Inflammatory Myopathies

26

Jan Verschuuren, Fieke M. Cox,
Baziel van Engelen, Marianne de Visser,
and Umesh A. Badrising

26.1 Introduction and Classification

Idiopathic inflammatory myopathies (IIMs) represent a heterogeneous group of muscular disorders characterized by acquired muscle weakness and inflammatory infiltrates in skeletal muscle tissue. The three main disease entities in this group are sporadic inclusion body myositis (IBM), polymyositis (PM), and dermatomyositis (DM). These diseases differ strongly from each other in terms of clinical and pathological features. Since 1975, the Bohan and Peter criteria have been applied, allowing only a distinction between dermatomyositis and polymyositis based on the presence or absence of skin abnormalities. Histopathologically, there was no difference between PM and DM. At that time, IBM was not generally recognized as a separate disease entity and usually was not differentiated from PM. It was considered a "treatment-resistant" polymyositis. In 1984, IIMs were looked at from a histopathological point of view, which allowed PM, DM, and IBM to be discriminated particularly on histopathological criteria. A cytotoxic CD8-positive T-cell reaction is the main feature of PM and IBM, whereas in DM a B-cell-mediated microangiopathy is most prominent. Recently, this classification has been challenged as numerous cases of histopathologically defined PM have been described that were nonresponsive to immunosuppressants and immunomodulating therapies, eventually mimicking the clinical picture of IBM. However, differentiation between PM and IBM is crucial because of the different therapeutic approaches required. This chapter focuses on the three most relevant IIMs: IBM, PM, and DM.

J. Verschuuren (✉) • F.M. Cox • U.A. Badrising
Department of Neurology, Leiden University Medical Center, Postbox 9600, 2300 RC Leiden, The Netherlands
e-mail: j.j.g.m.verschuuren@lumc.nl; m.devisser@amc.uva.nl

B. van Engelen
Department of Neurology, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands
e-mail: b.vanengelen@neuro.umcn.nl

M. de Visser
Department of Neurology, Academic Medical Center, Amsterdam, The Netherlands
e-mail: m.devisser@amc.uva.nl

26.2 Sporadic Inclusion Body Myositis

26.2.1 Synonyms, Abbreviations

IBM

26.2.2 Genetics and Pathophysiology

Sporadic inclusion body myositis is, as the name implies, not hereditary. There are rare descriptions of a familial form of IBM that is probably no more frequent than in other autoimmune diseases. There is a strong association with the auto-

M.P. Wattjes and D. Fischer (eds.), *Neuromuscular Imaging*, DOI 10.1007/978-1-4614-6552-2_26,

immune prone ancestral HLA 8.1 haplotype and with other autoimmune disorders, such as Sjögren's disease, thyroid disorders, celiac disease, rheumatoid arthritis, and type I diabetes mellitus. Hereditary IBMs are a group of rare myopathies with a genetic origin that share some histopathological characteristics such as inclusions and tubulofilamentous structures with sporadic IBM but lack cellular infiltrates on muscle biopsies. They include IBM1 (desmin-related myopathy), a form of myofibrillar myopathy caused by mutations in the *Desmin* gene on chromosome 2q35; Japanese distal myopathy with rimmed vacuoles or Nonaka myopathy, allelic to IBM2, with a similar clinical and pathological picture with quadriceps sparing and mutations in the UDP-*N*-acetylglucosamine-2-epimerase/*N*-acetylmannosamine kinase (*GNE*) gene mapped on chromosome 9p13-p12; IBM3 characterized by joint contractures, external opthalmoplegia, and proximal weakness resulting from mutations in the gene encoding myosin heavy chain IIa (MYHC2A or MYH2) on chromosome 17p13.1; and inclusion body myopathy with Paget disease and frontotemporal dementia, caused by missense mutations in the valosin-containing protein (*VCP*) gene on chromosome 9p13.3-p12. ZASPopathy, another subtype of myofibrillar myopathy, is a late-onset distal myopathy with its responsible gene located on chromosome 10q22.2-q23.3 and coding for Z-band alternatively spliced PDZ-motif containing protein (*ZASP*). It is a hereditary myopathy with overlap. These hereditary myopathies are not considered inflammatory muscle disorders or myositis. Most are discussed in Chap. 20 (myofibrillar myopathies) and Chap. 21 (distal myopathies).

The pathophysiology in IBM is still unknown. Histopathological features based on muscle biopsy findings suggest the presence of inflammation and degeneration. Which of these processes is the primary etiological factor is a matter of debate.

26.2.3 Histopathology

Muscle biopsy shows atrophic fibers and inflammatory and degenerative changes.

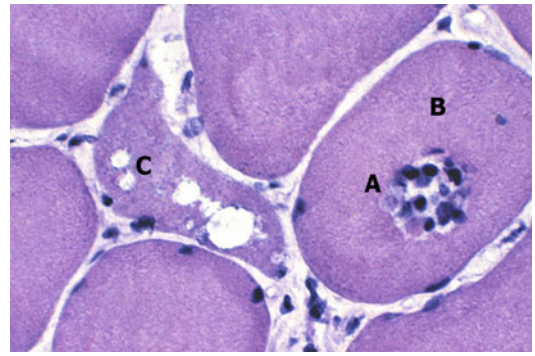

Fig. 26.1 Muscle biopsy of a patient with sporadic inclusion body myositis. This biopsy shows mononuclear cell invasion (*A*) of a non-necrotic muscle fiber (*B*) and rimmed vacuoles. (H&E)

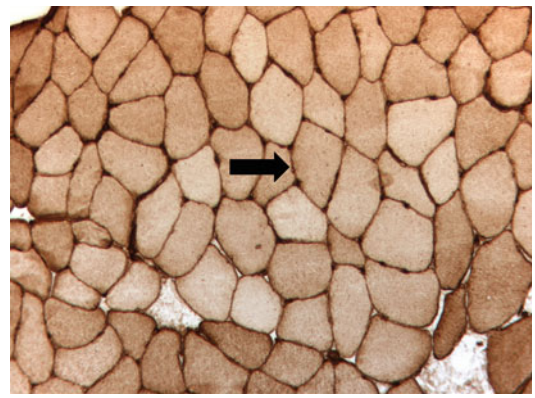

Fig. 26.2 Pathological sarcolemmal major histocompatibility complex type I (MHC-I) expression (*arrow*) in a muscle biopsy of a patient with sporadic inclusion body myositis. The muscle fiber membrane is darkly colored, as are capillaries. Normally, capillaries stain darker than the membrane (see Fig. 26.3)

