# Idiopathic Inflammatory Myopathies

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## Case-Based Questions (please see page 3 for answers)

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| 1. | A 67-year-old man with a history of diabetes and hyperlipidemia presents with a proximal muscle weakness of several weeks' duration. CK level is elevated (2756 U/L) and electromyography shows evidence of membrane instability suggestive of a necrotizing or inflammatory myopathy. A biopsy of quadriceps muscle is performed and shows frequent degenerating/regenerating muscle fibers, scant endomysial inflammation consisting mainly of CD8+ T cells, diffuse upregulation of MHC-1, and scattered fibers with sarcolemmal deposition of C5b9 (complement membrane attack complex). Myositis-specific antibody panel is negative. Which of the following histopathologic features was likely also seen in this patient's biopsy? | |
| | a. | Linear perimysial positivity on alkaline phosphatase stain |
| | b. | Randomly distributed fibers with densely packed, LC3- and p62-positive small puncta |
| | c. | Sarcoplasmic expression of MxA in perifascicular muscle fibers |
| | d. | TDP43-positive coarse sarcoplasmic aggregates |

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| 2. | A 37-year-old woman with no significant prior medical history presents with a shortness of breath, fingertip ulcers, and mild proximal muscle weakness. A muscle biopsy is performed and shows rare degenerating/regenerating muscle fibers in no particular distribution, mild diffuse upregulation of MHC-1, and mild diffuse MxA positivity in the fiber sarcoplasm. Which of these myositis-specific antibodies is most likely to be positive? | |
| | a. | Anti-MDA5 |
| | b. | Anti-Mi-2 |
| | c. | Anti-NXP2 |
| | d. | Anti-SAE |
| | e. | Anti-TIF1γ |

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| 3. | On your consultation neuromuscular pathology service, you receive an outside muscle biopsy with a clinical history "55-year-old woman with elevated creatine kinase level; rule out myositis"; no other clinical information is provided. The biopsy shows perifascicular fiber atrophy and perifascicular necrosis, perimysial edema and fragmentation, macrophage-rich, largely perimysial inflammatory infiltrate, and intranuclear actin inclusions in perifascicular muscle fibers. MxA, LC3, and p62 immunostains are negative. Which of the following is the most likely diagnosis? | |
| | a. | Anti-HMGCR-positive immune-mediated necrotizing myopathy |
| | b. | Anti-Jo-1-positive anti-synthetase syndrome-associated myositis |
| | c. | Anti-Mi-2-positive dermatomyositis |
| | d. | Anti-TIF1γ-associated dermatomyositis |
| | e. | Inclusion body myositis |

**Scroll to Page 3 for Answers**

Question 1: Correct answer and rationale: The correct answer is (b). The clinical and pathologic features of this case are characteristic of immune-mediated necrotizing myopathy (IMNM), which can be associated with anti-SRP or anti-HMGCR antibodies but can also be seronegative (as in this example). Regardless of the serotype, IMNMs show randomly distributed non-necrotic fibers with densely packed autophagic puncta, best demonstrated by immunohistochemistry for LC3 and p62 (but also detectable by electron microscopy). Linear alkaline phosphatase positivity in the perimysium is a feature of anti-synthetase syndrome-associated myositis (ASM), although it can also be seen in anti-Mi-2-assocaited dermatomyositis (DM). MxA upregulation is a marker of interferon type 1 (α/β) response and is seen in DM. TDP43-positive sarcoplasmic aggregates are a feature of inclusion body myositis (IBM).

Question 2: Correct answer and rationale: The correct answer is (a). The clinical and pathologic features of this case are most compatible with DM associated with anti-MDA antibodies, which is characterized by mucocutaneous ulceration, rapidly progressive interstitial lung disease, and mild (or absent) muscle weakness. Muscle biopsy findings are mild and lack perifascicular fiber atrophy that is seen in all other types of DM; unless there is patchy or diffuse MxA upregulation, they can be nonspecific / nondiagnostic. The other four listed antibodies (anti-Mi-2, anti-NXP2, anti-SAE and anti-TIF1γ) are associated with DM subtypes that show "classic" DM findings (perifascicular fiber atrophy and perifascicular MxA upregulation).

Question 3: Correct answer and rationale: The correct answer is (b). The pathologic features of this case are diagnostic of ASM, and would be compatible with any anti-synthetase antibody (including anti-Jo-1). The main differential diagnosis for ASM is anti-Mi-2-assocated DM, which can be histologically similar but shows perifascicular MxA upregulation and lacks intranuclear actin inclusions. Anti-TiF1γ-associated DM shows well-developed perifascicular atrophy and MxA positivity, but little or no inflammation and no perifascicular fiber necrosis. IMNM (regardless of the serotype) shows little to no inflammation, randomly distributed degenerating/regenerating muscle fibers, no MxA staining, and randomly distributed fibers with densely packed LC3/p62-positive autophagosomes. IBM shows endomysial inflammation (which consists of CD8+ T cells and macrophages and can be seen invading intact muscle fibers), chronic myopathic features, mitochondrial abnormalities, and LC3/p62/TDP43-positive rimmed vacuoles / coarse sarcoplasmic aggregates.