Chapter 5
A 45-Year-Old Woman with Proximal Limb Weakness and Skin Peeling on Fingertips

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History

A 45-year-old Caucasian woman presented to our neuromuscular clinic for evaluation of muscle stiffness and weakness. Seven months prior to the presentation, she developed stiffness and cramps in her hands and wrists. She saw a rheumatologist and did not receive a specific diagnosis. The symptoms partially resolved after taking a non-steroidal anti-inflammatory agent. She then developed stiffness in the muscles that surrounded her knees, especially in her hamstrings, which prevented her from doing yoga or squats. The symptom was worse in the morning and better after exercise. She subsequently experienced weakness getting out of a chair and walking up stairs. She also developed intermittent mild muscle pain around the shoulders and in the thighs. She returned to her rheumatologist who ordered serum creatine kinase (CK) level which came back markedly elevated at 13,000 U/L. She also saw a neurologist; the repeat CK level was 19,000 U/L. She denied pigmenturia or rigorous exercise prior to getting the CK checked. She underwent a left quadriceps muscle biopsy at a local hospital, which reportedly showed "a necrotizing myopathy consistent with rhabdomyolysis". She only took 3 days of steroids before the muscle

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biopsy, which helped a little. She denied chill, fever, weight loss, or breathing abnormalities. She denied febrile illness, myotoxic drug exposure, or foreign travel. She had no significant past medical history, and was on no medications. Family history was significant for hypothyroidism in her sister. She was an office worker.

Physical Examination

General examination was notable for the skin peeling at her fingertips and dupuytren's contracture involving the left digit 3. There was no skin rash. Cardiopulmonary examination was normal. Neurologic examination showed normal mental status, cranial nerve functions, sensation, coordination, and gait. Motor examination showed normal muscle tone, normal muscle bulk, and weakness in the bilateral deltoid (MRC 4+/5), infraspinatus (5−/5), and iliopsoas (4/5) muscles. Deep tendon reflexes were 2+ throughout. Toes were downgoing bilaterally.

Investigations

Serum CK level was 8,017 U/L. Complete blood count (CBC) and comprehensive metabolic panel were normal. Antinuclear antibodies (ANA), anti-extractable nuclear antigen antibodies (ENA), and rheumatoid factor were negative. Myositis antibody panel showed a positive anti-Jo-1 autoantibody. TSH and vitamin D levels were normal. Nerve conduction study (NCS) was normal. Needle electromyography (EMG) showed an irritable myopathy. A left deltoid muscle biopsy was performed.

Muscle Biopsy Findings

The left deltoid muscle biopsy (Fig. 5.1) showed an inflammatory myopathy with preferential perifascicular myofiber necrosis (Fig. 5.1a). The inflammation was predominantly perimysial, with focal extension into endomysium (Fig. 5.1b). The alkaline phosphatase reactivity was increased in perimysial connective tissue, indicating connective tissue damage (Fig. 5.1c). Perifascicular atrophy was present in several fascicles, which was more noticeable in the ATPase stains (Fig. 5.1d). There was no COX-deficient fiber. The findings are consistent with an inflammatory myopathy and compatible with antisynthetase syndrome (ASS).