Inflammation is mainly located endomysially and consists of mononuclear cells, including T lymphocytes and to a lesser extent B cells and macrophages. CD8-positive cytotoxic T cells invade non-necrotic muscle fibers (Fig. 26.1). Similar to PM, pathological expression of major histocompatibility complex type I (MHC-I) on the sarcolemma can be observed in sporadic IBM (Figs. 26.2 and 26.3). Degenerative changes include the "rimmed vacuoles," which are seen with hematoxylin-eosin (H&E) or Gomori trichrome staining of fresh frozen muscle biopsy specimens. The vacuoles are filled with

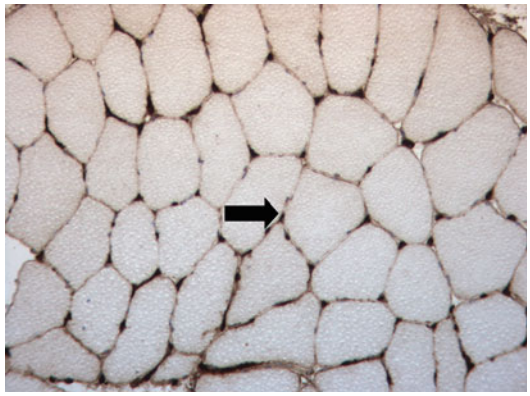

Fig. 26.3 Negative MHC-I stain to compare with Fig. 26.2. It was obtained using the same microscope and similar light exposure. Capillaries (*arrow*) normally take up more stain than does the muscle fiber membrane, as can be seen here

amorphous material. Eosinophilic inclusions are rarely seen in the nucleus or cytoplasm, and their presence is not mandatory for the diagnosis of IBM. On electron microscopy, tubulofilamentous structures can be visualized in the cytoplasm of 15- to 21-nm diameter, as well as in the nucleus or near the rimmed vacuoles. Degenerative proteins such as β-amyloid and hyperphosphorylated tau accumulate near these tubulofilamentous structures.

26.2.4 Clinical Presentation

Inclusion body myositis is the most frequent acquired myopathy after 50 years of age. The first symptoms of weakness usually start after age 40 years (average 60 years). The male to female ratio is 2:1. The most frequent first clinical manifestation is weakness of the quadriceps muscles, leading to falls onto the knees and difficulty rising from a chair. Other muscle groups that are frequently affected at clinical onset are the finger flexors and pharyngeal muscles, the latter leading to dysphagia with obstructive symptoms such as inability to swallow and aspiration. Weakness of the finger flexors results in the inability to make a tight fist in which the fingernails are no longer visible (Fig. 26.4). The clinical involvement pattern is often asymmetrical. As the disease progresses over time, preferential muscle involvement

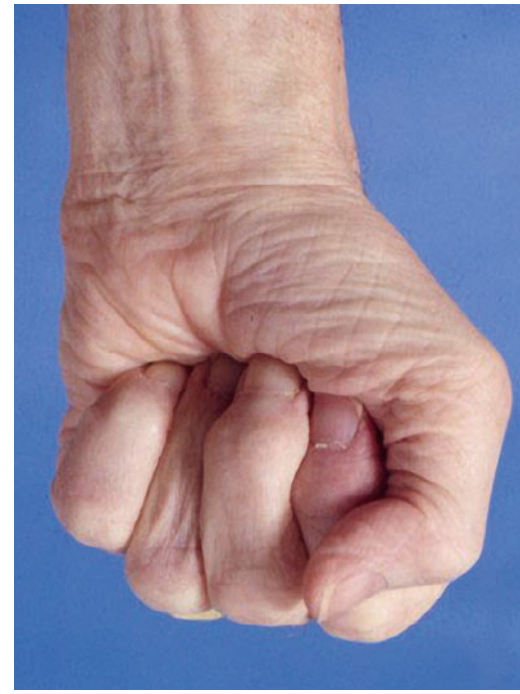

Fig. 26.4 Finger flexor weakness in inclusion body myositis. The patient is unable to conceal the fingernails when making a fist

continues, with ventral muscles of the legs and arms being most weakened. At the end stage, all muscles of the lower leg are experiencing weakness. Pain and malaise are usually not associated with IBM. IBM is slowly progressive and leads to major disabilities at the end-stage of the disease.

The serum creatine kinase (CK) activity is usually normal to mildly elevated (two to five times the upper limit). About half of IBM patients show reactivity toward a not yet specified 43-kDa muscle protein autoantigen.

26.2.5 Imaging Findings

26.2.5.1 Magnetic Resonance Imaging and Computed Tomography

The main findings visualized on magnetic resonance imaging (MRI) are fatty infiltration, inflammation, and atrophy of muscles. Fatty infiltration is the most common abnormality, and computed tomography (CT) can also be used to demonstrate it. The asymmetrical clinical

manifestations are reflected in an asymmetrical involvement pattern on CT and MRI. The degree of fatty infiltration correlates with the duration of symptoms, the severity of weakness, and the functional disabilities. The extent of fatty infiltration is much greater than that seen in polymyositis. Changes suggestive of muscle edema on fat-suppressed T2-weighted MRI sequences—which are considered to indicate inflammation—are seen less frequently and do not correlate with disease duration or with severity of the disease.

The deep finger flexor is the first muscle in the forearm that shows signs of fatty degeneration. In the case that the deep finger flexor muscle is unaffected, the other forearm muscles are not likely to show abnormalities. Signs of discrete fatty infiltration of the deep finger flexors on MRI or CT may be clinically silent and can precede clinical symptoms of weakness (Fig. 26.5).

Fatty infiltration in the upper arm has no distinct involvement pattern. The shoulder girdle is less frequently affected by fatty degeneration than the upper arm. The subscapular muscle is most frequently affected in the shoulder girdle.

