Autoantibodies in Immune Myopathies

Antibody testing results provide clinically useful information.

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Immune myopathies include dermatomyositis, polymyositis, myositis associated with antisynthetase syndrome, immune-mediated necrotizing myopathy, and inclusion body myositis. This article gives a brief overview of these syndromes with a more detailed discussion on the emerging role of autoantibodies in their evaluation.

Clinical Presentation

Dermatomyositis presents with subacute (days to months) relatively symmetric weakness in the proximal muscles of the arms and legs. Neck flexor weakness and dysphagia can also occur. Characteristic skin findings include an erythematous macular rash on the face, neck, and anterior chest (V-sign); shoulders and upper back (shawl sign); and extensor surfaces of the elbows, knuckles, and knees (Gottron sign). A periorbital purplish discoloration (heliotrope rash) or a papular erythematous rash over the knuckles (Gottron papules) is also common. Amyopathic dermatomyositis (ie, rash without notable muscle weakness) can occur in up to 20% of individuals; muscle weakness in the absence of rash can also occur. Cardiac symptoms (eg, arrhythmias, pericarditis, myocarditis, and diastolic heart failure) may occur and interstitial lung disease (ILD) is present in up to 20% of those affected. Rheumatologic, vasculitic, and other connective tissue diseases may be present. There is an increased risk of malignancy in adults, occurring in up to 15% of cases within 2 to 3 years of presentation; individuals with dermatomyositis should have comprehensive age-appropriate malignancy screening.

Polymyositis, similar to other autoimmune conditions, presents with predominantly proximal symmetric weakness in the arms and legs. Dysphagia and myalgias can also occur. Cardiac involvement, including conduction system defects and diastolic heart failure, are reported in up to 30% of cases, and ILD is present at a similar frequency to dermatomyositis.

Inflammatory myopathy in association with anti-aminocarboxyl-tRNA synthetase antibodies is termed antisynthetase syndrome and occurs in 30% of individuals with inflammatory myopathy. Antisynthetase syndrome includes relatively acute-onset myositis, ILD, constitutional symptoms (fever and weight loss), Raynaud’s phenomenon, nonerosive arthritis, and mechanic’s hands. When present, ILD tends to be severe and difficult to treat.

Immune-mediated necrotizing myopathy presents with acute or insidious onset of progressive proximal weakness of the upper and lower extremities and, sometimes, the facial muscles. This myopathy can occur within the context of cancer (paraneoplastic), be associated with connective tissue diseases (eg, scleroderma and mixed connective tissue disease), or be idiopathic. The 3 types, based on antibody status, are antibody negative, anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) positive, and anti-signal recognition particle (SRP) positive. Anti-HMGCR myopathy can occur in association with previous statin use, although not everyone affected has a history of statin exposure. Anyone with immune-mediated necrotizing myopathy should have comprehensive malignancy screening.

Inclusion body myositis is the most common acquired myopathy in people over age 50 to 60 and is the only immune myopathy that is more common in men. It presents with slowly progressive asymmetric weakness of proximal and distal muscles in the upper and lower extremities, with a predilection for early involvement of the deep wrist and finger flexors, ankle dorsiflexors, and knee extensors. Dysphagia occurs in up to 60% of cases and, rarely, may be the sole presenting feature.

Myositis Antibodies

Myositis antibodies are subdivided into myositis-specific antibodies (MSAs) and myositis-associated antibodies.

Myositis-Specific Antibodies

MSA status can help define specific clinical phenotypes, facilitate diagnosis, identify those at risk for
comorbidities and hence in need of surveillance screening, offer prognostic information and help predict treatment response (Table).

Approximately 60% to 70% of patients with dermatomyositis have an MSA, which may preclude the need for muscle biopsy. Anti-Mi-2 and anti NXP-antibody are associated with a better response to treatment, although anti-NXP-2 carries a higher risk of malignancy and typically has onset at an earlier age. Anti-MDA-5 positivity is associated with the poorest survival because of associated ILD; close monitoring for pulmonary complications is recommended. Anti-TIF1-γ antibodies are associated with a greatly increased risk of malignancy with a specificity of 89% and sensitivity of 78%. There is no clear consensus on the frequency of malignancy screening for those