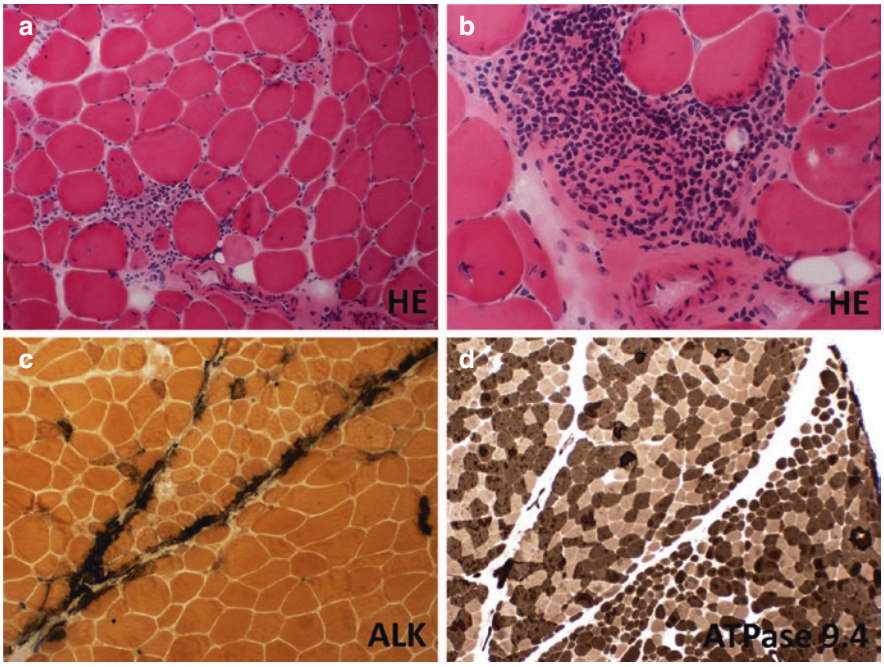

Fig. 5.1 Hematoxylin and eosin stain (HE) shows active myopathy with a large collection of lymphocytic infiltrates in perimysium and surrounding a perimysial blood vessel. Alkaline phosphatase stain (ALK) shows abnormal reactivity in scattered regenerating fibers and perimysium. APTase pH 9.4 stain (ATPase 9.4) shows 3 adjacent fascicles with perifascicular atrophy

Additional Investigation After the Muscle Biopsy Diagnosis

Given the biopsy findings and the presence of anti-Jo-1 autoantibody, the patient had computed tomography (CT) of chest, which showed patchy ground glass opacities, minimal reticulation, bronchiectasis, and mild honeycombing at the bilateral lung bases. Minimal ground glass opacities were also noted in the lingula. The findings are consistent with interstitial lung disease (ILD). CT of abdomen and pelvis was unremarkable. The age- and gender-appropriated cancer screening was unrevealing. During the follow up visit, she reported intermittent left hand coldness and cyanosis. Angiography revealed left brachial artery occlusion. Transesophageal echocardiogram (TEE) did not reveal any cardioembolic source.

Final Diagnosis

Antisynthetase Syndrome

Patient Follow-up

The patient was treated with Prednisone 40 mg once daily. She underwent left axillary-to-radial bypass using a non-reversed left greater saphenous vein harvested from the left leg. She was also treated with Coumadin. Her limb weakness and skin peeling at the fingertips (mechanic's hand) resolved 2 months after starting steroids. The symptoms of intermittent coldness and cyanosis of the left hand also resolved. She remained symptom free from her ILD standpoint. Chest CT abnormalities improved. The dose of prednisone was gradually tapered down to 20 mg daily. She tolerated the steroids well. She did not want to take a chronic immunosuppressive agent to spare the steroids use. She continued to do well 4 years after the initiation of the steroids treatment.

Discussion

The classification of idiopathic inflammatory myopathies (IIM) has been continuously evolving owing to the advances in the characterization of muscle inflammatory cell infiltrates, muscle pathology phenotypes, and autoantibody associations [1–12]. Based on the clinical presentation, muscle pathological features, and serological findings, IIM are currently classified into 5 distinct subtypes which include inclusion body myositis (IBM), polymyositis (PM), dermatomyositis (DM), immune-mediated necrotizing myopathy (IMNM), and antisynthetase syndrome (ASS) [1, 10, 13]. The percentage of each subtype varies in different study cohorts [9, 14]. IMNM is the most common subtype in the large Japanese (177/460, 38.5%) [14] and French (91/260, 35.0%) [9] cohorts. This is followed by IBM in the Japanese cohort (73/460, 15.9%) and French cohort (77/260, 29.6%). DM and ASS account for 12.2% and 11.1%, respectively, in the Japanese cohort, and 20.0% and 15.4%, respectively, in the French cohort. PM is rare, accounting for 4.1% in the Japanese cohort but none in the French cohort [9, 14], as most of the PM cases fall into IMNM or ASS after these 2 subtypes have been added to the IIM classification list [9]. In addition, PM associated with connective tissue diseases is often called "overlap myositis" rather than PM. Besides IIM, inflammatory myopathies also include rare eosinophilic fasciitis, focal myositis, and sarcoid granulomatous myositis [1].