The legs are more commonly and more severely affected than the upper extremities or the pelvis. Overall, the lower legs usually have relatively less preserved muscle bulk than the upper legs. Anterior thigh compartment muscles are more affected than the posterior compartment muscles. The quadriceps femoris muscle frequently exhibits severe fatty degeneration, with a relative sparing of the rectus femoris muscle. Complete sparing of the entire quadriceps muscle is rather rare (Fig. 26.6). In general, all muscles of the lower legs can be involved, in particular the medial head of the gastrocnemius muscle, although it may not appear to be the clinically most involved lower leg muscle. The anterior compartment muscles are usually those most involved clinically. The lateral head is often relatively spared (Fig. 26.7). Atrophy is a common finding and shows a pattern similar to that of fatty infiltration. A combination of severe fatty infiltration of the deep finger flexors and the medial head of the gastrocnemius muscle, with sparing of the rectus femoris muscle, in an elderly

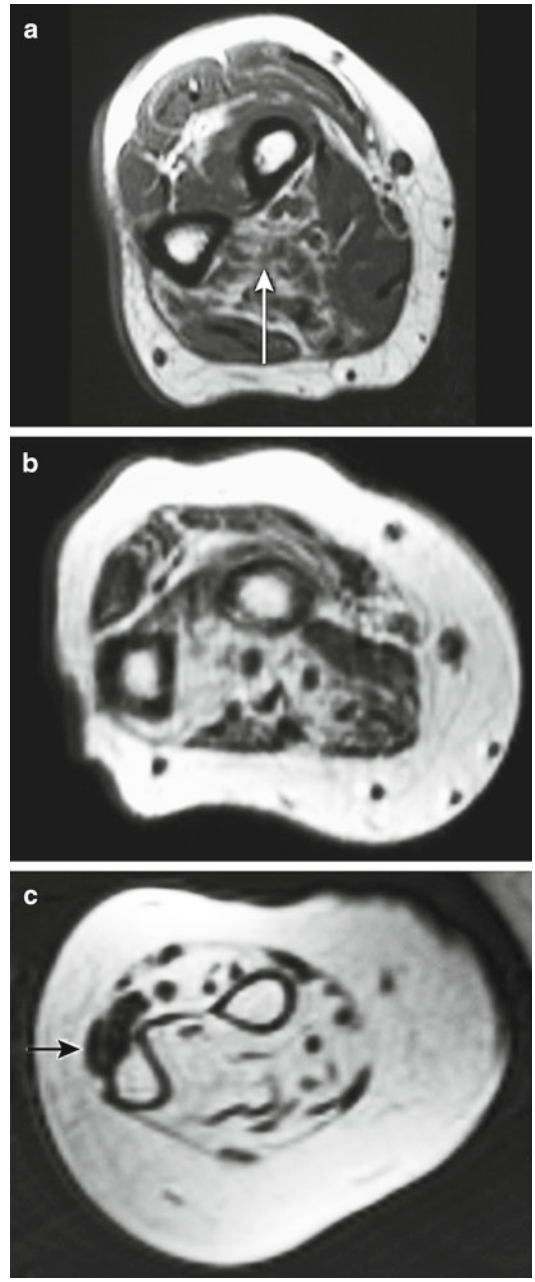

Fig. 26.5 Axial T1-weighted magnetic resonance imaging (MRI) scans of the right forearms of patients with inclusion body myositis. (**a**) Mild and isolated fatty infiltration of the deep finger flexor (*white arrow*). (**b**) Moderate fatty infiltration of the flexors (especially the deep finger flexors), in contrast to the less severely infiltrated extensor compartment. (**c**) Severely fatty infiltrated muscles, with relative sparing of the extensor carpi ulnaris (*black arrow*) muscle

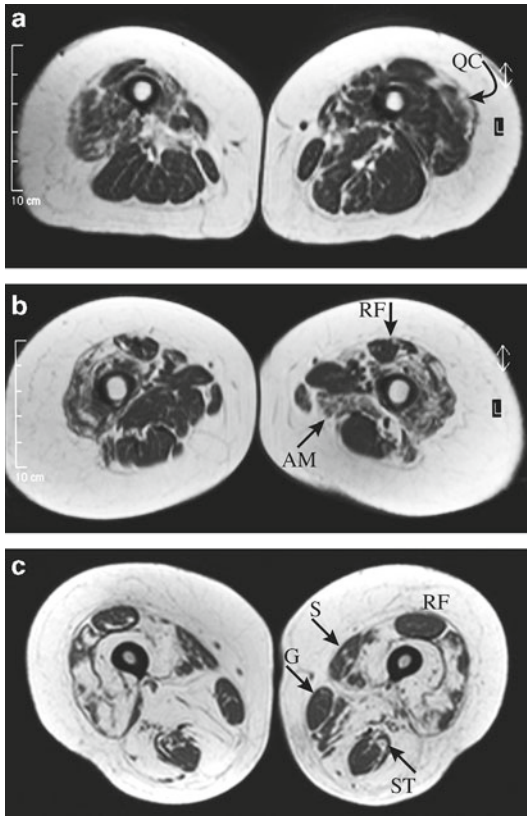

Fig. 26.6 Axial T1-weighted MRI scans of the thighs of patients with inclusion body myositis. (**a**) Mild, asymmetrical fatty infiltration of the quadriceps muscles (*QC*), with relative sparing of the rectus femoris muscle. (**b**) Moderate fatty infiltration of the quadriceps muscles with relative sparing of the rectus femoris muscle (*RF*). The left adductor magnus muscle (*AM*) is more severely affected than the right adductor magnus. (**c**) Severe fatty infiltration of almost all muscle groups with relative sparing of the rectus femoris (*RF*), semitendinosus (*ST*), sartorius (*S*), and gracilis (*G*) muscles

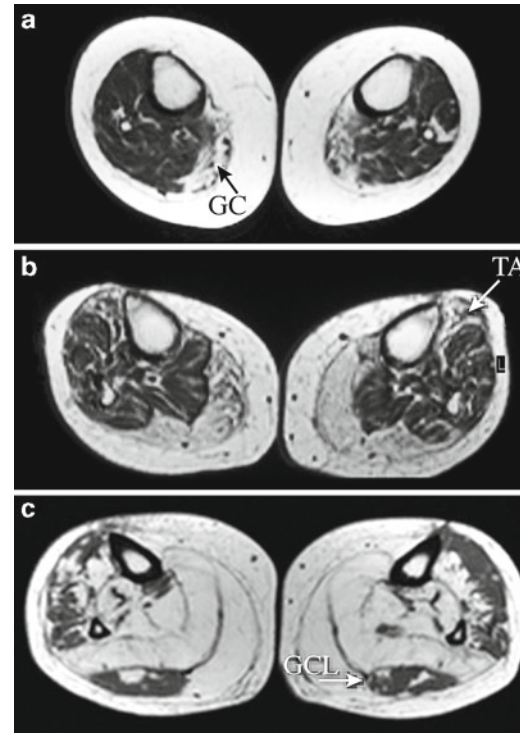

Fig. 26.7 Axial T1-weighted MRI scans of the lower legs of patients with inclusion body myositis. (**a**) Isolated fatty infiltration of the gastrocnemius muscles (*GC*). (**b**) More pronounced fatty infiltration of the gastrocnemius muscles and anterior tibial muscles (*TA*). (**c**) Severe, relatively symmetrical fatty infiltration of almost all posterior compartment muscles, with relative sparing of the lateral head of the gastrocnemius muscle (*GCL*). The anterolateral compartment is affected to a lesser degree

