Autoimmune myopathies: autoantibodies, phenotypes and pathogenesis

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Abstract | The different autoimmune myopathies—for example, dermatomyositis, polymyositis, and immune-mediated necrotizing myopathies (IMNM)—have unique muscle biopsy findings, but they also share specific clinical features, such as proximal muscle weakness and elevated serum levels of muscle enzymes. Furthermore, around 60% of patients with autoimmune myopathy have been shown to have a myositis-specific autoantibody, each of which is associated with a distinct clinical phenotype. The typical clinical presentations of the autoimmune myopathies are reviewed here, and the different myositis-specific autoantibodies, including the anti-synthetase antibodies, dermatomyositis-associated antibodies, and IMNM-associated antibodies, are discussed in detail. This Review also focuses on a newly recognized form of IMNM that is associated with statin use and the production of autoantibodies that recognize 3-hydroxy-3-methylglutaryl-coenzyme A reductase, the pharmacological target of statins. The contribution of interferon signaling to the development of dermatomyositis and the potential link between malignancies and the initiation of autoimmune myopathies are also assessed.

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Introduction

Autoimmune myopathies are a heterogeneous group of diseases, of which polymyositis and dermatomyositis are probably the best known.[1–3] These two entities share several clinical features, such as proximal muscle weakness that typically progresses over a period of weeks to months, and evidence of inflammation on muscle biopsy. Immune-mediated necrotizing myopathies (IMNMs) probably represent a distinct form of autoimmune myopathy that is not associated with the same levels of inflammatory infiltrates as polymyositis or dermatomyositis on muscle biopsy.[2–10] Inclusion body myositis (IBM) is also a disorder considered by some authors to be a member of this group of diseases.[2–11] Indeed, IBM muscle biopsies reveal inflammatory infiltrates similar to those found in polymyositis, and patients with IBM have other evidence of immune system activation.[3,11] Nevertheless, patients with IBM, unlike those with dermatomyositis, polymyositis or IMNM, have a unique pattern of weakness and lack a sustained response to immunosuppression, which is the treatment of choice for patients with these conditions.[3] Furthermore, pathological evidence suggests that IBM might actually be a myodegenerative disease that is associated with abnormal accumulation of amyloid-β[12] and/or TAR DNA-binding protein 43,[13] as seen in Alzheimer disease and amyotrophic lateral sclerosis, respectively.

Given that the primary role of the inflammatory response in IBM is currently under debate,[14,15] this Review focuses primarily on the clinical presentation and pathogenesis of adult-onset polymyositis, dermatomyositis, and IMNM. The association between distinct clinical phenotypes and autoantibodies is also reviewed. Furthermore, evidence that statins may trigger a unique form of autoimmune muscle disease is discussed, along with data highlighting the involvement of interferon (IFN) signaling and malignancies in the initiation and maintenance of specific autoimmune myopathies.

Competing interests
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Key points

- The autoimmune myopathies include dermatomyositis, polymyositis, and immune-mediated necrotizing myopathies
- Autoimmune muscle disease typically presents with subacute onset of proximal muscle weakness, elevated muscle enzyme levels, an irritable myopathy on electromyography, and inflammation and/or necrosis of myofibers on muscle biopsy
- The majority of patients with autoimmune myopathy have one of the myositis-specific autoantibodies, each of which is associated with a distinct clinical phenotype
- Statin-triggered autoimmune myopathy is a newly recognized form of muscle disease that is associated with autoantibodies recognizing 3-hydroxy-3-methylglutaryl-coenzyme A reductase, the pharmacological target of statins

Box 1 | Diagnostic criteria

The following diagnostic criteria for dermatomyositis and polymyositis were devised by Bohan and Peter:[1,16]

- Symmetric proximal muscle weakness, progressing over weeks to months, with or without dysphagia and/or diaphragmatic weakness
- Muscle biopsy demonstrating myofiber necrosis, phagocytosis, regeneration, variation in fiber diameter, and an inflammatory exudate
- Elevation of serum skeletal muscle enzymes including creatine kinase, aldolase, aspartate transaminase, alanine transaminase and/or lactate dehydrogenase
- Electromyography showing low-amplitude, small, polyphasic motor units; fibrillation potentials and/or positive sharp waves; increased insertional activity and complex repetitive discharges

Evidence of all four of the above criteria is required for a diagnosis of definite polymyositis, whereas evidence of two or three of the criteria is required for diagnoses of probable and possible polymyositis, respectively. By contrast, for a patient to be diagnosed with definite dermatomyositis they must have the dermatomyositis rash as well as three or four of the above criteria. Patients with dermatomyositis rash and two of the above criteria are diagnosed with probable dermatomyositis, and patients with dermatomyositis rash and one of the above criteria are diagnosed with possible dermatomyositis.

Clinical presentation

In 1975 and 1977, Bohan and Peter published a series of papers that established diagnostic criteria for dermatomyositis and polymyositis (Box 1).[1,16] Although these criteria are imperfect, they are still widely used in both clinical and research settings, and provide a useful starting point for discussing the typical clinical features associated with autoimmune myopathy.

Proximal muscle weakness

The most common clinical feature associated with autoimmune myopathies is symmetrical proximal muscle weakness that progresses over a time period of weeks to months.[1,16] A patient with such a disease may complain that they have difficulty rising from chairs, climbing stairs, or washing their hair. In severe cases of autoimmune myopathy, oropharyngeal weakness can result in dysphagia and/or dysphonia; in such cases diaphragmatic weakness may also occur and require mechanical ventilation. Although autoimmune myopathies are frequently characterized as 'painless weakness', some patients do have considerable myalgia; thus, the presence of muscle pain should not preclude a diagnosis of autoimmune myopathy.[17] By contrast, muscle weakness slowly evolving over years, asymmetric or distal muscle weakness, facial weakness or scapular winging are rarely associated with autoimmune myopathies and should strongly suggest the possibility of an alternative diagnosis such as limb-girdle muscular dystrophy, or other non-immune-mediated muscle disease.