Autoantibodies play an important role in shaping the current classification of IIM [1]. They correlate with the severity of muscle disease, extra-muscular manifestations, muscle pathology phenotypes, cancer risk, and treatment response [9, 14]. There are 16 myositis-specific autoantibodies associated with IIM, 8 with ASS, 5 with DM, 2 with IMNM, and 1 with IBM. The myositis-specific autoantibodies associated with ASS target aminoacyl-tRNA synthetases, including histidyl (Jo-1), threnyl (PL-7), alanyl (PL-12), isoleucyl (OJ), glycyl (EJ), asparaginyl (KS), phenylalanyl (ZO), and tyrosyl (YRS/HA) tRNA synthetases [15]. The 5 myositis-specific autoantibodies associated with DM target complex nucleosome remodeling histone deacetylase (Mi-2), melanoma differentiation-associated gene 5 (MDA5), small ubiquitin-like modifier activating enzyme (SAE), nuclear matrix protein 2

(NXP2), and transcription intermediary factor 1γ (TIF-1γ). The two myositis-specific autoantibodies associated with IMNM target signal recognition particle (SRP) and anti-3-hydroxy-3-methyglutaryl-coenzyme A reductase (HMGCR). Anti-NT5C1A antibody is associated with IBM, but it can also be present in Sjogren's syndrome and systemic lupus erythematosus (SLE). Myositis-associated antibodies include ANA, anti-Ro/SSA, anti-PM-Scl, anti-Ku, and anti-U2 snRNP.

IIM, except for IBM which is discussed in a separate chapter in this book, are autoimmune myopathies that manifest subacute, progressive, proximal limb weakness. While DM can affect both children and adults, PM, IMNM, and ASS predominantly affect adults. These subtypes also differ in the muscle disease severity, extra-muscular manifestations, serum autoantibody association, muscle biopsy features, and treatment response. In general, the muscle disease is mild in ASS but relatively severe in IMNM, especially in SRP-myopathy and statin-naïve HMGCR-myopathy which are discussed in a separate chapter. DM has a wide spectrum, which can be mild or refractory. Serum CK level is usually markedly elevated in IMNM and ASS, less elevated in PM and DM, and can be normal in DM. EMG typically shows an irritable myopathy. Extra-muscular manifestations are a feature of DM and ASS, less commonly seen in autoantibody-negative IMNM, and rare in autoantibody-positive IMNM. Typical skin lesions seen in DM include Gottron papules in finger knuckles, heliotrope erythema in eyelids, and rash in cheek, chest, shoulders, upper arms, and thighs. The presence of anti-MAD-5 autoantibody is associated with severe ILD, skin ulcers, and arthritis but mild muscle weakness. Calcinosis is mainly seen in juvenile DM and associated with anti-NXP-2 autoantibody. The presence of anti-TIF-1γ autoantibody is associated with a high risk of developing malignancies.

ASS is characterized by the presence of anti-tRNA synthetase autoantibodies, myositis, ILD, non-erosive arthritis, mechanic's hands, and Raynaud's phenomenon [8, 16]. The diagnostic criteria of ASS was developed in 2010 [17] and revised in 2011 [18]. To be diagnosed with ASS, one must have an anti-tRNA synthetase autoantibody and meet two major or one major and two minor criteria. The major criteria include ILD and myositis. The minor criteria include arthritis, Raynaud's phenomenon, and mechanic's hands. Therefore, the diagnosis of ASS requires clinical, serological, radiological, and pathological evaluation which may include serum CK and myositis antibody panel, NCS/EMG, high resolution computed tomography (HRCT) of chest, and muscle or lung biopsy. Our patient had anti-Jo-1 antibody and presented with myositis, arthralgia, mechanic's hands, and ILD, typical for ASS. In addition, our patient also had vasculopathy with left brachial artery occlusion. Vasculopathy is a known extra-muscular manifestation in dermatomyositis [19]; it has also been reportedly in association with ASS [20].

