Metabolic and Toxic Myopathies

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

1.	The patient is a 47-year-old man (he/him) with a history of "getting weaker" for several years. He gets tired more easily than he used to, and feels short of breath when he pushes himself. While these symptoms are relatively recent, he always found PE classes challenging and was told by his gym teacher that "he wasn't trying hard enough". On physical exam, there is moderate weakness of proximal and axial muscles. CK level is elevated (1353 U/L). A biopsy of quadriceps femoris is performed and appears relatively normal on routine muscle stains, with the exception of a few randomly distributed vacuolated fibers. Which of the following ultrastructural features would support the diagnosis of adult-onset Pompe disease?
a.	Curvilinear bodies
b.	Increase in membrane-bound glycogen and autophagic vacuoles
c.	Mitochondrial crystalline arrays
d.	Myofibrillar disarray with Z-band streaming
e.	Subsarcolemmal glycogen lakes

2.	On your neuromuscular pathology service, you receive a periocular muscle biopsy from a patient with a history of progressive external ophthalmoplegia; unfortunately, the entire specimen is submitted in formalin. Which of the following stains would help establish the diagnosis of mitochondrial myopathy in this case?
a.	COX-SDH enzyme histochemistry
b.	Desmin immunohistochemistry
c.	Dual slow/fast myosin immunohistochemistry
d.	p62 immunohistochemistry
e.	SDH-B immunohistochemistry

3.	A 38-year-old gender-queer person (they/them) with a history of long-standing systemic lupus erythematosus develops subacute proximal muscle weakness; their medications include steroids and hydroxychloroquine (HCQ). CK level is normal, while electromyography shows myopathy without evidence of membrane instability. A muscle biopsy is performed to evaluate for steroid myopathy vs. HCQ myopathy vs. immune-mediated myopathy. Which of the following staining patterns on LC3 immunohistochemistry would favor the diagnosis of autophagic vacuolar myopathy consistent with HCQ myopathy?
a.	Coarse sarcoplasmic puncta in the fiber center
b.	Densely distributed fine sarcoplasmic puncta
c.	Diffuse sarcoplasmic staining
d.	Large subsarcolemmal inclusions
e.	Rimmed vacuoles

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Question 1: Correct answer and rationale: Correct answer is (b) – increase in the membrane-bound (i.e. lysosomal) glycogen and autophagic vacuoles is characteristic of adult-onset Pompe disease; while subsarcolemmal (and intermyofibrillar) glycogen increase is usually also present, those features can also be present in non-lysosomal glycogen storage myopathies (or, when present to a lower degree, entirely nonspecific). Curvilinear bodies are seen in ceroid lipofuscinoses and in patients treated with chloroquine or hydroxychloroquine. Mitochondrial crystalline arrays are seen in mitochondrial myopathies. Myofibrillar disarray with Z-band streaming is seen in many congenital myopathies but can also be present in patients treated drugs that inhibit microtubule polymerization (colchicine and vincristine).

Question 2: Correct answer and rationale: Correct answer is (e) – SDH-B immunohistochemistry. This immunostain, which targets subunit B of the respiratory chain complex II, results in a staining pattern analogous to SDH frozen section enzyme histochemistry and can therefore help establish the presence of mitochondrial hyperplasia ("ragged red fibers") on the FFPE tissue. (This stain is also useful in diagnosis of tumors that carry SDH-B mutations, such as pheochromocytomas and paragangliomas in inherited paraganglioma syndromes.) While COX-SDH enzyme histochemistry is very useful for establishing the diagnosis of a mitochondrial disorder, it can only be performed on the frozen tissue. Desmin and dual myosin immunostains can highlight the absence of desmin filaments and myofibrils in the parts of the fiber where normal myofibrillar architecture is replaced by abnormal accumulations of intracellular organelles and/or sarcoplasmic substances, but this staining pattern is not specific for mitochondrial disorders. p62 (or LC3) immunohistochemistry would not be useful in the provided clinical scenario because mitochondrial dysfunction does not lead to autophagy impairment.

Question 3: Correct answer and rationale: Correct answer is (a) – randomly distributed fibers with coarse LC3-positive sarcoplasmic puncta are highly suggestive of an autophagic vacuolar myopathy (AVM), but are not specific for HCQ myopathy (a similar pattern can be seen in colchicine or vincristine myopathy, late-onset Pompe disease, and genetic AVMs such as Danon disease and X-linked myopathy with excessive autophagy). Randomly distributed muscle fibers with densely distributed fine LC3-positive sarcoplasmic puncta are highly suggestive of an immune-mediated necrotizing myopathy (for details, please review April 2021 lecture in this series). LC3-positive rimmed vacuoles and/or large subsarcolemmal inclusions can be seen in AVMs, but are more typical of disorders with impaired granulophagy (such as hereditary inclusion body myopathies and sporadic inclusion body myositis). Diffuse sarcoplasmic LC3 staining is nonspecific and should not be seen on a properly optimized muscle LC3 immunohistochemistry. (Of note, p62 and LC3 staining patterns are similar in each of the described conditions, so p62 and LC3 immunohistochemistries can be used interchangeably.)