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].

K. E. N. Clark · D. A. Isenberg (✉)
Centre for Rheumatology, Division of Medicine, University College London, London, UK
e-mail: david.isenberg@ucl.ac.uk

R. Aggarwal, C. V. Oddis (eds.), *Managing Myositis*, https://doi.org/10.1007/978-3-030-15820-0_9

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.

References

1. Bohan A, Peter JB. Polymyositis and dermatomyositis (first of two parts). N Engl J Med. 1975;292:344–7.
2. Hervier B, Devilliers H, Stanciu R, et al. Hierarchical cluster and survival analyses of antisynthetase syndrome: phenotype and outcome are correlated with anti-tRNA synthetase antibody specificity. Autoimmun Rev. 2012;12:210–7.
3. Meyer A, Lefevre G, Bierry G, et al. In antisynthetase syndrome, ACPA are associated with severe and erosive arthritis. Medicine (Baltimore). 2015;94:e523.
4. Labrador-Horrillo M, Martinez MA, Selva-O'Callaghan A, Delgado JF, Martinez-Gomez X, Trallero-Araguas E, Rodriguez-Sanchez JL, Vilardell-Tarres M. Anti-cyclic citrullinated peptide and anti-keratin antibodies in patients with

idiopathic inflammatory myopathy. Rheumatology. 2009;48:676–9.
5. Meyer O, Charlanne H, Cherin P, Allanore Y, Coquerelle P, Grardel B, Chamot A-M, Hachulla E, Inflammation CRE. Subluxing arthropathy: an unusual manifestation of the antisynthetase syndrome. Ann Rheum Dis. 2009;68:152–3.
6. Cavagna L, Nuño L, Scirè CA, et al. Serum Jo-1 autoantibody and isolated arthritis in the antisynthetase syndrome: review of the literature and report of the experience of AENEAS Collaborative Group. Clin Rev Allergy Immunol. 2017;52:71–80.
7. Cavagna L, Nuño L, Scirè CA, et al. Clinical spectrum time course in Anti Jo-1 positive antisynthetase syndrome: results from an international retrospective multicenter study. Medicine (Baltimore). 2015;94:e1144.
8. Oddis CV, Medsger TA, Cooperstein LA. A subluxing arthropathy associated with the anti-Jo-1 antibody in polymyositis/dermatomyositis. Arthritis Rheum. 1990;33:1640–5.
9. Kaneko Y, Hanaoka H, Hirakata M, Takeuchi T, Kuwana M. Distinct arthropathies of the hands in patients with anti-aminoacyl tRNA synthetase antibodies: usefulness of autoantibody profiles in classifying patients. Rheumatology (Oxford). 2014;53:1120–4.
10. Oztürk MA, Unverdi S, Goker B, Haznedaroglu S, Tunç L. A patient with antisynthetase syndrome associated with deforming arthritis and periarticular calcinosis sine myositis. Scand J Rheumatol. 2007;36:239–41.
11. Labirua-Iturburu A, Selva-O'Callaghan A, Vincze M, Dankó K, Vencovsky J, Fisher B, Charles P, Dastmalchi M, Lundberg IE. Anti-PL-7 (anti-threonyl-tRNA synthetase) antisynthetase syndrome. Medicine (Baltimore). 2012;91:206–11.
12. Dobloug C, Garen T, Bitter H, Stjärne J, Stenseth G, Grøvle L, Sem M, Gran JT, Molberg Ø. Prevalence and clinical characteristics of adult polymyositis and dermatomyositis; data from a large and unselected Norwegian cohort. Ann Rheum Dis. 2015;74:1551–6.
13. Aggarwal R, Cassidy E, Fertig N, Koontz DC, Lucas M, Ascherman DP, Oddis CV. Patients with non-Jo-1 anti-tRNA-synthetase autoantibodies have worse survival than Jo-1 positive patients. Ann Rheum Dis. 2014;73:227–32.
14. Dugar M, Cox S, Limaye V, Blumbergs P, Roberts-Thomson PJ. Clinical heterogeneity and prognostic features of South Australian patients with anti-synthetase autoantibodies. Intern Med J. 2011;41:674–9.
15. Hamaguchi Y, Fujimoto M, Matsushita T, et al. Common and distinct clinical features in adult patients with anti-aminoacyl-tRNA synthetase antibodies: heterogeneity within the syndrome. PLoS One. 2013;8:e60442.
16. Fiorentino DF, Kuo K, Chung L, Zaba L, Li S, Casciola-Rosen L. Distinctive cutaneous and systemic features associated with antitranscriptional intermediary factor-1γ antibodies in adults with dermatomyositis. J Am Acad Dermatol. 2015;72:449–55.