ASS has a female predominance with a mean age at onset of 60.2 years in one study cohort [21]. The most common manifestation in ASS is ILD with a prevalence of 86%, followed by myositis (73%) and arthritis (60%) [22]. Mechanic's hands with hyperkeratosis and scaling are common but often subtle. ILD is associated with the high morbidity and mortality of the disease. The cancer risk in ASS is low. Anti-Jo-1 autoantibody is by far the most common autoantibody in ASS. Anti-PL-7, anti-PL-12, anti-OJ, and anti-EJ autoantibodies are less common. Other autoantibodies are rare. While anti-Jo-1, anti-EJ, and anti-PL-7 autoantibodies are most often associated with myositis, anti-PL-12 autoantibody is often associated with amyopathic DM or ILD [23].

Muscle biopsy is useful to support the diagnosis of ASS myositis and to rule out other muscle diseases. The characteristic muscle pathological changes seen in ASS myositis are damages to both myofibers and perimysial connective tissue. Inflammation, when present, is most commonly perivascular in the perimysium (Figs. 5.1b and 5.2A1 and B1) that can extend into nearby endomysium. However, cases of predominantly endomysial inflammation with lymphocyte rimming viable myofibers are present (Fig. 5.2C1). Acute myofiber damages (i.e. necrotic fibers, myophagocytic fibers, regenerating fibers) can be scattered throughout but more frequent in the perifascicular region (Fig. 5.2A1). The preferential involvement of perimysial fibers is often more evident on the MHC1 and C5b-9 immunostains. MHC1 may show diffuse or patchy upregulation in myofibers, with perifascicular accentuation (Fig. 5.2A2, B2, and C2). C5b-9 shows strong sarcoplasmic reactivity in necrotic fibers (Fig. 5.2A3 black arrows), and sarcolemmal reactivity in viable but abnormal perifascicluar myofibers (Fig. 5.2A3 red arrows). True perifascicular atrophy with uniform small atrophic fibers (Fig. 5.1d) is uncommon in ASS myositis. Rather, the presence of frequent small regenerating fibers (highlighted by alkaline phosphatase stain, Fig. 5.2A4 arrows) interspersed by normal sized myofibers in the perifascicular region may give the appearance of patchy, uneven perifascicular atrophy (Fig. 5.2A1). Chronic myopathic changes (i.e. split fibers, hypertrophic fibers, interstitial fibrosis) are usually absent. The perimysial connective tissue damage is often widespread, best viewed in alkaline phosphatase stain (Figs. 5.1c, 5.2A4 and B4). Perimysial capillary abnormalities, including endothelial tubuloreticular inclusions (Fig. 5.2A5, arrow) and capillary C5b-9 deposition (Fig. 5.2A3, yellow arrows) are also common findings, although usually less pronounced than those in dermatomyositis. Intranuclear actin aggregate (Fig. 5.2B5, arrow) has been reported as a specific finding in ASS myositis [24].

Dermatomyositis shares many common pathological features with ASS myositis, including perifascicular atrophy, capillary C5b-9 deposition, endothelial tubuloreticular inclusions, and MHC1 upregulation in perifascicular fibers. ASS myositis usually has more widespread connective tissue damage evident on the alkaline phosphatase stain. Perifascicular atrophy in ASS is often irregular or patchy, composed of necrotic and regenerating fibers, with retained COX expression. DM, on the other hand, usually has uniform perifascicular atrophy that spans the full length of a fascicle (Fig. 5.3a, b). Perimysial connective tissue damage is minimal (Fig. 5.3c). The perifascicular atrophic fibers show zonal loss of COX reactivity and relatively retained SDH reactivity (Fig. 5.3d) [25], which is a useful distinctive feature [26]. MHC1 upregulation is usually restricted to perifascicular fibers rather than the diffuse upregulation with perifascicular accentuation seen in ASS myositis (Figs. 5.3e and 5.2A2, B2, and C2). Capillary C5b-9 deposition (Fig. 5.3f) and endothelial tubuloreticular inclusions are more abundant than ASS myositis.