Electromyography

In patients with dermatomyositis or polymyositis, electromyography (EMG) of the affected muscle typically reveals short-duration, small-amplitude, polyphasic motor units. These motor units are also evident in other myopathic processes, including muscle disuse. In addition, patients with active autoimmune myopathy usually have features on EMG associated with 'irritable myopathy', such as spontaneous activity (fibrillation potentials and positive sharp waves) and/or complex repetitive discharges.[18] Of note, in the experience of this reviewer, patients with partially treated dermatomyositis, polymyositis or steroid myopathy may have a non-irritable myopathy that lacks spontaneous activity on EMG.

Muscle biopsy

In patients with suspected autoimmune muscle disease, a muscle biopsy can provide valuable diagnostic information. Muscle biopsy findings that were recognized by Bohan and Peter to be associated with autoimmune myopathies include: degenerating and/or necrotic myofibers, regenerating muscle fibers, atrophic muscle cells, and evidence of inflammatory exudates.[1,16] These features are not, however, specific for immune-mediated myopathies, as they can also be found in patients with IBM and inflammatory muscular dystrophies, such as limb-girdle muscular dystrophy type 2B (also called dysferlinopathy).[19]

Since Bohan and Peter published their classification scheme, biopsies from patients with dermatomyositis, polymyositis and IMNM have been shown to have unique pathological features, indicating that different pathophysiological mechanisms underlie these distinct diseases. As discussed in detail below, evidence of atrophic, degenerating or regenerating fibers within the perifascicular area is pathognomonic for dermatomyositis (Figure 1).[20] By contrast, muscle biopsies from patients with polymyositis are characterized by the presence of cytotoxic T cells surrounding and invading non-necrotic myofibers (Figure 1b).[21,22] Muscle biopsies from patients with IMNM typically show marked myofiber necrosis, degeneration and regeneration, and few, if any, inflammatory cells are usually seen in muscle biopsies from these patients (Figure 1d).[4,8–14] Since toxic myopathies, endocrine-associated myopathies, paraneoplastic myopathies, and muscular dystrophies can also be associated with necrotic myofibers on muscle biopsy, the presence of myositis-specific autoantibodies (MSAs, see below) can help differentiate between these diseases and disorders that have an immune-mediated pathology. When specific features of dermatomyositis, polymyositis or IMNM are absent, non-immune-mediated muscle diseases should always be considered as an alternative diagnosis.

Moreover, features on muscle biopsies that are clearly characteristic of other muscle diseases, such as rimmed-vacuoles (as seen in IBM) or increased accumulation of glycogen (as seen in acid maltase deficiency), should suggest that the patient does not have dermatomyositis, polymyositis or IMNM.

Elevated muscle enzymes

Elevated serum levels of muscle enzymes such as creatine kinase, aldolase, aspartate transaminase and/or alanine transaminase are present in at least 90% of patients with autoimmune myopathy.[1,23] Although elevated levels of creatine kinase are believed to be the most sensitive and specific marker of muscle damage, patients with autoimmune myopathies can present with elevated serum aldolase levels without an accompanying increase in serum creatine kinase levels.[24,25]

In 2009, a series of 12 patients with elevated serum aldolase levels but normal levels of creatine kinase was studied in detail.[26] This analysis showed that many of these patients had muscle pain (92%) as well as arthralgias (75%) and interstitial lung disease (42%); only 50% of the patients had muscle weakness on examination.[26] Muscle biopsies showed that fragmentation of perimysial connective tissue and elevated acid phosphatase cellularity was prominent in those patients with selectively high serum aldolase levels. Furthermore, a few of the patients with high levels of serum aldolase were shown to have perifascicular atrophy on muscle biopsy, or skin rashes suggestive of dermatomyositis.[26] Importantly, all patients responded to corticosteroid therapy. Taken together, these findings indicate that in patients with muscle discomfort and normal serum levels of creatine kinase, measuring serum aldolase levels might help identify patients with a steroid-responsive autoimmune myopathy.

In patients with autoimmune myopathy, identifying whether elevated serum levels of transaminases are the result of muscle or liver disease can be challenging, particularly in those patients taking potentially hepatotoxic medications, such as methotrexate or azathioprine. However, as the liver enzyme γ-glutamyl transpeptidase (GGT) is not released by damaged muscle fibers,[27] elevated serum levels of GGT should suggest the possibility of concurrent liver damage.

MRI

Although not included in the Bohan and Peter criteria, MRI might help identify and, thus, aid the management of patients with autoimmune myopathy. On short tau inversion recovery (STIR) imaging, increased signal intensity within muscle tissue is consistent with the presence of muscle necrosis, degeneration, and/or inflammation (Figure 2).[28] As a result, this finding has been incorporated into contemporary diagnostic criteria for autoimmune myopathies.[10,29]

MRI can also identify when chronic muscle damage has resulted in fatty replacement of skeletal muscle (Figure 2); in my experience, muscles that have been extensively replaced by fatty tissue are unlikely to improve with immunosuppressive therapy. Since autoimmune myopathies can result in 'patchy' muscle involvement,[22] and considering that 'blind' muscle biopsies have a substantial false-negative rate of at least 12%,[1,30] some authors have suggested that MRI-guided muscle biopsies might

