFN]); activation and proliferation of B cells (IL-1, IL-6, and type I IFN); and survival and activation of autoreactive T cells, B cells, and plasma cells (IFN-γ, IL-17, CXCL-13, BAFF, and APRIL) [63, 75–80]. De Paepe and Zschuntzsch review the role of cytokines as potential therapeutic targets in IIM [81].

Tocilizumab (Actemra)

Tocilizumab is an antagonist of the IL-6 receptor that binds soluble and membrane-bound IL-6 receptors. Through the binding of the IL-6 receptor, IL-6 triggers several intracellular pathways leading to the release of inflammatory mediators and stimulation of the immune system including B- and T-cell growth and differentiation. There are case reports of tocilizumab efficacy involving two adult PM patients and one adult DM overlap patient as well as one JDM patient with an overlap myositis syndrome of polyarthritis and Raynaud phenomenon [82–84]. In the JDM case, no mention of a myositis flare was made when the patient developed overlap symptoms and tocilizumab was added for the treatment of refractory arthritis [84].

Anti-tumor Necrosis Factor (Anti-TNF)

Support for the use of anti-TNF treatment in IIM include polymorphisms in the TNFα-308A promoter region associated with an increased production of TNFα; association of the -308A allele with interferon-α (INF-α) activity; expression in muscle and elevated serum levels; increased TNF production in severe calcinosis; and specific risk-associated TNF genotypes [85–88]. Results of anti-TNF therapy in adults and children when treating IIM have been mixed: some studies report a benefit, while others report no response or even a worsening of disease [89]. The only published data of anti-TNF therapy in JDM are with infliximab and etanercept.

Infliximab (Remicade)

Treatment of five patients with severe refractory JDM with infliximab (3 mg/kg every 8 weeks to 6 mg/kg every 4 weeks) in a prospective study revealed promising results [16]. A sustained clinical improvement was reported at 30 weeks for all five patients as noted by improvement in strength, joint contractures, and calcinosis. Corticosteroids were weaned in all cases and discontinued in three. At the time of publication of the study, all patients remained on infliximab and at least one additional DMARD. Infliximab dosing ranges from 6 to 10 mg/kg IV every 2–8 weeks. Adverse effects include infusion reactions, most commonly occurring after the first infusion; systemic infections including reactivation of tuberculosis, as well as other opportunistic infections; and immunogenicity with the development of anti-infliximab antibodies.

Etanercept (Enbrel)

In the only published trial of etanercept to date in JDM, nine patients with disease activity for at least 12 months and refractory to initial therapy were prospectively treated with etanercept 0.4 mg/kg SC twice weekly [90]. Results at the 24-week follow-up revealed improvement in a validated Disease Activity Score (DAS) in three patients, stable DAS in one patient, and worsened DAS in two patients; these two patients were noted to have polymorphisms in the TNFα-308A promoter, which the authors speculated may have led to increased TNF production that, when inhibited by etanercept, led to alterations in the type I IFN expression and more active disease. In all patients, there was no significant improvement in serum muscle enzymes or Childhood Myositis Assessment Scale (CMAS). Enbrel is administered at a dose of 0.8 mg/kg/week subcutaneously. Adverse effects of treatment include injection site reaction and development of infection but with lower rates of reactivation of tuberculosis than infliximab.

Table 30.1 Future therapeutic targets

Therapeutic agent	Target	Pathogenic considerations
Belimumab	B-LyS aka BAFF receptor	B-Lys (BAFF) receptor primarily expressed by B cells [91, 92]. Increased BAFF in PM and DM [87]. BAFF mRNA expression significantly correlates with disease activity measures in adult and pediatric IIM [93]
Anakinra	IL-1receptor	Il-1 receptor upregulation identified in skeletal muscle biopsy tissue from PM and DM [94]. Three of four patients with DM had improvement in cutaneous findings after treatment with anakinra [95]. Child with JDM and MAS showed improvement in MAS parameters [96]; no reports of treatment in JDM for primary disease
Anti-IL-17	IL-17	IL-17-producing cells have been demonstrated in skeletal muscle biopsy tissue from patients with PM and DM [97–100]. There are no results in JDM to date
Sifalimumab	IFN-α	Differential type I IFN signature overexpression in skeletal muscle and peripheral blood [101–105]. These signatures were proposed as a biomarker of disease activity [106]. Sifalimumab suppressed the type-I IFN gene signature in blood and muscle in phase 1b trial of PM and DM [107]. There are no results in JDM to date
Interferon Kinoid (IFN-K)	IFN-α	As stated above [101–106]. IFN-K is a therapeutic vaccine. In patients with SLE, neutralizing anti-IFN-α antibody was significantly correlated with decreased IFN scores [108]. A study of IFN-K is currently enrolling patients with DM to evaluate the change from baseline in the expression of IFN-induced genes [NCT02980198]. There are no studies in JDM to date
Tofacitinib	JAK-1, 3	Blocks IFN signaling [109]. Reported as effective in treating refractory DM [110]. There is a proof-of-concept open-label study currently enrolling to measure safety and efficacy in adult patients with refractory DM treated with tofacitinib [NCT03002649]
Ruxolitinib	JAK-1, 2	Selective inhibitor of JAK 1 and JAK 2 kinase. Reported as effective in treating refractory DM [111]
IMO-8400	TLR-7, 8, 9	TLRs have been found to be expressed in skeletal muscle tissues from adult patients with PM and DM [112, 113]. Endogenous production of type I IFN in DM is generated by pDCs, mainly through the TLR-9 pathway and in part by TLR-7 [113]. There is an active phase 2 trial of IMO-8400 in probable or definite adult DM with cutaneous manifestations [NCT02612857]

B-Lys B lymphocyte stimulator, *BAFF* B-cell activating factor, *IL-1* interleukin 1, *IL-17* interleukin 17, *IFN-α* interferon-alpha, *JAK* Janus kinase, *TLR* Toll-like receptor, *PM* polymyositis, *DM* dermatomyositis, *IIM* idiopathic inflammatory myopathies, *MAS* macrophage activation syndrome, *pDC* plasmacytoid dendritic cell

Future Therapeutic Targets

Various novel therapeutic targets are under study as potential modulators of proposed pathogenic pathways in JDM with some of these currently in early clinical trials. Table 30.1 summarizes these potential novel therapies [91–113].

Additional Treatments

Stem Cell Transplantation

Inclusion criteria for the treatment of children with JDM with autologous stem cell transplantation (aSCT) were first proposed in 1999 [114]. Since that time, there remains limited experience with aSCT in JDM; however, the results of reported cases are encouraging. Enders et al. describe three JDM patients who received aSCT for severe refractory disease [115]. Two patients were reported in drug-free disease remission greater than 5 years following transplant, and the third patient remained without muscle disease, nearly 3 years after aSCT, but continued to have persistent skin disease including calcinosis. It is postulated that, in part, aSCT increases the repertoire of regulatory T cells and that this diversity is linked to suppressive function [116].

Physical Therapy and Exercise

In a study of physical activity, it has been demonstrated that physical capacity and health-related

quality of life are reduced in JDM patients when compared to those in controls [117]. It is now a recommendation that physical therapy be initiated at the diagnosis of JDM in an effort to maintain or correct range of motion affected by muscle and/or joint inflammation [118]. Recently published consensus-based recommendations for the management of JDM, as developed by 19 experts in pediatric rheumatology and two experts in physical therapy, include the implementation of an exercise program when it is determined to be safe [119]. Several studies have suggested safety and benefits of supervised exercise in adult patients with IIM including those with recent disease onset [120, 121].

A randomized controlled trial (RCT) evaluated the feasibility, safety, and efficacy of an exercise program in children and adolescents with JDM [122]. In addition to an improvement in physical performance, there was an increase in parental rating of well-being in the group of patients with exercise intervention. Moreover, there is evidence that aerobic capacity may promote muscle growth and, at the same time, suppress the inflammatory response in the patient's muscle [123, 124].

Skin Involvement

Calcinosis

Calcinosis in the post-corticosteroid era affects 17–47% of children during their course of JDM and is present in long-term follow-up in as many as 37% of patients [1, 3, 125, 126]. Calcinosis is a significant cause of morbidity including skin ulceration, contracture, and pain. The presence of calcinosis has been associated with male sex, persistent disease activity 6 months after diagnosis, prolonged time to diagnosis, inadequate therapy, and the presence of certain myositis-specific antibodies [127–131]. Additionally, polymorphisms of TNF-α and IL1-α are associated with calcinosis risk [88, 132]. Treatment of calcinosis is a challenge, as there is no consistently efficacious therapy which leads to any substantive response in JDM patients. Aggressive therapy at disease onset with appropriate first-line therapy including glucocorticoids appears to decrease the frequency and severity of calcinosis [5, 133]. Poorly controlled muscle disease is a risk factor for calcinosis; however, evidence for quiescent muscle disease does not guarantee remission of calcinosis. An exhaustive list of antirheumatic medications has been employed in an effort to address calcinosis in JDM and other autoimmune diseases. Use of anti-inflammatories (IVIG), medications that affect calcium and phosphate balance (bisphosphonates, diltiazem, probenecid, and sodium thiosulfate), and biologic therapies (anti-TNF, abatacept, and rituximab) are reported with varying efficacy in case reports [16, 19, 134–138].

Following reports of sodium thiosulfate (STS) in treatment of calciphylaxis as well as tumoral calcification in renal patients, topical, and topical plus intravenous sodium thiosulfate has been reported as being successful in treating ulcerative skin disease and progressive, refractory calcinosis in children with JDM in two case reports [19, 139].

Conclusion

Currently accepted therapy for the initial treatment of JDM includes corticosteroids and conventional oral immunosuppressive drugs with recent published evidence for methotrexate over cyclosporine as a first-line agent. IVIG is used most frequently for the initial treatment of severe disease and treatment of refractory disease and for pronounced skin disease. Additional immunosuppressive and immunomodulatory agents including biologics are being used in the treatment of recalcitrant disease and severe cutaneous manifestations such as calcinosis with varied success.

The role of exercise in not only improving gross measures of muscle health but also in changing the metabolic profile of muscle is intriguing from a pathogenic as well as therapeutic perspective.

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31 Management Considerations: Refractory Skin Rash and Calcinosis

Matthew A. Lewis and David F. Fiorentino

Key Points to Remember

- Knowledge of the patient's myositis-specific autoantibody is salient because it may inform the risk of malignancy or interstitial lung disease and therefore drive therapy selection.
- Topical therapies have a palliative role in reducing itch, erythema, and scale but are rarely effective in gaining complete control of the cutaneous manifestations of dermatomyositis.
- Antimalarials are only modestly effective agents in controlling cutaneous dermatomyositis and may result in a drug eruption in up to 30% of cases so their use may be most appropriate in patients with mildly active skin disease.
- Mycophenolate, methotrexate, and intravenous immune globulin are the most effective therapies for cutaneous dermatomyositis.
- Combining multiple systemic therapies is frequently necessary to control refractory cutaneous dermatomyositis.
- Treatment of calcinosis is challenging, and while surgical excision is the most effective, medical therapies may have some benefit in controlling disease activity and reducing the development of calcinosis.

Introduction

Cutaneous dermatomyositis negatively impacts quality of life primarily due to the pruritus and distribution of the pink to violaceous erythema to cosmetically sensitive areas such as the face, neck, chest, arms, and hands. The detriment to quality of life may exceed that of atopic dermatitis and psoriasis [1]. Before embarking on a specific therapy plan for refractory cutaneous dermatomyositis, several principles of management are worth considering.

Principles of Management of Cutaneous Dermatomyositis

Differentiate Active Skin Disease from Damage

It is important to identify to what extent the patient's current cutaneous manifestations repre-

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sent disease activity versus damage. This diagnostic step is analogous to evaluating muscle weakness, in that not all weakness is due to myositis but could be due to damage, deconditioning, pain, or steroid myopathy, for example. Disease activity will respond to medical therapy, whereas damage will not. It is important to make this distinction to avoid escalating medical therapy for what is primarily skin damage. Diffuse red or violaceous erythema on the skin, the presence of scale, and Gottron papules and cutaneous ulceration are signs of disease activity. The most common scenario for this is determining whether skin erythema is due to active inflammation or dilated blood vessels (telangiectasias)—the latter representing damage. This can be difficult, but often close inspection (with or without the aid of magnification) will reveal discrete blood vessels. Typically, telangiectatic damage has a deeper red color (Fig. 31.1) as opposed to either the pink or violaceous erythema that is seen in active inflammation (Fig. 31.2). In addition, any presence of itch, scaling, and elevation (papules or plaques) is usually a sign of active inflammation. Unfortunately, the absence of these features does not always indicate damage. Other more readily distinguishable forms of damage include (a) hyperpigmentation, which is a tan to brown post-inflammatory form of pigmentary damage, which generally improves with time (Fig. 31.3), and (b) poikiloderma (Fig. 31.4), which is the combination of epidermal atrophy, telangiectasias, hyperpigmentation, and hypopigmentation resulting from prior interface dermatitis and endothelial damage and will often improve over

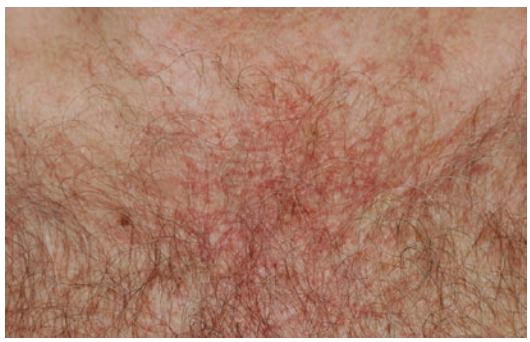

Fig. 31.1 Red telangiectatic patch on the chest representing damage

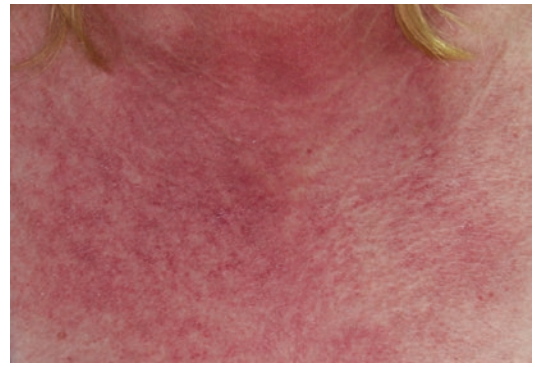

Fig. 31.2 Bright pink patches and scaly plaques of disease activity on the chest

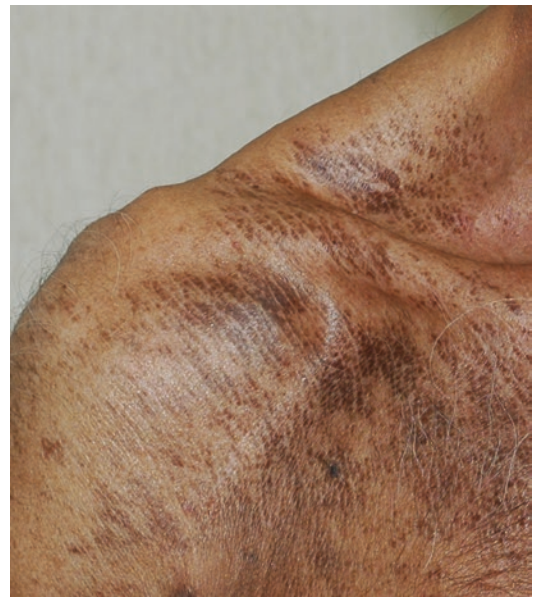

Fig. 31.3 Hyperpigmented, rippled patches on the shoulder demonstrating damage

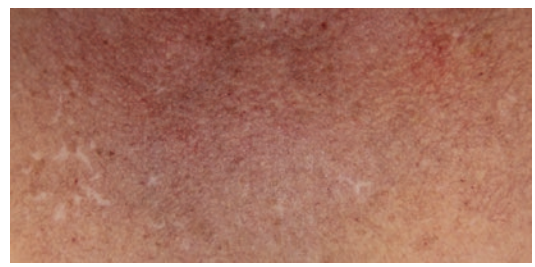

Fig. 31.4 Poikiloderma on the central chest consisting of deep red telangiectatic vessels, hyperpigmentation, and hypopigmentation on atrophic skin

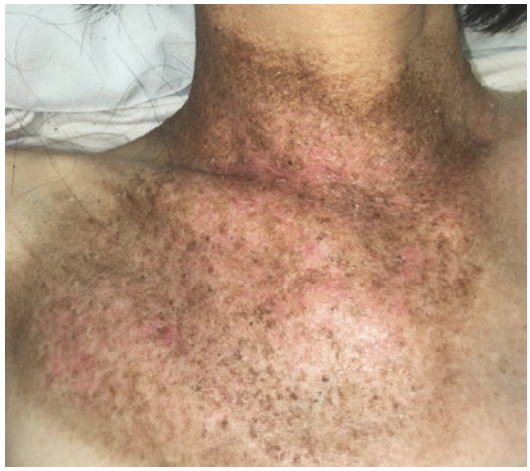

Fig. 31.5 Both the pink erythema and scale of disease activity in addition to reticulated, hyperpigmented brown patches of damage on the chest and neck

time. During the course of the patient's cutaneous disease, frequently both the inflammatory pink erythema of activity and the hyperpigmentation of damage will be present in the same location (Fig. 31.5).

Target all Organs Involved, Not Just the Skin

While considering your patient's medical comorbidities, select the treatments that will best target all affected organs by dermatomyositis in your patient, e.g., skin disease, interstitial lung disease, myositis, and arthritis. In patients in whom multiple organs are affected, it is key to establish an open line of communication between the treating dermatologist, rheumatologist, pulmonologist, and neurologist to create a timely and effective treatment plan while avoiding unnecessary medication toxicities.