Overlap myositis secondary to a systemic autoimmune disease such as lupus, systemic sclerosis, or Sjogren's syndrome may also demonstrate inflammatory myositis with perimysial connective tissue damage. The muscle biopsy in this setting often demonstrates pan-fascicular rather than perifascicular involvement (Fig. 5.4a). Regenerating fibers (Fig. 5.4b) and necrotic fibers (Fig. 5.4c) are ran-

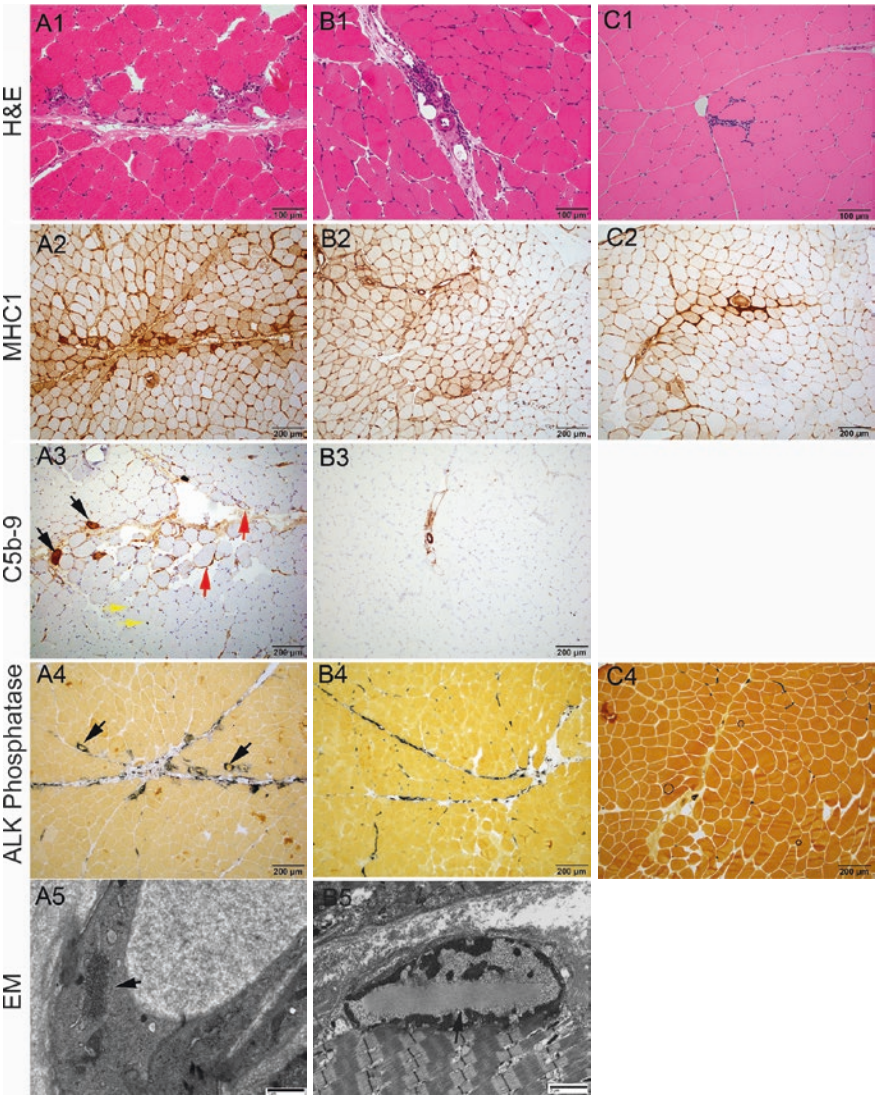

Fig. 5.2 Columns A-C represent three different patient's muscle biopsies, all with myopathy and confirmed presence of serum anti-Jo-1 autoantibody. Case A shows perifascicular necrotizing myopathy (**A1**) and diffuse MHC1 upregulation with perifascicular accentuation (**A2**). C5b-9 immunostain highlights necrotic fibers (**A3**, black arrows), sarcolemmal stain of some viable perifascicular fibers (**A3**, red arrows) and capillary reactivity (**A3**, yellow arrows). Alkaline phosphatase stain shows increased perimysial connective tissue reactivity and regenerating fibers (**A4**, black arrows). EM shows rare endothelial tubuloreticular inclusions (**A5**). Case B shows focal perivascular inflammation (**B1**) and patchy perifascicular myofiber MHC1 upregulation (**B2**). There is no significant myofiber necrosis (**B3**). Alkaline phosphatase stain shows increased perimysial connective tissue reactivity (**B4**). EM shows intranuclear actin aggregate (**B5**, arrow). Case C shows focal endomysial lymphocytic inflammation that rims a myofiber (**C1**). MHC1 immunostain shows patchy upregulation near the lymphocytic infiltrate and perimysium (**C2**). There is no significant myofiber necrosis or connective tissue alkaline phosphatase activity (**C4**)