17. Manfredi A, Sebastiani M, Cassone G, Pipitone N, Giuggioli D, Colaci M, Salvarani C, Ferri C. Nailfold capillaroscopic changes in dermatomyositis and polymyositis. Clin Rheumatol. 2015;34:279–84.
18. Selva-O'Callaghan A, Fonollosa-Pla V, Trallero-Araguás E, Martínez-Gómez X, Simeon-Aznar CP, Labrador-Horrillo M, Vilardell-Tarrés M. Nailfold capillary microscopy in adults with inflammatory myopathy. Semin Arthritis Rheum. 2010;39:398–404.
19. Mugii N, Hasegawa M, Matsushita T, Hamaguchi Y, Horie S, Yahata T, Inoue K, Someya F, Fujimoto M, Takehara K. Association between nail-fold capillary findings and disease activity in dermatomyositis. Rheumatology (Oxford). 2011;50:1091–8.
20. Pinal-Fernandez I, Fonollosa-Pla V, Selva-O'Callaghan A. Improvement of the nailfold capillaroscopy after immunosuppressive treatment in polymyositis. QJM. 2016;109:205–6.
21. de SFHC, Barros TBM, Levy-Neto M, Shinjo SK. Adult dermatomyositis: experience of a Brazilian tertiary care center. Rev Bras Reumatol. 2012;52:897–902.
22. De Souza FHC, Miossi R, Shinjo SK. Necrotising myopathy associated with anti-signal recognition particle (anti-SRP) antibody. Clin Exp Rheumatol. 2017;35:766.
23. Lorenzoni PJ, Scola RH, Kay CSK, Prevedello PG, Espíndola G, Werneck LC. Idiopathic inflammatory myopathies in childhood: a brief review of 27 cases. Pediatr Neurol. 2011;45:17–22.
24. Shinjo SK, Levy-Neto M. Anti-Jo-1 antisynthetase syndrome. Rev Bras Reumatol. 50:492–500.
25. Park JK, Mecoli CA, Alexanderson H, et al. Advancing the development of patient-reported outcomes for adult myositis at OMERACT 2016: An International Delphi Study. J Rheumatol. 2017:jrheum.161252.
26. Sultan SM, Ioannou Y, Moss K, Isenberg DA. Outcome in patients with idiopathic inflammatory myositis: morbidity and mortality. Rheumatology (Oxford). 2002;41:22–6.
27. Weinstein AA, Drinkard BM, Diao G, Furst G, Dale JK, Straus SE, Gerber LH. Exploratory analysis of the relationships between aerobic capacity and self-reported fatigue in patients with rheumatoid arthritis, polymyositis, and chronic fatigue syndrome. PM R. 2009;1:620–8.
28. Campbell R, Gordon P, Ward K, Reilly C, Scott DL, Rafferty GF. Nonvolitional assessment of muscle endurance in idiopathic inflammatory myopathies: there is no relationship between patient-reported fatigue and muscle fatigability. Muscle Nerve. 2014;50:401–6.
29. Butbul Aviel Y, Stremler R, Benseler SM, et al. Sleep and fatigue and the relationship to pain, disease activity and quality of life in juvenile idiopathic arthritis and juvenile dermatomyositis. Rheumatology (Oxford). 2011;50:2051–60.

30. Ramkumar S, Raghunath A, Raghunath S. Statin therapy: review of safety and potential side effects. Acta Cardiol Sin. 2016;32:631–9.
31. Zhan Q, Wang G, Liu X, et al. A multi-center retrospective study of organ involvement in adult patients with polymyositis or dermatomyositis. Zhonghua Yi Xue Za Zhi. 2014;94:43–6.
32. Elam MB, Majumdar G, Mozhui K, Gerling IC, Vera SR, Fish-Trotter H, Williams RW, Childress RD, Raghow R. Patients experiencing statin-induced myalgia exhibit a unique program of skeletal muscle gene expression following statin re-challenge. PLoS One. 2017;12:e0181308.
33. Michalska-Kasiczak M, Sahebkar A, Mikhailidis DP, et al. Analysis of vitamin D levels in patients with and without statin-associated myalgia — a systematic review and meta-analysis of 7 studies with 2420 patients. Int J Cardiol. 2015;178:111–6.
34. Taylor BA, Lorson L, White CM, Thompson PD. Low vitamin D does not predict statin associated muscle symptoms but is associated with transient increases in muscle damage and pain. Atherosclerosis. 2017;256:100–4.