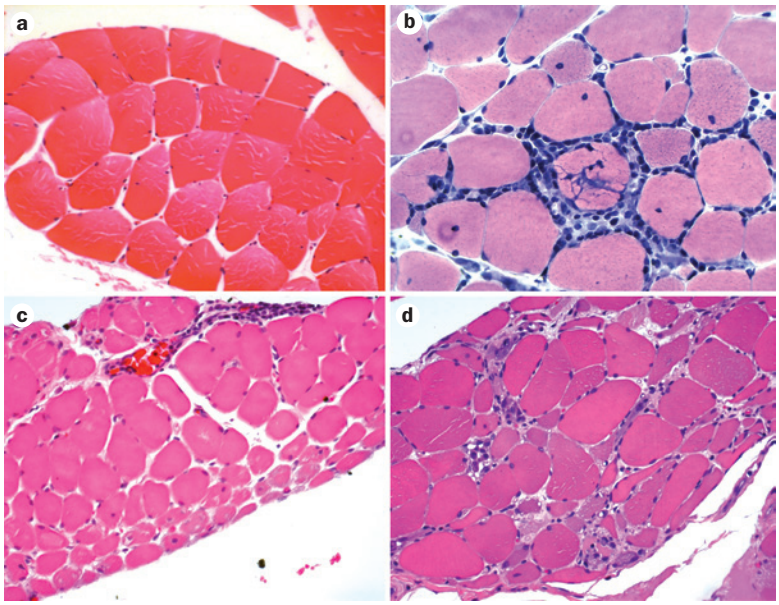

Figure 1 | Muscle biopsies from patients with polymyositis, dermatomyositis or immune-mediated necrotic myopathy. **a** | A typical muscle fascicle from a normal muscle biopsy specimen includes myofibers of uniform size. **b** | The presence of lymphocytes (the small blue cells in this hematoxylin and eosin stain) surrounding and invading muscle fibers is a characteristic feature of polymyositis muscle biopsies, whereas **c** | perifascicular atrophy is typically seen in muscle biopsies from patients with dermatomyositis. **d** | Degenerating, necrotic and regenerating muscle fibers are a characteristic feature of muscle biopsies from patients with immune-mediated necrotic myopathy.

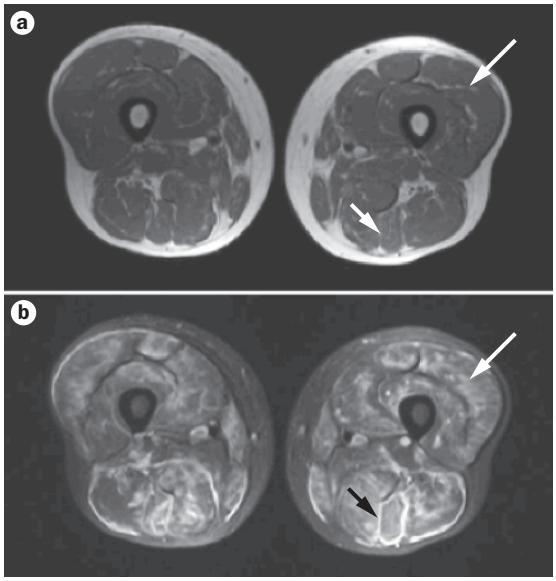

Figure 2 | Thigh MRI from a patient with dermatomyositis. **a** | In T1-weighted images, fat is bright and muscle is dark. **b** | In short tau inversion recovery sequences, normal muscle is dark and inflamed muscle is bright. Long arrows indicate the inflamed left vastus lateralis muscle. Short arrows highlight the left biceps femoris muscle; the bright rim around this muscle is consistent with fascial inflammation.

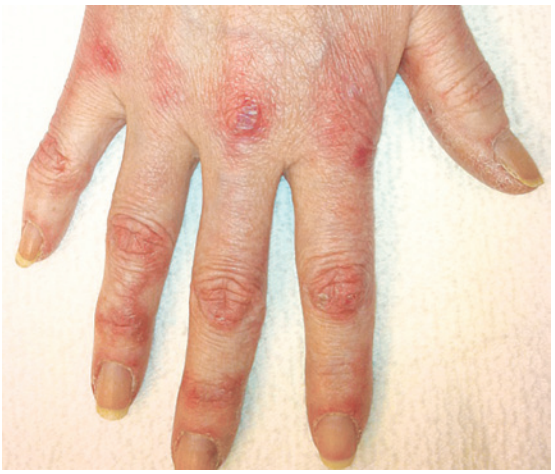

Figure 3 | Gottron papules. In a patient with dermatomyositis, Gottron papules—pathognomonic cutaneous manifestations of dermatomyositis—are evident on the extensor surfaces of the metacarpophalangeal, proximal interphalangeal and distal interphalangeal joints.

improve diagnostic accuracy. In one small study, five of 11 patients with polymyositis who underwent blind biopsies were falsely identified as not having this disorder. By contrast, only one of 14 patients with polymyositis who had an MRI-guided biopsy had a false-negative result.[31] A study of patients with autoimmune myopathy (polymyositis or dermatomyositis) has revealed that inflammatory cells are abundant in areas with high-intensity STIR signal on MRI;[32] however, inflammatory cells, albeit fewer in number, were also shown to be present in areas deemed not to be affected on MRI. The same investigators also found that MRI signal intensity decreased in patients with dermatomyositis or polymyositis after treatment had been initiated;[33] this finding suggests that MRI could help the treating clinician to assess a clinical response. Nevertheless, further studies are required before the utility of MRI in informing decision-making relating to the treatment of autoimmune myopathies is known.

Dermatomyositis rash

Characteristic cutaneous features often help the treating clinician to differentiate patients with dermatomyositis from those with polymyositis or IMNM.[34–36] Purplish discoloration around the eyes known as a heliotrope rash and/or an erythematous rash over the extensor surfaces of the metacarpophalangeal, proximal interphalangeal and distal interphalangeal joints referred to as Gottron papules (Figure 3) are both features of dermatomyositis. In fact, the heliotrope rash and Gottron papules are the only two cutaneous findings that are specific for this disorder. Indeed, patients with these features who lack muscle involvement are referred to as having 'amyopathic' dermatomyositis.[10,37]

Although less specific than the cutaneous features mentioned above, patients with dermatomyositis might also present with skin atrophy, dyspigmentation, and telangectasias on the upper back (the 'shawl sign') or the upper chest (the 'V-sign').[34–36] Changes in the nail beds, including periungual telangiectasias and cuticular hypertrophy, might be seen in patients with dermatomyositis, but these cutaneous features are also commonly found in patients with scleroderma. Of note, dermatomyositis rashes can be exacerbated by exposure to ultraviolet light.[38,39] When performed, skin biopsies taken from patients with this condition frequently show inflammatory cells at the dermoepidermal junction,[40] or around small blood vessels in the dermis;[41] however, these pathological findings may also be seen in patients with lupus erythematosus. Finally, patients with dermatomyositis may develop painful subcutaneous calcifications, although these calcifications are most commonly found in juvenile cases.[42]