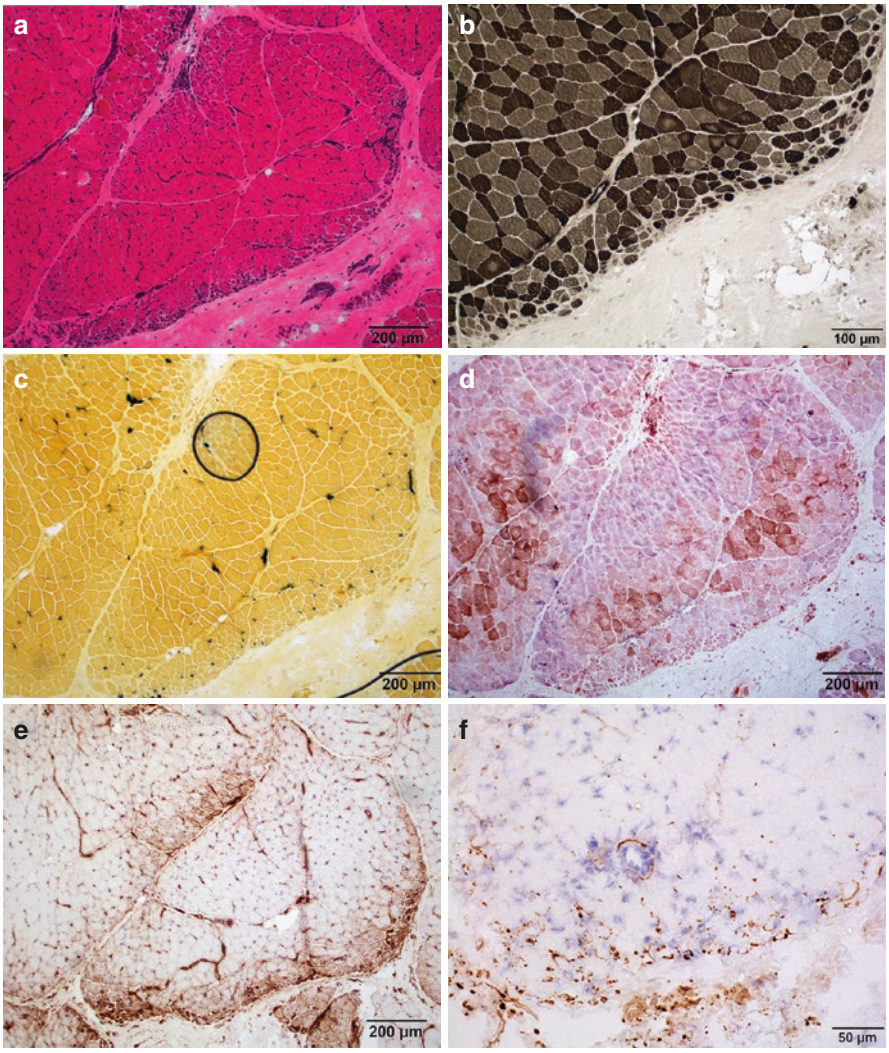

Fig. 5.3 Quadriceps muscle biopsy from an 8-year-old girl with dermatomyositis. (**a**) H&E shows uniform perifascicular atrophy with no skipping areas. (**b**) ATPase 9.4 highlights perifascicular atrophy and type 2 fiber atrophy. (**c**) Alkaline phosphatase shows no perimysial connective tissue damage or regenerating fibers in the perifascicular myofibers. (**d**) COX/SDH combination stain shows zonal loss of COX reactivity (brown) in the perifascicular fibers and relatively retained SDH reactivity (blue). (**e**) MHC class I immunostain shows selective upregulation in perifascicular fibers but not the fibers in the center of the fascicle. (**f**) C5b-9 immunostain shows terminal complement complex deposition in capillaries. There is no significant myofiber necrosis