Topical Therapy Is Mainly Adjunctive Therapy

While topical glucocorticoids and topical calcineurin inhibitors are commonly used for cutaneous dermatomyositis, they are rarely used as monotherapy for skin disease except in the mildest of cases. Class I and class II high-potency topical glucocorticoids such as clobetasol propionate 0.05% and fluocinonide 0.05%, respectively, are the most effective creams for affected areas on the body when applied twice daily. Table 31.1 displays a list of topical glucocorticoids arranged by their potency. These high-potency topical agents may result in skin atrophy and hypopigmentation, which are reversible once the cream is stopped. Advising the patient to routinely stop the medication for 1–2 weeks per month will prevent these adverse effects. Milder class V and class VI topical corticosteroids such as mometasone furoate 0.1% cream and desonide 0.05% cream, respectively, may be effective on the face when applied twice daily. Topical calcineurin inhibitors such as tacrolimus 0.1% ointment and pimecrolimus 1% cream may be modestly helpful for facial involvement in cutaneous dermatomyositis [2, 3]. They have comparable efficacy to class IV to VI topical steroids and are preferable for the eyelids given that they do not carry the risk of skin atrophy or elevating intraocular pressure as do topical glucocorticoids. Topical calcineurin inhibitors often produce a transient burning sensation, which typically resolves after 3–5 days of

Table 31.1 Topical glucocorticoid potency chart

Class I (superpotent)—Scalp, Gottron papules
Clobetasol 0.05% ointment and cream
Betamethasone dipropionate 0.05% ointment, augmented
Halobetasol propionate 0.05% ointment and cream
Class II (potent)—Recalcitrant areas on extremities/back
Betamethasone dipropionate 0.05% ointment and cream
Fluocinonide 0.05% ointment and solution
Desoximetasone 0.25% ointment and cream
Class III–V (middle strength)—Chest/neck, mild involvement of extremities/back
Desoximetasone 0.05% cream
Mometasone furoate 0.1% cream
Triamcinolone acetonide 0.1% cream/ointment
Betamethasone valerate 0.1% cream/ointment
Class VI–VII (mild)—Face, groin, folds of skin
Desonide 0.05% ointment and cream
Fluocinolone acetonide 0.01% cream and solution
Hydrocortisone 1–2.5% cream and ointment

consecutive use and may be minimized by storing the medication in the refrigerator. Although there is a boxed warning for lymphoma on the package insert based on a theoretical risk of lymphoma, multiple epidemiologic studies and post-marketing surveillance have failed to demonstrate any risk of lymphoma [4]. Ultimately, for cutaneous dermatomyositis, although topical agents have a palliative role in reducing itch, erythema, and scale, they are rarely effective in gaining complete cutaneous disease control except in very mild disease.

Discuss the Importance of Photoprotection

Although patients vary in terms of their perceived photosensitivity, [5, 6]. It is still important to discuss photoprotection with the patient. It is helpful to counsel patients to avoid hours of peak ultraviolet radiation intensity (10 am–4 pm), wear sun-protective clothing, and seek a sunscreen that has a broad spectrum, i.e., reduces UVA and UVB exposure, with sun protection factor of 50 or higher. Also, even in shaded areas, reflective sunlight from sand, pavement, or other surfaces can still result in significant ultraviolet radiation exposure.

Knowing the Patient's Dermatomyositis-Specific Antibody May Be Useful

Knowing the patient's dermatomyositis-specific autoantibody may indirectly guide management. For myositis treatment, based on findings from the Rituximab in Myositis (RIM) Trial [7], dermatomyositis patients with anti-synthetase antibodies, particularly anti-Jo-1 antibodies, and also anti-Mi-2 antibodies, have improved clinical responses in myositis after receiving rituximab compared to dermatomyositis patients without these autoantibodies [8]. Unfortunately, there are no data available regarding comparative efficacies of various treatments for skin disease among the different autoantibody groups. Nonetheless, these autoantibodies can be valuable in risk stratification such as the increased risk of developing an associated cancer with antinuclear matrix protein 2 (NXP2) and anti-transcriptional intermediary factor-1 gamma (TIF1-γ) antibodies [9, 10] and the increased risk of interstitial lung disease with anti-melanoma differentiation-associated gene 5 (MDA5) antibodies [11, 12] and anti-synthetase antibodies. This information may guide therapy as predicting the involvement of another organ may drive therapy selection.

Most Treatment Guidelines for Cutaneous Dermatomyositis Are Expert Opinions

We present a suggested treatment ladder (Table 31.2) for management cutaneous dermatomyositis. It should be stressed that this algorithm is not based on comparative effectiveness studies but instead expert opinion, and consideration of the patient's medical comorbidities, and preferences are tantamount in selecting a treatment regimen to reduce the morbidity of cutaneous dermato-

Table 31.2 Treatment ladder for inflammatory erythema of cutaneous dermatomyositis

Mild disease
Photoprotection
Topical corticosteroids
Topical calcineurin inhibitors
Antimalarials
Moderate-to-severe disease
First line
Mycophenolate mofetil
Methotrexate
Second line
Intravenous immune globulin
Third line
Leflunomide
Azathioprine
Combination therapy
Fourth line
Tofacitinib
Rituximab
Cyclosporine
Cyclophosphamide

myositis. In addition, treatment of prototypical active skin disease (erythema, scale, papules) may vary from that of cutaneous ulcers (a manifestation of vasculopathy). The latter scenario will be discussed separately, as will management of calcinosis.

Treatment Ladder for the Inflammatory Erythema of Cutaneous Dermatomyositis

Antimalarials Antimalarials are often mentioned as first-line agents for skin disease and thus deserve initial mention. They are modestly effective for cutaneous dermatomyositis with 30–50% of patients having some positive response after 4–6 months [13]. Typical dosing for hydroxychloroquine is 4–5 mg/kg/day based on actual bodyweight. The safest dosing regimen for chloroquine is unknown but has been suggested to be less than 2.3 mg/kg/day. Quinacrine can be added to either of the above antimalarials at 100 mg daily. One important observation to note is a report that up to 30% of dermatomyositis patients will have a cutaneous drug eruption after starting hydroxychloroquine [14]. This drug eruption ranges from a morbilliform rash to actual worsening of cutaneous dermatomyositis and can be quite severe requiring systemic glucocorticoids to achieve resolution. Given this issue and their modest efficacy, we consider them first-line agents only for patients with mild skin disease or as adjunctive therapy with other medications. For patients with moderate-to-severe skin disease, these agents would be second line and usually used in combination therapy with other steroid-sparing agents.

Antimalarials are modestly effective for cutaneous dermatomyositis and but some studies suggest an association with skin eruptions in 30% of cases.

Mycophenolate Mofetil Mycophenolate mofetil is a first-line agent for moderate-to-severe cutaneous dermatomyositis (Table 31.2) [15, 16]. In the authors' retrospective cohort, mycophenolate was the only medication significantly associated with cutaneous disease remission [70]. It is ideal for the dermatomyositis patient with both highly active skin disease and confirmed or suspected interstitial lung disease as it is also first-line treatment for early interstitial lung disease in dermatomyositis [17]. The authors start at a dose of 500 mg twice daily and check a complete blood count and renal and hepatic function panels after 1 month. If the patient is tolerating the medication well, then the dose may be increased to 2000–3000 mg daily. The therapeutic effect typically becomes evident after 3–4 months, although continued improvement of skin disease is often observed even 6–12 months after therapy. If partial improvement is seen after 3 months, then increasing the dose to 1500 mg twice daily is recommended to further reduce disease activity. If no improvement in the skin disease is seen after 4 months of therapy with at least 2 g daily, then mycophenolate mofetil is unlikely to be of significant benefit. The major side effects include nausea, weight loss, vomiting, and diarrhea, which affect 20–50% of patients. Patients can also experience insomnia and rarely hypertension. Infections, especially viral such as herpes simplex and herpes zoster, can be seen and are likely attributable to inhibition of inosine monophosphate dehydrogenase which is necessary for B- and T-lymphocyte maturation.

Although absorption is best if taken 1 h before or 2 h after eating, many patients need to take it with food to mitigate the gastrointestinal side effects. Instruct patients to avoid taking calcium, magnesium, and zinc at the same time as they inhibit its absorption. If patients have significant upper gastrointestinal symptoms, then switching to mycophenolic acid (Myfortic®), a delayed release preparation of mycophenolate, will often alleviate those symptoms and allow the patient to tolerate the medication. If a patient is switched from mycophenolate mofetil to mycophenolic

acid, 360 mg of mycophenolic acid is equivalent to 500 mg of mycophenolate mofetil.

Mycophenolate mofetil is a first-line agent for moderate-to-severe cutaneous dermatomyositis. GI intolerance and viral infections are common.

Methotrexate Methotrexate is also an effective treatment for refractory cutaneous dermatomyositis [74–76]. It is an ideal agent for the dermatomyositis patient who also has an accompanying inflammatory arthritis. However, because it can be associated with pulmonary fibrosis, it is often avoided in patients with known or evolving interstitial lung disease. It may be challenging for some patients to tolerate due to nausea, abdominal pain, and fatigue after the weekly doses. Switching to subcutaneous administration will ameliorate but may not eliminate the gastrointestinal side effects. Also, taking folinic acid (leucovorin) 5–15 mg 12 h after the methotrexate dose may lessen the fatigue, in addition to daily folic acid. Increasing the folic acid dose to 2–5 mg daily may also reduce fatigue, hair loss, and mucositis associated with methotrexate. Patients with comorbid depression may benefit from taking 7.5–15 mg of L-methylfolate daily, which has improved central nervous system penetration [18] and is used as an adjunctive treatment for depression [19, 20].

Methotrexate is an effective treatment for cutaneous dermatomyositis. Subcutaneous administration and higher doses of folic acid may reduce GI upset, fatigue, and hair loss.

Azathioprine Azathioprine is commonly started for myositis and interstitial lung disease, but there have been no reports that specifically evaluate its efficacy in cutaneous dermatomyositis. Although azathioprine has been shown to be equivalent to methotrexate for myositis and inhibits purine synthesis, like mycophenolate, its effectiveness in skin disease is not well documented.

Intravenous Immune Globulin Intravenous immune globulin (IVIG) is typically highly effective for cutaneous dermatomyositis with 70–80% of patients achieving partial or complete remission [21–23]. The relative lack of immunosuppression makes it an ideal therapy for patients with a history or suspicion of internal malignancy. Although mild improvement in skin disease may occur after the first or second month of IVIG, it often takes 3–4 months for the full effect of IVIG to be evident. If no improvement is seen after 4 months of IVIG, then it is unlikely to provide any clinical benefit. Checking serum IgA prior to infusion is recommended to avoid anaphylaxis in patients with selective IgA deficiency due to trace amounts of IgA in IVIG. Also, patients receiving IVIG may transiently show positive hepatitis B core antibodies [105]. This result may be from passive transfer of hepatitis B core antibodies within the IVIG or possibly false-positive testing of hepatitis B core antibodies following infusion [106]. Therefore, checking a hepatitis B panel prior to IVIG is important so the patient will not be unnecessarily given antiviral medication for hepatitis B reactivation prophylaxis when hepatitis B core antibodies are found in subsequent blood tests. Given the cost, tolerability issues, and lack of ease of administration, IVIG is considered a second-line agent for skin disease in DM.

Headaches affect between 30% and 60% of patients receiving IVIG and range from mild-to-severe migraines to aseptic meningitis, which limit the use of the medication. The rate of infusion, total dose, hydration status, and brand may all influence the incidence of headaches, and slowing the infusion, lowering the total dose per day, and increasing the amount of IV fluids may all diminish the headache severity. Cyproheptadine is an antihistamine with anti-serotonergic properties that may prevent or reduce the severity of headaches if taken before the infusion is started and every 4–6 h during the infusion. IVIG also may commonly cause an infusion reaction with fever, chills, nausea, myalgias, hypertension or hypotension, or urticaria which typically resolves. Temporary cessation of IVIG and symptom-

directed treatment may be necessary. Less frequent complications include acute kidney injury, particularly in those with advanced age or baseline chronic renal insufficiency. Additionally, venous and arterial thrombotic events have been reported during the infusion up to 1 week following IVIG infusion [24]. Risk factors for venous and arterial thrombotic events are advanced age, underlying hyperviscosity states, thrombophilias, and coronary artery disease.

- IVIG is a highly effective treatment for cutaneous dermatomyositis.
- Cost, tolerability, and route of administration make it a second-line agent.

Leflunomide Leflunomide may be a valuable alternative to methotrexate. It has been reported to improve both skin and muscle disease in four dermatomyositis cases at 20 mg daily dose [25, 26]. Like methotrexate and tofacitinib, leflunomide is a preferred treatment choice in the setting of coexisting arthritis. Leflunomide may trigger interstitial pneumonitis, although less commonly than methotrexate, and so may not be preferable in patients with known interstitial lung disease. Diarrhea and nausea are the most common side effects in 25% and 10% of patients, respectively. Alopecia and hepatotoxicity may also occur in 10% and 5% of patients, respectively. The authors typically start at 10 mg daily to assess tolerability, check labs in 4–8 weeks, and if necessary will increase to 20 mg daily.

Combination Therapy Combining multiple traditional systemic therapies is frequently necessary to control refractory cutaneous dermatomyositis. Methotrexate and mycophenolate mofetil is a useful combination to control recalcitrant skin disease, typically both given at submaximal doses to reduce risk of infection. The authors have also had success with combination therapy with azathioprine and either mycophenolate mofetil or methotrexate for cutaneous dermatomyositis. This combination of methotrexate with azathioprine has been shown to help refractory myositis in patients who failed monotherapy with either methotrexate or azathioprine alone [71]. As discussed earlier, antimalarials can also be added in combination with systemic immunosuppressive therapy. IVIG is commonly added to either methotrexate or mycophenolate mofetil to gain control of cutaneous disease without increasing the risk of infection.

Combination Therapy in Refractory Cutaneous Dermatomyositis Is More Effective than Monotherapy

Commonly used combinations:

- Mycophenolate + IVIG
- Mycophenolate + methotrexate
- Mycophenolate + azathioprine
- Methotrexate + tofacitinib
- Mycophenolate + tofacitinib + IVIG

Biologics and Other Agents

Rituximab The data regarding efficacy of rituximab for cutaneous dermatomyositis are conflicting. Aggarwal et al. analyzed data from the RIM Trial with 72 adult dermatomyositis patients and found a 20% reduction in the frequency of the classic dermatomyositis signs such as the heliotrope sign and Gottron papules at 36 weeks of follow-up [27]. However, there was no effect on cutaneous ulceration, panniculitis, or alopecia. Although regarding myositis, patients with anti-Mi-2 and anti-synthetase antibodies have improved responses to rituximab as compared to dermatomyositis patients without those antibodies [7], it is not clear that this association extends to cutaneous disease. Prior evidence for rituximab in cutaneous dermatomyositis was mixed with one report of three patients (two juvenile-onset and one adult patient) showing moderate improvement in poikilodermatous changes [28] and another open label trial with eight adult patients showing no benefit in inflammatory erythema of dermatomyositis [29]. Dosing in DM typically follows the rheumatoid arthritis protocol of

1000 mg IV at day 0 and day 14. The therapeutic effect of rituximab is typically not evident until at least 2–3 months following administration. Infectious complications are the most frequent serious adverse effects in dermatomyositis patients, and prophylaxis for pneumocystis pneumonia is warranted after rituximab for 6 months. Progressive multifocal leukoencephalopathy, a demyelinating disease due to reactivation of the JC virus, is one of the dreaded complications and is fortunately extremely rare. Based on Medicare/Medicaid data between 2000 and 2009, the incidence of this infection among patients with rheumatic diseases without malignancy or HIV treated with rituximab is estimated at 0.2 per 100,000 [30].

Rituximab has mixed results on refractory cutaneous dermatomyositis; therefore, further studies are needed to evaluate its efficacy.

Tofacitinib Janus kinase inhibitors are an exciting class of medications, and those targeting JAK1 or TYK2 inhibit signaling through type I interferon receptors may be particularly effective for dermatomyositis. Ruxolitinib was reported to improve patients with cutaneous dermatomyositis in two reports when given for concomitant polycythemia vera [31, 32]. Tofacitinib was reported to improve three refractory cutaneous dermatomyositis patients from moderate or severe cutaneous disease activity to mild disease activity over 4 weeks [33] at 5 mg or 10 mg twice daily. Tofacitinib has also been reported to reduce arthritis and myositis in addition to cutaneous dermatomyositis in one patient [34]. Tofacitinib may result in increased risk of infection (including herpes family viruses), bone marrow suppression, transaminitis, and elevated cholesterol so checking a complete blood count, comprehensive metabolic panel, and a lipid panel is recommended 4–8 weeks after initiation. Current data are limited to case reports and small case series. Larger studies are required to confirm its potential therapeutic benefit.

Cyclophosphamide Cyclophosphamide is an alkylating agent that is rarely needed to arrest recalcitrant cutaneous dermatomyositis. It has been reported to be useful in a case with progressive vasculitis [35], and the authors have used it for refractory ulceration in patients with anti-MDA5 antibodies. If given orally, it is typically started at 1–2 mg/kg daily with a minimum of 2 liters per day to prevent hemorrhagic cystitis. It may be increased to 2 mg/kg if an insufficient response is seen at 1 mg/kg. Cyclophosphamide induces several immediate toxicities including nausea and vomiting and at higher doses alopecia, myelosuppression, and rarely hemorrhagic cystitis. Vigilant monitoring with serial blood tests and urinalyses is necessary to monitor for these adverse effects. Long-term risks include malignancy (skin, bladder, and hematologic), infertility, and gonadal failure.

Systemic Glucocorticoids A word should be given regarding the use of systemic glucocorticoids for cutaneous dermatomyositis. These are generally not used for chronic control of disease, although they may be helpful in the acute reduction of pruritus and erythema. They may be started simultaneously as a steroid-sparing agent and tapered off over 1–2 months while the steroid-sparing agent takes effect. They are poor choices for long-term therapy of skin disease due to their association with well-known side effects that include weight gain, osteopenia, hypertension, diabetes, and cataracts.

Other therapies There are several therapies, discussed later, which are not uniformly effective or readily used for cutaneous dermatomyositis.

Dapsone is a sulfone antibiotic that inhibits neutrophil activation through blockade of myeloperoxidase [36]. The evidence for its use in cutaneous dermatomyositis is limited to three case reports in which its addition resulted in a moderate improvement in the cutaneous disease activity [37–39]. Treatment should likely be reserved in cases of mild skin disease that has failed other agents.