patient with no family history should prompt for a search for IBM. Hyperintensity on fat-suppressed T2-weighted images indicating edema suggestive of inflammation is randomly present. It is most frequently found in the extensor carpi ulnaris muscle in the forearms and the dorsal muscles of the lower leg (Fig. 26.8). In a series of 32 patients, inflammation was absent in the gluteal, obturatorius, and pectineus muscles and therefore should be regarded as highly uncommon in sporadic IBM.

26.2.5.2 Swallowing Video-fluoroscopy

Dysphagia, as described above, is common in IBM and can be visualized by video-fluoroscopy of the patient swallowing. Typically, repetitive swallowing, residues in the vallecular and piriform sinuses, and cricopharyngeal dysfunction (Fig. 26.9) can be observed. Diverticula and frank aspiration are seen less frequently.

26.2.6 Therapy

There is no effective treatment to slow progression of the disease. Immunosuppressive and immunomodulating therapy, including corticosteroids,

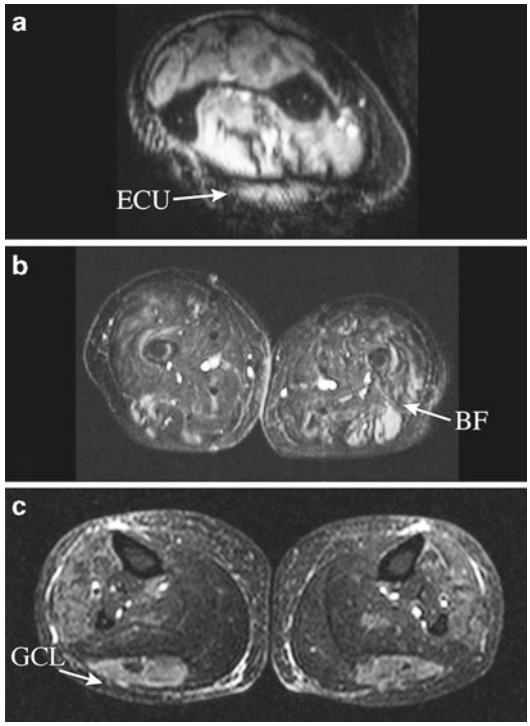

Fig. 26.8 Axial fat-suppressed T2-weighted MRI (short tau inversion recovery, STIR) scans of patients with inclusion body myositis. (**a**) Edema in the right extensor carpi ulnaris muscle (*ECU*). (**b**) Edema in the biceps femoris muscle (*BF*). (**c**) Edema in the lateral head of the gastrocnemius muscle (*GCL*). Corresponding T1-weighted images are shown in Fig. 26.7c

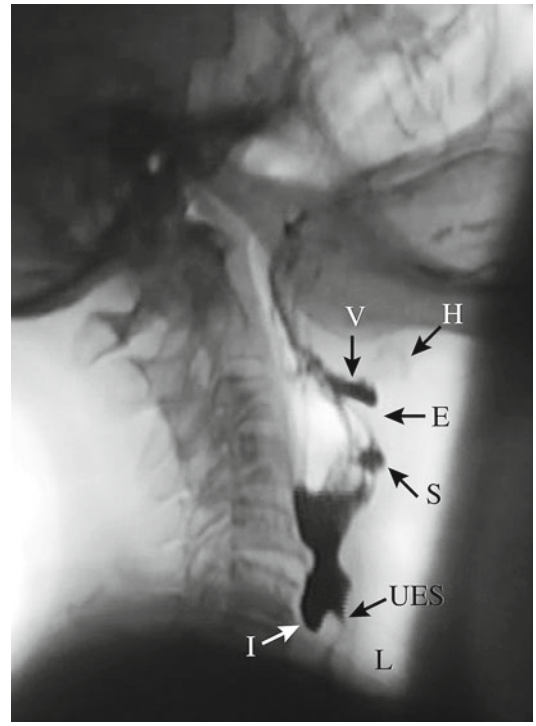

Fig. 26.9 Video-fluoroscopy of swallowing radiopaque fluid in upright position. Note the indentation (*I*) of the cricopharyngeal muscle near the upper esophageal sphincter (*UES*) and residues in the vallecular (*V*) and piriform (*S*) sinuses. Also shown are the hyoid bone (*H*), epiglottis (*E*), and larynx (*L*)

azathioprine, methotrexate, intravenous immunoglobulins, and β-interferon have not been shown to be effective. Obstructive dysphagia can sometimes be treated by cricopharyngeal myotomy or botulinum toxin injections. A percutaneous endoscopic gastrostomy tube is sometimes necessary in others to maintain nutrition and to prevent aspiration of oral intake.

26.2.7 Differential Diagnosis

Differentiation from polymyositis (PM) (see Sect. 26.3) is based on clinical information—presence or absence of pain and malaise, symmetrical versus asymmetrical weakness, waddling gait versus nonwaddling gait, high versus low serum CK activity—and histopathological criteria. However, the histopathological findings in IBM, particularly early in the disease course, are not always conclusive according to current diagnostic criteria. Muscle MRI can be helpful in the distinction as it shows more fatty infiltration in sporadic IBM than in PM. Furthermore, the combination of fatty infiltration of the flexor digitorum profundus and medial gastrocnemius muscles, with relative sparing of the rectus femoris muscle, may be highly indicative of sporadic IBM.

Compared to sporadic IBM, motor neuron disease (see Sect. 29.3) is a rapidly progressive disorder often presenting also with muscle cramps and fasciculations. The distribution of weakness is different, finger extensors are usually more affected than finger flexors—in contrast to the usual pattern in sporadic IBM. Welander myopathy (see Sect. 21.2.2), an autosomal dominantly inherited late-onset myopathy, presents with sim-

ilar predominantly finger extensor weakness. Miyoshi myopathy (see Sect. 19.3) has early adult onset in the distal lower leg. It is caused by mutations in the dysferlin gene. Inflammation in muscle tissue may also be evident both histopathologically and on MRI. Markedly elevated serum CK activity, often 10–100 times normal, is usually present. Multifocal motor neuropathy presents with asymmetrical selective muscle weakness, often initially affecting the finger extensors. In contrast to sporadic IBM, electromyography often shows conduction blocks.