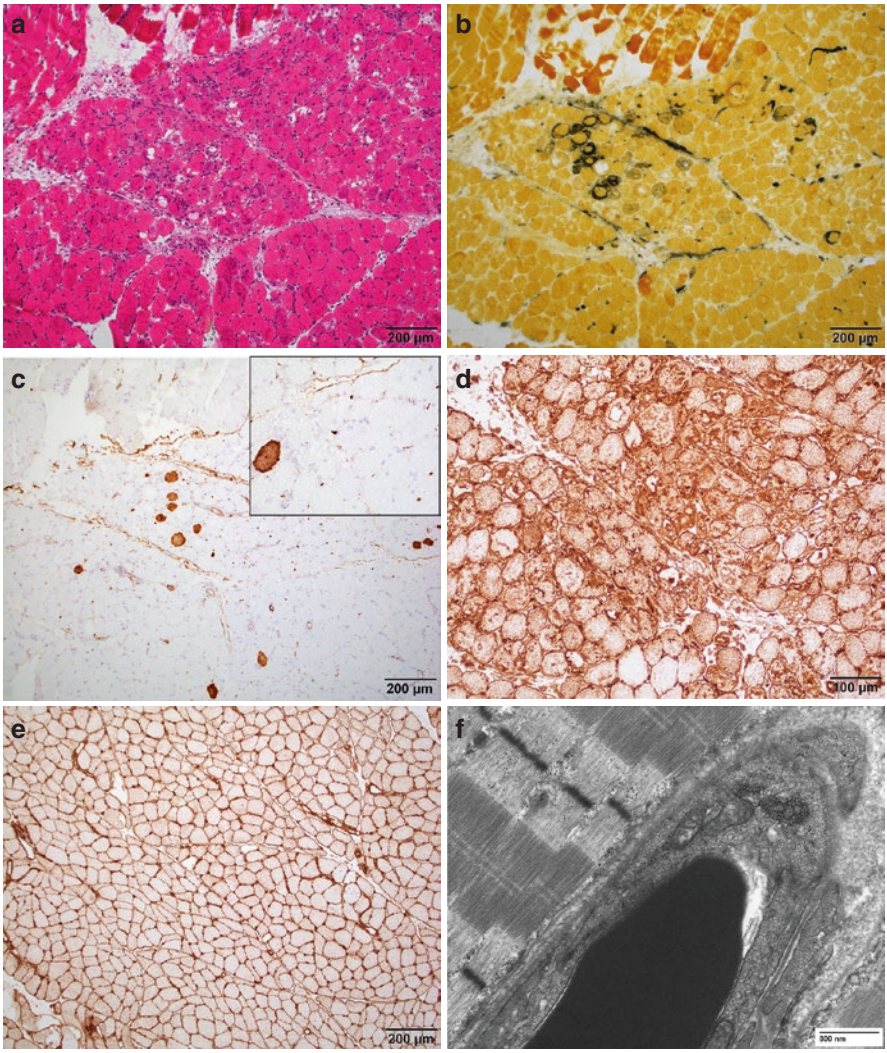

Fig. 5.4 Quadriceps muscle biopsy from a 35-year-old woman with lupus myositis. (**a**) H&E shows inflammatory myositis with pan-fascicular involvement. There is no perifascicular atrophy. (**b**) Alkaline phosphatase shows perimysial reactivity and frequent regenerating fibers. (**c**) C5b-9 immunostain shows frequent scattered necrotic fibers and capillary C5b-9 reactivity (inset). (**d**, **e**) MHC class I immunostain shows diffuse myofiber reactivity in both the myopathic region (**d**) and histologically normal region (**e**). (**f**) EM shows frequent endothelial tubuloreticular inclusions in capillaries

domly distributed. Capillary complement complex deposition is random (Fig. 5.4c). MHC1 is diffusely upregulated, even in histologically normal regions (Fig. 5.4d, e). Tubuloreticular inclusions (Fig. 5.4f) are frequently seen in patients with lupus, but rarely seen in patients with scleroderma or Sjogren's syndrome [27]. It should be noted that a wide range of overlapping pathology can be seen in ASS myositis, DM, and overlap myositis, and distinction is not always possible on the basis of pathology alone. Correlation with clinical symptomatology and serum autoantibody status is highly recommended.

Management of patients with ASS often requires multidisciplinary care provided by specialists in neurology, rheumatology, pulmonology, and rehabilitation. Corticosteroids is typically used as the first-line therapy, which can be used as monotherapy in mild cases. Additional immunosuppressive agents, such as azathioprine, mycophenolate mofeti, tacrolimus, rituximab, and cyclophosphamide, may be used for treating severe and refractory cases or as steroids-sparing agents. Once the disease symptoms improve and stabilize, immunosuppressive agents can be tapered. There are no research data, however, to guide the length of the immunosuppressive therapy or the rate of tapering. Myositis in ASS is usually mild, and it responds relatively well to immunosuppressive therapy [21] as seen in our patient.

