Chapter 17
A 65-Year-Old Man with Asymmetrical Leg Weakness and Foot Tingling

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History

A 65-year-old Caucasian man was referred for evaluation of neuropathy. Nine years prior to the presentation, he developed tingling in both feet. He then developed aching pain in the thighs. Two years prior to the presentation, he developed leg weakness with difficulty climbing stairs and picking up his feet, worse on the left. He noticed atrophy in the left calf muscles but no fasciculations. He also developed pain but not numbness or weakness in his hands. He admitted to chronic low back pain and hip pain, which was non-radiating. He denied bowel or bladder symptoms. He was evaluated by an outside neurologist and had nerve conduction study (NCS) and electromyography (EMG) done three times. They all reportedly showed chronic, predominantly axonal, sensorimotor polyneuropathy and right carpal tunnel syndrome. Lumbosacral spine MRI only showed a small disc protrusion at L5/S1 with no spinal canal or neural foraminal stenosis. He had been on a statin drug for 25 years for hyperlipidemia. He stopped it for 1 month at one time with no change of his symptoms. He had a past medical history of hypertension, hyperlipidemia, mitral valve prolapse, and right carpal tunnel syndrome. The only surgery that he had was the right carpal tunnel release. His medications included aspirin, carvedilol, lisinopril, zocor, and gabapentin. His family history was positive for hypertension

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and hyperlipidemia but negative for muscle or nerve diseases. He was married with two children. He did not drink alcohol or smoke cigarettes. He was a retired real estate agent.

Physical Examination

General examination was unremarkable. There was no cataract, spine tenderness, spine scoliosis, or joint contracture. Neurologic examination showed normal mental status and cranial nerve functions. Motor examination revealed reduced muscle tone in the left leg with atrophy in the distal leg muscles. Weakness was detected in the bilateral hip flexors (MRC: 4+/5), left foot and toe dorsiflexors (MRC 4−/5), left foot and toe plantar flexors (3/5), left foot evertor (4−/5), and right toe dorsiflexors (4+/5). There was no muscle fasciculation or scapular winging. Pinprick sensation was reduced from the toes to ankles. Vibratory sensation was reduced at the toes. Joint position sense was intact. Deep tendon reflexes were 2+ at the biceps, triceps, brachioradialis, and knees, and absent at the ankles. Toes were downgoing bilaterally. He was able to walk but could not walk on his heels, toes, or in tandem.

Investigations

A repeat NCS showed reduced bilateral peroneal and tibial compound muscle action potential (CMAP) amplitudes, worse on the left, and normal distal motor latencies and conduction velocities. Left sural conduction response was absent, and right sural sensory nerve action potential (SNAP) amplitude was markedly reduced with normal peak latency and conduction velocity. Needle EMG of selected left lower limb muscles showed a few fibrillation potentials and positive sharp waves in the tibialis anterior and medial gastrocnemius muscles, early recruitment of small-amplitude and short-duration motor unit potentials in the tibialis anterior, medial gastrocnemius, and vastus lateralis muscles. Needle EMG of the right flexor digitorum profundus muscles also showed a few small-amplitude and short-duration motor unit potentials but normal recruitment and no abnormal spontaneous activities. Overall, the NCS/EMG showed an irritable myopathy mainly affecting distal leg muscles, and a distal sensory polyneuropathy. Serum creatine kinase (CK) level was elevated at 481 U/L. Aldolase level was also elevated at 8.5 U/L (normal <7.7). Complete blood count (CBC), comprehensive metabolic panel (CMP), ESR, TSH, free T4, HbA1C, vitamin B12, and serum immunofixation were all normal. ANA, ENA, ANCAs, myositis antibody panel, anti-cytosolic 5′-nucleotide 1A (cN1A; NT5C1A) autoantibody, and anti-3-hydroxy-3-methyglutaryl-coenzyme A reductase (HMGCR) autoantibody were all negative. A right vastus lateralis muscle biopsy was performed.