Overlap syndromes

Patients with autoimmune myopathy can present with, or develop, an overlap autoimmune rheumatic disease such as scleroderma, systemic lupus erythematosus, Sjögren syndrome, rheumatoid arthritis, or mixed connective disease.[22,43] Thus, patients with autoimmune myopathy can have typical features of the coexisting rheumatic disease; for example, dryness of the eyes and mouth (Sjögren syndrome) or kidney involvement (systemic lupus erythematosus), as well as symptoms associated with immune-mediated muscle disease. The frequency with which autoimmune muscle disease occurs in the context of other rheumatic diseases has not been well-defined. For example, in the case of scleroderma, skeletal muscle involvement has been reported to occur in 16–93% of patients, depending on the diagnostic criteria used to classify the condition.[44,45]

Patients with autoimmune myopathies, especially those with dermatomyositis or polymyositis, might also present with cardiological symptoms including conduction defects, arrhythmias, and reduced ejection fractions.[2,46–52] Furthermore, interstitial lung disease (ILD) occurs in a substantial number of patients with dermatomyositis or polymyositis. This condition is typically thought to occur in 5–46% of patients with either of these conditions,[23,53–59] and the incidence of pulmonary symptoms seems to depend on the clinical setting and the criteria used to determine pulmonary involvement. In one study, when abnormalities on high-resolution CT and/or pulmonary function tests were used to diagnose ILD (even in the absence of symptoms), 11 of 17 (65%) patients with dermatomyositis or polymyositis were shown to have ILD.[60] Importantly, ILD most often occurs in the context of anti-Jo-1 or one of the other antisynthetase autoantibodies (see below).

Autoantibodies

Since Bohan and Peter's diagnostic criteria for dermatomyositis and polymyositis were developed, it has become clear that patients with autoimmune myopathies frequently have autoantibodies. Myositis-associated autoantibodies (for example, anti-Ro and anti-La) are associated with both immune-mediated myopathies and other connective tissue disorders and will not be discussed further here. By contrast, each MSA is associated with

a unique clinical phenotype, and these autoantibodies are found almost exclusively in patients with immune-mediated myopathy or antisynthetase syndrome. New autoantibodies are continually being identified and, to date, around 60–80% of patients with autoimmune myopathy seem to have at least one MSA.[61] In fact, several classification schemes have proposed that the presence of MSAs be included in inclusion criteria for dermatomyositis and polymyositis.[10,29,62] Interestingly, with the exception of anti-155/140, MSAs are associated with a decreased risk of malignancy.[63] The individual MSAs are discussed in detail below.

Antisynthetase autoantibodies

Several antisynthetase autoantibodies exist, each of which recognizes a distinct aminoacyl-tRNA synthetase (ARS).[64–71] These ubiquitous enzymes are expressed within the cytoplasm, where they attach amino acids to their cognate transfer RNA (tRNA). For example, histidyl-tRNA synthetase catalyzes the esterification of histidine to the correct tRNA; this process leads to the formation of a histidyl-tRNA complex. As the coding sequence of a messenger RNA molecule is 'read' by the ribosome, the appropriate aminoacyl-tRNA complex transfers its amino acid to the growing polypeptide chain.

Autoantibodies that recognize histidyl-tRNA synthetase (for example, Jo-1) were first described in 1980;[64] they are the most common type of MSA, and 25–30% of patients with dermatomyositis or polymyositis have these antibodies.[65] Antibodies that target threonyl-tRNA-synthetase (anti-PL-7),[66] alanyl-tRNA synthetase (anti-PL-12),[67] glycyl-tRNA synthetase (anti-EJ),[68] isoleucyl-tRNA synthetase (anti-OJ),[68] asparaginyl-tRNA synthetase (anti-KS),[69] tyrosyl-tRNA synthetase,[70] and phenylalanyl-tRNA synthetase (anti-Zo)[71] have also been identified. The prevalence of each of these anti-ARS autoantibodies in patients with dermatomyositis or polymyositis is around 1–5%.[65]

Interestingly, patients with autoantibodies against the aminoacyl-tRNA synthetases share a common constellation of clinical features, including autoimmune myopathy, ILD, nonerosive arthritis and fever, as well as 'mechanic's hands', which are characterized by hyperkeratotic lesions located predominantly on the lateral and palmar aspects of affected fingers (Figure 4).[72,73] Collectively, these diverse manifestations are referred to as the antisynthetase syndrome. However, not every patient that has an antisynthetase autoantibody has every feature of the syndrome. For example, one study showed that while around 90% of patients who were anti-Jo-1-positive had muscle involvement, only 16 of 31 (52%) patients with anti-PL-12 autoantibodies had myopathy.[74] Patients with anti-PL-12 autoantibodies also had lower rates of fever, mechanic's hands and arthritis than patients with anti-Jo-1. By contrast, 90% of patients with anti-PL-12 autoantibodies had ILD, whereas only 50–75% of patients shown to have anti-Jo-1 had ILD.[74] As not all patients with antisynthetase autoantibodies have myopathy, some authors have objected to the use of the term 'myositis-specific autoantibody' to describe this group of antibodies. Indeed, referring to these autoantibodies as being 'antisynthetase syndrome-specific' might be more accurate.

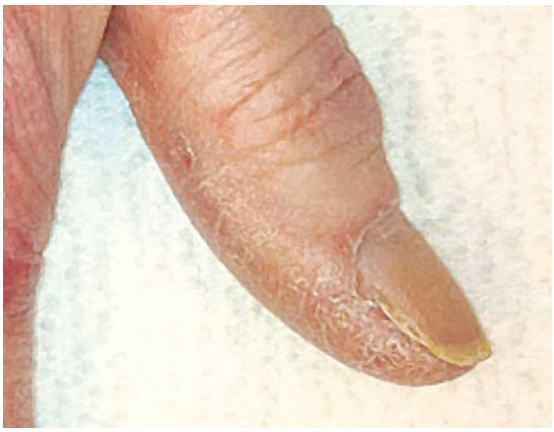

Figure 4 | Hyperkeratotic lesions associated with antisynthetase syndrome. In this patient with antisynthetase syndrome, hyperkeratotic lesions can be seen on the thumb.