Tacrolimus, a potent inhibitor of T-cell activation, typically used for interstitial lung disease was reported to simultaneously improve cutaneous dermatomyositis in two case series with a total of nine juvenile dermatomyositis patients [40, 41]. Tacrolimus, like cyclosporine, has a low therapeutic index and requires frequent lab monitoring to avoid nephrotoxicity [42].

Abatacept is a fusion protein with cytotoxic T-lymphocyte antigen-4 (CTLA-4) and the Fc portion of human IgG1. There is a single case report of abatacept and intravenous sodium thiosulfate started in a juvenile dermatomyositis patient with severe cutaneous ulcerations, which resulted in complete healing of the cutaneous ulcerations after 6 months [72]. However, the ulcer healing may be largely attributable to sodium thiosulfate in this case. Although abatacept demonstrated reduction in refractory myositis in a delayed start trial [73], cutaneous disease was not an outcome measure, so further study is needed to determine the efficacy of abatacept in cutaneous dermatomyositis.

Anti-tumor necrosis factor-alpha inhibitors should be avoided as a treatment for disease activity as they have been reported to trigger dermatomyositis [43] and exacerbate preexisting cutaneous dermatomyositis [44, 45]. Exposure to these agents may occur when the dermatomyositis patient initially presents with an inflammatory arthritis and anti-tumor necrosis factor-alpha therapy is started for suspected rheumatoid arthritis.

Specific Scenarios

Scalp Pruritus Scalp pruritus is the most common and frequently the most bothersome symptom affecting 90% of patients. The severity and intractability often compel patients to seek evaluation and treatment. The symptoms may manifest with a neuropathic quality such as burning or crawling sensation, likely due to structural damage to epidermal nerve fibers resulting in a small fiber neuropathy [46]. Scalp pruritus or dysesthesia in dermatomyositis typically represents active disease so treatment requires anti-inflammatory medications. Topical corticosteroid solutions such as clobetasol propionate 0.05% solution, fluocinonide 0.05% solution, or fluocinolone acetonide 0.01% oil under occlusion with a wet head wrap have a palliative effect but are unlikely to fully control moderate-to-severe pruritus. In severe cases, systemic agents (e.g., methotrexate, mycophenolate mofetil, and IVIG) are often necessary. Antihistamines such as hydroxyzine and doxepin have a mild benefit for pruritus and largely assist with sleep induction. Medications for neuropathic pain such as gabapentin, amitriptyline, nortriptyline, and pregabalin may also be useful temporizing measures to help lessen the intensity of pruritus until the active disease is fully controlled.

Cutaneous Ulceration Cutaneous ulceration is present in roughly 20% of dermatomyositis, and many of these patients have anti-MDA5 antibodies [49]. Ulceration reflects a severe microangiopathy—although often referred to as "vasculitis," these ulcers rarely are due to typical leukocytoclastic vasculitis but instead a pauci-inflammatory disease of the small vessels. At times, severe cutaneous ulceration (in the form of necrosis) portends a poorer prognosis in DM and can be linked with severe disease or underlying malignancy. Mucocutaneous ulceration is more common in the anti-MDA5 group [47], and these patients have a marked increased risk of developing interstitial lung disease [48–50]. In that serotype, treatment of cutaneous ulceration, therefore, should involve prompt evaluation for interstitial lung disease, which may direct therapy, depending upon the severity. Other risk factors to consider for ulceration are the presence of a coexisting thrombophilia such as a protein C or S deficiency, or antiphospholipid antibodies, which may create ulceration that is refractory to immunosuppression alone and requires concomitant anticoagulation as well. Also, with immunosuppression, secondary bacterial or viral infection may exacerbate existing ulcers so cultures of recalcitrant ulcers may be indicated in the appropriate clinical setting.

Regarding treatment of the ulceration, this is a difficult problem as it is unclear how the inflammation of dermatomyositis is related to these

associated vasculopathic lesions. The authors still primarily follow the primary objective of controlling skin disease activity with the above agents mentioned in the algorithm, but patients may require an aggressive immunosuppressive approach and frequent follow-up for cutaneous ulceration. There may also be a role for agents that specifically target blood vessels. For example, there is anecdotal evidence that starting vasodilators such as phosphodiesterase-5 inhibitors may accelerate healing of these ulcers, particularly those on the digits or elbows in dermatomyositis patients with anti-MDA5 autoantibodies. The authors use sildenafil 20 mg given three times daily in these settings of refractory cutaneous ulceration, and if necessary gradually increase the dose in 20 mg increments over 2–3 months to maximum of 80 mg three times daily. Additionally, other fibrinolytic agents such as pentoxifylline 400 mg three times daily, cilostazol 100 mg twice daily, or the combination of these medications may assist in healing of ulceration. Platelet inhibitors such as aspirin and clopidogrel also may be added on as well to reduce the propensity to form microthrombi and allow for wound healing.

Early Versus Late Treatment of Dermatomyositis Delay in treatment of refractory dermatomyositis may result in increased skin damage including hyperpigmentation, scarring, and calcinosis. Although data in juvenile DM supports the notion that aggressive, early treatment of disease decreases the risk of calcinosis [51], it is unclear if this effect relates to better control of inflammatory skin disease per se. In addition, the link between inflammation and calcinosis may be stronger in juvenile versus adult DM patients. Similarly, there are little data to inform us if earlier or more effective treatment of inflammatory skin disease would decrease the risk of other complications, such as myositis or interstitial lung disease. Certainly, the disease can begin with skin inflammation months or even years before onset of myositis, which would be consistent with the notion that unrestrained skin inflammation could eventually lead to muscle disease. Although common sense might predict that aggressive treatment of skin disease would help prevent myositis, this is not always the case [52]. It is now clear that burden of skin disease often has little correlation with that of muscle inflammation, and so these are not necessarily linked. Indeed, most cases of clinically amyopathic dermatomyositis for greater than 6 months' duration do not progress to involved muscle inflammation [53].

Calcinosis

Calcinosis affects approximately 20% of adult [78] and 40% of juvenile dermatomyositis patients [79]. It occurs on average 2–3 years after disease onset in juvenile patients [79] and 8 years after disease onset in adult dermatomyositis patients [91]. Calcinosis continues to be the most challenging cutaneous manifestation of dermatomyositis to modify with medical management. Calcinosis in dermatomyositis is classified as dystrophic calcification and tends to occur at sites of prior cutaneous damage from dermatomyositis such as the extensor surfaces or the elbows, or at sites of prior ulceration, but also often involves the proximal extremities and trunk. In juvenile dermatomyositis patients, the disease duration, severity of skin disease, delay in diagnosis, and therapy are risk factors for the development of calcinosis [103, 104]. In both juvenile and adult dermatomyositis, the presence of antinuclear matrix protein 2 (NXP2) antibodies are associated with an increased risk of developing calcinosis [54–56]. In adult dermatomyositis patients, in addition to disease duration, fingertip ulceration was also associated with calcinosis, suggesting that there may be an underlying vascular mechanism to calcinosis [54].

Although multiple medications have been attempted to treat calcinosis, none of them is uniformly effective. Current evidence for treatment is limited to uncontrolled case reports and case series.

Procedural Options

Surgical excision remains the standard of care for symptomatic calcinosis [91]. Excision of localized

lesions is highly effective with a low risk of recurrence. However, success of surgical excision and likelihood of complications may depend on the expertise of the surgeon performing the procedure.

Electric shock wave lithotripsy has been reported to alleviate pain in two patients with dermatomyositis but may only be effective with smaller calcinosis nodules in which surgical excision is not an option [59, 60].

Calcium Modulators and Vasoactive Medications

Diltiazem, a calcium channel blocker, has variable results in the treatment of calcinosis. Calcium channel blockers are thought to act by reducing influx of intracellular calcium. Although several authors report cases of regression or existing calcinosis and cessation of new calcinosis with doses between 1–3 mg/kg/day [87–90], Balin et al. from the Mayo Clinic found only 9 of 17 (53%) responded [91].

Bisphosphonates have been reported to reduce the size of calcinosis in several case reports with 15 of 28 juvenile dermatomyositis patients responding [57, 58, 80–83, 91, 92]. Although the mechanism of action is unclear, bisphosphonates reduce ectopic calcium originating from bone sources and inhibit macrophages, which have been found at sites of calcinosis. Reduction in size of calcinosis was determined by physical exam, serial photography, X-ray, technetium 99 bone scan, or computed tomography. In juvenile dermatomyositis patients, pamidronate was given at doses ranging from 1 mg/kg to 3 mg/kg IV every 3 months [57, 77, 81], and alendronate was given at 10 mg/day [83, 84]. Reduction in calcinosis size was seen as early as 1 month, and maximal benefit was typically reported at 1 year. By contrast, Balin et al., from the Mayo Clinic, reported that zero of two patients receiving alendronate showed a response, and one patient receiving disodium etidronate had a partial response [91]. Disodium etidronate failed to show any benefit to calcinosis in a report of six patients [92]. Randomized clinical trials are needed to determine the true effectiveness of bisphosphonate therapy for calcinosis.

Sodium thiosulfate has been used both intravenously [68] and intralesionally [69, 84] and topically [95–97] with improvement of calcinosis. The mechanism of sodium thiosulfate is unclear for calcinosis but may involve increasing calcium solubility and vasodilation. Intralesional sodium thiosulfate treatment is limited by the pain and high frequency of injections usually given weekly for 6–12 months and therefore is not suitable for many patients. Also, failure of intravenous sodium thiosulfate was also reported in two dermatomyositis patients and one patient with mixed connective tissue disease [98].

Topical sodium thiosulfate compounded at a strength of 25% may be most effective for smaller, superficial lesions [97]. Similarly, topical sodium metabisulfite compounded at 25% in cream was effective in reducing the inflammatory reaction, pain, and size of calcinosis after 4–8 weeks in four patients with calcinosis, two of whom had dermatomyositis, one with systemic sclerosis, and one patient with radiation dermatitis [99]. Similarly, sodium metabisulfite 25% ointment was effective in healing a large ulcerated idiopathic calcinosis plaque on the arm after 3 months of twice daily application [100]. Sodium metabisulfite is less expensive and more readily available than sodium thiosulfate. It becomes sodium sulfate, a metabolite of sodium thiosulfate with similar properties when exposed to oxygen and may be a reasonable substitution for sodium thiosulfate when used in topical application [99].

Low-dose warfarin at 1 mg daily was used in a double-blind, placebo-controlled study, which included five dermatomyositis patients and two systemic sclerosis patients [93]. In this study, Berger et al. reported that the two juvenile dermatomyositis patients receiving warfarin showed clinical and radiographic improvement in calcinosis on bone scan, as opposed to none of the three dermatomyositis patients receiving placebo [93]. Warfarin lowers γ-carboxyglutamic acid levels, which are found in high levels in calcinosis lesions, and may bind calcium and result in calcification. Alternatively, a study reported no benefit of low-dose warfarin after a mean of 14 months in six patients, five of whom had dermatomyo-

sitis and one had scleroderma [94]. Also, Balin et al. reported only one in four patients showing a partial response to low-dose warfarin. No complications involving hemorrhage were reported in these studies.

Anti-inflammatory Medications

IVIG has been reported to reduce the size of existing calcinosis in a few studies [61–64] but was reported to not halt calcinosis in two patients. IVIG is given monthly at doses of 2 g/kg/month divided over 2–3 days in these reports. Reduction in the size of calcinosis was reported as early as 2 weeks following initiation of IVIG, but average time to improvement was 2–3 months [61–64]. However, the true effect of IVIG on calcinosis remains unclear.

Minocycline has been reported to reduce the inflammatory reaction associated with calcinosis and the frequency of new calcinosis lesions in a retrospective report of nine systemic sclerosis patients [67]. Colchicine, 0.6 mg twice daily, also has been reported to reduce the local inflammatory reaction and pain associated with the calcinosis nodules in two juvenile dermatomyositis patients [85, 86]. In the case reported by Fuchs et al., addition of colchicine resulted in healing of ulcerations overlying the calcinosis [85].

Much of the other evidence on efficacy for calcinosis comes from systemic sclerosis. Rituximab has been reported to improve calcinosis in a single patient with limited cutaneous systemic sclerosis [66], but in a case series of two patients with overlap syndrome of systemic sclerosis and myositis, it failed to halt the progression.

The tumor necrosis factor-alpha inhibitor, infliximab, was reported to help reduce the size and soften preexisting calcinosis nodules in four of five patients with juvenile dermatomyositis after 12 months of therapy given at 3 mg/kg with loading doses at 0, 2, and 6 weeks and then every 8 weeks [101]. All five patients were on pamidronate during this study, but only one patient was started on pamidronate simultaneously with infliximab, suggesting the improvement seen in the study could largely be attributed to infliximab. Another case of the effective use of infliximab in calcinosis was in a patient with limited systemic sclerosis with myositis, with a reduction in the extent of the calcinosis and cessation of new calcinosis after 7 months of therapy, given at 3 mg/kg with loading doses at 0, 2, and 6 weeks and every 8 weeks thereafter [102]. However, infliximab should be used with caution because of the known reports of exacerbating and triggering dermatomyositis with etanercept and adalimumab in adult dermatomyositis patients [43–45].

Regarding a treatment approach to calcinosis in a typical dermatomyositis patient, first, it may be more helpful in the JDM patient to make sure active skin disease has been controlled and utilization of immunosuppressant agents may be first-line therapy for this population. Second, assess their surgical candidacy as surgical excision remains the most effective palliative and curative treatment. Third, consider treatments above based on the individual patient comorbidities and the extent of inflammation at the sites of calcinosis.

Treatment approach for calcinosis in dermatomyositis
1. Treat disease activity (juvenile DM > adult DM).
Methotrexate, mycophenolate, IVIG
Combination immunosuppression
2. Surgical resection, if feasible.
Most effective therapy
3. If calcinosis is inflamed or ulcerated.
Colchicine
Minocycline
Topical sodium thiosulfate or sodium metabisulfite
4. Consider additional therapies with some evidence of efficacy.
Bisphosphonates
Diltiazem
Sodium thiosulfate or sodium metabisulfite
Infliximab
Low-dose warfarin
Extracorporeal lithotripsy

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Management Considerations: Interstitial Lung Disease

32

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Key Points to Remember

- Interstitial lung disease is a significant contributor to the morbidity and mortality associated with idiopathic inflammatory myopathy, especially the anti-synthetase syndrome and MDA5 antibody-associated myositis.
- An assessment of the extent and type of radiographic involvement, coupled with functional status and physiologic parameters, can help guide initial therapy.
- Asymptomatic patients with <10% of disease on CT with normal PFTs (limited disease) do not require treatment.
- First-line treatment of symptomatic myositis-associated ILD often includes glucocorticoids with the addition of a second agent, such as azathioprine or mycophenolate mofetil; Calcineurin inhibitors, cyclophosphamide, or rituximab are alternative agents for progressive disease not responding to combination therapy.
- Rapidly progressive ILD may require high-dose glucocorticoids with the addition of rituximab and/or cyclophosphamide.
- Emerging concepts in treatment include biologics, such as basiliximab and abatacept, as well as antifibrotics for predominantly fibrotic disease, such as pirfenidone and nintedanib.

Introduction

Glucocorticoids (GC) are initially used in nearly all patients with IIM-ILD. Prevailing practice is to subsequently utilize a second agent, most commonly azathioprine (AZA) or mycophenolate mofetil (MMF), in patients with significant ILD though prospective trials comparing GC alone versus GC combined with another agent are lacking. In patients where ILD responds poorly to GC and AZA or MMF, switching to a calcineurin inhibitor such as tacrolimus or cyclosporine is typically

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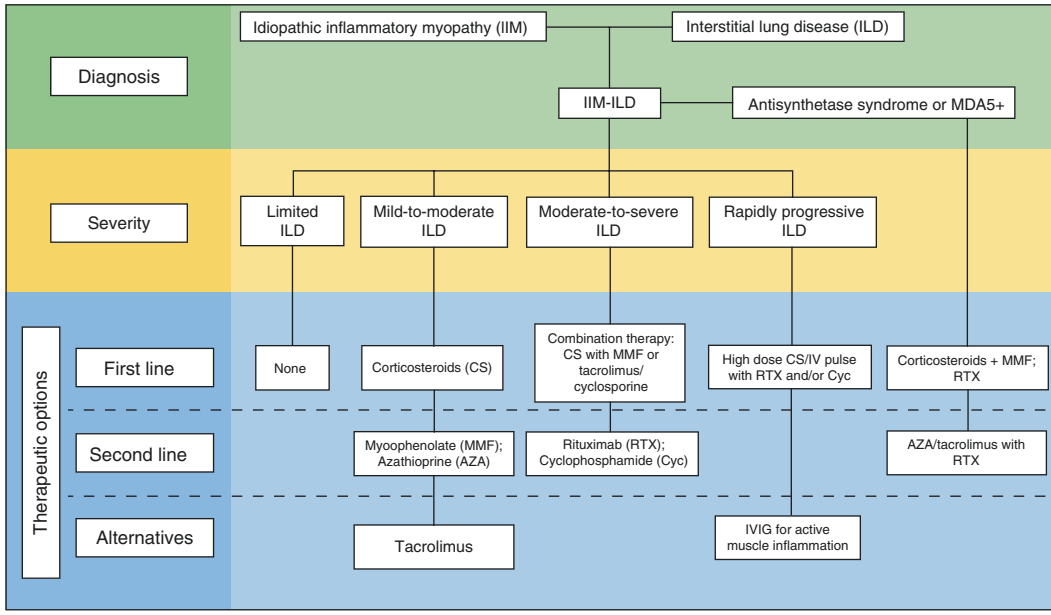

Fig. 32.1 Therapeutic approach to interstitial lung disease associated with idiopathic inflammatory myopathy

attempted first. If that fails or severe decline ensues, then other agents such as cyclophosphamide (Cyc) or rituximab (RTX) should be considered (Fig. 32.1). There are currently no trials comparing the relative efficacy of these agents to treat IIM-ILD. For those patients with profound muscle weakness, severe dysphagia, or concomitant infections, intravenous immunoglobulin (IVIG) may be useful as an adjunct though its role in treating ILD is not documented outside of sparse case reports [3–5]. In patients where fibrosis is the predominant component of disease based on a CT scan (UIP or fibrotic NSIP pattern), none of these agents may be effective, and consideration for antifibrotic agents, such as pirfenidone and nintedanib used in idiopathic pulmonary fibrosis, if available, may be reasonable. Finally, other causes of dyspnea such as concomitant heart failure, pulmonary hypertension, infection, and respiratory muscle weakness should also be considered and assessed before contemplating additional or alternative immunomodulatory therapy. In all patients, vaccination for influenza and pneumococcal pneumonia are important, as are an assessment of bone density and osteoporosis prevention. Prophylaxis for pneumocystis jiroveci pneumonia (PJP) should be considered in any patient on greater than 20 mg of prednisone or equivalent or in a patient on a combination of GC (equivalent to 10 mg of prednisone or more) and a second agent.