Muscle Biopsy Findings

The right vastus lateralis muscle biopsy (Fig. 17.1) showed a chronic active myopathy with marked fiber size variation, rare rimmed vacuoles and occasional scattered necrotic and regenerating fibers. The most distinctive feature was the presence of over a dozen of myofibers containing small sarcoplasmic spherical proteinaceous aggregates, which were eosinophilic on the H&E stain (Fig. 17.1a), dark blue on the Gomori

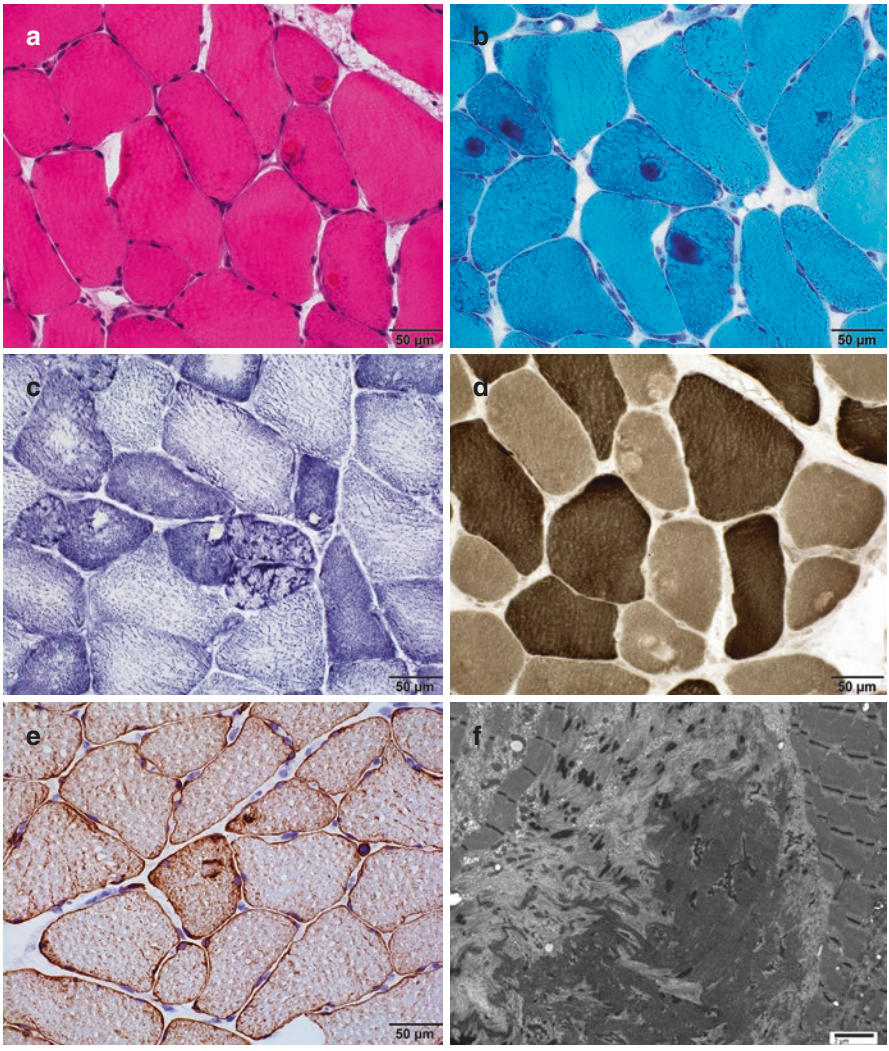

Fig. 17.1 Myofibrillar myopathy. (**a**) H&E stain. (**b**) Gomori trichrome stain. (**c**) NADH-TR stain. (**d**) ATPase stain at pH 9.4. (**e**) Desmin immunostain. (**f**) Granulofilamentous material on electron microscopy

trichrome stain (Fig. 17.1b), metachromatic on the crystal violet stain, and pale on the NADH-TR (Fig. 17.1c), SDH, COX and ATPase (Fig. 17.1d) stains, involving predominantly type 1 myofibers. The protein aggregates in most of the fibers were immunoreactive to desmin (Fig. 17.1e). A small focus of endomysial lymphocytic inflammation was present. There was no diffuse upregulation of class I major histocompatibility complex (MHC1), except for focal reactivity in the necrotic fibers and near the inflammatory cells. There was no excessive COX-deficient fibers. Very mild neurogenic changes including rare esterase positive denervated atrophic fibers and subtle fiber type grouping were also present. Electron microscopy (EM) showed a sarcoplasmic accumulation of granulofilamentous materials which appeared to be a mixture of Z-line material, electron dense material, and disrupted myofilaments (Fig. 17.1f). The findings are characteristic of myofibrillar myopathy. Focal areas of maldistribution of mitochondria were also noted with streaks separating myofibrils, rendering a lobulated appearance on light microscopy.