Dermatomyositis-specific autoantibodies

Anti-Mi-2

Anti-Mi-2 autoantibodies were first discovered in 1976,[75] but the autoantigen was not identified as a critical component of the nucleosome-remodeling deacetylase (NuRD) complex until 1995.[76–79] The NuRD complex regulates transcription via histone deacetylation and ATP-dependent nucleosome remodeling,[80] and the Mi-2 subunit of the NuRD complex has been shown to act as a DNA-dependent, nucleosome-stimulated ATPase that acts primarily as a transcriptional repressor.[81] Mi-2 seems to have a role in several developmental processes, including the establishment of the epidermal basal cell layer,[82] and B-cell and T-cell differentiation.[83–86] Work in my laboratory has also suggested that this complex might also be involved in muscle repair.[87]

Unlike the antisynthetases, which can be found in patients with either dermatomyositis or polymyositis, anti-Mi-2 is almost exclusively found in patients with dermatomyositis; and in this patient population the prevalence of anti-Mi-2 is around 20%.[88–94] Patients with dermatomyositis who are anti-Mi-2-positive have a characteristic clinical phenotype. Although these patients typically have more-severe skin rashes, they also have a better response to steroid therapy and a decreased risk of malignancy compared with patients with dermatomyositis who are anti-Mi-2-negative.[89,91,95–97]

Anti-p155/140 and anti-MJ (anti-NXP-2)

In the past decade, another dermatomyositis-specific autoantibody has been identified. This antibody, which recognizes proteins with molecular weights of 155 kDa and 140 kDa, was originally discovered by two different groups and found to be present in 13–21% of patients.[98,99] The 155 kDa autoantigen has been presumptively identified as transcriptional intermediary factor 1-γ.[100] Of note, several studies have shown that adult patients with dermatomyositis who have anti-p155/140 autoantibodies

have an increased risk of cancer compared with those patients with dermatomyositis who lack these antibodies.[98,99,101,102] This increased risk of cancer might be substantial; in one study the prevalence of malignancy in anti-p155/140-positive patients was 71%, compared with 11% in patients with dermatomyositis who lacked this antibody.[99] Interestingly, these antibodies were also detected in around 23% of juvenile patients with dermatomyositis, a group in which autoantibodies were previously thought to be exceptionally rare.[98,103] Although these children did not have cancer, those with p155/140 had more-severe cutaneous involvement than those who lacked these antibodies.

Children with dermatomyositis have also been shown to have other autoantibodies. For example, anti-MJ is an autoantibody that recognizes nuclear matrix protein 2 (NXP-2) and has been found exclusively in patients with juvenile dermatomyositis.[104–106] In contrast to pediatric patients with dermatomyositis who lack these autoantibodies, those with this antibody have a significantly increased risk of developing calcinosis (54% versus 15%).[106] It is now appreciated that around 40% of juvenile dermatomyositis cases are associated with known autoantibodies, such as anti-155/140 and anti-NXP-2.[103,104]

Anti-MDA5

In 2005, Sato and colleagues were the first group to identify antibodies recognizing melanoma differentiation-associated gene 5 (MDA5), an RNA helicase involved in the innate immune response against viruses, in a cohort of Japanese patients.[25] Interestingly, this antibody was found exclusively in patients with amyopathic dermatomyositis,[25,102,107] most of whom had rapidly progressive ILD.[107] Research suggests that these patients, particularly those with high ferritin levels, have more-severe ILD and a lower survival rates than patients with lower ferritin levels.[108]

Anti-SUMO-1

Several years ago, two patients presented with skin manifestations typically associated with dermatomyositis. They subsequently developed both myositis and ILD, and were eventually found to have autoantibodies that recognize small ubiquitin-like modifier 1 (SUMO-1), an enzyme involved in post-translational protein modification.[109] A larger study established that this autoantibody is exclusively found in patients with dermatomyositis, and that the prevalence of this antibody in this patient cohort was around 8%.[110] Most anti-SUMO-1 patients presented with skin manifestations before muscle involvement, and many experienced dysphagia.[110]

Autoantibodies associated with IMNM

The signal recognition particle (SRP) is a cytoplasmic protein that binds the signal sequences of newly synthesized proteins and facilitates their translocation into the endoplasmic reticulum. The SRP comprises six subunits, and in 1986 Reeves *et al.* were the first group to discover, in serum from a patient with polymyositis, an autoantibody that recognized the 54 kDa subunit of this protein complex.[111] Later studies showed that some patients with myopathy have autoantibodies that recognize the 7SL RNA component of the SRP[112] and/or other protein subunits of the SRP complex.[113] Anti-SRP autoantibodies have been estimated to occur in around 4% of patients with autoimmune myopathy;[113] however, these antibodies might not be entirely specific for patients with myopathy, as at least two studies have reported that patients with systemic sclerosis—an antisynthetase-like syndrome—or rheumatoid arthritis had anti-SRP antibodies, but not muscle weakness.[114,115]

Several studies have described the clinical and/or pathological phenotypes of patients with anti-SRP in detail[4,113–116] and, taken together, these analyses indicate that anti-SRP autoantibodies are associated with an immune-mediated necrotizing myopathy. For example, muscle biopsies taken from patients with anti-SRP antibodies are characterized by abundant degenerating, regenerating and necrotic cells; by contrast, these muscle biopsies are rarely shown to have collections of inflammatory cells. Of note, these studies have shown that patients who are anti-SRP-positive usually have a rapidly progressive disease course, and most of these patients have severe muscle weakness.