Specific Agents, Dosage, and Side Effects

Glucocorticoids (GC) Prednisone or methylprednisolone in equivalent doses are commonly used in most patients with ILD in IIM [Table 32.1]. The efficacy of using GC alone without a disease modifying anti-rheumatic disease (DMARD) or biologic agent is unknown as there are no controlled trials comparing monotherapy with GC vs. GC with an additional agent. However, early data suggested a significant failure of using GC as sole therapy [6]. Further, only up to 50% of ILD patients with myositis respond to GC, with early diagnosis associated with an improved response [7]. When using GC, a dose of 1 mg/kg for at least 1 month is recommended, and with stabilization, the dose is gradually tapered in approximate 10 mg per month increments with careful attention not to stop GC suddenly and precipitate an adrenal crisis. The rate

Table 32.1 Therapeutic agents used to treat interstitial lung disease (ILD) associated with idiopathic inflammatory myopathy

Therapeutic agent	Target dosage	Major side effects	Notes
Glucocorticoids (GC)	1 mg/kg (pulse dosing 1 g/day × 3 days for severe or rapidly progressive ILD)	Infections; hypertension, hyperglycemia, osteoporosis, cataracts/glaucoma, weight gain, Cushing's, adrenal insufficiency, steroid myopathy	First-line therapy; consider prophylaxis for PJP at doses >20 mg/day
Azathioprine (AZA)	2 mg/kg	Infections, bone marrow suppression, GI issues (nausea/vomiting/diarrhea)	Check TPMT level Monitor CBC, LFT, and serum creatinine every 2–3 months
Mycophenolate mofetil (MMF)	2–3 g/day in divided doses	Infections, GI issues (nausea, abdominal pain, diarrhea)	Monitor CBC, LFT, and serum creatinine every 2–3 months
Tacrolimus	Start at 1 mg twice daily; slowly increase to trough levels of 5–10 ng/ml	Infections, renal insufficiency, hyperkalemia, hypertension, neuropathy	Monitor serum levels, potassium, phosphorus, magnesium, CBC, LFT, and serum creatinine
Cyclophosphamide (Cyc)	Oral: 2 mg/kg IV: 500–1000 mg/m^2 q4weeks	Infections, bladder cancer (oral), lymphoma	Dose adjust for renal failure
Rituximab (RTX)	1000 mg IV × 2 (2 weeks apart), can repeat q6 months as needed	Infections, including progressive multifocal leukoencephalopathy, infusion reactions	Consider monitoring CD19 counts and quantitative immunoglobulins before repeat dose
Intravenous immunoglobulin (IVIG)	2 g/kg monthly with dose adjustment based on severity and response	Headaches, infusion reactions, aseptic meningitis	Useful as adjunct for patients with profound muscle weakness, severe dysphagia, or concomitant infections

of taper varies and may continue for up to a year, with some patients requiring a very low dose (i.e., 5 mg) indefinitely. More rapid tapers have anecdotally been associated with more flares. However, there are some circumstances where shorter and less intense courses of steroid therapy may be justified due to side effects or less severe ILD as long as a second agent is concomitantly administered. In hospitalized patients with severe or rapidly progressive disease, pulse dosing of 1 g per day intravenously for 3 days is reasonable prior to initiating oral dosing [8, 9]. Major side effects of GC include infections, hypertension, hyperglycemia, weight gain, insomnia, and mood changes and, with longer courses, osteoporosis and cataracts/glaucoma.

Azathioprine (AZA) Azathioprine is a purine inhibitor that has been used historically for a wide variety of autoimmune diseases including autoimmune ILD. In the 1980s, AZA was frequently used as a second agent to treat patients with ILD either as a steroid-sparing agent or in steroid-refractory patients [10]. More recently, it has been used less given the emergence of MMF and is mainly used early with less severe ILD in combination with GC. Retrospective studies on myositis-associated ILD showed clinical efficacy and survival benefit with AZA including a cohort analysis of 54 patients with connective tissue disease (CTD)-associated ILD (CTD-ILD) [15 with polymyositis (PM)/dermatomyositis (DM)] demonstrating pulmonary function stability and a tendency for improvement with AZA [11]. Complications of AZA include infections, gastrointestinal intolerance, and the risk for bone marrow suppression. The average dose is 2 mg/kg daily with adjustments based on careful monitoring of the white blood cell count and checking a thiopurine methyl transferase (TPMT) level prior to initiating therapy.

MycophenolateMofetil(MMF) Mycophenolate mofetil is a purine inhibitor that reversibly inhibits inosine monophosphate dehydrogenase. MMF has anti-inflammatory (inhibiting B and T lymphocyte proliferation) and possibly antifibrotic effects that make it more efficacious and more frequently utilized in ILD associated with autoimmunity, and with fewer side effects including cytopenia [12, 13]. A prospective study of 125 patients assessed the efficacy of MMF in CTD-ILD, including 32 with PM- or DM-associated ILD. There were significant improvements in forced vital capacity (FVC) and diffusing capacity of carbon monoxide (DLCO) at 1 and 2 years with the most noticeable improvement seen in the 32 myositis-associated ILD cases despite decreases in the steroid dose [13]. The usual effective dose is between 2 and 3 g per day in divided doses with most side effects related to gastrointestinal upset, including nausea, abdominal pain, and diarrhea in addition to risks of infection related to its immunosuppressive effects. Another version of this drug, mycophenolic acid, may be successfully used when gastrointestinal side effects result from MMF. Some practitioners will measure mycophenolate levels in patients who developed significant side effects but appear to have either improving or stabilizing lung function.

Tacrolimus Tacrolimus inhibits calcineurin, which is important in the activation of T cells and cytokine expression. It has occasionally supplanted cyclophosphamide and is commonly used to prevent organ rejection in transplant patients but has been utilized in patients with myositis-associated ILD, especially in those unresponsive to either MMF or AZA [14]. In a prospective study of 13 patients with anti-synthetase-associated ILD treated with tacrolimus, lung function improved significantly [15]. Tacrolimus also significantly improved survival rates of myositis-associated ILD in another retrospective controlled study [16]. Dosing begins at 1mg twice a day, and tacrolimus serum levels are monitored to obtain a therapeutic trough level of 5–10 ng/ml. Toxicities include renal insufficiency, hyperkalemia, neuropathy, and hypertension, which not infrequently may lead to cessation of this medication. Cyclosporine is an alternative calcineurin inhibitor, but it is used less due to tolerance and side effects.

Cyclophosphamide (Cyc) Cyclophosphamide is an alkylating agent and is used as either oral therapy (2 mg/kg with adjustment for renal failure) or intravenously (500–1000 mg/m^2) every 4 weeks. Given its higher risk for infection including opportunistic infections and bladder cancer (when given orally), it is reserved for cases of severe ILD associated with IIM where there is rapid deterioration or failure of efficacy of other agents [17]. In a comparative retrospective case series of 10 DM patients with acute or subacute ILD, there was 50% survival with early prednisolone plus IV Cyc, which was a significantly better outcome than subjects without early immunosuppressive therapy [18]. In a systematic review of 12 non-randomized studies on Cyc used for myositis and myositis-associated ILD, improving lung function was noted by both PFTs and chest HRCT scan [19].

Rituximab (RTX) Rituximab is a chimeric anti-CD20 molecule that depletes B cells. While its efficacy in the treatment of muscle disease in IIM is uncertain, there is support for its use in ILD associated with IIM [20], specifically in the anti-synthetase syndrome with an identifiable antibody such as Jo-1 [21, 22]. A recent open-label phase II trial for rituximab in 12 anti-synthetase-positive patients with ILD showed improvement or stabilization of PFTs in most cases [22]. In addition, there are many small retrospective studies demonstrating radiologic and physiologic improvement [23–25]. Further, a B cell-depleting regimen with RTX may be reasonable when a lymphoid plasmacytic infiltrate with lymphoid follicles are noted on lung biopsy. Standard dosing is 1000 mg intravenously for two doses 2 weeks apart, but RTX can be repeated at 6-month

intervals as needed. Risks associated with this agent include infusion reactions, and a wide variety of infections including the very rare occurrence of progressive multifocal leukoencephalopathy (PML) related to JC virus, which is a very rare event.

Emerging Concepts in Treatment There is growing interest in exploring additional therapies for IIM and IIM-ILD, particularly with biologics that target appropriate pathogenic pathways [5]. Basiliximab is a monoclonal antibody that blocks the alpha chain (CD25) of the interleukin-2 (IL-2) receptor complex and has been used in patients with ILD related to IIM who have refractory disease [26]. Abatacept, which targets CD80 and CD86 on antigen-presenting molecules, and tocilizumab, which inhibits IL-6, have been noted in case reports to be efficacious in refractory inflammatory myopathy and are potential therapeutic agents in ILD associated with myositis [27, 28]. Finally, in those patients where significant fibrotic disease develops or where fibrosis is the predominant feature, it may be appropriate to try the FDA-approved antifibrotic agents pirfenidone and nintedanib, currently used in idiopathic pulmonary fibrosis [29].

Treatment Consideration for Distinct Clinical Scenarios

Although there are no therapeutic options that are specifically recommended for ILD associated with IIM, certain circumstances might suggest choosing one available agent over another. Careful assessment of functional status, physiologic parameters, extent and type of radiographic involvement, and pathologic data, when available, can aid in deciding when treatment is necessary and to guide the choice of therapy. In those patients where there are significant functional and physiologic decrements, aggressive treatment with GC and often a second agent is standard of care (Table 32.2; Fig. 32.1).

Limited Disease Some patients with limited disease (less than 10%) on HRCT, normal or near normal PFTs (>70% FVC), and no complaints of dyspnea do not require treatment. Based on data accumulated in scleroderma, these patients have a lower risk for mortality and progression, though similar prognostic data has not been accumulated in IIM-ILD [30]. In such cases, close surveillance with routine functional assessment and serial physiologic/radiologic data is required every 3–6 months, with initiation of therapy at any signs of progression.

Table 32.2 Management of distinct clinical scenarios in interstitial lung disease (ILD) associated with idiopathic inflammatory myopathy

Clinical scenario	Definition	Management
Limited ILD	<10% disease on CT chest, normal or near normal PFTs (>70% FVC), no complaints of dyspnea	No treatment indicated; close surveillance q3–6 months with routine function assessment and serial physiologic/radiologic data
Mild-to-moderate ILD	FVC <70% or decline >10%, exertional dyspnea, modest desaturation with exercise without need for oxygen	GC as initial therapy with a second agent, such as MMF or AZA. Tacrolimus considered if treatment failure with above
Moderate-to-severe ILD	FVC <50%, significant dyspnea, oxygen required	Stronger consideration for starting with combination therapy, such as GC and MMF and/or tacrolimus/cyclosporine. Cyc or RTX if combination therapy has failed
Rapidly progressive ILD	Rapidly progressive ILD over a few months or ILD flare that precipitates rapid decline	High-dose GC with consideration for pulse IV GC with RTX and/or Cyc. In critical illness, consider IV GC, IV Cyc, RTX, and IVIG (if active muscle inflammation)

ILD interstitial lung disease, *CT* computed tomography, *PFT* pulmonary function test, *FVC* forced vital capacity, *MMF* mycophenolate, *AZA* azathioprine, *Cyc* cyclophosphamide, *RTX* rituximab, *IVIG* intravenous immunoglobulins, *GC* glucocorticoids

Mild-to-Moderate ILD In this case, the patient is typically dyspneic with activity and will have an FVC <70% or a decline of 10% or more from previous PFTs. At this point, they are unlikely to need oxygen or have only modest desaturation with exercise. If the CT suggests NSIP or OP or a combination without significant honeycombing, then the choice of therapy would include prednisone at 1 mg/kg/day and a second agent such as MMF or AZA. If either of these agents is ineffective, then tacrolimus would be the next choice. If the CT or pathology is consistent with a UIP pattern, the role for anti-inflammatory therapy is less clear [31], but evidence suggests that myositis-associated UIP (treated with immunosuppression) has a better outcome than UIP associated with IPF. Therefore, given the possible less aggressive UIP pattern seen in myositis, anti-inflammatory therapy may still have a role with or without consideration of antifibrotics [32]. In severe fibrotic disease, lung transplant evaluation should strongly be considered. In the case of anti-synthetase syndrome, rituximab could be used initially with emerging trials examining this agent as first-line [33].

Moderate-to-Severe ILD In this patient, the FVC is typically <50%, and the patient has significant dyspnea with ambulation and often desaturates to the extent that oxygen is required. Therapy is similar to that noted above with a stronger consideration for combination therapy including different agents such as high-dose (1 mg/kg/day) or IV pulse GC (1 g for 3 days) with MMF or a calcineurin inhibitor. Often the combination of GC with two other immunosuppressive agents is required including MMF and tacrolimus. Cyc or rituximab should be considered if combination therapy has failed [18] or especially in the anti-synthetase syndrome or in those with anti-MDA5 positivity, where there is a lower threshold to add rituximab in addition to either MMF, AZA, or tacrolimus. A combination of Cyc and rituximab is also used in more severe cases. Pulmonary rehabilitation should be utilized and transplant evaluation should be considered.

Rapidly Progressive ILD This typical scenario is a patient who presents with ILD that progresses rapidly in a matter of days to months or one who has slowly progressive disease with a flare precipitating rapid decline. If CT scanning or lung biopsy still suggests predominately inflammatory disease, then high-dose GC is the treatment of choice with consideration for pulse IV GC (1 g for 3 days) plus either rituximab or Cyc; in some severe cases with respiratory failure, both may be warranted. In the case of patients with the MDA5 autoantibody who present with severe ILD requiring high-flow oxygen or mechanical ventilation, there is a low threshold for considering dual therapy as noted above. In the context of critical illness, often a combination of high-dose GC with intravenous cyclophosphamide is utilized, which may take effect within 7 days, and rituximab may also be added, which may require several weeks to take effect. If there is active muscle inflammation with weakness, intravenous immunoglobulin may be beneficial in the early stages of treatment [4].

Monitoring of Therapy

In addition to routine laboratory monitoring to assess for medication toxicity/adverse effects, patients should be clinically monitored every 2–4 weeks when starting therapy. Serial PFTs are often undertaken every 3 months, primarily following the FVC, TLC, and the DLCO, as well as oxygen saturation with ambulation (exercise desaturation study). The use of repeat or recurrent CT scanning is guided by worsening clinical symptoms or physiologic data, evaluation of response to therapy, and suspicion for other concomitant processes (infection, pulmonary embolism, etc.). Echocardiography is recommended at baseline and periodically with any change in clinical symptoms, especially in patients with anti-synthetase syndrome and advanced ILD, to evaluate for pulmonary artery hypertension, a known complication of myositis and a contributor to morbidity and mortality in IIM [34]. Stability or improvements in physiologic parameters are generally seen as a rationale to continue the ongoing regimen, whereas a decline may prompt an adjustment of the therapeutic

approach. While it is unclear what constitutes a clinically significant decline in lung functional parameters, >10% decline in FVC or smaller declines in FVC in combination with >15% in DLCO have been suggested as guidelines to determine the efficacy of therapy and to help decide whether to continue or change to another agent [35]. Emerging research suggests that serum biomarkers may be useful in measuring disease activity outside of physiologic and radiographic testing and in determining response to therapy. Serum lactate dehydrogenase (LDH), Krebs von den Lungen-6 (KL-6), surfactant protein-D (SP-D), interleukin-18 (IL-18), and ferritin levels have all been proposed as prognostic biomarkers that can help measure response to therapy in ILD associated with IIM [36–39]. Typically, at least 3–6 months is needed to ascertain efficacy of any particular treatment strategy.

Conclusion

In summary, ILD associated with IIM presents unique challenges and contributes to significant morbidity and mortality. A vigilant surveillance for this complication in patients with inflammatory myopathy and prompt recognition and treatment can result in substantial improvement in some patients and clinical stability in many others.

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Role of Exercise in the Management of Myositis

33

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Key Points to Remember

- Exercise, individually adapted, is safe for all individuals with adult and juvenile myositis.
- Intensive exercise can reduce disease activity and inflammation. Initiate all exercise with low intensity and progress slowly.
- Initiate exercise under the supervision of a physical therapist and measure muscle function and other outcomes before starting and follow-up the effects of exercise regularly using validated outcome measures.
- Myositis affects activities of daily living and quality of life, and OT assessment and treatment are important to improve outcome.
- Work ability is limited in patients with myositis, and assessment of work ability and interventions is important to incorporate in the care.
- Best care is delivered by an inter-professional and multidisciplinary team including the patient.

Introduction

The idiopathic inflammatory myopathies (IIM) are a heterogeneous group of rare diseases that lead to muscle inflammation and damage. Although many patients respond to medical treatment, a majority develop some level of sustained disability. Patients are left with longstanding muscle impairment, fatigue, pain and reduced quality of life, affecting all areas of life. To provide holistic care, an inter-professional team of physicians, nurses, social workers, physical and occupational therapists is needed. For example, the nurse could be the primary contact to provide information on pharmaceutical treatment and support, whereas the social worker could provide support in accepting and coping with a chronic, life-changing disease that impacts family, friends and work. Regular inter-professional and multidisciplinary team conferences could enhance the care of myositis patients through shared knowledge, collab-

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orative goal setting and shared decision-making. This chapter focuses on the role of exercise, physical therapy and occupational therapy as part of an interdisciplinary team.