Final Diagnosis

Myofibrillar Myopathy

Patient Follow-up

The patient underwent genetic testing. The muscular dystrophy gene panel showed one copy of a possible pathogenic variant, c.5568T > A (p.C1856X), in the *SMCHD1* gene. The *DUX4* gene expression-permissive 4q35 haplotype was not tested, as his presentation was atypical for facioscapulohumeral muscular dystrophy. There was no mutation detected in the *desmin*, *myotilin*, *FHL1, or DNAJB6* gene. The other genes, mutations in which could also cause myofibrillar myopathy, including *αB-crystallin*, Z-line alternatively spliced PDZ motif-containing protein (*ZASP*), *filamin C*, and *bcl-2-associated athanogene 3 (Bag3)* genes were not included in this muscular dystrophy gene panel. Due to the patient's insurance status, these genes had not been tested. The patient underwent physical therapy, and his weakness slightly progressed over the next 1–1/2 years. But his gait improved after wearing ankle foot orthotic brace (AFO). He was referred to cardiology for cardiac evaluation which revealed a very mild dilated cardiomyopathy, and it was treated. His pulmonary function test was unremarkable.

Discussion

Myofibrillar myopathies are a group of heterogeneous genetic myopathies that share distinct muscle pathology features [1]. They are caused by mutations in the genes that encode proteins in Z line or associated with Z line, which play important roles

in maintaining intermyofibrillar architecture. The genes that are primarily involved in myofibrillar myopathies include *desmin* (*DES*), *αB-crystallin* (*CRYAB*), *myotilin (MYOT)*, *ZASP (LDB3)*, *filamin C (FLNC)*, *Bag3 (BAG3)*, and *four-and-a-half-LIM domain 1 protein (FHL1)*. Many cases are sporadic. The inheritance in the majority of the cases with a positive family history is autosome dominant except for the FHL1-associated cases which are X-linked. Recessive mutations are very rare. A large number of cases with myofibrillar myopathies have no gene mutations found, which indicates that some causative genes have not been identified yet [2–5].

Age of symptom onset in myofibrillar myopathies is variable, ranging from childhood to late adulthood with adult onset being more common [4], especially in the cases with mutations in the *LDB3*, *MYOT*, and *FLNC* genes. Childhood cases are often severe and the progression is rapid. Myofibrillar myopathies can affect skeletal muscles and cardiac muscles. Limb weakness is often distal starting from lower limbs. It gradually progresses to involve upper limb muscles and proximal limb muscles. Some patients may show Achilles and finger contractures and atypical predominant scapuloperoneal weakness. Facial weakness is uncommon. Some older patients may report slurred speech and difficulty swallowing. Cardiac involvement is relatively common in the disease that is caused by mutations in the *DES*, *FLNC*, *FHL1*, or *BAG3* gene. Patients may have arrhythmia, conduction defects, and/or dilated or hypertrophic cardiomyopathy. Cardiac involvement is rare in the disease that is caused by mutations in the *MYOT* or *LDB3* gene. Respiratory weakness is mainly seen in early-onset severe cases and is also common in cases with *FLNC* mutations. Peripheral neuropathy is common especially in patients with *BAG3* mutations. Early-onset cataract is a feature associated with *CRYAB* mutations.

The common causes of distal limb numbness and asymmetrical distal lower limb weakness in an elderly patient like ours include polyradiculopathy, lumbosacral plexopathy, and polyneuropathy. Myofibrillar myopathy is often misdiagnosed with these conditions and a correct diagnosis is often delayed. EMG plays a pivotal role in raising a suspicion for a myopathy. EMG in myofibrillar myopathies usually shows myopathic changes more prominent in the affected distal lower limb muscles as seen in our case. It may also show a coexisting distal polyneuropathy [4]. CK in myofibrillar myopathies is either normal or mildly elevated. The combination of a distal predominant myopathy and a distal polyneuropathy should raise a suspicion for a myofibrillar myopathy. The differential diagnosis in this setting includes sporadic inclusion body myositis (sIBM) and other distal myopathies [6]. For the distal limb muscles, sIBM more affects finger flexors than foot dorsiflexors. The more severe foot and toe plantar flexor weakness seen in our patient is atypical for sIBM. Muscle MRI may show different patterns of muscle involvement in myofibrillar myopathies caused by different gene mutations.

Muscle biopsy plays a key role in making a diagnosis of a myofibrillar myopathy and differentiating it from other distal myopathies. Subsequent genetic testing can identify genetic causes in many patients but not all [3]. As the disease more affects distal limb muscles and the muscle involvement can be asymmetrical, choosing an affected muscle for biopsy based on the clinical weakness, EMG findings, and muscle MRI findings is important as it can increase the biopsy yield.