Two studies have reported that a subset of patients with anti-SRP develop dermatomyositis-like rashes.[115,116] However, perifascicular atrophy was not evident in this cohort, raising the possibility that these individuals might not have had a true dermatomyositis rash. A further two studies comprising a total of 26 patients with myopathy reported that the membrane attack complex (MAC), an effector of the alternative pathway of the complement system, which can disrupt cell membranes, was present on muscle capillaries in patients with anti-SRP myopathy.[4,114] This result suggests that microvascular injury might underlie or contribute to muscle necrosis seen in patients with IMNM. A third group, however, did not observe MAC on muscle capillaries in a cohort of 23 anti-SRP-positive patients with IMNM.[116] As is the case in patients with dermatomyositis, malignancies have been reported in a subset of patients who have anti-SRP antibodies; in one study, two of 23 anti-SRP patients developed malignancies, although these occurred 7 years or more after the onset of weakness.[115]

Statin-associated IMNM

Musculoskeletal symptoms such as myalgia and cramp are quite common in patients taking statins (9–20%), but they are usually mild.[117–119] By contrast, rhabdomyolysis is a well-known severe adverse event associated with statin use. Fortunately, however, this adverse event occurs rarely in patients taking this medication, at a rate of around 0.4 per 10,000 patient years.[120] In most cases, statin-associated muscle complaints improve when the treatment is discontinued, and complete recovery can be expected within a few weeks or months after discontinuation of the drug.[121] Nevertheless, over the past two decades, numerous case reports have indicated that statins might cause dermatomyositis or polymyositis in some patients, and the identification of inflammatory cells in muscle biopsies taken

from these patients supports this hypothesis.[122–124] Several compelling studies have also shown that patients can develop IMNMs after taking statins.

In one case series, eight patients were shown to develop myopathy while taking statins, and in some cases the myopathy persisted or even progressed despite discontinuation of the medication.[125] In fact, seven of the eight patients only improved on initiation of immunosuppressive therapy. Seven of the eight cases had numerous necrotic and regenerating fibers on muscle biopsy, indicating that they might have had statin-associated IMNM. In five cases, marked inflammation on muscle biopsy was absent, indicating that these patients did not have clinical features associated with dermatomyositis or polymyositis. In all eight cases, major histocompatibility complex class I (MHC-I) expression was present in non-necrotic muscle fibers; this finding is a characteristic feature of immune-mediated muscle diseases, and is not seen in patients with other forms of muscle disease such as the muscular dystrophies.[126–128]

In a second case series, 24 patients were identified who had progressive proximal muscle weakness after starting statins, which progressed even after these medications were discontinued.[8] These patients had elevated serum creatine kinase levels, and muscle biopsies revealed marked myofiber necrosis and regeneration in the absence of prominent lymphocytic infiltrates, consistent with a necrotizing myopathy. The patients' symptoms improved with immunosuppressive medications; however, over 50% of the patients worsened when immunosuppressive therapy was tapered. This series also demonstrated that the prevalence of statin exposure was markedly higher in patients with IMNM than in control patients with dermatomyositis, polymyositis or IBM.

Taking a different approach, researchers at Johns Hopkins University (including myself) have identified novel autoantibodies that recognize 200 kDa and 100 kDa proteins in 16 of 26 patients who presented to our department with a necrotizing myopathy. No other autoantibodies or alternative diagnoses were identified in these patients.[9] The patients who expressed these novel antibodies had proximal muscle weakness and high serum levels of creatine kinase, and responded to immunosuppressive therapy—clinical symptoms worsened in many of the patients when immunosuppressive treatment was tapered. Analysis of muscle biopsies taken from these patients revealed that 75% of the cases had abnormal capillary morphologies, 50% had evidence of MAC deposition on non-necrotic muscle cells, and 50% had MHC-I expression in non-necrotic myofibers.[9] Of note, 63% of the patients who had these novel antibodies had been exposed to statins before developing myopathy. Furthermore, compared with age-matched control patients with myopathy, the prevalence of statin use in patients with anti-200/100 autoantibodies (83%) was significantly higher than in patients with dermatomyositis (25%), polymyositis (37%) or IBM (34%).[9]

In a follow-up study, we identified the autoantigen recognized by the anti-200/100 autoantibody as 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR)—the pharmacological target of statins.[129] Statins are known to dramatically upregulate HMGCR protein levels; thus, in some patients, increased HMGCR expression could trigger anti-HMGCR autoimmunity. Why some statin-naive patients with IMNM also develop anti-HMGCR autoantibodies remains to be determined.

Of note, elevated HMGCR expression is required for muscle differentiation *in vitro*.[130] We have shown that in muscle biopsy specimens, regenerating human muscle fibers also express high levels of HMGCR.[129] This finding suggests that after statin medications are discontinued, high levels of HMGCR expression in regenerating muscle tissue might continue to drive the autoimmune response.

Together, the studies mentioned above strongly suggest that an environmental factor—statin medication—is associated with a distinct form of autoimmune necrotizing myopathy that is characterized by the production of anti-HMGCR autoantibodies. Since associations between environmental factors and the development of sustained autoimmunity are rare, this distinct form of autoimmune necrotizing myopathy might prove to be a model system for studying this phenomenon.

Risk of malignancy

Several large studies have established that patients with autoimmune myopathy—in particular, those with dermatomyositis—have an increased risk of developing a malignancy. For example, in an analysis of 537 Australian patients, those with dermatomyositis or polymyositis had standardized incidence ratios (SIRs) for cancers of 6.2 and 2.0, respectively, compared with the rest of the population.[130] In these patients, the greatest risk of developing a malignancy was shown to be within the first year after dermatomyositis or polymyositis diagnosis. Moreover, in the largest population-based study of autoimmune myopathy to date, 618 patients with dermatomyositis and 914 patients with polymyositis were identified in the national medical databases of Sweden, Denmark and Finland.[62] In this cohort, 32% of patients with dermatomyositis and 15% of patients with polymyositis were found to have cancer, representing SIRs of 3.0 and 1.3, respectively. The risk of cancer was highest in the 2 years before and after the diagnosis of autoimmune myopathy, but patients with dermatomyositis continued to have a higher than expected risk of developing malignancy for up to 5 years after skin and/or muscle disease became apparent.[131] Malignancies of the ovaries, lung, pancreas, stomach and colon were among the most common cancers seen in patients with dermatomyositis. In patients with polymyositis, the most commonly seen malignancies were non-Hodgkin lymphoma, as well as lung and bladder cancers.[131]

Polymyositis: lumping or splitting?

