



Necrotizing myopathies: beyond statins

Andrew L. Mammen

Purpose of review

This review discusses the spectrum of diseases associated with a necrotizing muscle biopsy. Although patients with toxic myopathies, endocrine dysfunction, and heritable myopathies may have prominent necrosis on muscle biopsy, immune-mediated myopathies are emphasized here.

Recent findings

A decade ago, immune-mediated necrotizing myopathy was recognized as a distinct form of myositis. Recent evidence now suggests that immune-mediated necrotizing myopathy is not one disease, but can be divided on the basis of the presence of distinct autoantibodies recognizing either the signal recognition particle or 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. Anti-HMG-CoA reductase-positive patients can be further subdivided into those with and without statin exposure, the latter of which may be particularly refractory to immunosuppressive therapy.

Summary

A significant number of patients with autoimmune myopathy have a predominantly necrotizing muscle biopsy with minimal lymphocytic infiltration. This biopsy finding occurs in various forms myositis, including the antisynthetase syndrome, scleroderma-associated myopathy, antisignal recognition particle-associated myopathy, statin-associated anti-HMG-CoA reductase-positive autoimmune myopathy, and statin-naïve anti-HMG-CoA reductase-positive myopathy. Future progress in elucidating pathogenic mechanisms and defining optimal treatment strategies may depend upon recognizing these distinct forms of myositis and analyzing them as separate entities.

Keywords

anti-HMG-CoA reductase, autoimmune, muscle, myopathy, myositis, necrotizing, signal recognition particle, statin

INTRODUCTION

The idiopathic inflammatory myopathies (IIMs), including polymyositis and dermatomyositis, are systemic autoimmune diseases affecting skeletal muscle. Patients with one of these conditions usually present with symmetric proximal muscle weakness, elevated muscle enzyme levels, autoantibodies, and responsiveness to immunosuppression. Muscle biopsies from patients with IIM have typically been described as revealing prominent lymphocytic infiltration. However, it has been emphasized recently that some patients with other clinical features of autoimmune myopathy have abundant myofiber necrosis, degeneration, and regeneration with only minimal, if any, inflammation on muscle biopsy. On the basis of their distinctive muscle biopsies, these patients are often referred to as having immune-mediated necrotizing myopathy (IMNM). This designation implies that IMNM patients have a unique form of myositis that can be diagnosed on the basis of muscle biopsy findings alone. In the last few years, particular

attention has been focused on those patients who develop IMNM in the context of statin use and have antibodies recognizing 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR).

Here, we will review how our understanding of necrotizing myopathy and myositis-specific autoantibodies has evolved over the last 40 years. We will also suggest an approach to the patient with a necrotizing muscle biopsy, recognizing that this histologic feature is neither sensitive nor specific for a particular subtype of autoimmune myopathy.

Muscle Disease Unit, Laboratory of Muscle Stem Cells and Gene Expression, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, Maryland, USA

Correspondence to Andrew L. Mammen, MD, PhD, Muscle Disease Unit, Laboratory of Muscle Stem Cells and Gene Expression, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, 50 South Drive, Room 1146, Building 50, MSC 8024, Bethesda, MD 20892, USA. Tel: +1 301 402 6956; fax: +1 301 594 0305; e-mail: andrew.mammen@nih.gov

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KEY POINTS

- Some patients with autoimmune muscle disease have muscle biopsies revealing prominent myofiber necrosis with minimal lymphocytic infiltration.
- Anti-HMGCR and anti-SRP are the most common autoantibodies found in patients with autoimmune necrotizing myopathies.
- Compared with those without statin exposure, statin-exposed patients with anti-HMGCR antibodies may respond better to immunosuppressive therapy.
- Further studies are required to define the mechanism of myofiber injury and optimal treatment strategies for patients with necrotizing myopathies.

RECOGNITION OF NECROTIZING MYOPATHY AS A HISTOLOGICALLY DISTINCT FORM OF MYOSITIS

In their classic 1975 description of the IIMs, Bohan and Peter [1] expressed the then widely held view that ‘polymyositis is an inflammatory myopathy of unknown cause to which the term dermatomyositis is applied in the presence of the characteristic skin rash’. Recognizing no histologic features that could distinguish between patients with polymyositis and dermatomyositis, these authors offered the following characterization of muscle biopsies from patients with either disease: ‘necrosis of type I and II fibers, phagocytosis, regeneration with basophilia, large vesicular sarcolemmal nuclei and prominent nucleoli, atrophy in a perifascicular distribution, variation in fiber size, and an inflammatory exudate, often perivascular.’ Over the last 40 years, further work has shown that polymyositis and dermatomyositis are actually distinct entities with unique histological findings on muscle biopsy. Thus, the perifascicular atrophy described by Bohan and Peter is now widely regarded as the pathognomonic feature of dermatomyositis and not found in patients with polymyositis [2]. In contrast, more recent diagnostic classification schemes recognize the invasion of nonnecrotic muscle fibers by CD8⁺ T cells as the hallmark histologic feature of polymyositis [3].