The defining feature of myofibrillar myopathy is the presence of sarcoplasmic protein aggregates in a background of chronic myopathy. These protein aggregates have been referred to as hyaline structures, spheroid bodies, or Mallory bodies. They are eosinophilic on H&E, dark blue on Gomori trichrome, but pale on mitochondria enzyme stains (NADH-TR, SDH, and COX) and ATPase stains (Fig. 17.1). Cytoplasmic bodies can also be seen in myofibrillar myopathy, but much less specific. Cytoplasmic bodies are usually smaller than hyaline structures, composed of a dark red core surrounded by a pale halo on Gomori trichrome (Fig. 17.2a). On EM, cytoplasmic bodies are composed of an electron dense core surrounded by a halo of radiating filaments that show continuity with myofibrils (Fig. 17.2b). Replicated triads can be prominent (Fig. 17.2b). NADH-TR stain may also reveal widespread myofibrillar disarray (Fig. 17.2c), sometimes referred to as nonhyaline structures [7]. Both hyaline and nonhyaline structures are immunoreactive to desmin (Fig. 17.2d). These aggregates are also reported to be immunoreactive to alpha B crystalline, myotilin and dystrophin [4]. On EM, both hyaline and nonhyaline structures are composed of disintegrated Z band material, electron dense material, and disorganized myofilaments, which are collectively referred to as granulofilamentous material (Fig. 17.2e). Vacuoles containing degenerating membranous organelles can also be seen in some cases of myofibrillar myopathy (Fig. 17.2f); those vacuoles typically lack tubulofilamentous inclusions seen in inclusion body myositis (IBM).

Morphological differential considerations of myofibrillar myopathy include target/targetoid fibers, central cores, multi-minicores, lobulated myofibers, and chronic myopathies from any cause with markedly abnormal myofibrillar architecture. Most of those lack well-formed hyaline structures. Target/targetoid fibers are seen in chronic active denervation atrophy, and they often coexist with angular atrophic fibers and fiber type grouping. Central cores and multi-minicores are most common in children. The muscle biopsy usually shows type 1 fiber predominance and lacks active myopathic changes such as necrotic, myophagocytic, or regenerating fibers. Lobulated fibers (Fig. 17.2g) have been commonly associated with calpain deficiency but can be seen in a variety of hereditary and nonhereditary conditions. On EM, the lobulated appearance is rendered by maldistribution of mitochondria from their normal Z-band location into streaks that separate myofibrils into bundles (Fig. 17.2h). The presence of specific diagnostic features of other chronic myopathies, such as lymphocytic invasion and diffuse myofiber MHC1 upregulation in IBM and polymyositis, and muscle dystrophic changes with detectable membrane protein defects by immunostaining panel in various muscular dystrophies, overrides the morphological diagnosis of myofibrillar myopathy.

There is no effective disease-modifying therapy for myofibrillar myopathies currently. Several disease animal models have been generated to study the disease-causing mechanisms and to develop targeted therapies to control sarcomere disruption and protein aggregation [2]. At this point, the management of patients with myofibrillar myopathies is mainly supportive to maximize functions and prevent falls. Since cardiac involvement is relatively common in patients with myofibrillar myopathies, these patients should be referred to cardiology for a thorough