In their criteria, Bohan and Peter define polymyositis as a myopathy that is associated with proximal muscle weakness, elevated muscle enzymes, irritable myopathy on EMG, and degenerating, necrotic or regenerating myofibers on muscle biopsy.[1,16] Since this definition was proposed, several autoantibodies have been identified

in patients with autoimmune myopathies, and these autoantibodies are strongly correlated with specific disease phenotypes.[3] Indeed, as outlined above, accumulating evidence suggests that these autoantibodies are associated with distinct disease states. For example, patients with anti-synthetase autoantibodies have a constellation of systemic features, including arthritis, interstitial lung disease and an inflammatory myopathy.[72,73] By contrast, patients with anti-SRP autoantibodies have a severe necrotizing myopathy, and minimal, if any, systemic involvement.[111–116] Finally, patients with anti-HMGCR-associated myopathy have a necrotizing myopathy frequently triggered by statin exposure.[9,129]

To date, most scientific studies and clinical trials have grouped patients with the above symptoms and antibodies together under the umbrella term 'polymyositis' (the 'lumping' approach). However, further progress in our understanding of these diseases and how best to treat them might rely on our ability to recognize them as distinct entities ('splitting').

Pathological mechanisms

Vascular pathology in dermatomyositis

Atrophic, degenerating and/or regenerating myofibers identified in perifascicular regions are characteristic features of dermatomyositis muscle. Selective depletion of capillaries in these perifascicular regions has been proposed to result in hypoxia and observed myofiber pathology.[2] The possibility that vasculopathy could contribute to dermatomyositis is supported by research showing that 'tubuloreticular inclusions'—abnormal filamentous structures seen on electron microscopy—are found within capillary endothelial cells in dermatomyositis.[132] Furthermore, capillary damage and dropout occurs early in the disease process in autoimmune myopathy and may be preceded by the deposition of MAC on endothelial cells.[133–137] Interestingly, evidence indicates that neovascularization often occurs in dermatomyositis muscle.[138] This process might be facilitated by hypoxia, as vascular endothelial growth factor (VEGF) is known to rise in hypoxic conditions and elevated levels of VEGF have been observed in muscle tissue and serum in patients with myositis.[139]

Further evidence indicating that vascular damage may contribute to dermatomyositis pathology comes from an elegant study of dermatomyositis muscle biopsy specimens.[140] This study showed that intermediate-sized blood vessels are unevenly distributed within dermatomyositis muscle, and often have pathological features including perivascular inflammation. Importantly, both abnormal capillaries—capillaries that were reduced in size and had endothelial loss and MAC deposition—and perifascicular atrophy were located in regions within the dermatomyositis muscle distant from intermediate-sized perimysial blood vessels.[140] Thus, Pestronk *et al.*, the authors of this study, hypothesized that these intermediate-sized blood vessels might be the primary target of the immune response. Damage to these vessels could lead to ischemia in 'watershed' areas of muscle tissue, and lead to subsequent capillary and myofiber damage.

Interferons and dermatomyositis

Inflammatory cells located around intermediate-sized blood vessels are a typical (but not pathognomonic) feature of dermatomyositis muscle biopsies. The majority of these inflammatory cells are $CD4^+$ plasmacytoid dendritic cells (PDCs),[141] which are known to be a source of IFN-α.[142] The presence of PDCs within the epidermis of dermatomyositis skin[143] suggests that IFN-mediated processes might contribute to both the muscular and cutaneous manifestations of this disease. This hypothesis is supported by numerous lines of evidence.

First, IFN-induced genes, such as *MxA* and IFN-stimulated gene 15 (*ISG15*), and ISG15-conjugated proteins are highly expressed in atrophic perifascicular myofibers and capillary endothelial cells within dermatomyositis muscle.[141,144] Elevated levels of *MxA* have also been shown to be present within basal keratinocytes in dermatomyositis skin biopsies.[145] Second, as has been commented on by others,[146] tubuloreticular inclusions of the type found in endothelial cells in dermatomyositis muscle can develop in blood cells of patients treated with IFN;[147] furthermore, cultured endothelial cells develop similar structures when exposed to type I IFNs.[148,149] Third, autoantibodies against melanoma differentiation-associated gene 5 protein—an IFN-inducible protein—were recently discovered in patients with amyopathic dermatomyositis,[107] raising the possibility that this protein might be abnormally expressed in dermatomyositis skin. Finally, IFN-inducible gene expression in blood correlates with dermatomyositis disease activity.[150,151] Taken together, these observations strongly suggest a causal link between IFN signaling and dermatomyositis pathophysiology.

MSAs, autoantigens and cancer

Although the exact role of MSA in the pathogenesis of autoimmune myopathies remains unknown, evidence suggests that the production of these antibodies reflects changes in autoantigen expression within the tissue that has been targeted by the immune response. This relationship is probably best described in patients with statin-associated IMNM. Statins are known to upregulate the expression of the HMGCR protein, and this increased protein expression has been hypothesized to induce the production of anti-HMGCR autoantibodies.[129] Furthermore, once the myopathic process has been initiated (and after statins have been discontinued), the anti-HMGCR immune response might be sustained by persistently high levels of HMGCR protein in regenerating fibers.[129]

Studies have shown that several myositis autoantigens, including anti-Jo-1, are expressed at relatively low levels within normal muscle, but at high levels in regenerating muscle fibers in patients with dermatomyositis or polymyositis.[152] In fact, Mi-2 protein is expressed at high levels only in dermatomyositis muscle and, more specifically, in perifascicular myofibers that express markers of regeneration.[87] Of note, myositis autoantigens are typically expressed at low levels in 'normal' tissues (for example, breast tissue), but at high levels in tumors derived from those tissues (such as breast cancer).[152] As an increased risk of cancer has been associated with several autoimmune

myopathies,[153] this finding suggests that an autoimmune response originally directed against a tumor might become redirected to regenerating muscle tissue under certain circumstances. Once initiated, the autoimmune response could lead to additional muscle injury and repair and, consequently, further increases in the expression of autoantigens, and persistent stimulation of the immune response.[154] A feed-forward cycle as described in the preceding text might help explain how an autoimmune response targeting muscle is sustained (Figure 5).

