

# Clinical Reasoning: A 70-year-old man with walking difficulties

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## SECTION 1

A 70-year-old man presented with progressive gait unsteadiness for 5 years. He also had to use his arms to climb stairs or to get up from a chair. He reported no pain, sensory symptoms, or fatigue. He had pulmonary sarcoidosis at age 24 years, which remained in remission after treatment with corticotropin and prednisone. There was no family history of autoimmune or muscle diseases.

Clinical examination showed 4/5 strength of the iliopsoas and quadriceps muscles and slight weakness of

the biceps brachii muscles. The results of gait examination, including stance, stride, posture and arm swing, were normal. Toe and heel walking were normal, but the patient was unable to squat. The Romberg sign was negative. Ankle tendon reflexes were absent. The rest of the results of the neurologic examination, particularly the sensory examination, were normal.

### Questions for consideration:

1. What is the cause of the walking difficulty?
2. What is the differential diagnosis?

**GO TO SECTION 2**

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*Disclosure:* Author disclosures are provided at the end of the article.

## SECTION 2

Because there was no impairment in the sensory, cerebellar, or extrapyramidal systems, the walking difficulty was most likely due to the proximal leg muscle weakness, which also explains why the patient used his arms when climbing stairs and rising up from a chair. A pure motor disorder in an elderly patient could be secondary to a motor neuron disorder (MND), pure motor neuropathy, neuromuscular junction (NMJ) dysfunction, or myopathy. An acquired MND typically presents with asymmetric distal limb weakness. Hereditary spinal muscular atrophy is characterized by proximal muscle weakness but usually presents at an earlier age. Multifocal motor neuropathy (MMN) with conduction block starts at age 30 to 50 years and usually presents with distal more than proximal weakness of the arms more than the legs. Lambert-Eaton myasthenic syndrome (LEMS), a rare but treatable NMJ disorder, usually presents with proximal leg weakness, low or absent tendon reflexes, and autonomic dysfunction.

Myopathies could be toxic, such as those associated with alcohol, steroid, or statins; metabolic, such

as thyroid myopathy and Pompe disease; or inflammatory. Inflammatory myopathies include polymyositis (PM), inclusion body myositis (IBM), and sarcoid myopathy. In rare cases, genetically determined dystrophinopathies are the cause of limb-girdle weakness at this age. For example, Becker muscular dystrophy (BMD) can present with late-onset limb-girdle weakness. Furthermore, limb-girdle muscular dystrophies (LGMDs) can be considered, although onset of symptoms at older age is rare. A negative family history, as is the case in this patient, could suggest an autosomal recessive LGMD or a new mutation. The level of the serum creatine kinase (CK) is often very high in the recessive form of LGMD, whereas in its autosomal dominant form, the CK is normal or moderately increased.

The prevalence of these disorders at older age and the presence of an associated autoimmune disorder should be considered.

### Questions for consideration:

1. Which investigations are at your disposal?
2. Which would you use and in what order?

**GO TO SECTION 3**

### SECTION 3

The next step is to further differentiate between MND, MMN, LEMS, or a myopathy.

CK levels are high in dystrophinopathies, Pompe disease, and thyroid dysfunction but are usually normal in MND, MMN, LEMS, steroid myopathy, and IBM. Thyrotropin testing helps to indicate thyroid myopathy. Anti-voltage-gated P/Q-type calcium channel (VGCC) serum antibodies are specific for LEMS. Alpha-glucosidase level and DNA testing of the dystrophin gene are optional in Pompe disease and BMD.

Electrophysiologic studies would help to differentiate between MND, MMN, LEMS, and myopathy. A muscle biopsy of an affected muscle may suggest the type of myopathy.

In our patient, thyrotropin and CK levels were normal. Nerve conduction studies were normal and

did not show conduction block. Needle electromyography of the left rectus femoris muscle showed no abnormalities. The soleus muscle showed spontaneous muscle fiber activity with high-amplitude, polyphasic motor unit action potentials (MUAPs), more compatible with an axonal neuropathy than with a myopathy. Repetitive nerve stimulation was normal, making LEMS improbable.<sup>1</sup> Anti-VGCC antibodies were not tested. Biopsy of a symptomatic anterior tibial muscle showed nonspecific myopathic changes. DNA testing for BMD showed no deletion or duplication in the dystrophin gene.

#### Questions for consideration:

1. What is the most likely diagnosis, and does the clinical course help you in the diagnostic process?
2. What would be your therapeutic advice?

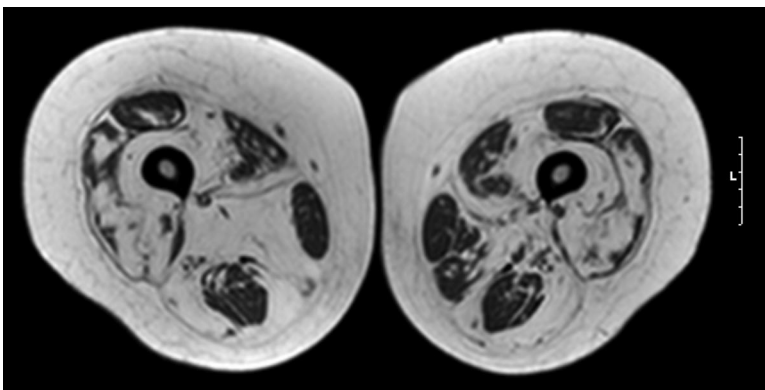
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#### SECTION 4