The Role of Physical and Occupational Therapy

Physical therapy (PT) mainly consists of adapted exercise targeting muscle impairment, reduced aerobic capacity and balance, but also aiming to reduce pain and fatigue and improve quality of life. Occupational therapy (OT) aims to facilitate valued life activities regarding the needs and wants of the myositis patient. Routine activities are affected by reduced hand function, pain, muscle weakness, and fatigue and OT intervention includes a hand exercise program, prescription of assistive devices, orthoses, and teaching strategies for energy saving and optimizing ergonomics (Table 33.1).

Physical Therapy

The Anti-inflammatory Effects of Exercise Intervention

Previously, patients with IIM were discouraged from exercise, especially in the active phase of disease, due to fear of increased disease activity and inflammation. This notion was based on studies of healthy athletes where marathon runners elevated their serum CK in association with inflammatory infiltrates being detected in their muscle tissue [1]. Elevated serum CK and IL-6 levels are normal responses to exercise and return to normal within 24 h after concentric exercise, while eccentric exercise leads to more prolonged levels [2]. An inflammatory response in muscle tissue after exercise implies repair and regeneration of the muscle and IL-6 is usually considered a pro-inflammatory cytokine but in muscle, IL-6 has an anti-inflammatory effect [3]. Intensive aerobic exercise performed three times weekly can reduce pro-inflammatory cytokines in healthy individuals [4]. Similarly, intensive resistance training of 8–12 repetitions reduces expression of pro-inflammatory cytokines (IL-8) while increasing lean body mass in young individuals [5].

The anti-inflammatory effect of exercise has been shown in myositis patients as intensive resistance training 3 days/week reduced disease activity leading to improvement in dyspnoea and strength [6]. Furthermore, microarray analyses of post-exercise muscle biopsies revealed down-regulation of pro-inflammatory genes and genes regulating fibrosis as well as down-regulation of anti-inflammatory genes [7]. Levels of serum CK

Table 33.1 Types of exercise programs and definitions

Aerobic exercise
Exercise involving several, larger muscle groups, such as biking, walking/running, swimming, leading to increased heart rate, preferably above 60% of predicted maximal heart rate.
Intensive resistance training
Resistance training performed with the goal to improve muscle strength, often involving a few large or small muscles exercised against a resistance of 8–12 voluntary repetition maximum (VRM), allowing 8–12 repetitions before exhaustion. For example, exercising using gym equipment, free weights or against gravity.
Endurance-based resistance training
Resistance training performed with the goal to improve muscle endurance in specific muscle groups, large or small, using somewhat lower loads allowing >15 repetitions before exhaustion, see examples of intensive resistance training.
Maximal heart rate
The maximal number of heart beats per minute. Maximal heart rate (HR) is tested with a maximal test on a stationary bike or a treadmill. Loads are increased every minute until exhaustion. The HR, registered by an echocardiogram, at the point of exhaustion is defined as the true maximal HR. Predicted maximal HR is defined as 220-age.
Easy-moderate intensity home exercise
Home exercise performed with non-specific intensity with low-moderate exertion and far below a maximal effort. The home exercise program described in this chapter contains resistance training only, but can be combined with aerobic walking at 60% of predicted maximal HR.

and inflammatory infiltrates in the vastus lateralis remained unchanged throughout a 7-week exercise program. Our unpublished data also reveal that CK levels were elevated following a submaximal pool exercise session, but quickly returned to baseline values 24 h later in a small group of patients with established myositis.

Exercise has an anti-inflammatory effect on muscle in myositis patients.

Exercise as a Treatment Modality in PM and DM: A Randomized Controlled Trial

Given that myositis patients have reduced muscle endurance, an aerobic intensive exercise protocol was tested in a randomized controlled trial in patients with established PM and DM [8]. Thirty minutes of stationary biking at 70% of maximal capacity followed by endurance-based resistance training 3 days a week for 12 weeks resulted in reduced myositis disease activity and inflammation. A majority of the 11 patients in the intensive exercise group demonstrated reduced myositis disease activity using the IMACS response criteria (≥20% improvement in three of the six myositis core set measures) compared to 0 of 10 patients in the non-exercising control group. Genes related to mitochondrial biogenesis, cytoskeletal remodelling, muscle hypertrophy, capillary growth and protein synthesis were upregulated in the exercise group, while genes related to inflammation and immune response and ER stress were downregulated by exercise. In contrast, the non-exercising control group showed no similar gene expression changes [9]. Further, intensive endurance exercise reduced intra-muscular lactate levels at exhaustion along with markedly improved endurance, while increased mitochondrial enzyme activity indicated improved aerobic metabolism in muscle tissue [10]. Although acute effects of exercise on CK were not investigated in these studies, it would be expected they would elevate as in healthy individuals. Thus, serum CK levels and other inflammatory markers should not be assessed within 24 h of high-intensity exercise.

Effects of Exercise in PM and DM

Although it is clear that exercise is beneficial in myositis, a common question asked is how soon we can initiate exercise in myositis patients. That is, is it safe to begin exercise early in myositis?

A home-based resistance training program performed 5 days/week for at least 12 weeks is one of the most evaluated exercise programs (Fig. 33.1) targeting muscle groups most affected by PM and DM including the shoulder, neck, hip girdle and thigh muscles. Preferably, this program is combined with sub-maximal aerobic physical activity such as walking or stationary biking at 50–70% of predicted maximal heart rate [11, 12]. In a randomized controlled study, this home exercise program and aerobic walking in combination with standard medical treatment including prednisone and immunosuppressive agents was proven safe, but not more effective, short term, than standard medical treatment. However, the combination of exercise with medical therapy demonstrated higher physical function in subjects at a 2-year follow-up [12] highlighting the benefit and safety of early exercise intervention. Moreover, this reinforces the benefit of regular exercise and an active lifestyle for myositis patients. A more intensive exercise program (aerobic exercise at 70% of maximal capacity and resistance training with 8–12 VRM) was similarly well tolerated by three patients with high CK levels and persistent muscle weakness who showed clinically relevant improvement in physical capacity [13]. All studies noted positive effects on physical and aerobic capacity, muscle strength and endurance and less limitation in daily activities [14]. Exercise improves the quality of life in PM and DM as self-reported physical function improves while fatigue lessens [8]. Today, exercise has become a very important part of the treatment in patients with PM and DM in all phases of the disease [14]. Creatine supplements in combination with exercise can further improve physical capacity in patients with established PM and DM [15] (Table 33.2).

Fig. 33.1 Fifteen-minute home exercise program on low to moderate intensity. Use extra free weights or just work against gravity. Use loads allowing 10–15 repetitions initially generating moderate perceived exertion. If possible, increase the weight over several weeks. You can combine this program with a 15–20 min walk at 60% of predicted maximal heart rate (220 age). Perform home exercise program and walks 3–5 days a week. (**a**) Two minutes of warm-up climbing up and down a stool or step-up board to slightly increase the heart rate. (**b**) Range of motion exercise in case of severe muscle weakness in the shoulder muscles. (**c**) Squeeze a soft exercise ball for increased grip strength. (**d**) Sit on a chair with full thigh support, extend the knee, and hold for a couple of seconds, and go slowly back. Use a weight-cuff or work against gravity. (**e**) Sitting or standing. Lift one arm up to the ceiling and back. Use a free weight (weight cuff, dumbbell or rubber band). (**f**) Lying on the floor or on a bench with knees bent, lift the pelvis, hold 1–2 s, and return slowly. (**g**) Sit-ups. If possible, start by lifting without neck support, then continue with neck support. (**h**) Lift one leg up and down. Have the other knee bent if you have lower back pain

Table 33.2 Creatine supplementation during exercise program

A loading dose of 8 g/day for 3 days is followed by a maintenance dose of 3 g/day of pure creatine administered for 3 months, followed by 4 weeks without creatine supplements, but continued exercise.
Then another period of supplementation can be started using the same loading and maintenance dose.
Patients should consult with their physician before starting creatine supplementations to discuss this in relation to medical treatment and also to assess baseline muscle strength. If possible, consult with a physical therapist for additional tests of muscle endurance.
There is no rationale for creatine supplements without a minimum of twice a week exercise.

Exercise can and should be initiated as soon as possible in myositis patients.

Exercise Programs in Inclusion Body Myositis

A few smaller and short duration studies evaluating exercise in inclusion body myositis (IBM) report safety without increased CK levels though improvement of muscle strength and/or function have been somewhat divergent. Resistance training 3 days/week for 12 weeks improved strength primarily in muscle groups less affected by the disease, with only marginal improvement in affected muscle groups such as the knee extensors and wrist/finger flexors [16]. A home exercise program employed twice daily for 16 weeks was well tolerated leading to a statistically significant and clinically relevant improvement in strength in all tested muscle groups including the quadriceps and wrist and finger flexors compared to baseline (Fig. 33.2) as well as improved walking and stair climbing [17]. Another home exercise program (4 days/week) combined with stationary biking at 80% maximal capacity (3 days/week) resulted in significantly improved aerobic capacity, but not in muscle strength or physical function [18]. These studies support exercise intervention in IBM, a myopathy with progressive decline of muscle mass and muscle strength. Further studies are necessary regarding longer duration programs and the role of balance exercise in fall prevention.

Exercise is currently the only proven therapy for IBM.

Individually adapted exercise program especially range of motion exercises is safe and important in JDM.

Exercise Programs in Juvenile Dermatomyositis (JDM)

All case reports, small open-label studies and the first RCT indicate safety of exercise regimens in JDM with no signs of increased disease activity or inflammation [14]. Twelve weeks of an intensive, progressive aerobic exercise program which combined treadmill walking with squats, sit-ups and push-ups improved muscle strength and the HAQ compared to control groups [19], but there was no difference in aerobic capacity, isometric muscle strength or fatigue between groups. Range of motion exercises remain important in juvenile patients to maintain full range of motion and prevention of contractures.

Health-Enhancing Physical Activity. Health-enhancing physical activity (HEPA) is defined as 150 min of physical activity of moderate intensity or 75 min of high-intensity physical activity weekly with additional resistance training twice weekly [20]. This intervention not only promotes cardiovascular health but should be used in IIM patients at risk for osteoporosis and type II diabetes.

Health-enhancing physical activity is recommended in all patients with myositis to prevent osteoporosis, glucose intolerance, and reduce cardiovascular risk.

Fig. 33.2 Home exercise program in IBM. Perform each task of the program bilaterally twice a day for 16 weeks. Number of repetitions need to be adapted to muscle strength with frequent follow-up to ensure safety and optimal exercise loads. Start exercising once a day if twice a day is too demanding. Use an exercise diary to keep track of numbers of repetitions, loads and exercise frequency. A vast majority of individuals with IBM tolerate this program well; however, clinical experience indicates that reduced muscle strength and increased pain have occurred in rare cases. If the patient has previously experienced these symptoms after easy to moderate intensity exercise, start with a less intense regimen than that suggested above. (**a**) Sit-to-stand. If possible stand up without arm support, or use a chair without arm support. Try to sit down as slowly as possible. Having a table in front of you could improve the feeling of safety. Make sure that the chair is locked. (**b**) Sitting down, supporting one arm on the thigh. Flex the wrist while not moving the elbow. Hold on to a free weight or work against gravity alone. (**c**) Sitting on a chair or bench with full thigh support. Lean back a little and extend the knee as much as possible. Hold for a few seconds and return slowly. Work against gravity or use a weight-cuff. In case of severe quadriceps weakness, lie down on a bench and lift one leg up, try to keep the knee as straight as possible. (**d**) Sit or stand. Bend the elbow, lifting the hand up to the shoulder, return slowly. Work against gravity or use a free weight/rubber band. (**e**) Heel lifts. Standing close to a steady chair or a wall as balance support. Lift the heels as high as possible and go down rather slowly. Try to keep knees straight. (**f**) Sitting down. Lift one arm up to the ceiling and return slowly. Try to sit straight up tightening the core muscles. Work against gravity or use a free weight/rubber band. (**g**) Toe lifts. Stand up with the back against a wall and heels 10–20 cm from the wall. Lift the toe joints from the floor and return slowly. If this is not possible, sit down and do the same exercise, put a weight-cuff on the feet for extra resistance if needed

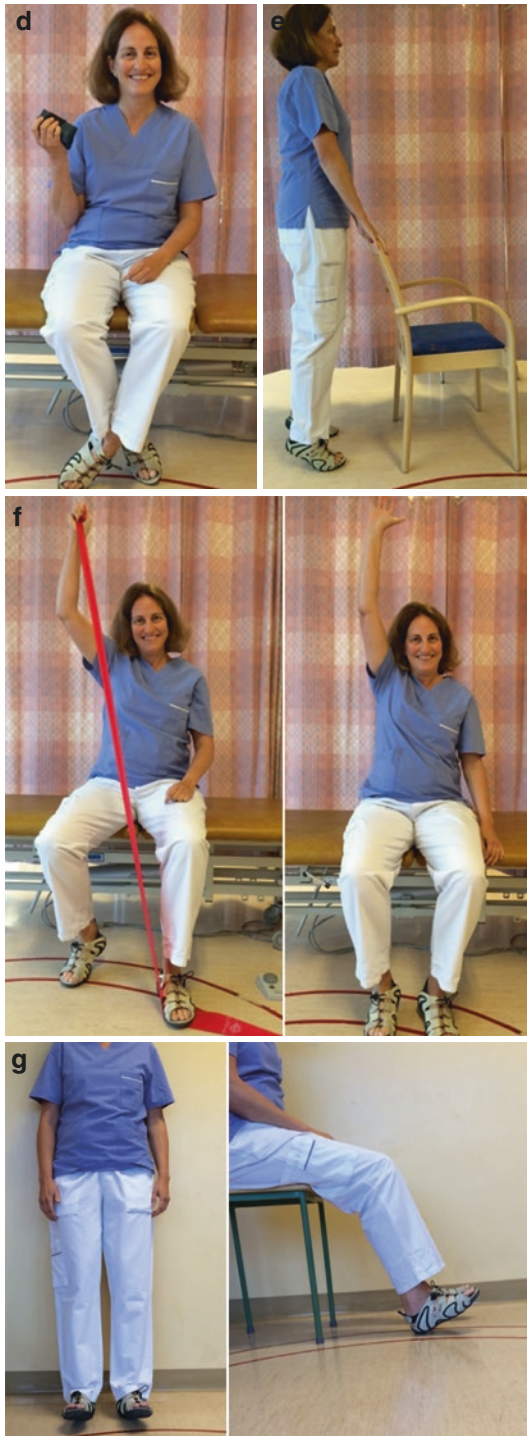


Fig. 33.2 (continued)

Introducing Exercise to a Patient

If possible, refer the patient to a physical therapist for prescription of exercise and measures of baseline physical capacity and follow-up. A physically active lifestyle prior to a rheumatoid arthritis diagnosis is the only factor predicting physical activity levels later on [21]. Our hypothesis is that this is true for most chronic diseases, including IIM. Therefore, it is very important to ask your patient about previous physical activity habits. Set goals of physical activity and exercise together with the patient, for example using SMART goals; Specific, Measurable, Attainable, Realistic, and Timely.

In patients with recent onset PM or DM, in flaring patients or in patients with severe muscle weakness, initiate an easy-moderate intensity home exercise program and 20 min. of walking 5 days/week as soon as possible [14]. Adapt the number of repetitions or loads to your patient's current status and divide the program in two parts in a day if necessary. Use the Borg CR-10-scale, [22] or another scale to estimate starting load/intensity. Begin with a low-moderate exertion program. Patients with recent onset PM and DM need more frequent follow-up along with exercise adaptation according to changes in muscle function.

Patients in a more established phase of the disease with previous exercise experience can start with pool training, gym training or other more intensive home exercise using free weights or rubber bands. Again, adapt the exercise to current disease activity and disability. Begin with a moderate exertion program. The patient should be able to incorporate the exercise program in their daily life.

Progress the exercise program over weeks to months to reach an individual goal intensity generating perceived exertion "rather heavy" to "heavy/very heavy exertion". Based on current evidence, the recommended exercise intensity and frequency for patients with established, low-disease activity

PM and DM do not differ from the recommended dose for healthy population [23].

Level of Exercise for Different Goals in a Patient

- To improve muscle strength – resistance training 2–3 days/week with 8–12 VRM
- To improve muscle endurance – resistance training 2–3 days/week with 30–40 VRM
- To improve aerobic capacity – aerobic exercise 20 min, 3 days/week at ≥60% of predicted max HR

Occupational Therapy

Occupational therapy is based on the theory that performing meaningful activities enables wellbeing and quality of life. Activities of daily living include all the different tasks a person does during a day from the time they wake up in the morning to the time they go to bed.

Activities of Daily Living in Myositis

Polymyositis and Dermatomyositis

Proximal muscle weakness in PM and DM [24] leads to difficulties getting up from sitting, rising from a toilet or a chair and getting in and out of a bathtub etc. Dressing is adversely affected as well as whole-body washing. Many patients describe reduced muscle endurance which can influence prolonged activities such as cooking, cleaning and washing clothes. Fatigue and pain are important symptoms in PM and DM, and these factors also impact the ability to perform daily activities and quality of life.

A majority of individuals with PM and DM still experience activity limitation despite low or no disease activity [25]. Most patients (62%) with PM and DM rated their work ability as poor or less good. Those working with their arms and hands or those walking long distances experience more sick-leave [26]. Therefore, it is important to investigate the workplace as well as the home to provide the best possible adaptation. Reduced grip force and dexterity in PM and DM have a negative influence on daily activities and quality of life [25, 27].

Inclusion Body Myositis

IBM leads to slow progression of muscle weakness of the proximal and distal muscles, ultimately limiting activities of daily living and reduction in quality of life [28, 29]. The loss of muscle power is most prominent in the knee extensors affecting the ability to walk, and many patients may become dependent on a wheelchair [28]. Like PM and DM, individuals with IBM may also have difficulty getting up from sitting. The most common activities of daily living affected are personal care, moving around, household activities, work and leisure activities. Reduced grip strength and ultimately reduced active range of motion of the hands are common affecting the ability to perform daily activities [28].

