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Which non-autoimmune myopathies are most frequently misdiagnosed as myositis?

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Abstract

Purpose of review—To discuss the spectrum of non-autoimmune myopathies that may be misdiagnosed as autoimmune myopathy.

Recent findings—Inherited myopathies such as dysferlinopathy, calpainopathy, and facioscapulohumeral dystrophy may be misdiagnosed as autoimmune myopathy, especially when they have inflammatory muscle biopsies. Inclusion body myositis is frequently misdiagnosed as polymyositis when rimmed vacuoles are absent on muscle biopsy and a careful neuromuscular evaluation is not performed. Hypothyroid myopathy can be misdiagnosed as immune-mediated necrotizing myopathy if thyroid function tests, including a T4 level, are not obtained. Self-limited statin myopathy can be distinguished from statin-associated autoimmune myopathy because patients with the former do not have autoantibodies recognizing HMG-CoA reductase.

Summary—Autoimmune myopathies can usually be distinguished from non-autoimmune myopathies based on a combination of the patient history, neuromuscular exam, laboratory findings, and/or muscle biopsy features.

Keywords

Autoimmune myopathy; polymyositis; inclusion body myositis; muscular dystrophy; endocrine myopathy

INTRODUCTION

The autoimmune myopathies include dermatomyositis (DM), polymyositis (PM), and immune-mediated necrotizing myopathy (IMNM) [1]. In contrast, non-autoimmune myopathies include inherited, endocrine, and toxic myopathies. Distinguishing autoimmune from non-autoimmune myopathies is essential since, in general, only the former respond to immunosuppressive therapy. This review will focus on those non-autoimmune myopathies that are frequently misdiagnosed as an autoimmune myopathy. Of note, although emerging

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Conflicts of interest

Until 2014, Dr. Andrew Mammen received royalties from INOVA Diagnostics for a patent on anti-HMGCR autoantibody testing entitled “Compositions and Methods for Characterizing a Myopathy”.

evidence suggests that sporadic inclusion body myositis (IBM) may have a significant autoimmune component [2], this disease will be treated as a non-autoimmune myopathy given that it rarely, if ever, improves with existing immunosuppressive therapies.

INHERITED MYOPATHIES

The inherited myopathies can be divided into two main groups, metabolic myopathies and muscular dystrophies. The metabolic myopathies include disorders of glycogen storage and fatty acid oxidation. Patients with either of these can experience episodic muscle weakness, muscle pain, and elevated serum muscle enzyme levels. Such episodes are typically triggered by exercise, fasting, or illness. In addition, patients with glycogen storage disorders may have proximal weakness and elevated muscle enzyme levels between episodes of more severe muscle symptoms; these patients are occasionally misdiagnosed as having an autoimmune myopathy. However, as disorders of fatty acid oxidation are only rarely accompanied by fixed weakness and/or elevated creatine kinase (CK) levels, they are not discussed further here.

Although more than a dozen different glycogen storage disorders have been identified, myophosphorylase deficiency (i.e., McArdle's disease) and adult-onset acid maltase deficiency (i.e., Pompe disease) are the most common and most likely to be misdiagnosed as autoimmune myopathy. Myophosphorylase deficiency is an autosomal recessive disorder caused by mutations in *PYGM*, a gene that encodes a muscle-specific glycogen phosphorylase [3]. Affected patients are unable to utilize glycogen stores for energy and present in childhood or early adulthood with exercise-induced cramping, markedly elevated CK levels (often over 10,000 IU/L), and myoglobinuria. Interestingly, after ~10 minutes of exercise, these symptoms may spontaneously improve or resolve. This unique characteristic of myophosphorylase deficiency, known as the "second wind phenomenon", distinguishes it from other metabolic myopathies. Although younger myophosphorylase deficiency patients are usually strong between episodes, they may have moderately elevated CK levels even when resting. Moreover, older patients can develop progressive proximal muscle weakness that, in association with elevated muscle enzyme levels, may lead to a misdiagnosis of autoimmune myopathy. This diagnostic error can usually be avoided by eliciting a history of exercise-induced cramping with the second-wind phenomenon. In patients with this unique feature, a diagnosis of myophosphorylase deficiency can be confirmed directly by sequencing the *PGYM* gene. The diagnosis should also be suspected in patients who have muscle biopsies that reveal subsarcolemmal glycogen deposits best seen with periodic acid-Schiff (PAS) staining. In these cases, the diagnosis can be confirmed by demonstrating the absence of myophosphorylase activity on frozen muscle sections. Unfortunately, effective therapies for myophosphorylase deficiency are not yet available.