Although Bohan and Peter [4] were aware that some myositis patients had a necrotizing myopathy with muscle biopsies characterized by a ‘lack of inflammation and phagocytosis, despite massive muscle necrosis’, this was thought to be the case primarily in patients with cancer-associated myositis. By 2003, however, a working group of the European Neuromuscular Centre established a diagnostic classification scheme recognizing IMNM as a distinct form of myositis, not necessarily associated with

malignancy, in which muscle biopsies revealed muscle fiber necrosis as the predominant abnormal histological feature [5]. Although muscle biopsies from patients with toxic myopathies, hypothyroidism, metabolic myopathies (after an episode of rhabdomyolysis), and muscular dystrophies may also be predominantly necrotizing, a 2012 study by Preuß *et al.* [6] suggested that upregulation of the major histocompatibility class I antigen in non-necrotic muscle fibers can be used to help identify those who have IMNM. These investigators also found that complement deposition on capillaries and on the sarcolemma of nonnecrotic fibers is more characteristic of an immune-mediated process in patients with a necrotizing muscle biopsy.

DISCOVERY OF AUTOANTIBODIES ASSOCIATED WITH NECROTIZING MYOPATHIES

During the same time period in which predominantly necrotizing muscle biopsies were identified as representing a distinct histological subgroup of myositis patients, additional work revealed that individual myositis-specific autoantibodies are associated with distinct clinical phenotypes. For example, dermatomyositis-specific Mi-2 autoantibodies were identified in 1976 [7] and anti-Jo-1 autoantibodies, associated with a unique clinical syndrome including myositis, interstitial lung disease, nonerosive arthritis, fever, and mechanic’s hands, were first described in 1980 [8]. In 1986, Reeves and colleagues [9,10] discovered antibodies recognizing components of the signal recognition complex (SRP) in a patient characterized as having ‘typical polymyositis’. Subsequent studies by Miller [10], Kao [11], Hengstman [12], and their colleagues revealed that anti-SRP-positive patients have a distinctive phenotype characterized by severe, rapidly progressive weakness, very high creatine kinase (CK) levels, minimal extramuscular manifestations, and a necrotizing myopathy with relatively sparse inflammation. Thus, anti-SRP autoantibodies were the first myositis autoantibodies identified as specifically associated with IMNM.

Recognizing that not all patients with necrotizing myopathies have anti-SRP autoantibodies, Christopher-Stine *et al.* [13] identified patients with this muscle biopsy feature and screened their sera for novel autoantibodies. Among 26 patients with a necrotizing muscle biopsy and no previously identified autoantibody, a cohort of 16 was found to have autoantibodies recognizing 200-kd and 100-kd proteins. Patients with this specificity were similar to anti-SRP patients on the basis of their muscle biopsy characteristics, high CK levels, response to immunosuppressive therapy, and lack

of extramuscular manifestations. Surprisingly, however, the anti-200/100-kd-positive patients were found to have a particularly high prevalence of statin exposure. Indeed, among anti-200/100-kd-positive patients aged 50 or over, 83% had a prior exposure to this class of medications. In contrast, similarly aged patients with dermatomyositis and polymyositis had significantly lower statin exposure rates of 25 and 37%, respectively. These findings were consistent with those of Grable-Esposito *et al.* [14], who described 25 patients who developed an IMNM following exposure to statins. This cohort of patients, like those with anti-200/100-kd autoantibodies, developed a necrotizing myopathy following statin exposure that continued to progress despite discontinuation of statins and required immunosuppressive therapy to control. Based primarily on the findings of these two groups, statin-associated IMNM was identified as a unique subtype of myositis associated with antibodies recognizing the 200-kd and 100-kd autoantigens.

Further work by Mammen *et al.* [15] revealed that the 100-kd autoantigen is HMGCR, the pharmacologic target of statin drugs, and that the 200-kd autoantigen is most likely an HMGCR dimer. These investigators subsequently showed that anti-HMGCR antibodies are not found in the vast majority of patients with statin exposure, including those who develop self-limited form of statin myotoxicity that abates spontaneously with statin discontinuation [16]. Thus, anti-HMGCR antibodies, the second antibody to be associated with IMNM, appear to be specific for those with an autoimmune process.

THE PLOT THICKENS . . .