This patient has a slowly progressive pure motor disorder with myopathic and neurogenic aspects. MMN, LEMS, metabolic myopathies, LGMD, and BMD are unlikely as discussed above. Steroid myopathy was also unlikely, because the prednisone was stopped several years previously.<sup>2</sup> The lack of muscle inflammation on the biopsy and the normal CK rule out PM and sarcoid myopathy. MND and IBM remain possible, IBM being the more likely based on the slow clinical course, autoimmune-prone history, absence of fasciculations, absence of neuropathic features in the muscle biopsy, and the knowledge that in IBM, the EMG may show a neurogenic process and that the muscle biopsy can be negative. Because pharmacotherapeutic options were lacking, the patient was followed up. Over the following years, his muscle weakness progressed and spread to the distal legs and finger flexor of 2 digits of his right hand. Three years later, the patient was partially wheelchair bound. He reported difficulties with swallowing solid foods but did not develop fasciculations, cramps, or pyramidal tract signs.

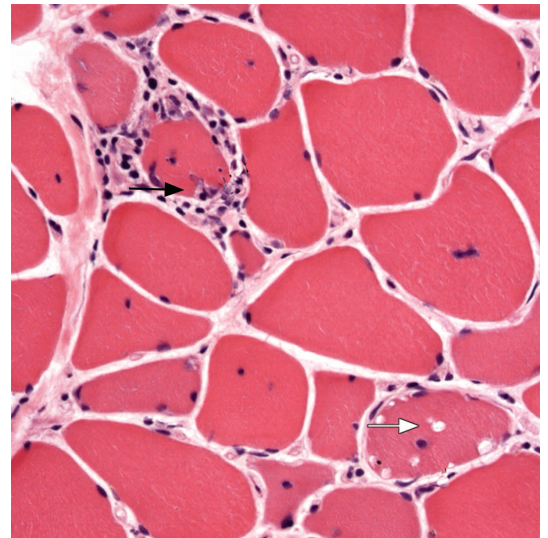
The clinical picture of an elderly patient presenting with slowly progressive, painless proximal leg and finger flexor weakness with dysphagia suggests IBM. A second biopsy of the vastus lateralis muscle showed only fat. A muscle MRI was performed, after 2 negative muscle biopsies, to select an appropriate muscle for a third muscle biopsy<sup>3</sup> and to investigate whether a specific pattern of muscle involvement could be detected, which could be helpful in the diagnostic process. The MRI of the muscles showed extensive fatty infiltration of the shoulder, limb-girdle, and leg musculature (figure 1). Muscles in the legs not showing fatty infiltration had a high signal on short-

**Figure 1** MRI of the proximal femur



Axial T1-weighted image of the proximal femur of both legs shows fatty infiltration and atrophy of the quadriceps femoris, hamstrings, and adductor muscles. The gracilis muscle is relatively normal, with only minor fatty infiltration. There is asymmetric involvement of the adductor muscles, more pronounced on the right side.

**Figure 2** Muscle biopsy



Muscle biopsy in hematoxylin & eosin stain, showing the rimmed vacuoles (white arrow) and invasion of lymphocytes in nonnecrotic muscle fibers (black arrow).

inversion time inversion recovery, indicative of inflammation.

The third biopsy of the anterior tibial muscle showed myopathic changes including mononuclear inflammatory infiltrates with invasion of nonnecrotic fibers and rimmed vacuoles, supporting the diagnosis of IBM (figure 2).

**DISCUSSION** IBM is an idiopathic inflammatory myopathy with an onset after age 40 years and a male predominance. Although the prevalence is low (5 to 10 patients per million inhabitants), it is considered one of the most frequently acquired myopathies in the elderly. Most patients present with weakness of quadriceps muscles or finger flexors or dysphagia. The onset is insidious, and the course is slowly progressive, painless, and mostly asymmetric.<sup>4</sup> Diagnosis can be confirmed by the presence of rimmed vacuoles in the muscle biopsy in combination with invasion of lymphocytes in nonnecrotic muscle fibers and interstitial infiltrates. Some criteria also require positive amyloid staining or 16- to 20-nm tubulofilaments on electromicroscopy.<sup>5</sup>

Initially, slight quadriceps weakness can be missed or ascribed to age, leading to diagnostic delay. Important clues for quadriceps weakness are difficulties when climbing stairs, repetitive falls on the knees, and difficulty with rising from a chair.

Diagnostic pitfalls lead to further delay. Electromyography can be misleading because it might suggest a neurogenic origin (in one third of the IBM patients, large polyphasic MUAPs can be demonstrated). It is not unusual for patients with clinically

defined IBM to lack the canonical histologic features of IBM.<sup>6</sup> This can be because the rimmed vacuoles seem to be more prominent in a later stage of the disease or due to the patchy nature of the histologic abnormalities.<sup>7</sup> Therefore, after a negative muscle biopsy, additional biopsies may be needed to get confirmation. This case illustrates that the clinical picture was diagnostically more helpful than the histopathologic criteria.

The pathogenesis of IBM remains enigmatic, but there are clues suggesting an autoimmune and degenerative pathway.<sup>8,9</sup> IBM is associated with other autoimmune disorders. No effective drug therapy is currently available.

### DISCLOSURE

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