Inflammatory Myopathies: Sporadic Inclusion Body Myositis

Key Points

- IBM is the most frequent acquired myopathy of the elderly.
- Fatty infiltration is far more extensive than inflammation on muscle MRI.
- Fatty infiltration is present proximally as well as distally, and asymmetry is common.
- Signs of fatty degeneration are seen more frequently in anterior thigh muscles (with relative sparing of the rectus femoris) than in posterior thigh compartment (hamstring) muscles.
- Deep finger flexors are the first muscles in the forearm to be involved.
- A combination of severe fatty infiltration of the medial head of the gastrocnemius muscle, with relative sparing of the rectus femoris, and affliction of the deep finger flexors are indicative of IBM.

Suggestions for Further Reading

Cox FM, Verschuuren JJ, Verbist BM, et al. Detecting dysphagia in inclusion body myositis. J Neurol. 2009;256:2009–13.

Cox FM, Reijnierse M, van Rijswijk CS, et al. Magnetic resonance imaging of skeletal muscles in sporadic inclusion body myositis. Rheumatology (Oxford). 2011;50:1153–61.

Degardin A, Morillon D, Lacour A, et al. Morphologic imaging in muscular dystrophies and inflammatory myopathies. Skeletal Radiol. 2010;7:1219–27.

Dion E, Cherin P, Payan C, et al. Magnetic resonance imaging criteria for distinguishing between inclusion body myositis and polymyositis. J Rheumatol. 2002;29:1897–1906.

Needham M, Mastaglia FL. Inclusion body myositis: current pathogenetic concepts and diagnostic and therapeutic approaches. Lancet Neurol. 2007; 6:620–31.

Phillips BA, Cala LA, Thickbroom GW, et al. Patterns of muscle involvement in inclusion body myositis: clinical and magnetic resonance imaging study. Muscle Nerve. 2001;24:1526–34.

Sekul EA, Chow C, Dalakas MC. Magnetic resonance imaging of the forearm as a diagnostic aid in patients with sporadic inclusion body myositis. Neurology. 1997;48:863–66.

26.3 Polymyositis

26.3.1 Synonyms, Abbreviations

PM

26.3.2 Genetics and Pathophysiology

Polymyositis (PM) is an inflammatory myopathy with presumed autoimmune pathogenesis. The current pathophysiological concept is based on CD8-positive cytotoxic T cells that attack non-necrotic muscle fibers. The presence of pro-inflammatory cytokines and chemokines and overexpression of MHC-I on the surface of muscle fibers seem to play a key role in the formation of infiltrates of CD8-positive T cells, which persist over time. The antigenic target of the autoimmune attack is still unknown. Viruses are a potential trigger of the immune response, but auto-antigens expressed on the sarcolemma of the muscle fiber itself may be involved. Myositis-specific antibodies (MSAs) (e.g., anti-Jo antibodies) directed against histidyl-tRNA synthetase and antibodies against anti-aminoacyl-tRNA synthetases (ARS) have been found. The latter are rare and include anti-PL-7, anti-PL-12, anti-EJ, anti-OJ, anti-KS, anti-ZO, and anti-tyrosyl-tRNA synthetase antibodies. Patients usually do not have more than one of these anti-synthetase

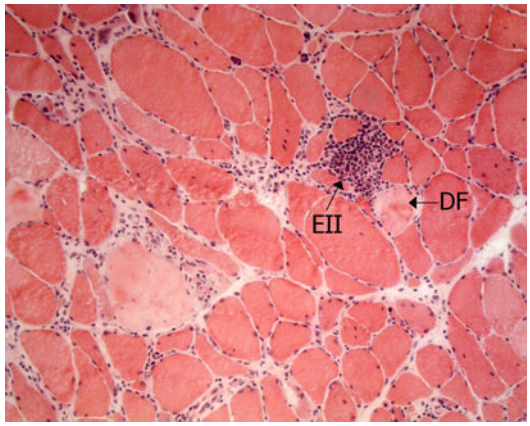

Fig. 26.10 Muscle biopsy of a patient with polymyositis. Note the variation in fiber size, degenerating muscle fibers (*DF*), and endomysial mononuclear inflammatory infiltrates (*EII*). (H&E)

antibodies. MSAs are present in around 40 % of PM patients. Anti Jo-1 is associated with the antisynthetase syndrome, a combination of interstitial lung disease, myositis, Raynaud phenomenon, and nonerosive arthritis. Patients with anti-SRP antibodies are clinically more diverse. They have a worse treatment effect and are associated with higher mortality. This antibody has lately become more frequently associated with necrotizing myopathy.

Polymyositis occurs as an isolated entity or in association with a connective tissue disease (CTD) or cancer. A retrospective study showed that fewer than 2 % of patients with an inflammatory myopathy had the histopathological features of definitive PM. Most patients have a histopathologically unspecified myositis, partly in conjunction with a CTD. PM is therefore considered an overdiagnosed entity. PM usually occurs sporadically, although familial clustering can occur, suggesting a genetic predisposition. PM is associated with the 8.1 HLA haplotype.

26.3.3 Histopathology

Polymyositis is histopathologically characterized by the presence of predominantly endomysial mononuclear infiltrates (Fig. 26.10) penetrating non-necrotic muscle fibers that express MHC-I molecules on the sarcolemma. These mononuclear infiltrates consist of mainly CD8-positive T cells, macrophages, and to a lesser degree B cells.

26.3.4 Clinical Presentation

Polymyositis presents with a subacute (weeks to months) onset of symmetrical weakness of proximal muscles, which can be accompanied by muscle pain, tenderness, fever, and nondestructive arthritis. It usually presents after the second decade of life. Onset before the age of 20 years should prompt a search for an alternative diagnosis, such as a muscular dystrophy with secondary inflammatory infiltrates (e.g., dysferlinopathy or facioscapulohumeral dystrophy). In about one-third of patients, PM is associated with a CTD according to the literature, but these groups most likely include patients with unspecified myositis. PM patients may have a higher chance of developing malignancy, but this is debatable. Accurate data are lacking because of the ill-defined entity of PM. If left untreated, the disease is progressive, leading to severe disability. Self-limiting disease has been reported in untreated patients. Often, however, it gives rise to severe chronic disability. MSA levels correlate with disease severity. Serum CK activity can be elevated to as high as 50 times the normal limit.