Pearls

Clinical Pearls

1. IIM are currently classified into IBM, PM, DM, IMNM, and ASS with distinct clinical, serological, and muscle pathological features in each subtype.
2. Diagnostic evaluation of patients with IIM includes serum CK, myositis antibody panel, NCS/EMG, and muscle biopsy. High resolution chest CT is also important in evaluating patients with ASS.
3. ASS is characterized by the presence of anti-tRNA synthetase autoantibodies, myositis, ILD, arthritis, mechanic's hands, and Raynaud's phenomenon. The most common antisynthetase antibody detected in ASS is anti-Jo-1 autoantibody.
4. Muscle involvement in ASS manifests subacute, progressive, proximal limb weakness. Muscle weakness in ASS is usually mild and responds well to immunosuppression.
5. CK is often markedly elevated in ASS, EMG usually shows an irritable myopathy, and a muscle biopsy is useful to support the diagnosis and to rule out other muscle diseases.
6. Patients with ASS often require multidisciplinary care provided by neurologists, rheumatologists, pulmonologists, and physiatrists.

Pathology Pearls

1. The hallmarks of ASS myositis are perifascicular myofiber necrosis, perimysial connective tissue damage, and perivascular lymphocytic inflammation.
2. Muscle involvement is patchy in ASS. The presence of the above diagnostic features may be variable.
3. Diagnostic features on EM include myofiber intranuclear actin aggregates and capillary endothelial tubuloreticular inclusions. The former is reported to be specific for AAS myositis. The latter is usually less abundant and less well-formed than those seen in dermatomyositis.
4. Compared with dermatomyositis, ASS myositis often has more prominent perifascicular connective tissue damage and myofiber necrosis, less uniform perifascicular atrophy, and no zonal loss of COX reactivity in perifascicular fibers.

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