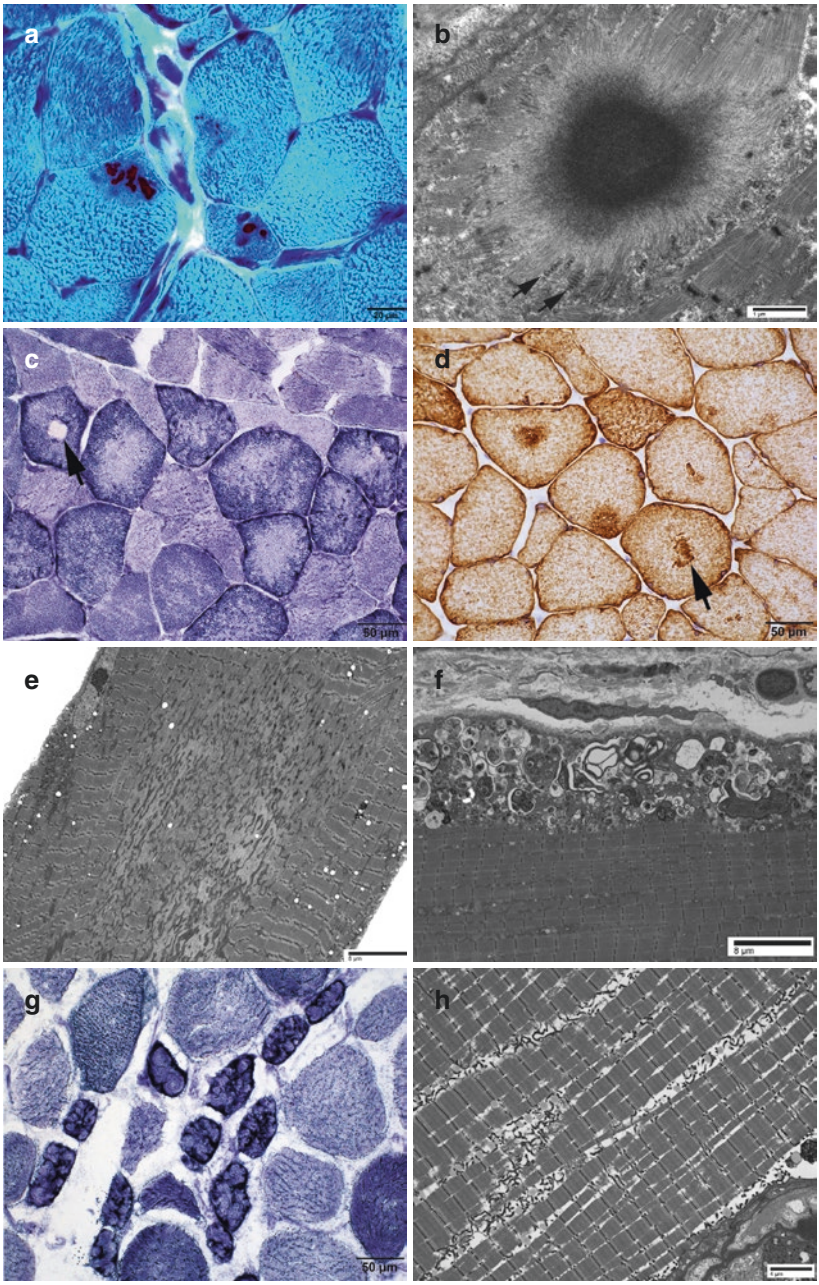

Fig. 17.2 (**a**, **b**) Cytoplasmic bodies from an 8-year-old girl with plectin (PLEC) associated muscular dystrophy. (**a**) Gomori trichrome and (**b**) EM (arrows: replicated triads). (**c–e**) Hyaline and Non-hyaline structures from a 72-year-old man with myofibrillar myopathy. (**c**) NADH-TR, (**d**) Desmin immunostaining, and (**e**) EM (arrows: hyaline structures). (**f**) A vacuole with degenerating membranous organelles in an 83-year-old man with myofibrillar myopathy. (**g–h**) Myopathy with lobulated fibers from a 67-year-old woman. (**g**) NADH-TR shows prominent lobulated changes in type 1 myofibers. (**h**) EM shows maldistribution of mitochondria that form subsarcolemmal and sarcoplasmic bands

cardiac evaluation and for the management of associated cardiac defects if present. These patients may also undergo swallow evaluation and pulmonary function test. Genetic counseling should be provided.

Pearls

Clinical Pearls

1. Myofibrillar myopathies are a group of heterogeneous genetic myopathies that are primarily caused by mutations in the genes encoding desmin, αB-crystallin, myotilin, ZASP, filamin C, Bag3, and FHL1. The disease is mainly autosomal dominant except for the FHL1-associated disease which is X-linked.
2. Patients with myofibrillar myopathies commonly show adult onset of symptoms. The onset is often late. The early-onset disease is usually more severe and rapidly progressive.
3. Myofibrillar myopathies predominantly affect distal limb muscles with initial weakness in the distal lower limb muscles. Cardiac involvement is common which may manifest arrhythmia, conduction defects, and/or dilated or hypertrophic cardiomyopathy. Peripheral neuropathy is common especially in patients with *BAG3* mutations.
4. The combination of a distal predominant myopathy and a distal polyneuropathy should raise a suspicion for a myofibrillar myopathy.
5. Muscle biopsy plays a key role in the diagnosis of a myofibrillar myopathy. Subsequent genetic testing can identify genetic causes in many patients but not all.
6. Currently there is no effective therapy for myofibrillar myopathies. The management is mainly supportive. Patients should be referred to cardiology for a thorough cardiac evaluation and for the management of associated cardiac defects if present.

Pathology Pearls

1. The characteristic feature of myofibrillar myopathy is the presence of sarcoplasmic hyaline structures in a background of chronic myopathy. Cytoplasmic bodies, non-hyaline structures, rimmed vacuoles, and uneven oxidative enzyme staining are common findings in myofibrillar myopathy but less specific.

2. The hyaline structures are dark on Gomori trichrome, pale on ATPase, NADH-TR, COX, and SDH stains, and immunoreactive to desmin.
3. On EM, the hyaline and non-hyaline structures are composed of disorganized filaments, Z-disk material, and electron dense material, which are collectively referred to as granulofilamentous material.

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