Acid maltase deficiency is an autosomal recessive disease caused by mutations in *GAA*, the gene encoding the lysosomal enzyme acid alpha-glucosidase. Individuals with *GAA* mutations resulting in severe reductions in enzymatic activity (<1% of normal) typically present as infants with hypotonia, diaphragmatic weakness, and cardiac involvement; these patients may die within one year of birth. Patients with 1-6% of normal enzymatic activity may not present until childhood, but still develop severe proximal muscle weakness and may

die from respiratory failure within 5 to 20 years. In contrast, patients with 1-29% of normal acid alpha-glucosidase activity may be asymptomatic until middle age and only then develop gradually progressive proximal muscle weakness [4,5]. While these patients may be misdiagnosed as having an autoimmune myopathy, several clues may suggest the possibility of adult onset acid maltase deficiency instead. First, myotonic discharges on electromyography (EMG) can be seen in acid maltase deficiency but are rare in patients with autoimmune myopathy. Second, as the diaphragm tends to be more severely involved than other skeletal muscles, a low forced vital capacity on pulmonary function testing should raise a suspicion for acid maltase deficiency. And finally, muscle biopsies from patients with acid maltase deficiency usually reveal PAS-positive vacuoles and do not have inflammatory infiltrates as seen in those with autoimmune myopathy. The diagnosis of acid maltase deficiency can be confirmed using an enzyme activity assay and the precise mutations subsequently identified by gene sequencing. Since an FDA-approved enzyme replacement therapy is now approved for this condition, making the correct diagnosis is especially important.

Muscular dystrophies represent the second main group of inherited conditions that may be confused with autoimmune myopathy. While there are more than a hundred different types of muscular dystrophy, this review will focus on a few that are most often misdiagnosed as autoimmune myopathy because they can present with proximal muscle weakness, elevated serum muscle enzyme levels, muscle biopsies including prominent collections of inflammatory cells, and/or no family history due to an autosomal recessive inheritance pattern. These include dysferlinopathy, calpainopathy, and facioscapulohumeral dystrophy.

Dysferlinopathy patients have pathogenic mutations on both copies of their *DYSF* gene, resulting in a defective protein unable to participate in its usual role in muscle membrane repair. Such patients most often present in their teens or early twenties with slowly progressive proximal muscle weakness and CK levels over 10,000 IU/L. A subset of dysferlinopathy patients present with distal weakness and thus are rarely misdiagnosed as autoimmune myopathy. The majority of dysferlinopathy patients have muscle biopsies that include cellular infiltrates and upregulation of major histocompatibility complex (MHC) class I molecules [6] as frequently described in autoimmune myopathies; these patients are most vulnerable to misdiagnosis. Indeed, one study revealed that 10 out of 40 dysferlinopathy patients were initially treated with corticosteroids and other immunosuppressive agents because they were misdiagnosed with polymyositis [7]. Such therapeutic misadventures can be avoided by immunostaining muscle biopsies for dysferlin protein, which is absent in patients with dysferlinopathy. Alternatively, genetic testing revealing pathogenic mutations in each *DYSF* gene can also confirm the diagnosis of dysferlinopathy.

The *CAPN3* gene encodes calpain-3, a calcium-dependent protease that plays a role in cytoskeletal remodeling and membrane repair. Patients with homozygous pathogenic *CAPN3* mutations have calpainopathy and typically present in childhood with progressive proximal muscle weakness and mildly to moderately elevated CK levels. Individuals with calpainopathy also often have scapular winging, which is only rarely present in patients with autoimmune myopathy. However, as muscle biopsies may reveal infiltrates consisting of

eosinophils [8] or macrophages and lymphocytes [9], this occasionally leads to an erroneous diagnosis of autoimmune myopathy. This error can be avoided by immunohistochemical staining for calpain-3 on muscle biopsy (staining is reduced in those with calpainopathy) or by *CAPN3* gene sequencing.