26.3.5 Imaging Findings

26.3.5.1 Magnetic Resonance Imaging

There are quite a few MRI studies on PM, especially those imaging the legs. However, a substantial number of these studies used the Bohan and Peter criteria and thus may have included IBM patients in their description of muscle involvement. Studies in which IBM patients are excluded show that inflammation and fatty infiltration are the most common findings in PM. Inflammation is far more common than fatty infiltration. Therefore, T2-weighted MRI with fat suppression provides the most useful sequences for detecting abnormalities in PM. As MRI findings in PM and dermatomyositis are

similar, we refer the reader to the figures on dermatomyositis later in the Sect. 26.4.5.

Inflammation and fatty infiltration are both proximally and symmetrically located in the upper and lower extremities. Inflammation is frequently present in the vastus muscles, medial head of the gastrocnemius, and the tibialis anterior muscle. The gracilis muscles, extensor digitorum, tibial posterior muscle, flexor digitorum, flexor hallucis longus, and peroneal muscles are least affected. In contrast to IBM, there can be isolated inflammation in the absence of fatty infiltration, suggesting that inflammation seems to precede fatty infiltration.

The degree of fatty infiltration in the anterior part of the lower extremity is comparable to that in the posterior part. Preferentially, fatty infiltration can be observed in the vastus muscles, hamstrings, and gastrocnemius muscles. Relatively spared from fatty infiltration are the gracilis, rectus femoris, posterior tibial, and soleus muscles. These descriptions of fatty infiltration, however, should be interpreted cautiously, as wrongly included IBM cases may have corrupted these data.

Inflammatory changes have been reported to normalize after treatment, without a clinical correlation. However, this subject has not been investigated in large series.

For a final diagnosis, muscle biopsy is still the gold standard. However, it is not uncommon that a first muscle biopsy shows nonspecific changes, without the required inflammatory changes. Pathological sarcolemmal expression of MHC-I molecules may facilitate the diagnosis of PM. Weakness—in contrast to fatty infiltration—does not correlate with inflammatory changes on MRI. Sampling error may occur even in weak muscles because of the patchy distribution of the inflammation. Some authors advise muscle MRI scanning prior to biopsy to identify muscles that show inflammation and thus increase the yield of the muscle biopsy.

26.3.5.2 Ultrasonography

Although MRI is probably more sensitive for detecting inflammation than ultrasonography (US) because more muscles are investigated at once, and MRI imaging can better visualize the global pattern of muscle involvement, US can also be used to detect inflammation in muscles (see Chap. 2). Features in PM include increased muscle echo intensity and altered architecture of the fasciae/septa. Contrast-enhanced US is a way to measure blood flow in tissues. One study showed significantly higher blood flow velocity and blood volume in patients with PM and DM than in patients with comparable clinical characteristics who had a different myopathy or motor neuron disease.

26.3.6 Therapy

The initial goal of treatment is to improve muscle strength. Based on empirical data, high-dose prednisone for 6–8 weeks and then in tapering doses for approximately 1 year is the first-line treatment strategy. Alternatively, cycles of high-dose pulsed dexamethasone for 6 months can be given. Only 10 % of PM patients have an immediate remission after treatment with prednisone. In case of treatment failure, relapse, or unacceptable side effects, other immunosuppressive agents (e.g., azathioprine, methotrexate, cyclosporin A, cyclophosphamide) can be added. Treatment failure may be explained by a wrong diagnosis (see Differential Diagnosis, below), possibly due to a concurrent neoplasm or inadequate immunosuppressive treatment.

26.3.7 Differential Diagnosis

The differential diagnosis of PM includes DM and IBM. Chronic or treatment-resistant PM may have a clinical resemblance to sporadic IBM, apart from the histopathological overlap. It remains questionable whether these patients should be regarded as having sporadic IBM. DM is clinically similar but is distinguished by its cutaneous manifestations and different histopathology (discussed later in the chapter). Based on histopathology, muscular dystrophies such as the limb-girdle muscular dystrophies (see Chap. 19), facioscapulohumeral dystrophy (see Chap. 23),

and dysferlinopathy (see Sect. 19.3)—which may show inflammatory changes suggestive of PM at first sight in the muscle biopsy—should be considered in the differential diagnosis. Pathological sarcolemmal MHC-I expression in the muscle biopsy may be helpful for discriminating between inflammatory myopathies and dystrophies. Endocrine, toxic, and infectious myopathies should also be considered in the differential diagnosis as they may have a clinical resemblance with subacute onset. Hypothyroid myopathy, for example, can resemble PM clinically. Infectious mimicking myopathies include human immunodeficiency virus (HIV)-related myopathy. Myopathies caused by toxins include corticosteroids, statins, antimalarials, and antipsychotics among others. Statins can cause rhabdomyolysis and nowadays are often linked to necrotizing myopathy (see Chap. 27). Autoimmune necrotizing myopathy is increasingly recognized as a separate disorder, different from PM.

Diseases of the neuromuscular junction, especially Lambert–Eaton myasthenic syndrome, can present with subacute proximal leg muscle weakness. Electrophysiological examination and the presence of antibodies against P/Q calcium channels lead to the correct diagnosis.

Inflammatory Myopathies: Polymyositis

Key Points

- Histopathologically definitive polymyositis is a rare disorder.
- MRI and ultrasound are of value in confirming the presence of inflammation.
- Abnormalities are proximal and symmetrical, with no preference for the anterior or posterior part of the upper leg.
- Inflammation seen on MRI scans can resolve with immunosuppressive treatment.

Suggestions for Further Reading

Bronner IM, van der Meulen MF, de VM, et al. Long-term outcome in polymyositis and dermatomyositis. Ann Rheum Dis. 2006;65:1456–61.

Dalakas MC. Inflammatory muscle diseases: a critical review on pathogenesis and therapies. Curr Opin Pharmacol. 2010;10:346–52.

Dion E, Cherin P, Payan C, et al. Magnetic resonance imaging criteria for distinguishing between inclusion body myositis and polymyositis. J Rheumatol. 2002;29:1897–1906.