Occupational Therapy Treatment

Occupational therapy assessments should include hand function (grip strength/force, dexterity and grip ability) in both PM/DM as well as in IBM. It is also importance to assess activities of daily living including not only personal care and household activities but also work, leisure and sleep. Since fatigue together with muscle weakness and reduced muscle endurance affect persons with myositis, one should investigate the ability of a person to perform various activities throughout

the whole day. A person may be able to perform an individual task or activity in isolation well, but performing multiple such activities through a whole day may be difficult.

Compensating assistive devices such as a raised toilet seat or a reacher are used in order to maintain good activity performance. Similarly, work-related assistive devices and ergonomic advice are recommended. A good balance between activities and rest enhances the ability to perform meaningful activities and improves well-being (Table 33.3).

A pilot study reported that a hand exercise program is safe to perform in PM and DM (Figs. 33.3 and 33.4) [26]. Specific exercises for grip strength and endurance may help to improve hand function (Fig. 33.4). In addition, range of motion exercises for finger and thumb flexors are essential in IBM to avoid contractures due to severe muscle weakness (Fig. 33.3). Occasionally, wrist splints to help support the hand to improve grip ability and to relieve pain are needed in PM and DM patients with arthritis. A swan neck splint (Fig. 33.5) may help to increase the ability to flex finger joints and prevent overextension in a person with IBM.

Table 33.3 List of assistive devices that may be useful in patients with myositis

Raised toilet seat
Reacher
Walker or wheelchair
Stair lift
Jar opener
Ergonomically adapted tools (enlarged grip)

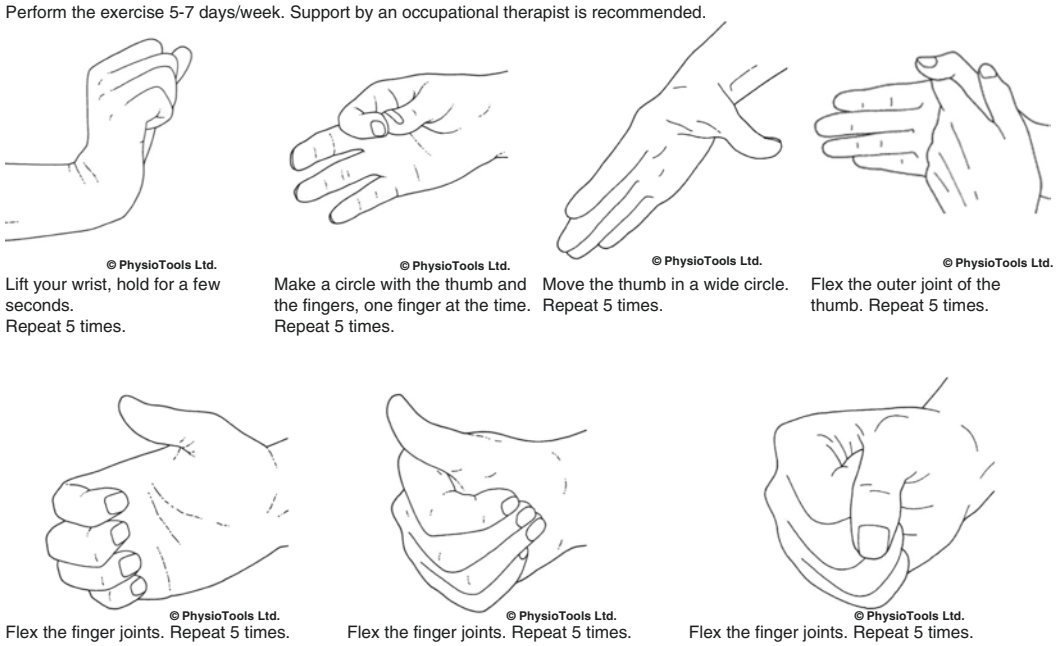
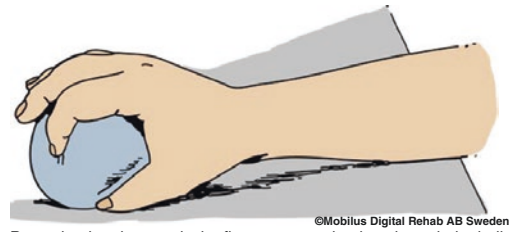


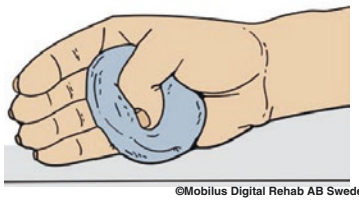
Fig. 33.3 Hand mobility exercise program for patients with myositis. (PhysioTools Online. Genral exercised 2nd edition. Retrieved June 25, 2018)

Hand exercise for strength should be performed 3-5 days per week. The ball or the dough need to have suitable resistance for the patient, preferably prescribed by an occupational therapist. The exercise should be supervised by an occupational therapist to enable individualization

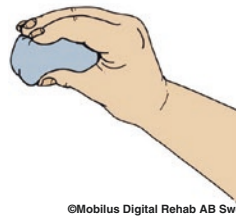
Squeeze the ball or the dough, flexing all fingers and the thumb. Repeat 10-15 times.



Press the thumb towards the fingers one at the time through the ball or dough and try to make circles. Repeat 10 times/finger.



Press the thumb through the ball or the dough towards the base of the little finger. Repeat 10 times.



Press the thumb towards the index- and middle finger through the ball or the dough. Repeat 10 times.

Press the thumb while holding the ball or the dough (key grip). Repeat 10 times.

Fig. 33.4 Hand strength exercise program for patients with myositis (Copyright Mobilus Digital Rehab AB Sweden www.gomobilus.com)

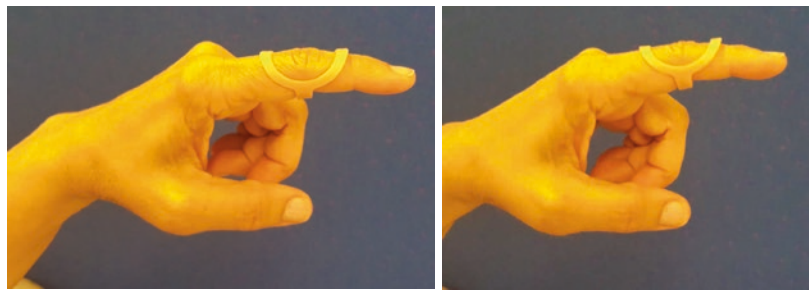


Fig. 33.5 Swan neck splint that may prevent overextension in the proximal interphalangeal joint and enable finger flexion in patients with IBM. (Photo: Karin Åström Stockholm Sweden)

Conclusion

Patients with myositis are affected in their activities of daily living due to reduced muscle function and aerobic capacity, fatigue and pain, often despite low disease activity. Exercise is important in all IIM patients despite the heterogeneity associated with myositis to optimize function and the quality of life. Intensive exercise can even be regarded as therapeutic, reducing disease activity. Exercise should be recommended early with gradual progression based on the individual response. Exercise is perhaps the only proven treatment in IBM patients and most patients tolerate exercise without adverse effects. The inter-professional-multidisciplinary team including the patient is crucial for the best treatment. Further research is needed to understand predictors for exercise response in the idiopathic inflammatory myopathies.

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Dietary Considerations in Myositis

34

Kun Huang and Rohit Aggarwal

Key Points to Remember

- There is an increased incidence of celiac disease in patients with myositis, so a gluten-free diet should be considered if symptomatic.
- Low serum vitamin D levels have been reported in myositis patients, but it is unclear whether vitamin D supplementation has any therapeutic effect on myositis. We recommend vitamin D intake at 600–800 IU/day for the prevention and treatment of glucocorticoid-induced osteoporosis.
- Evidence is lacking to recommend creatine supplementation or a protein-rich diet as adjunctive therapy in myositis.
- Retinoids, as a treatment of acute promyelocytic leukemia (APL), may cause autoimmune myositis and therefore should be avoided as a supplement in patients with myositis.
- Dietary statin is abundant in red yeast rice, oyster mushroom, soy products, and various grains which can be a source of exogenous statin in patients with anti-HMGCR-positive immune-mediated necrotizing myopathy; therefore these should be avoided in this subset of myositis.
- There is no definitive evidence that an anti-inflammatory diet helps myositis or of dysbiosis in myositis.

Introduction

Diet has long been known to have a crucial impact on human health and disease. It is possible that the complex interaction of diet and other environmental factors with genetic milieu may play a role in the pathogenesis of autoimmune rheumatic diseases including myositis. The dietary effects of the human gut microbiome, which harbors up to 1012 cells per gram of tissue [1], and its effect on autoimmune disease, are growing rapidly and are implicated in many autoimmune diseases, including RA, SLE, multiple sclerosis (MS), type 1 diabetes, and inflammatory bowel disease (IBD)

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[2–11]. In idiopathic inflammatory myopathies (IIM), dietary contributions are poorly understood, and this chapter will review the role of gluten, vitamin D, creatine, retinoid acid, protein-rich diets, dietary statins, anti-inflammatory diets, and the gut microbiome in IIM.

Gluten Sensitivity and Gluten-Free Diet

"Celiac disease" specifically refers to gluten-sensitive enteropathy with characteristic findings on small bowel histology. However, gluten sensitivity can affect systems beyond the gastrointestinal (GI) tract including skin (i.e., dermatitis herpetiformis) and neurological disorders (e.g., gluten ataxia, neuropathy, and myopathy being the most common and IIM being rare) [12].

Celiac disease is reported in adult polymyositis (PM) and dermatomyositis (DM) along with juvenile DM [13–15]. Henriksson first identified PM and celiac disease in a 33-year-old woman in 1975 where treatment with a gluten-free diet led to the resolution of both muscular and GI symptoms [16]. A subsequent study identified 14 adult PM patients confirming 5 with clinical signs and a jejunal biopsy consistent with celiac disease, while several case reports support this association in adults [17]. In a UK cohort of 300 patients with gluten sensitivity and neurological manifestations, 13 had myopathic symptoms [18], while 4 (4.5%) patients in a Swedish cohort of 88 IIM patients had biopsy-confirmed celiac disease, a higher than expected prevalence than the general population [19]. Interestingly, 3 of these 4 patients had inclusion body myositis (IBM) such that 3 of 18 (17%) patients with IBM had celiac disease. Other studies have also indicated a high prevalence of celiac disease in IBM patients [20, 21]. Further, immunogenetic findings demonstrate an association between the HLA class II extended haplotypes, DQ2 [22, 23], DR3 or DR5 [24, 25] in both DM/PM and celiac disease while IBM and celiac disease share an association with HLA B8-DR3 [20]. Despite the association there is no causal relationship between myositis and gluten.

> Celiac disease is common in myositis especially JDM and should be suspected in myositis patients with GI symptoms.

In most cases of celiac-associated myositis, IIM is diagnosed first with some exceptions [26]. Many patients have no overt signs or symptoms of celiac disease, which may be found incidentally during endoscopy or a malignancy workup [17, 18, 27]. Similarly, gluten avoidance alone does not typically improve IIM [16, 19, 27], and a gluten-free diet to avoid malabsorption and malnutrition is simply an adjunctive therapy if celiac disease was found. In clinical practice, a high degree of suspicion is necessary to detect celiac disease in patients with IIM as GI symptoms are usually silent. Antibody testing for celiac disease may be helpful but not diagnostic, as tissue transglutamine antibody, the most specific and sensitive serological screening test for celiac disease, is usually negative [21]. Selva-O'Callaghan and colleagues recommended bowel biopsy to exclude celiac disease in patients with moderate anti-gliadin values (>7 mg/L) [21].

Vitamin D Deficiency

The active form of vitamin D inhibits T-cell proliferation, reduces secretion of interleukin 2 (IL-2) and interferon γ (IFNγ) by CD4+ T lymphocytes, and suppresses antibody secretion from B cells [28]. Vitamin D is a powerful blocker of dendritic cell differentiation and modulates the macrophage response such as the release of inflammatory cytokines and chemokines [29, 30]. As vitamin D is an endogenous immune modulator [31], it is not surprising that low levels of vitamin D have been associated with many cancers, infectious diseases, IBD, type 1 diabetes, and MS [32–35]. Based on serum samples collected during similar months, vitamin D deficiency was reported in a cohort of Swedish DM/PM and IBM (149 patients) compared to a gender-matched control population with an odds ratio exceeding that observed for MS [36].

Epidemiological data cannot answer the question of whether vitamin D deficiency is the cause

or the effect. Intuitively, myositis therapies including prolonged exposure to glucocorticoids and sun avoidance may result in vitamin D deficiency, arguing for the effect rather than the cause. However, in SLE subjects, independent of steroid use, the correlation of low vitamin D levels and active disease persisted [37, 38] and low vitamin D levels predated the diagnosis of SLE and predicted progression [39]. Vitamin D supplementation in SLE patients led to a reduction in inflammatory cytokines [40], decrease in autoantibodies, and increase in complements level [40, 41]. Nevertheless, the benefit of vitamin D supplementation in SLE in randomized controlled trials is minimal [40, 42]. No controlled trials of vitamin D supplementation have been done in myositis.

Immunogenetic factors are implicated in the association between vitamin D deficiency and autoimmunity. Single nuclear polymorphisms (SNP) in genes that modulate either vitamin D degradation or vitamin D receptor (VDR) signaling are associated with an increased risk of developing SLE [39, 43, 44]. Similarly, some IIM patients harbor VDR polymorphisms that affect VDR gene expression, implying a potential role of VDR signaling in disease pathogenesis [45–47]. Luigi and colleagues proposed that enhancing the VDR signaling pathway may be a potentially new pharmacological tool for myositis treatment [48, 49].

There is no consensus for vitamin D supplementation beyond the maintenance of bone health and for adults taking prednisone at a dose of ≥2.5 mg/day for ≥3 months [50], the 2017 American College of Rheumatology guidelines suggest calcium supplementation at 1000–1200 mg/day and vitamin D intake at 600–800 IU/day for osteoporosis prevention [51].

Many questions remain including the degree of vitamin D supplementation, the clinical relevance of measuring the aforementioned gene SNPs, and the possibility of vitamin D supplementation worsening calcinosis. More data on long-term safety and the need for monitoring vitamin D levels rather than simply recommending chronic supplementation is necessary.

> The role of vitamin D supplementation is unclear in myositis beyond the prevention of osteoporosis in patients on steroids.

Creatine Supplementation

Oral creatine supplements are generally considered to improve athletic performance, albeit with variable effects. Randomized controlled trials have demonstrated positive effects of creatine supplementation in muscular dystrophies [52, 53] and no efficacy in metabolic myopathies [53]. Given low total creatine and phosphocreatine levels in IIM [54, 55], it is postulated that creatine supplements may positively impact muscle bioenergetics despite rare and conflicting trial results.

In a randomized double-blind study to evaluate the efficacy of creatine monohydrate therapy versus placebo, 37 PM or DM patients on stable immunosuppression and a home exercise program were given 20 g of creatine/day for 8 days followed by more than 3 g/day for 6 months [56]. The creatine therapy group showed a modest improvement in functional performance and muscle energy parameters. However, creatine supplementation in a small cohort of 15 JDM patients (0.1 g/kg/day) vs. controls in a randomized, crossover, double-blind short duration trial of only 12 weeks showed no effect on muscle function, intramuscular phosphocreatine content, body composition, aerobic conditioning, or health-related quality of life [57].

No adverse effects were observed in long-term studies in adult athletes with the administration of 5–10 g creatine/day but the effects in more sedentary myositis subjects are unknown. Most authorities note that an intake of 3 g creatine/day, similar to the daily endogenous turnover of 2 g creatine, is unlikely to pose a risk [58]. Further, some forms of creatine may be unsafe as the degradation product, creatinine, as well as other toxic ingredients may be found at unacceptable levels [59].

Creatine supplementation (3 gm/day) in myositis has conflicting results, with at least one study showing modest improvement in functional status.

Protein Supplementation

Protein supplementation has long been used as a nutritional strategy in muscle building especially when combined with resistance-type exercises [60]. This is mainly due to postprandial aminoacidemia, which is known to stimulate skeletal muscle protein synthesis [61, 62]. In the elderly, age-dependent muscle loss is attenuated serving to maintain the quality of life [63]. In theory, protein supplementation may facilitate the recovery of muscle function and performance, but protein supplements in healthy individuals fail to demonstrate measurable reductions in muscle damage or enhanced recovery of muscle function.

Protein supplementation in patients with muscle disuse or disease is also disappointing. In a small trial of healthy older men immobilized for 5 days, dietary protein supplementation (~20 g twice daily) did not attenuate muscle loss [64] and in patients with facioscapulohumeral muscular dystrophy, post-exercise protein supplementation in a randomized control trial led to no improvement in training effects [65].

Since there are no studies to evaluate the utility of protein supplementation in patients with IIM, we recommend the same protein supplementation for healthy adults with minimal physical activity at 0.8 g protein/kg/day. To promote skeletal-muscle protein accretion and physical strength, dietary intake of 1.0, 1.3, and 1.6 g protein/kg/day is recommended for individuals with minimal, moderate, and intense physical activity, respectively [66].

There is no evidence that protein supplementation helps myopathy or IIM.

Retinoid Acid

Retinoids bind to the retinoic acid binding site of retinoic acid receptors and have biologic activities similar to those of vitamin A. They suppress the differentiation of Th1/Th17 cells, induce the development of Th1/regulatory T cells, and influence the proliferation of B cells. Retinoids reduce disease activity in animal models of RA [67, 68], lupus nephritis [69], vasculitis [70], and autoimmune myositis [71]. Although four clinical trials have been conducted on retinoid therapy in RA [72, 73], lupus nephritis [74], and systemic sclerosis [75], they were small with many subjects withdrawing due to hepatic toxicity with no significant improvement in arthritis symptoms or inflammatory markers. A small study of 31 patients suggested that etretinate may help skin involvement in systemic sclerosis [75]. There have been no retinoid trials for myositis.