Facioscapulohumeral dystrophy typically presents in young adults who complain of arm weakness. This weakness is often asymmetric and the forearm muscles may be dramatically atrophied despite relatively normal deltoid muscles, resulting in characteristic “Popeye” arms. In addition, weakness of the shoulder girdle muscles often results in scapular winging. Finally, facial weakness is usually present on examination even if it is not noted by the patient. Although asymmetric weakness, sparing of deltoid muscles, scapular winging, and facial weakness would all be atypical in a patient with autoimmune myopathy, one-third of facioscapulohumeral dystrophy patients have inflammatory muscle biopsies with CD4+ and CD8+ T-cells [10,11]; these patients are occasionally diagnosed as having polymyositis. The correct diagnosis can be confirmed by genetic testing. In contrast to dysferlinopathy or calpainopathy, facioscapulohumeral dystrophy is most often inherited in an autosomal dominant fashion because of deletions in the D4Z4 repeat sequence in chromosome 4. However, as several genetically distinct forms of facioscapulohumeral dystrophy have been identified, additional genetic tests may be utilized to confirm the diagnosis.

INCLUSION BODY MYOSITIS

Sporadic IBM is the most common myopathy presenting in older adults and probably the muscle disease most frequently misdiagnosed as a treatable autoimmune myopathy. In one study, up to 50% of IBM patients were initially diagnosed as having polymyositis or another muscle disease [12]. In most cases, the typical features of IBM should help clinicians who perform a detailed neuromuscular exam distinguish IBM from polymyositis and other forms of autoimmune muscle disease. First, IBM patients have a unique pattern of muscle involvement including not only proximal muscle weakness, but also weakness of the deep finger flexors, wrist flexors, and ankle dorsiflexors. In many cases, the quadriceps are weaker than the hip flexors, which would be highly unusual in patients with autoimmune muscle disease. Also, many IBM patients have orbicularis oculi weakness which is rare in patients with autoimmune myopathies. Finally, whereas symmetric muscle involvement is the rule in patients with autoimmune myopathy, asymmetric muscle weakness is often noted in IBM patients. Importantly, about half of IBM patients have dysphagia. However, as this can also be present in patients with autoimmune myopathy, it may not be less helpful in distinguishing between the two conditions.

The typical muscle biopsy features of inclusion body myositis include not only invasion of healthy myofibers by cytotoxic CD8+ T cells, as described in polymyositis, but also rimmed vacuoles and evidence of mitochondrial dysfunction. When present, this combination of features should strongly suggest the diagnosis of IBM. However, approximately 20% of patients with otherwise typical clinical features of IBM have inflammation but no rimmed vacuoles on muscle biopsy [13]. These patients can easily be misdiagnosed as having polymyositis if asymmetric weakness, distal weakness, and/or orbicularis oculi weakness are not revealed by a careful neuromuscular exam.

It has been noted that some patients initially presenting with symmetric proximal muscle weakness, high serum CK levels, inflammatory muscle biopsies, and responsiveness to immunosuppressive therapy eventually evolve into a typical IBM phenotype. For example, we recently described 5 patients with myositis in the context of HIV infection who presented with both proximal and distal weakness and who had improved proximal muscle strength following immunosuppressive therapy. However, each of these patients went on to develop weakness primarily affecting wrist flexors, finger flexors, knee extensors, and/or ankle dorsiflexors as commonly seen in IBM [14*]. Thus, even patients with an established diagnosis of treatment-responsive polymyositis should be carefully monitored over time for the development of weakness in an IBM pattern. Whether such patients should continue to be treated with immunosuppressive agents remains unknown and may require an empiric trial of drug tapering.

ENDOCRINE MYOPATHIES

While mild hypothyroidism may be associated with fatigue, muscle pain, and cramping, patients with severe hypothyroidism can have proximal muscle weakness, markedly elevated CK levels, and a necrotizing muscle biopsy [15]. Such patients can easily be misdiagnosed as having immune-mediated necrotizing myopathy if thyroid function tests are not ordered. Importantly, patients with central hypothyroidism may have a necrotizing myopathy even the context of a normal TSH level [16]. In these cases, low or absent circulating T4 levels should suggest the correct diagnosis. While hyperthyroidism is less frequently a cause of myopathy, this should also be considered. Finally, hyperadrenocorticism associated with Cushing syndrome can cause a myopathy with proximal muscle weakness. However, other features of Cushing syndrome such as abdominal stria and moon facies should alert clinicians to this condition. Moreover, since patients with myopathy caused by Cushing syndrome have normal CK levels and non-inflammatory muscle biopsies, they should only rarely be misdiagnosed with an autoimmune myopathy.