Although anti-HMGCR antibodies are frequently associated with statin-triggered autoimmune myopathy, this is not always the case. Indeed, Mammen *et al.* [15] screened 750 patients enrolled in a longitudinal study at the Johns Hopkins Myositis Center and found that among 45 anti-HMGCR-positive study participants, only 30 (67%) had a prior statin exposure. And in a European cohort of myositis patients, just 20 of 45 (44%) anti-HMGCR-positive study participants had a prior statin exposure [17^{***}]. Interestingly, statin-naïve anti-HMGCR-positive patients have distinct clinical characteristics. Compared with those with statin exposure, these patients are significantly younger, have higher CK levels, and are less likely to be of white race. In a separate study, Werner *et al.* [18] also found that statin-naïve anti-HMGCR-positive patients respond less well to treatment than those with statin exposure [18].

Importantly, one must note that not all anti-HMGCR and anti-SRP-positive patients have exclusively necrotizing muscle biopsies. Indeed, in

addition to myofiber necrosis, 11% of statin-exposed and 39% of statin-naïve anti-HMGCR-positive patients had collections of inflammatory cells, predominantly in a perivascular distribution [15]. Similarly, in one study [10], two out of seven (22%) anti-SRP-positive study participants had endomysial and/or perivascular lymphocytic inflammation.

Just as not all anti-SRP and anti-HMGCR-positive patients have a necrotizing myopathy, not all myositis patients with predominantly necrotizing muscle biopsies have one of these two autoantibodies. For example, in a series of 38 patients with a necrotizing myopathy on muscle biopsy, there were 16 (42%) anti-HMGCR, six (16%) anti-SRP, two (5%) anti-PL-12, one (3%) anti-PL-7, and one (3%) anti-Jo-1-positive patients [13]. Subsequent studies have confirmed antisynthetase syndrome patients may present with necrotizing muscle biopsies [19,20]. Interestingly, Bhansing *et al.* [21^{***}] recently reported that among 24 patients with scleroderma myopathy, four (17%) had muscle fiber necrosis without inflammation. Thus, a histologic diagnosis of necrotizing myopathy may also be reached in patients who have myositis and an overlapping connective tissue disease. Finally, the author has noted that occasional patients with typical clinical features of dermatomyositis may also have a necrotizing muscle biopsy.

APPROACH TO THE PATIENT WITH A NECROTIZING MYOPATHY

A necrotizing muscle biopsy is a relatively non-specific finding that can be seen in patients with endocrinopathy (e.g. hypothyroidism), exposure to myotoxins (e.g. statins), muscular dystrophies, and a variety of autoimmune myopathies. Conditions associated with a necrotizing muscle biopsy are as follows:

- (1) autoimmune myopathies (in approximate descending order of prevalence):
 - (a) statin-associated anti-HMGCR-positive myopathy,
 - (b) statin-naïve anti-HMGCR-positive myopathy,
 - (c) anti-SRP-positive myopathy,
 - (d) scleroderma myopathy,
 - (e) antisynthetase syndrome,
 - (f) dermatomyositis,
- (2) nonautoimmune myopathies (arbitrary order):
 - (a) toxic myopathies,
 - (b) hypothyroidism,
 - (c) heritable myopathies.

Although upregulation of major histocompatibility class I and the deposition of complement on

capillaries and nonnecrotic muscle fibers may suggest the probability of an immune-mediated process [6], the possibility of a nonimmune-mediated myopathic processes should always be considered in patients who have a necrotizing muscle biopsy.

In those patients with a necrotizing muscle biopsy who have normal thyroid stimulating hormone and thyroxine, an absence of myotoxic exposures, and a lack of other family members with muscle disease, an autoimmune process should be high on the differential. When a careful examination of the patient also reveals an absence of prominent distal weakness, asymmetric weakness, facial weakness, and extraocular muscle involvement, the possibility of an autoimmune myopathy should be strongly considered even in the absence of inflammatory cells on muscle biopsy.

In our series of patients with autoimmune necrotizing myopathy, the majority had either anti-HMGCR or anti-SRP autoantibodies [13]. These patients frequently have no extramuscular manifestations to suggest the possibility of a systemic autoimmune process. Although anti-HMGCR-associated myopathy should be a strong consideration in any patient developing a myopathy while on statins that progresses despite statin discontinuation, at least one-third of anti-HMGCR-positive patients have no history of statin exposure. Consequently, testing for anti-HMGCR and anti-SRP autoantibodies may play a key role in making the correct diagnosis of patients who have isolated skeletal muscle involvement and a necrotizing muscle biopsy.

In patients with a necrotizing myopathy in the context of arthritis, interstitial lung disease, fever, and/or mechanic's hands, the antisynthetase syndrome should be strongly suspected. Confirmation of the diagnosis can be achieved by testing for anti-Jo-1, anti-PL-7, and anti-PL-12 autoantibodies.