All-trans retinoic acid (ATRA)-induced myositis in APL patients has been reported in children and adults, commonly involving the lower extremities with a median time to onset of 18 days (9–24 days) [76–82]. Many patients required high-dose glucocorticoid therapy in addition to ATRA discontinuation.

Avoid all trans retinoic acid supplements in myositis patients.

Dietary Statin

Statins are the most commonly prescribed category of drugs worldwide. While generally well tolerated, 2–10% of patients on statin medication develop toxic myopathy characterized by significant myalgia or muscle enzyme elevation, which resolves soon after discontinuation of statin. In rare cases, some may develop immune-mediated necrotizing myopathy (IMNM) associated with autoantiboidies to HMG-CoA reductase [83] (see Chap. 24).

Natural statins can be found in the normal diet or in supplements, which may induce toxic myopathy or IMNM in the same manner as

synthetic statins. Red yeast rice was utilized in the original production of lovastatin, the first marketed pharmaceutical statin, and oyster mushroom contains up to 2.8% lovastatin equivalent on a dry weight basis. Relatively high amounts of lovastatin were found in Shiitake mushrooms [84] whereas other studies failed to substantiate this finding [85]. These mushrooms are frequently served worldwide. Cumulatively, a mushroom soup recipe could greatly exceed the standard daily lovastatin prescription dose. Other natural occurring statins are found in soy products and various grains including wheat germ [86, 87], and some statins are even found in public water supplies [88]. Although these natural sources of statin may provide a health benefit in lowering cholesterol, they may also contribute to statin-related side effects that may be overlooked when assessing a patient with myopathy.

A comprehensive dietary history should be taken in patient with immune-mediated necrotizing myopathy (especially those with anti-HMGCR autoantibodies).

Anti-inflammatory Diet and Gut Microbiome

Hippocrates once said, "Let food be thy medicine." Diet shapes the gut bacterial ecology and diversity [89, 90], also known as the gut microbiome. The concept of an anti-inflammatory diet has been very popular. Although there is no strict definition of what composes an anti-inflammatory diet, it is believed that the foods with the highest anti-inflammatory benefits are fruits, green leafy vegetables, nuts, omega-3 fatty acids found in fatty fish, healthy fats and high fiber whole grains, all of which are found in a Mediterranean diet. A dietary basis for managing inflammatory disease is most likely explained by interactions between the gut microbiome and the immune system. For example, omega-3 fatty acids can decrease the production of reactive oxygen species, inhibit T-cell proliferation and IL-2 production, and decrease MHC class II expression and antigen presentation [91]. Conversely, high-fat diet alters the epithelial cells of the intestinal barrier and promotes the translocation of lipopolysaccharide-bearing bacteria which in turn induces toll-like receptor (TLR) activation of macrophages in the gut, adipose tissue, and skeletal muscles [92]. The gut microbiome is implicated in a variety of autoimmune diseases, including RA [11, 93, 94], SLE [6, 7], Sjogren syndrome [95–98], Behcet disease [5, 99, 100], and ankylosing spondylitis [101–104].

A meta-analysis that reviewed 10 randomized controlled trials concluded that the consumption of >2.7 g/day of omega-3 fatty acids for >3 months reduced the use of NSAIDs in RA subjects [105]. Other clinical trials have also shown a beneficial effect of omega-3 fatty acids in RA with a reduction in the number of swollen joint counts and duration of morning stiffness [91].

Despite the pathogenic pathway of high-fat diet in gut microbiome and skeletal muscles, there is little to no evidence to support the role of dysbiosis (i.e., alteration in the composition, diversity, or metabolites of the microbiome), in the onset or evolution of inflammatory myopathies. No studies have investigated the differences in microbial taxonomic composition and the role of an anti-inflammatory diet in myositis. Nevertheless, we recommend a Mediterranean diet to everyone given its beneficial effect on cardiovascular health.

An anti-inflammatory or any other special diet has no role in the management of myositis, but a Mediterranean diet is reasonable to pursue from a cardiovascular perspective.

Conclusion

Diet plays a role in attenuating or accentuating autoimmunity in both the innate and adaptive immune systems. This chapter summarizes evidence related to gluten, vitamin D, creatine, protein-rich diets, retinoids, anti-inflammatory

diets, and dysbiosis in the pathogenesis and treatment of IIM. Taken together, we lack the requisite evidence to confidently recommend specific dietary habits or nutritional supplementations in the management of myositis. However, the human gut microbiome is emerging as a key contributor to the immune system and the development of immune-mediated diseases, and the next step certainly involves unraveling the role of dysbiosis in the pathogenesis or treatment response in IIM.

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Distinguishing Disease Activity and Damage in Myositis

35

Rodolfo Curiel and Lisa G. Rider

Key Points to Remember

- There is no single gold-standard measure for assessing disease activity and damage in myositis, and both activity and damage must be comprehensively assessed.
- Disease activity and damage may be discordant in different organs at any point in time.
- Measurement of muscle enzymes in combination with magnetic resonance imaging, a careful history and physical examination, and determination of changes in muscle strength and other organ manifestations over time are required to differentiate active disease from chronic damage.
- A beneficial response to recent therapies and disease flares generally indicates active disease.
- Occasionally, a repeat biopsy of the muscle is required to determine active muscle disease.
- The assessment of other organ systems, including pulmonary, the skin, and joints, is also critical.

Introduction

To determine optimal therapy, responses to treatment, and the long-term effects of disease and medications in patients with idiopathic inflammatory myopathies (IIM), physicians must distinguish disease activity from disease damage. *Disease activity* includes the inflammatory manifestations of illness in the muscles, skin, lungs, joints, and other systems that are potentially reversible with treatment, whereas *disease damage* encompasses changes from prior inflammation that are often irreversible, particularly in adults (e.g., scarring, fibrosis, and atrophy) and adverse effects that accumulate after long-term medication (e.g., osteoporosis, steroid myopathy, etc.) [1]. Assessment of disease activity and damage requires a careful history and physical examination; evaluation of responses to recent therapies and relapses; recent changes in organ manifestation and severity; frequent laboratory testing such as muscle enzymes or inflammatory markers; sometimes specialized procedures including electromyography, pulmonary

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function testing, echocardiography, and imaging; and occasionally repeating muscle biopsies. Often, it is difficult to differentiate disease activity from damage. The evaluations of muscle strength and physical function, two of the key elements in the assessment of myositis, cannot by themselves distinguish disease activity from damage, without incorporating the results of other assessments in myositis patients. At disease onset, patients primarily have active disease, whereas later in the illness course, damage often exceeds activity. Damage is generally cumulative over time leading to an insidious decline in patients. However, most patients have a combination of active disease and disease damage at any given time, so it is imperative that physicians caring for myositis patients evaluate the proportion of active disease vs. damage that is responsible for a patient's clinical presentation. At times, the rate of change in assessments after a trial of immunosuppressive medication can distinguish active disease, which responds to immunosuppressive therapies, from damage, which should not change after such therapies. Further, an acute or subacute change in clinical features including the onset of arthritis or rash is also supportive of underlying active disease. A delicate balance always exists between undertreating a patient with active disease, which may lead to an increase in disease activity and damage over time, and overtreating a patient with chronic damage, with the risk of serious side effects from inappropriate therapy.

Because the IIMs are complex, heterogeneous, multisystem conditions, there is no gold-standard measure for assessing disease activity and damage. Multiple measures have been developed for use in clinical practice and therapeutic trials. The International Myositis Assessment and Clinical Studies Group (IMACS) established core set measures to assess disease activity and cumulative damage, which are recommended for use in all myositis therapeutic trials and outcome studies, but may also be used in the clinical care of

Table 35.1 Core set measures of disease activity and damage [1, 2]

Core set measures of disease activity in myositis	Measure details
Physician global disease activity	Overall rating of myositis disease activity by the physician based on all available clinical and laboratory measures. Assessment on a Likert scale or 10-cm visual analogue scale
Patient/parent global disease activity	Overall rating of myositis disease activity by the patient/parent. Assessment on a Likert scale or 10-cm visual analogue scale
Manual muscle testing	Measures muscle strength by applying pressure to muscle groups tested against gravity or through a range of motion for muscle groups with less than antigravity strength. 0–10-point or expanded 0–5-point Medical Research Council scale includes proximal, distal, and axial muscles
Physical function	Validated patient/parent questionnaire of activities of daily living. The (Childhood) Health Assessment Questionnaire (HAQ/CHAQ) assesses physical function in eight domains of daily activities
Laboratory assessment	At least two muscle enzyme elevations from the following: creatine kinase, aldolase, lactate dehydrogenase, aspartate aminotransferase, alanine aminotransferase [1, 3]
Extra-skeletal muscle disease activity	The Myositis Disease Activity Assessment Tool assesses 6 extra-muscular organs (cutaneous, constitutional, gastrointestinal, joint, cardiac, and pulmonary activity) to produce a physician-rated global extra-muscular assessment on a Likert scale or 10-cm visual analogue scale [2]
Core set measures of disease damage in myositis	**Measure details**
Physician global damage	Overall rating of myositis disease damage by the physician based on all available clinical and laboratory measures. Assessment on a Likert scale or 10-cm visual analogue scale
Myositis Damage Index	Physician assessment of damage in 11 organ systems (muscle, skeletal, cutaneous, gastrointestinal, pulmonary, cardiovascular, peripheral vascular, endocrine, ocular, infections, malignancy), with specific items assessed in each domain. Each domain is further evaluated by visual analogue scales for severity of damage [2]
Physical function	Validated patient/parent questionnaire of activity of daily living (HAQ/CHAQ)

Based on: https://www.niehs.nih.gov/research/resources/imacs/diseaseactivity/index.cfm https://www.niehs.nih.gov/research/resources/imacs/diseasedamage/index.cfm

IIM patients (Table 35.1) [1, 2]. Muscle strength and function are the core assessments of myositis, but assessment of disease activity and damage in other target organs, including skin, lungs, joints, gastrointestinal, cardiac, and other organ systems, is essential. Active disease in these target organs may run in parallel with muscle disease, but in some patients, certain organ systems dominate their illness course, and these systems are often associated with the myositis-specific autoantibody phenotypes. Disease activity and damage may be discordant in different organs at any point in time. Some key features that may help to differentiate between disease activity and damage in the individual organs involved in myositis are described below.

Muscle Weakness: Activity vs. Damage

Muscle weakness in IIM could result from active muscle inflammation or necrosis (active disease) or represent disease damage due to loss of muscle mass (atrophy, deconditioning, or steroid) or fibro-fatty replacement of muscle [as seen with inclusion body myositis (IBM) or long-standing polymyositis (PM)]. Although a single muscle strength measure cannot be used to distinguish between disease activity vs. damage, serial measurement showing either a beneficial response to immunosuppressive therapy or a rapid decline from relatively stable manual muscle testing (MMT) (flare up) is usually indicative of active disease. An exception could be a steroid myopathy. Serial measures of muscle strength with no change in a weak patient or a slow, insidious decline due to cumulative muscle mass loss usually indicate muscle damage. However, new or worsening dysphagia or dysphonia or respiratory muscle weakness often signals active or worsening muscle disease.

Testing Muscle Strength and Function An important component in the assessment of myositis is the examination of muscle strength based on the effective performance of a movement in relation to the forces of gravity and manual resistance. When MMT is used to assess strength, the muscle is scored as "weak" or "strong" based on the muscle's ability to resist externally applied force. Several grading systems exist for MMT, including the 0 to 5 expanded Medical Research Council scale and the 0 (no visible movement) to 10 (holds test position against maximal resistance) Kendall grading scale. MMT is one of six core set measures recommended for use in all myositis therapeutic trials and outcome studies (Table 35.1). We caution that the grades obtained with MMT are largely subjective and depend on several factors, including the effect of gravity, the manual force used by the clinician, the patient's age and level of fatigue, comorbid conditions, and cognitive and emotional factors of both the patient and tester. Nevertheless, it is a reliable and valid method when performed by an experienced clinician [2–4]. A shortened MMT test consisting of 8 axial, proximal, and distal muscles (i.e., MMT-8) is relatively easy to use in a clinical setting and closely approximates the more detailed testing of 26 muscle groups [2–4].

Another assessment of disease activity and damage is the physical function, a rating of the patient's ability to perform the activities of daily living. Physical function is commonly assessed in therapeutic trials and standard patient care using the Health Assessment Questionnaire (HAQ-DI), which is one of the core set measures in myositis. Vital areas of function, such as the ability to dress oneself, to toilet, to eat, and to go up and down stairs, are evaluated by self- or parent-reported questionnaires and by observational analysis (Table 35.2) [2]. Observational functional tests, such as the Myositis Functional Index-2 (FI-2) and the Childhood Myositis Assessment Scale (CMAS), are also used to measure fatigue and endurance, which, in addition to pure strength, are important elements of muscle function [2]. Tests of muscle strength and physical function, however, cannot distinguish active inflammation from chronic damage [1, 2], although rapid decline or improvement is generally due to active disease.

Muscle Enzymes Serum levels of creatine kinase (CK), aldolase, lactate dehydrogenase (LDH), and transaminases are often elevated in patients with myositis and correlate relatively well with disease activity, especially in PM and

Table 35.2 Measures of physical function used in myositis [2]

Measure	Myositis group	Description
Childhood Myositis Assessment Scale (CMAS)	Juvenile myositis	Observational tool of muscle function, strength, and endurance
Myositis Functional Index-2	Adult dermatomyositis and polymyositis	Observational tool of muscle function. Assesses dynamic muscle endurance and repetition in seven muscle groups
(Childhood) Health Assessment Questionnaire	Juvenile and adult dermatomyositis and polymyositis	Assesses activities of daily living by parent/patient questionnaire. A core set measure of activity and damage
Inclusion Body Myositis Functional Rating Scale	Inclusion body myositis	Patient functional rating scale about swallowing, handwriting, fine motor tasks, hygiene, dressing, position changes, walking, etc.
Inclusion Body Myositis Weakness Composite Index	Inclusion body myositis	Nine-item scale combining evaluation of hand flexor and quadriceps strength, timed functional assessment of limb girdle and axial weakness, and evaluation of walking and swallowing

immune-mediated necrotizing myopathy (IMNM). Of all the core set measures (Table 35.1), serum levels of muscle enzymes are among the few tests that discriminate active disease from disease damage or remission. On average, CK is highest in patients with polymyositis and IMNM, intermediate in patients with DM, and lowest in patients with JDM or IBM [5, 6]. In some myositis subsets (especially JDM) other muscle enzymes, such as aldolase, LDH, aspartate aminotransferase (AST), and alanine aminotransferase (ALT), may be better surrogates for muscle inflammation or activity [3]. Although serum CK has been used frequently to assess myositis disease activity, overall CK levels may not correlate well with muscle strength, endurance, or physical function in patients with DM or JDM or IBM, and is normal in up to 30% of DM and 70% of JDM patients despite active muscle disease. As the disease evolves into a chronic condition with significant muscle atrophy and damage, the serum CK level becomes an even less reliable marker of disease activity and may be normal, even when disease is active, due to loss of muscle mass. A lower serum creatinine, a nonprotein product of creatine phosphate metabolism by skeletal muscle tissue, is usually seen in patients with significant muscle atrophy and decreased muscle bulk [7]. Therefore, the serum creatinine is a reasonable measure to consider when evaluating serum CK levels in association with disease activity and damage.

Conversely, any elevation in the serum levels of these enzymes most often reflects ongoing disease activity; however, elevation of transaminases, LDH, and aldolase must also be distinguished from liver disease and LDH from pulmonary disease, which can co-occur in myositis patients [6]. Enzyme levels often improve weeks before muscle strength and function improve, while an increase can predict a clinical relapse.

Muscle Imaging Magnetic resonance imaging (MRI) of thighs, pelvis, and other proximal muscle groups can demonstrate areas of muscle edema on T2-weighted or short tau inversion recovery (STIR) images, which is suggestive of inflammation and active disease. Areas of muscle atrophy, fatty replacement, fibrosis, or calcification on T1-weighted images reflect chronic changes or damage [8] (Fig. 35.1). MRI can show areas of inflammation, even when enzymes and other biologic markers have returned to normal. Conversely, MRI can appear normal even when there is ongoing muscle inflammation documented by muscle biopsy [8]. Currently, proximal thigh muscle MRI is being used in some centers to evaluate active disease vs. damage despite its limitations.

Muscle Biopsy In PM and IBM, muscle fibers are often surrounded and invaded by mononuclear cells, most often CD8+ T lymphocytes (Fig. 35.2a). IBM has other characteristic changes on biopsy, including the presence of rimmed vacuoles. In DM and JDM, the mononuclear infiltrates, most often CD4+ T cells and dendritic

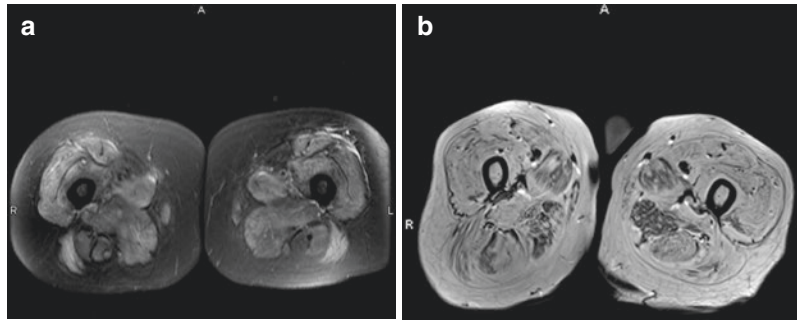

Fig. 35.1 (**a**) An axial T2 fast spin echo fat saturation image of the thighs showing active myositis with increased water or edema signal in the muscles, which is bright. (Courtesy of Dr. Kathleen Brindle). (**b**) An axial T1-weighted image of the thighs showing chronic myositis with extensive fatty atrophy and fibrofatty replacement of many muscles. (Courtesy of Dr. Kathleen Brindle)

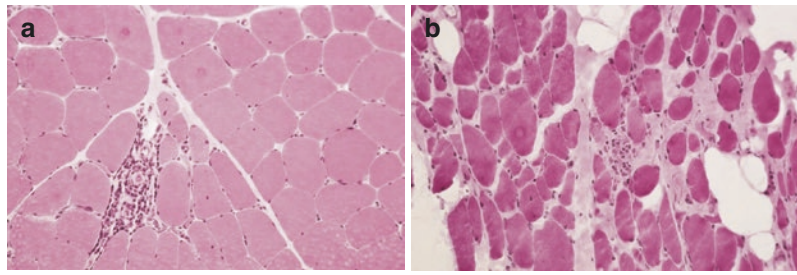

Fig. 35.2 (**a**) A focus of endomysial chronic muscle inflammation from a muscle biopsy of a patient with polymyositis. There is fiber atrophy and myophagocytosis. (Courtesy of Dr. Adam Schiffenbauer). (**b**) A muscle biopsy from a polymyositis patient with several signs of chronic change, including atrophy of myofibers in which the muscle cells are diminished in size, fibrofatty replacement of muscle evident by the large white cells, and a patch in which myofibers have been replaced by fibrotic tissue. On this biopsy there are also a few areas of myophagocytosis. (Courtesy of Dr. Adam Schiffenbauer)

cells, surround muscle blood vessels (perivascular inflammation), and there is frequent perifascicular myofiber atrophy. Degeneration, regeneration, necrosis, and myophagocytosis can also be present in the muscle biopsies of myositis patients. In INMN, muscle necrosis with little or no inflammation is a dominant feature, although the other changes may also be present. All the above-mentioned changes on muscle biopsy suggest active disease. Chronic changes that suggest muscle damage include fiber destruction, atrophy, and fatty replacement and expansion of connective tissue in between the muscle fibers (Fig. 35.2b). Very few patients require a repeat muscle biopsy to assist in clarifying active disease vs. damage, or to reassess a patient's diagnosis. Muscle histopathology provides information that can be of prognostic value, particularly in juvenile IIM [9, 10].