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<td><strong>Dermatomyositis</strong></td>
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<tr>
<td>Anti-Mi-2</td>
<td>Subacute onset of classic dermatomyositis, typical skin involvement</td>
<td>Good response to corticosteroids, which may be sufficient alone</td>
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<tr>
<td>Anti-MDA5</td>
<td>Severe skin involvement, can present as amyopathic form, rapidly progressive interstitial lung disease (ILD), vasculopathy (digital ulcerations)³</td>
<td>Poorest survival of all DM types due to ILD, avoid methotrexate (pulmonary toxicity), annual pulmonary function test (PFT), chest CT if suspicion of ILD</td>
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<tr>
<td>Anti-NXP-2</td>
<td>Mild-to-moderate weakness, classic skin rash, calcinosis, increased malignancy risk</td>
<td>Good response to treatment, monitor for malignancy</td>
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<tr>
<td>Anti-SAE</td>
<td>Mild-to-moderate muscle involvement and typical skin findings</td>
<td>Monitor for malignancy</td>
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<tr>
<td>Anti-TIF1-γ</td>
<td>Severe skin manifestations (hyperkeratotic papules, hypopigmentation, telangiectasia) greatly increased malignancy risk</td>
<td>Monitor for malignancy</td>
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<td><strong>Myositis overlap syndromes</strong></td>
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<td>Antisynthetase</td>
<td>ILD, nonerosive arthritis, Raynaud’s phenomenon, mechanic’s hands, fever, occasional rash, no known increased malignancy risk⁴</td>
<td>Often requires 2nd-line agent, avoid methotrexate (pulmonary toxicity); anti-Jo associated with lower likelihood of treatment-free remission; obtain annual PFT, chest CT if clinical suspicion of ILD</td>
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<td>Anti-La, PM-Scl, Ro, Ku, U1-RNP</td>
<td>Myositis overlap syndromes; also associated with Sjögren’s syndrome, systemic lupus erythematosus (SLE), scleroderma, mixed connective tissue disease (MCTD), rheumatoid arthritis (RA)</td>
<td>Typically responds well to immunotherapy</td>
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<td><strong>Immune-mediated necrotizing myopathy</strong></td>
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<td>Anti-SRP</td>
<td>Immune-mediated necrotizing myopathy (IMNM), aggressive disease, severe weakness, pulmonary involvement, dysphagia, axial muscle weakness, more cardiac complication risk with earlier onset, not associated with malignancy⁷</td>
<td>Poor response to corticosteroids, consider 2nd-line agent at presentation; consider rituximab early for those unresponsive to combination of corticosteroids and 2nd-line agents</td>
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<td>Anti-HMGCR</td>
<td>IMNM, prior statin exposure (60%), potentially increased malignancy risk, HMGCR-myopathy can mimic limb-girdle muscular dystrophy (LGMD)⁸</td>
<td>Poor response to corticosteroid, consider 2nd-line agent at presentation or in 1st month, consider intravenous immunoglobulin (IVIG) at presentation, add IVIG at 6 months if no response to monotherapy⁹</td>
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<td><strong>Inclusion body myositis</strong></td>
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<td>Anti-cN1A</td>
<td>Inclusion body myositis (IBM; 70% of patients); also associated with Sjögren’s syndrome or SLE; rarely found in persons with dermatomyositis or polymyositis and healthy people</td>
<td>Positive test result may preclude need for muscle biopsy; no response to current clinically available immunomodulatory treatment</td>
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with dermatomyositis who have undergone initial screening on presentation. It is judicious to monitor patients with anti-TIF1-γ and anti-NXP-2 antibodies closely for malignancy, particularly in the first 5 years of diagnosis. The most common antisynthetase antibody, anti-Jo-1 is also the most common MSA, and testing for antisynthetase antibodies is important to consider in anyone presenting with myositis, given the high prevalence of severe ILD. It is also advisable to closely monitor antibody-positive individuals for pulmonary complications. Treatment of antisynthetase antibody-associated disease often requires second-line agents in addition to corticosteroids, particularly for those with anti-Jo-1 antibodies. It is advisable to avoid methotrexate as a second-line agent if possible, given the additional risk of pulmonary toxicity with methotrexate.

Anti-SRP antibodies are associated with immune-mediated necrotizing myopathy, an aggressive disease that can be challenging to control. Individuals with anti-SRP myopathy have less predictable response to corticosteroids compared with those with anti-HMGCR myopathy, and more aggressive treatment may be warranted.9

Myositis-Associated Antibodies
Detection of MAA supports a diagnosis of myositis overlap syndrome (Table). In up to 15% of people with a myositis overlap syndrome, MAAs are present at initial presentation but clinical features of the overlapping rheumatologic condition are not evident, developing over time. Routine testing for the MAAs is recommended at initial presentation of inflammatory myopathy, even in the absence of supporting clinical features of rheumatologic disease.

Anti-cN1A antibodies have a sensitivity of 70% and specificity of 92% for diagnosis of inclusion body myositis,11,12 and anti-cN1A positivity with clinical features of inclusion body myositis may preclude the need for an invasive muscle biopsy. Anti-cN1A is not specific for inclusion body myositis, however, and can also occur in people with other rheumatologic disease and healthy individuals.

Anti-HMGCR are present in 20% to 60% of people with IMNM,13,14 and approximately two-thirds of individuals with anti-HMGCR positivity have a history of prior statin use. Expert consensus suggests treating anti-HMGCR myopathy with both corticosteroids and a second-line agent, either at initial presentation or within 1 month thereof, depending on symptom severity and corticosteroid response. Intravenous immunoglobulin (IVIG) therapy should be added within 6 months of presentation if there is no improvement with initial measures.10 In those with anti-HMGCR myopathy who have contraindications to steroids, or prefer to avoid steroids, IVIG has been beneficial as initial first-line monotherapy.15

Conclusion
Results of antibody testing offer useful adjunctive clinical information when evaluating patients with potential immune-mediated myopathies, including clinical characterization, diagnosis, guidance of additional workup and screening, prognosis, and therapeutic decision making. Given the greater availability of immunoassays for myositis antibodies in current clinical practice, it is important for clinicians to be familiar with their interpretation and their potential clinical roles.