TOXIC MYOPATHIES

Among the more than 39 million adults in the United States currently prescribed a statin [17], most tolerate them well. However, muscle symptoms may occur in as many as 10% of patients and this is a common reason for stopping statin therapy [18]. Given that the overwhelming majority of those with statin-related muscle symptoms do not have weakness or elevated CK levels, these individuals are not typically misdiagnosed with autoimmune myopathy. However, rare patients will experience more severe statin toxicity with elevated CK levels and proximal muscle weakness. This more severe statin-related toxicity, which some evidence suggests may result from mitochondrial dysfunction [19*], occurs at an estimated rate of 0.4 per 10,000 person years of statin treatment [20]. Fortunately, most patients with this form of self-limited statin myopathy will recover spontaneously after stopping the statin. However, especially since the discovery of statin-associated autoimmune myopathy [21], some patients with self-limited statin toxicity may be misdiagnosed as having an autoimmune process and treated inappropriately with corticosteroids and/or other immunosuppressive treatments. Distinguishing patients with statin-associated autoimmune myopathy from those with either mild or severe self-limited statin toxicity can be

accomplished by testing for autoantibodies recognizing HMG-CoA reductase, since only the former patients have these autoantibodies [22–24*].

In addition to statins, several other drugs are known to cause myopathy; in rare these individuals might be suspected of having an autoimmune myopathy. For example, colchicine can cause a myopathy characterized by vacuolization on biopsy [25]. Since the potential for toxicity is related to circulating levels of colchicine and this drug is excreted by the kidneys, renal dysfunction may precipitate toxicity in individuals who have been taking colchicine without difficulty for years.

Amphiphilic drugs such as chloroquine, hydroxychloroquine, amiodarone, procainamide, and doxorubicin may cause myopathy by disrupting the muscle cell membrane. Particularly in patients taking hydroxychloroquine for lupus, the possibility of co-existing autoimmune myopathy may be considered when weakness develops. If discontinuing the medication does not lead to resolution of weakness within a few weeks or weakness progresses despite drug cessation, then a muscle biopsy may be considered. In patients with drug-induced myopathy, the biopsy should show vacuoles that stain positively for lipids and acid phosphatase rather than inflammation.

Although in the developed world zidovudine is rarely used to treat HIV infection, it's low cost makes it an attractive treatment in poorer countries. Myopathy is a well-described adverse effect of zidovudine and can present with high CK levels and proximal weakness. Since HIV-infected patients may also develop autoimmune myositis, it may be difficult to distinguish drug toxicity from an autoimmune process. In these cases, muscle biopsies showing ragged red fibers and numerous cytochrome oxidase-negative fibers reflecting mitochondrial dysfunction should suggest zidovudine toxicity. In contrast, an inflammatory muscle biopsy would be more consistent with an autoimmune process.

CONCLUSIONS

A variety of different disease processes can mimic an autoimmune myopathy. However, the history and expert neuromuscular examination can usually help distinguish these. For example, a careful drug history can suggest the possibility of a toxic myopathy. Similarly, a history of muscle cramping with exercise should prompt an evaluation for metabolic myopathies. The presence of facial weakness, asymmetric weakness, scapular winging, or distal weakness out of proportion to proximal weakness should suggest the possibility of inclusion body myositis or a muscular dystrophy. Laboratory testing may also be helpful in excluding endocrine myopathies. It's also helpful to remember that most patients with autoimmune myopathy have multisystem disease with skin, joint, or lung involvement whereas those with non-autoimmune myopathy do not. Therefore, the absence of extramuscular symptoms should always prompt a search for a non-autoimmune cause of the myopathy. An exception to this rule would be patients with immune-mediated necrotizing myopathy, who rarely have extramuscular manifestations [26,27]. However, these patients can usually be identified based on the presence of autoantibodies recognizing the signal recognition particle or HMG-CoA reductase. Finally, when a patient with a diagnosis of autoimmune myopathy worsens or does not improve despite aggressive immunosuppressive

therapy, the possibility of a different or co-existing non-autoimmune condition should be considered.

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KEY POINTS

- Facial weakness, asymmetric weakness, scapular winging, and/or prominent distal weakness are uncommon features of autoimmune myopathies and suggest the possibility of inclusion body myositis or a muscular dystrophy.
- Exercise-induced muscle cramping and/or CK elevations should prompt an evaluation for metabolic myopathies.
- A careful review of medications is required to exclude the possibility of a toxic myopathy caused by statins, colchicine, hydroxychloroquine, and others.
- A non-autoimmune etiology should be suspected in patients with muscle disease who do not have extra-muscular manifestations or a myositis autoantibody.