Electromyography Electromyography (EMG) is a sensitive but nonspecific tool to evaluate myositis, as it may be abnormal in noninflammatory myopathies and fails to differentiate the various subtypes of IIM. It is helpful in determining the presence or absence of myopathy, but does not always distinguish between active disease vs. damage-related weakness. The presence of spontaneous activity, with insertional activity, fibrillation potentials, and positive sharp waves in the setting of otherwise typical myopathy (short duration, low amplitude polyphasic motor unit potentials) is indicative of active muscle inflammation or necrosis. However, these changes may be absent in active or inactive myopathy. Motor unit potentials of increased duration and reduced mean amplitude usually indicate muscle damage [3, 11].

Differentiating Activity from Damage Based on Muscle Testing

Using one muscle test is often not adequate to discriminate activity vs. damage in the muscles of patients with IIM. Multiple tests, serial assessments over time, and monitoring the response to immunosuppressive therapy by examining trends in the results can all be helpful adjuncts in this discrimination. At any given time in the disease course, to differentiate active disease from chronic damage, it is necessary to consider the measurement of muscle enzymes in combination with MRI, as well as the change in muscle strength and function over time (improvement vs. worsening) in response to glucocorticoids and other immunosuppressive therapies (Table 35.3). Repeat EMG and/or muscle biopsy is sometimes used to evaluate active vs. chronic disease, when other clinical and laboratory parameters are unrevealing (Fig. 35.3).

Dyspnea: Activity vs. Damage

A patient with persistent dyspnea may have ongoing parenchymal lung inflammation within the lung potentially responsive to immunosuppressive treatment, or chronic, irreversible parenchymal fibrosis that will not benefit from continued immunosuppressive treatment.

Moreover, dyspnea in IIM patients may be related to pulmonary or non-pulmonary causes. Pulmonary manifestations include interstitial lung disease (ILD), aspiration pneumonia often related to dysphagia, drug-induced lung disease, alveolar hemorrhage, pneumomediastinum and pneumothorax (resulting from rupture of alveoli or pleural

Table 35.3 Discriminating muscle activity versus damage in myositis [1, 2, 4]

	Activity	Damage
Muscle strength (manual muscle testing) (MMT)	Decreased, but improves with immunosuppressive therapy with rapid improvement (response) or worsening (flare up) in strength	Decreased, but no change with immunosuppressive therapy. Slow insidious decline
Muscle strength, endurance, and physical function (CMAS, CHAQ in juvenile, HAQ in adults, FI-2 in adults)	Decreased, but improves with immunosuppressive therapy or may worsen acutely in case of a relapse	Decreased, but no change with immunosuppressive therapy. May worsen slowly in case of cumulative muscle damage
Serum muscle enzymes (CK, aldolase, LDH, AST, ALT)	Increased especially in PM, IMNM; less often in DM, JDM, IBM Or normal (especially CK) in DM, JDM, IBM Increase or decrease in levels over weeks to months	Normal or low Steady levels or very slow insidious decline over months to years
Muscle magnetic resonance imaging	Increased edema signal on STIR or T2-weighted images	Decreased muscle bulk and fibro-fatty replacement on T1-weighted images
Serum creatinine	Normal	Decreased (decreased muscle mass and muscle atrophy)
Muscle biopsy	Inflammatory infiltrates, muscle fiber degeneration/regeneration, vascular swelling/thrombosis, muscle infarction, overexpression of class I MHC on myofibers	Muscle atrophy, increased connective tissue, and fatty infiltration of muscle
Electromyography	Insertional activity, fibrillation potentials, and positive sharp wave motor unit potentials of increased frequency and decreased duration	Motor unit potentials of increased duration and reduced mean amplitude

CMAS Childhood Myositis Assessment Scale, *CK* creatine kinase, *LDH* lactate dehydrogenase, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *PM* polymyositis, *IMNM* immune-mediated necrotizing myopathy, *DM* dermatomyositis, JDM juvenile dermatomyositis, *IBM,* inclusion body myositis, *STIR* short tau inversion recovery, *MHC* major histocompatibility complex

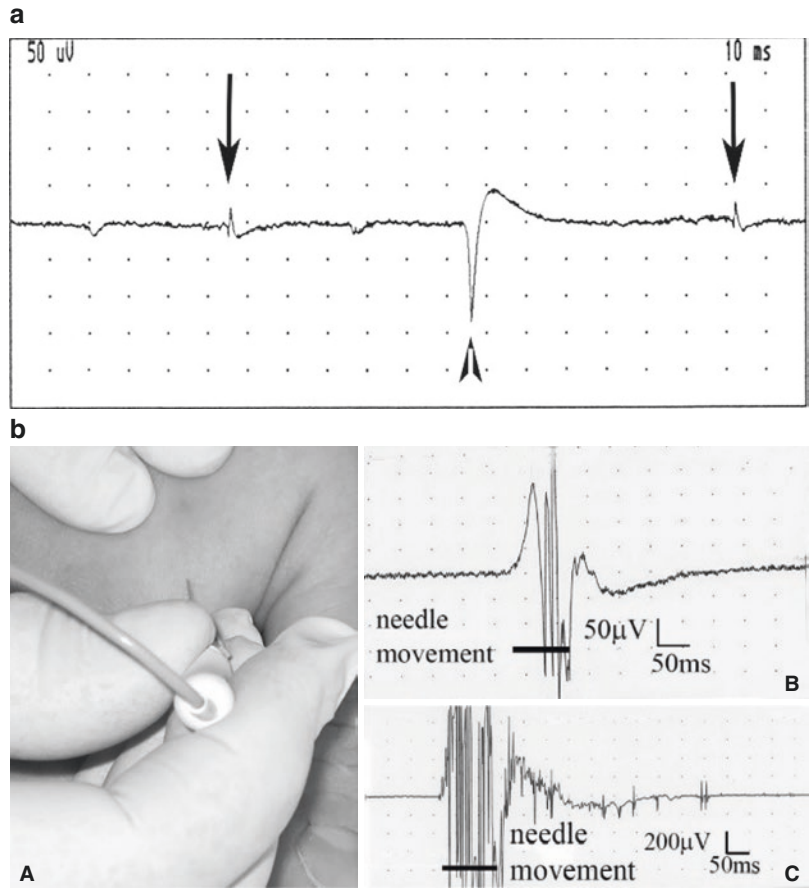

Fig. 35.3 (**a**) Electromyographic (EMG) findings of insertional activity, positive sharp wave, and fibrillation potentials, indicative of an active myopathy. In resting muscle, a positive sharp wave (arrowhead) and fibrillation potentials (long arrows) are shown. (**b**) (*A*) A needle EMG electrode is inserted into a relaxed first dorsal interosseous (hand) muscle. (*B*) Needle movement (bar denotes timeline) is associated with a burst of spikes. (*C*) With increased insertional activity, the spikes continue for about 500ms after needle movement (bar) ceases

blebs), as well as nonparenchymal abnormalities, such as respiratory failure due to muscle weakness and pulmonary artery hypertension. ILD is the most common form of pulmonary involvement in IIM and responsible for the greatest morbidity and mortality. Early detection of ILD, especially in high-risk groups like the anti-synthetase syndrome and anti-MDA5-associated disease, may improve outcomes [12]. Cardiac causes should be considered as well including left and right ventricular dysfunction, pericardial tamponade, coronary artery disease, and arrhythmias [13].

High-resolution computed tomography (HRCT) of the chest provides the most detailed images of the lungs along with the quantitative extent of lung involvement [14]. Changes in the extent or pattern of parenchymal involvement on serial chest HRCT over a short interval of 3–6 months, especially changes in ground-glass opacities or consolidation, may indicate active disease. A usual interstitial pneumonia HRCT pattern (more fibrosis, less response to immunosuppressive therapy) is fairly specific and includes the presence of septal thickening, honeycombing with traction bronchiectasis in a subpleural, basal distribution, and little or no ground-glass opacity. The HRCT pattern of nonspecific interstitial pneumonia (less fibrosis, more response to immunosuppressive therapy) includes patchy ground-glass opacity and consolidation, with minimal traction bronchiectasis, septal thickening, and honeycombing (Table 35.4).

Pulmonary function testing (PFT) is required for diagnosis, long-term follow-up, and monitoring the response to treatment in patients with ILD and other pulmonary complications. Restrictive physiology on PFTs (indicative of ILD) is characterized by a decrease in one or more of the following parameters: total lung capacity, functional residual capacity, forced vital capacity, forced expiratory volume in 1 second, and the diffusion capacity for carbon monoxide (DLCO). Morbidity and mortality in IIM have been linked to the baseline presence of ILD and restrictive physiology. Routine spirometry and gas-transfer monitoring

Table 35.4 Signs of active interstitial lung disease versus parenchymal damage

	Activity	Damage
Decreased DLCO/V_A on PFT	+++	+++
Decreased TLC/FVC on PFT	+++	+++
Rapid change in PFT parameters	+++	–
Ground-glass opacity on HRCT	+++	–
Consolidation on HRCT	+++	–
Septal thickening on HRCT	–	+++
Honeycombing on HRCT	–	+++
Traction bronchiectasis on HRCT	–	+++

DLCO diffusion capacity of carbon monoxide, V_A, alveolar volume, *TLC* total lung capacity, *FVC* forced vital capacity, *PFT* pulmonary function testing, *HRCT* high-resolution computed tomography of chest

Table 35.5 Signs of skin activity versus damage [2, 16]

	Activity	Damage
Erythema	+++	–
Erosion/ulceration	+++	–
Scale	+	+++
Dyspigmentation (hypopigmentation or hyperpigmentation)	–	+++
Telangiectasia	+	+++
Scar	–	+++
Nailfold capillary abnormalities (dilated blood vessels, decreased capillary density, tortuous capillaries)	+++	++
Calcinosis	–	+++

(i.e., DLCO) is central to routinely monitoring ILD in IIM patients or those at high risk for developing ILD [15]. While these parameters do not distinguish activity from damage in isolation, a rapid decline or improvement in PFT parameters may be a sign of worsening or improving activity, whereas stable parameters in certain settings would indicate irreversible changes (Table 35.4).

Dyspnea and exercise limitations in myositis-related ILD are, in most cases, multifactorial. Contributing factors include impaired gas exchange and pulmonary circulation, ventilatory dysfunction, and muscle dysfunction. A comprehensive evaluation is required including serial echocardiography, chest HRCT, and PFTs. Echocardiography is used to assess ventricular function and pulmonary pressure, while HRCT will distinguish inflammatory parenchymal disease characterized by ground-glass opacities from chronic irreversible lung damage indicated by the presence of fibrosis/honeycombing. Acute or subacute changes in respiratory physiology on PFTs suggest active disease, whereas PFTs will remain stable in patients with chronic disease. Periodic testing is required not only to assess response to treatment and prognosis but also to determine reversible (disease activity-related) changes from those that are irreversible (damage-related).

Assessment of the Skin

It is possible to distinguish disease activity from disease damage by carefully examining skin rashes (Table 35.5). Erythema, erosions, and ulcerations nearly always indicate active disease. Generally, the greater the intensity of erythema, the more active is the rash; for example, dark red erythema is more active than a faint pink rash. Occasionally, a faint pink discoloration from underlying skin vascular damage may persist after successful treatment of more active erythematous rashes. Erosions and ulcerations often indicate more active and severe disease and have been associated with a poorer prognosis, cancer-associated DM, and certain autoantibody subsets. Calcinosis often indicates skin damage, and we currently lack any effective therapies. It may persist for long periods of time, even with the resolution of other active rashes. However, the development of new calcinosis or the worsening of existing calcinosis often indicates underlying active disease. Skin atrophy and a scarring, hypopigmented rash is clearly a sign of disease damage (Fig. 35.4).

Leading dermatologists and rheumatologists with an expertise in DM/JDM have developed several tools to assess the cutaneous manifestations of myositis, including the Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI), Cutaneous Assessment Tool (CAT), the Disease Activity Score (DAS), and the Dermatomyositis Skin Severity Index (DSSI) [2]. The CDASI assesses activity and damage separately in the skin of DM/JDM patients over 15 anatomic sites and has three activity domains (erythema, scale, and excoriation/ulceration) and two damage domains (calcinosis and poikiloderma, defined as areas of hypopigmentation, hyperpigmentation, telangiectasia, and atrophy). Gottron papules on the hands are assessed

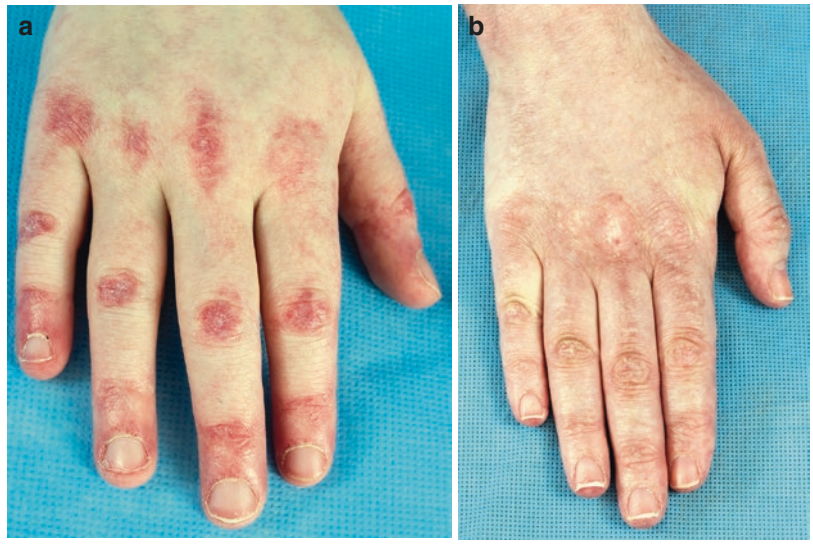

Fig. 35.4 (**a**) Gottron papules overlying the metacarpal phalangeal, proximal, and distal interphalangeal joints. The papules are primarily erythematous but with some mild telangiectasia and focal mild atrophy. This largely is consistent with active disease. (**b**) Atrophic and hyperpigmented Gottron papules overlying the metacarpal phalangeal and proximal phalangeal joints as well as in the linear extensor region between these joints. There is no erythema. This is consistent with disease damage, not activity

separately for activity (erythema and ulceration) and damage (dyspigmentation or scarring). Periungual erythema and telangiectasia and erythema and scale on the scalp are also assessed as elements of skin activity. The CDASI has been validated in clinical practice and therapeutic trials [2, 16].

Improvement in muscle strength, endurance, and physical function with an improved but persistently active rash is a common problem encountered by physicians caring for patients with IIM. Persistent rash, a sign of active disease, should be treated, but it is unclear if an untreated mild active rash is a predictor for future flare in non-cutaneous organs. The therapeutic target in IIM should be complete remission, meaning no evidence of disease activity in any organ system with the goal of mitigating further damage.

Assessment of Joints

The joints are common targets in myositis, most frequently leading to synovitis with complaints of pain, swelling, stiffness, and limited range of motion. The presence of an anti-aminoacyl-tRNA synthetase, anti-PM-Scl and anti-MDA-5 autoantibodies has been associated with frequent arthritis, particularly in the small joints of the hands [17, 18]. Radiographs are usually normal without joint space narrowing or erosions [19].

Joint contracture, a frequent complication of patients with juvenile myositis, is linked to muscle and surrounding connective tissue inflammation or scarring with or without calcium deposition. Significant joint contractures occur in up to 60% of children with juvenile myositis [20]. Ankles, hips, elbows, shoulders, and wrists are most often involved with joint contractures in JDM with serious and refractory disease [20]. Joint contractures related to muscle and connective tissue inflammation usually improve with immunosuppressive therapy, but contractures resulting from muscle scarring or calcinosis are only partially responsive to intervention and require physical therapy. Although rare, avascular necrosis, usually affecting the knees or hips, results from prolonged exposure to glucocorticoids, which is a sign of damage.

Conclusions

Clinical manifestations in individual patients with IIM at any point in time may result from a combination of active disease and chronic

damage. There is no gold-standard measure to differentiate disease activity and damage. Often a combination of modalities, which includes a careful clinical history and physical examination in addition to laboratory testing and imaging, is required to distinguish activity from damage. Serial assessments of the target organs over time (skin, muscles, lungs, joints) and monitoring the response to immunosuppressive therapy can be helpful in distinguishing activity from damage.

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