Although most patients with dermatomyositis have a characteristic rash to suggest the correct diagnosis, it's possible that a rare patient could present without a rash (dermatomyositis sine dermatitis) and with a necrotizing muscle biopsy. As ~80% of dermatomyositis patients will have a dermatomyositis-specific (i.e. Mi-2, transcriptional intermediary factor 1 γ , nuclear matrix protein 2) or dermatomyositis-associated (i.e. Jo-1 or polymyositis-Scl) autoantibody, testing for these would most likely confirm the diagnosis.

FUTURE DIRECTIONS

The IIMs are a family of diseases and each may have its own underlying pathophysiology and optimal treatment approach. Further progress in elucidating disease mechanisms and assessing response to therapeutic interventions will likely depend upon our

ability to appropriately separate patients into relatively homogenous groups.

The classification criteria for IIMs proposed by the European Neuromuscular Centre in 2004 recognized that an underlying autoimmune process could cause a predominantly necrotizing myopathy and labeled these patients as having IMNM. This represented a significant step forward in subcategorizing the different forms of myositis. However, subsequent observations suggest that IMNM is probably not one, but at least several different diseases. For example, we have observed that refractory anti-SRP patients usually respond well to treatment with rituximab [22], whereas statin-naïve anti-HMGCR patients frequently do not (personal observation); this suggests that patients with anti-SRP-associated IMNM are inherently different from those with anti-HMGCR-associated IMNM. Similarly, statin-exposed anti-HMGCR-positive patients often improve dramatically with intravenous immunoglobulin (personal observation), whereas statin-naïve anti-HMGCR patients may be quite refractory to any immunosuppressive therapy [18]. These retrospective and anecdotal observations will need to be confirmed in formal clinical trials that separate IMNM patients into distinct subsets on the basis of muscle biopsy features, autoantibody type, and statin exposure status. Only then will we be able to make evidence-based therapeutic recommendations for different necrotizing myopathy subtypes.

Although our understanding of pathophysiology is limited in polymyositis and dermatomyositis, some progress has been made. For example, cytolytic T cells probably directly damage muscle fibers in polymyositis [23], and recent studies suggest that interferon may play a pathophysiological role in dermatomyositis [24]. In contrast, mechanisms underlying cell death in patients with the various forms of IMNM remain obscure. Although autoantibody titers correlate with disease activity in anti-SRP [25] and statin-associated anti-HMGCR patients [18], it has not been demonstrated that these antibodies are directly pathogenic. Future experiments could address this issue by determining whether these antibodies cause or exacerbate muscle damage when transferred into experimental animals. In the event that autoantibodies are not pathogenic in IMNM, then the analysis (e.g. gene expression profiling) of muscle biopsy tissue from patients with different forms of IMNM may uncover distinct pathogenic pathways.

Finally, it remains to be determined whether anti-SRP and anti-HMGCR patients who have significant inflammatory infiltrates on muscle biopsy have a different disease than those with

the same autoantibody profiles, but with predominantly necrotizing myopathies.

CONCLUSION

We now recognize that myositis is not one disease, but a complex and heterogeneous group of diseases. One might hope that some readily identifiable histologic feature on muscle biopsy would allow a specific diagnosis. However, our review of the evidence suggests this is not the case for those who have a necrotizing myopathy on muscle biopsy. Rather, we have seen that patients with an auto-immune necrotizing myopathy may have statin-triggered myositis, the antisynthetase syndrome, scleroderma myopathy, or dermatomyositis, among others. As patients with each of these diseases may also have inflammatory muscle biopsies, the biopsy is of limited utility in making a specific diagnosis.

If muscle biopsy is not sufficient for diagnosis, can we look to myositis-specific autoantibodies to completely subtype myositis patients? Although these autoantibodies are diagnostically and prognostically useful, they also have limitations. For example, statin-exposed and statin-naïve anti-HMGCR-positive patients have the same autoantibody but may have different diseases as suggested by the observation that the latter do not reliably respond to immunosuppression. It remains to be shown whether patients who share other myositis-specific autoantibodies could also have distinct disease subtypes.

Significant progress has been made in understanding and recognizing the different subtypes of IIMs. In the future, a single biomarker may allow different forms of myositis to be unequivocally diagnosed. However, as when Bohan and Peter published their diagnostic criteria, clinicians today must often incorporate the history, physical exam findings, laboratory values, and muscle biopsy features to diagnose myositis and to distinguish between patients with different forms of this disease.

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None.

Conflicts of interest

A.L.M. holds a patent for anti-HMGCR antibody testing.

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