Garcia J. MRI in inflammatory myopathies. Skeletal Radiol. 2000;29:425–38.

van der Meulen MF, Bronner IM, Hoogendijk JE, et al. Polymyositis: an overdiagnosed entity. Neurology. 2003;61:316–21.

van der Pas J, Hengstman GJ, ter Laak, HJ, et al. Diagnostic value of MHC class I staining in idiopathic inflammatory myopathies. J Neurol Neurosurg Psychiatry. 2004;75:136–9.

26.4 Dermatomyositis

26.4.1 Synonyms, Abbreviations

DM

26.4.2 Genetics and Pathophysiology

The pathogenetic molecular mechanisms leading to the initiation of autoimmunity in dermatomyositis (DM) remain unclear. DM is thought to be a complement-mediated microangiopathy. There is an association with cancer and with MSAs. Regenerating muscle fibers express high levels of MSAs, in contrast to normal muscle cells. MSAs are expressed in cancerous tissue as well. Possibly, an anticancer response not only targeting cancer cells but regenerating myofibers as well leads to an autoimmune attack against muscle tissue. The most common MSAs are anti-Mi-2 autoantibodies and anti-Jo-1 (associated with the antisynthetase syndrome), which are found in 25–30 % of DM patients. A more recently discovered autoantibody, anti-155/140, present in 13–21 % of DM patients, is associated with a markedly

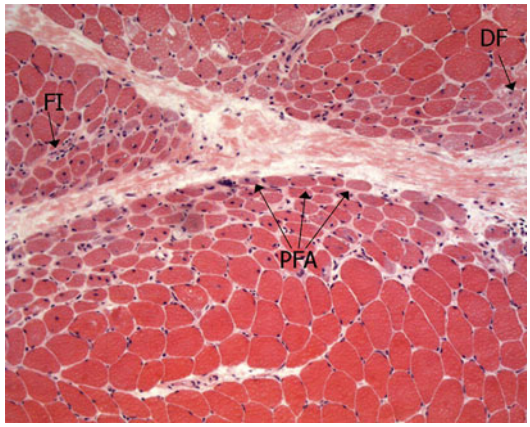

Fig. 26.11 Muscle biopsy of a patient with dermatomyositis. This biopsy shows perifascicular atrophy (*PFA*) with degenerating myofibers (*DF*) and scarce focal inflammation (*FI*). (H&E)

high risk of developing a malignancy. Melanoma differentiation-associated gene 5 is another MSA in DM patients, associated with only mild inflammation in the biopsy. DM is also associated with the 8.1 ancestral HLA haplotype.

26.4.3 Histopathology

Muscle biopsy may show a perifascicular distribution of atrophic, degenerating, and regenerating myofibers, especially in late stages of the disease (Fig. 26.11). The perifascicular location is probably due to destruction of capillaries in this region caused by a pathological deposition of immune complexes, such as membrane attack complex (MAC) of complement C5b-9. B cells are the predominant inflammatory cells found, together with plasmacytoid dendritic cells. They are part of the innate immune system, which plays an important role in antiviral and antitumor immune response. Skin biopsies reveal a cell-poor vacuolar interface dermatitis, where the inflammatory cells are located at the dermoepidermal junction as well as along vessel walls of the dermis. Because the immune response seen in muscle and skin biopsy specimens seems to be concentrated on the microvasculature, it is thought that capillaries are the primary target of the immune reaction in DM.

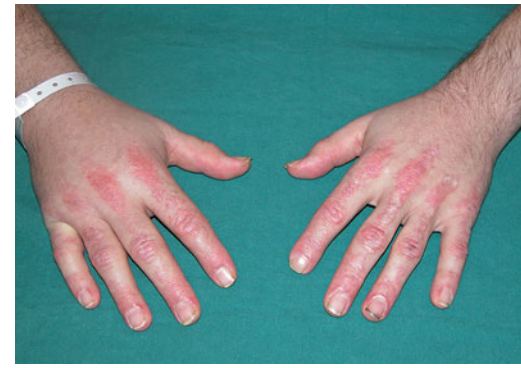

Fig. 26.12 Gottron's sign and papules in a patient with dermatomyositis

26.4.4 Clinical Presentation

The classic clinical presentation of DM is a subacute onset (weeks to months) of proximal and symmetrical muscle weakness. The first clinical manifestation can occur at any age, but peak incidence lies between 30 and 50 years of age. Women are affected twice as much as men. Muscle pain, especially exercise-induced pain, may be present. Characteristic for DM are the heliotrope rash: purplish discoloration around the eyes, sometimes with periorbital edema. Also characteristic is Gottron's sign, an erythematous or violet-colored symmetrical rash over the extensor surfaces of the metacarpophalangeal and interphalangeal joints, elbows, knees, and medial maleoli. This rash can evolve into a scaly eruption, called Gottron's papules (Fig. 26.12). Other characteristic skin abnormalities are a symmetrical rash in the neck area (the "shawl sign"); a rash on the cheeks, shoulders, back, or dorsal part of the extremities that is often aggravated by exposure to ultraviolet light; and poikiloderma atrophicans vasculare. Compatible other features are periungual erythema, skin ulcerations, lipodystrophy, alopecia, acanthosis nigrans, mechanics' hands, and livedo reticularis. The skin abnormalities may precede, occur in combination with, or appear after muscle involvement.

Dermatomyositis sine myositis, or amyopathic dermatomyositis, refers to a condition that shows the typical cutaneous manifestations of DM but no evidence of muscle weakness. However, when

these patients are followed for up to 5 years, about 20 % of them are found to have developed muscle weakness. Patients who have muscle involvement based on evaluation of a muscle biopsy, electromyography, or MRI, but who have no apparent muscle weakness, are usually diagnosed as having hypomyopathic dermatomyositis.

Patients with DM have a higher risk of developing cancer compared to the general population, especially adenocarcinoma of the lung, colon, or rectum as well as ovarian and breast cancer. The overall risk of developing an associated cancer is highest during the first 3 years after the diagnosis, with a trend toward a decreased risk over time. Cancer can precede, occur simultaneously with, or appear after the diagnosis of DM. It is recommended that DM patients be screened for cancer at diagnosis and yearly thereafter for at least 3 years. Interstitial lung fibrosis and in rare cases cardiomyositis are also associated with DM.

In adults, the serum CK is slightly to moderately elevated (<10 times the upper limit of normal in 20–90 % of patients).