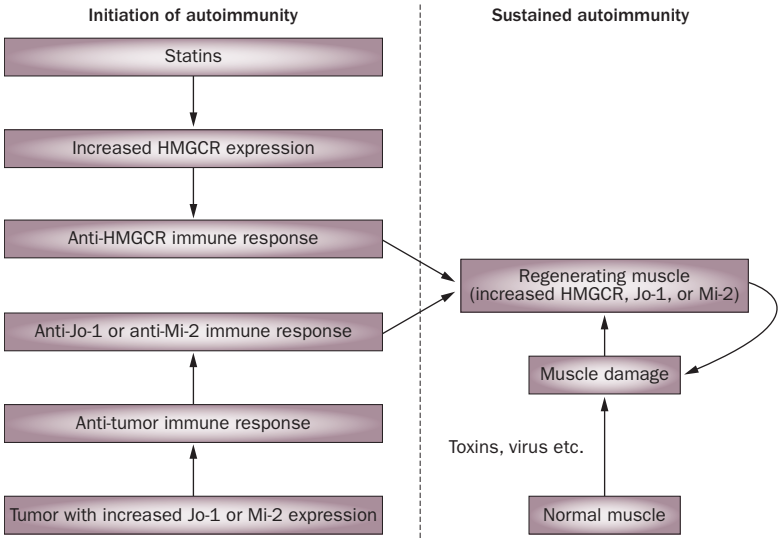

Figure 5 | Initiation and maintenance of autoantibody production. Statin exposure increases HMGCR expression and triggers an anti-HMGCR immune response. Similarly, overexpression of autoantigens such as Jo-1 and Mi-2 in tumors may provoke an antitumor immune response and the production of anti-Jo-1 or anti-Mi-2 autoantibodies. Under certain circumstances (for example, myotoxic exposure or viral infection) the immune response could be redirected to regenerating muscle cells expressing high levels of myositis autoantigens. This process could precipitate a feed-forward loop that is characterized by further muscle damage, continued muscle regeneration, and persistently elevated levels of autoantigens in muscle. Abbreviation: HMGCR, 3-hydroxy-3-methylglutaryl-coenzyme A reductase.

Immunogenetics

As in other systemic autoimmune diseases, an interaction between environmental and genetic factors is thought to be the initiating mechanism underlying various autoimmune myopathies. A thorough overview of the immunogenetics of autoimmune myopathies is beyond the scope of this review and a discussion of progress in this area can be found elsewhere.[155] However, it should be noted that considerable evidence links the presence of various human leukocyte antigen alleles with either an increased or decreased risk of developing autoimmune myopathy. Moreover, specific alleles of the ancestral haplotype 8.1 are known to confer risk for the development of particular autoantibodies. For example, the DRB1*0301 allele is associated with an odds ratio of 3.6 for developing autoimmune myopathy in general and, in particular, with a 15.5-fold increased risk of developing anti-Jo-1 autoantibodies.[156] By contrast, the DQA1*0201 and DRB1*0701 alleles are associated with an increased risk of developing anti-Mi-2 autoantibodies, but protect against the development of autoimmunity against Jo-1.[91,156–159] Other MHC alleles are known to be associated with the development of anti-PL-7, anti-SRP and other autoantibodies found in patients with immune-mediated muscle disease.[155]

Other gene polymorphisms have been shown to affect the risk of developing autoimmune myopathy. For example, in white individuals, the immunoglobulin γ heavy chain 13 allotype is positively correlated with dermatomyositis.[160] Furthermore, polymorphisms in the genes for several proinflammatory cytokines have been shown to be association with myositis. For example, the tumor necrosis factor (TNF) promoter 308A polymorphism is associated with an increased risk of juvenile dermatomyositis, whereas the TNF promoter 238A polymorphism has been shown to decrease the risk of juvenile dermatomyositis.[161] Similarly, the interleukin (IL)-1α +4845G allele decreases the risk of developing juvenile dermatomyositis, whereas the IL-1β +3953T allele confers an increased risk of developing the same disease.[161] Further studies will be required to elucidate the mechanistic link between the above polymorphisms and other immunogenetic risk factors, exposure to environmental triggers, and the development of autoimmune myopathy.

Conclusions

Our understanding of the underlying processes associated with autoimmune myopathies has substantially increased since Bohan and Peter outlined their diagnostic criteria for polymyositis and dermatomyositis 35 years ago. We now appreciate the diagnostic utility of the MSAs that are evident in the majority of patients with autoimmune myopathy. These MSAs are each associated with specific clinical phenotypes and, in all likelihood, different pathological mechanisms. Although the mechanisms underlying autoimmune myopathy remain poorly understood, important clues have emerged. For example, in one form of IMNM that is associated with novel autoantibodies, statins may trigger an immune response by stimulating the expression of HMGCR. Furthermore, in patients with dermatomyositis, IFN-producing cells and the increased expression of IFN-induced proteins in both skin and muscle may damage tissue and, in such situations, blood vessels seem to be a major target. Despite these advances in our knowledge of autoimmune myopathies, these diseases are still treated, as they were 35 years ago, with relatively nonspecific immunosuppressive therapies. As the pathological mechanisms that underlie autoimmune myopathies are elucidated, we expect that novel therapeutic targets will be identified.

Review criteria

References for this Review were selected from PubMed (1980 to present) and were restricted to publications in English. Original manuscripts and review articles were reviewed. Search terms included "autoimmune myopathy", "myositis", "dermatomyositis", "polymyositis" and "autoantibodies". Reference lists from identified papers were used also used.

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