26.4.5 Imaging Findings

26.4.5.1 Magnetic Resonance Imaging

The published data on imaging findings in DM are limited. In general, MRI findings for DM are comparable to those found for PM. The most frequent abnormalities are areas with high signal intensities on fat-suppressed T2-weighted images, indicating edema suggestive of inflammation. These changes tend to be located proximally and are symmetrical (Figs. 26.13 and 26.14). Particularly, all four heads of the quadriceps femoris and the anterior part of the lower legs are involved. The thigh adductors, short head of the biceps femoris, pectineus, obturatorius, gracilis, soleus, and lateral head of the gastrocnemius are relatively spared. The inflammatory changes on MRI can be diffuse or focal. In the latter case, changes can be missed when only certain parts of the body are examined. Muscle calcification is rare in adults but more common after juvenile onset.

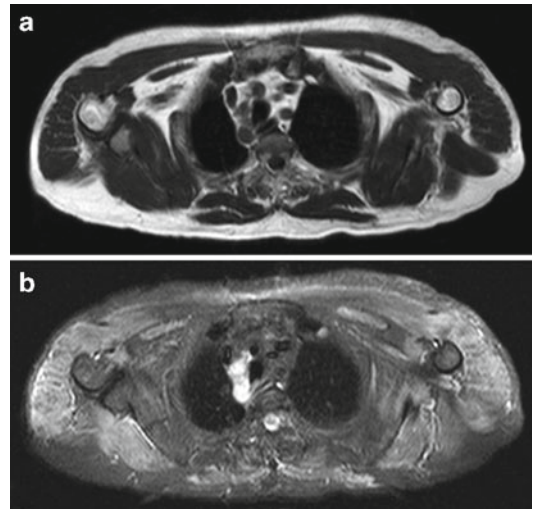

Fig. 26.13 Patient with dermatomyositis who complained of malaise, pain, and weakness lasting 7 weeks. (**a**) Axial T1-weighted MRI scans of the shoulder girdle show no signs of fatty infiltration. (**b**) Fat-suppressed T2-weighted images of the shoulder girdle show diffuse, symmetrical edematous abnormalities of all skeletal muscle groups including the pectoral muscles

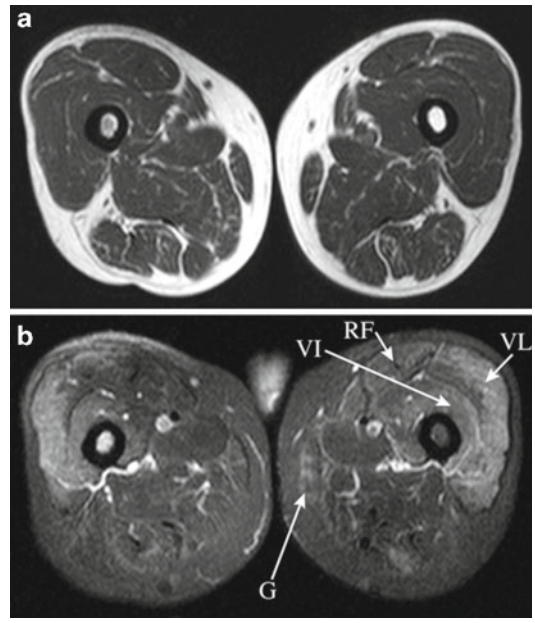

Fig. 26.14 Same patient as in Fig 26.13 with dermatomyositis. (**a**) Axial T1-weighted MRI scans of the upper leg show no signs of fatty infiltration. (**b**) Fat-suppressed T2-weighted images of the upper leg with more-or-less symmetrical edematous changes, compatible with inflammation, in the rectus femoris (*RF*), vastus intermedius (*VI*), vastus lateralis (*VL*), and gracilis (*G*) muscles

26.4.6 Therapy

Dermatomyositis can be treated with immunosuppressive agents such as corticosteroids. Immunosuppressive therapy should not always be the only therapeutic approach. As DM patients are at significant risk of having or developing a neoplasm, especially during the first 3 years after diagnosis, screening for cancer is mandatory. Such screening includes obtaining a thorough medical history, physical examination (including breast examination and rectal palpation), and laboratory testing. Age-appropriate cancer tests including CT of chest and abdomen, colonoscopy, and mammography are part of the screening. If DM is part of a paraneoplastic syndrome, surgical removal or pharmacological treatment of the primary neoplasm can result in disappearance of the clinical symptoms.

26.4.7 Differential Diagnosis

The differential diagnosis of DM includes PM (see Sect. 26.3) and IBM (see Sect. 26.2). The main clinical difference between PM/IBM and DM is the presence or absence of specific skin abnormalities. Also, the muscle biopsy shows discriminatory abnormalities, such as the mainly endomysial infiltrates in PM and IBM versus the mainly perimysial and perivascular infiltrates in DM. Systemic lupus erythematosus (SLE) may be difficult to discriminate on dermatological grounds. A skin biopsy can help differentiate between DM and SLE as the absence of immunoglobulin depositions at the dermoepidermal junctions makes SLE unlikely (although not impossible).

As for PM, other myopathies should also be considered, including muscular dystrophies and endocrine, toxic, and infectious myopathies.

Inflammatory Myopathies: Dermatomyositis

Key Points

- Dermatomyositis presents with proximal muscle weakness and characteristic cutaneous manifestations.
- Dermatomyositis is associated with malignancies, so screening for cancer is obligatory.
- Inflammation is the abnormality most commonly seen on MRI, possibly with a slight preference for the anterior thigh muscles in contrast to the posterior thigh muscles.

Suggestions for Further Reading

Dalakas MC. Review: an update on inflammatory and autoimmune myopathies. Neuropathol Appl Neurobiol. 2011;37:226–42.

Fujino H, Kobayashi T, Goto I, et al. Magnetic resonance imaging of the muscles in patients with polymyositis and dermatomyositis. Muscle Nerve. 1991; 14:716–20.

Mammen AL. Dermatomyositis and polymyositis: clinical presentation, autoantibodies, and pathogenesis. Ann N Y Acad Sci. 2010;1184:134–53.

Reimers CD, Schedel H, Fleckenstein JL et al. Magnetic resonance imaging of skeletal muscles in idiopathic inflammatory myopathies of adults. J Neurol. 1994;241:306–14.

Tomasová Studynková J, Charvát F, Jarosová K, et al. The role of MRI in the assessment of polymyositis and dermatomyositis. Rheumatology (Oxford). 2007;46: 1174–79.

Zampieri S, Valente M, Adami N et al. Polymyositis, dermatomyositis and malignancy: a further intriguing link. Autoimmun Rev. 2010;9:449–53.