Clinical Reasoning: Progressive proximal weakness in a 56-year-old man with bone pain

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Section 1

A 56-year-old man was admitted to an outside hospital for worsening weakness and fatigue in the setting of upper respiratory infection. He had noticed gradually progressive weakness over the last year. Initially, he experienced difficulty lifting both arms above his shoulder; this progressed to difficulty walking, getting up from a low seated position, and climbing stairs for the last 6 months. In addition, he endorsed worsening bone and joint pain that had started approximately 1.5 years ago.

The patient was a current smoker and had been smoking 1/2 pack of cigarettes a day since the age of 18. His medical history was notable for chronic obstructive pulmonary disease. He denied any recent vaccinations. There was no known family history of neurologic disease. His father died from a heart attack at age 56 and his mother from early-onset Alzheimer disease. Birth history was unrevealing, and he achieved motor milestones in time.

Given the patient's worsening weakness in the setting of acute respiratory illness, chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) with an acute flare was initially suspected. However, there were no sensory symptoms and reflexes were intact, thus MRI of spine with contrast was performed before considering lumbar puncture. MRI spine was unremarkable except for sclerotic lesions in C4 and C7 vertebra. MRI brain was also normal. Bone scan performed to investigate these vertebral lesions revealed several foci of increased activity in the cervical, thoracic, and lumbar spine, along with an inhomogeneous sclerotic and lytic lesion of the left radius (figure, D).

Laboratory workup showed mild elevation of alkaline phosphatase (135 IU/L, normal 40–115 U/L). Creatinine kinase (CK) (121 U/L, normal 44–196 U/L), aldolase (4.8 U/L, normal 1.0–7.5 U/L), and serum calcium (9.7 mg/dL, normal 8.6–10.3 mg/dL) were normal. Inflammatory and rheumatologic markers were negative and there was no evidence of an endocrinopathy. Serum kappa and lambda light chains were mildly elevated but serum protein electrophoresis and immunofixation were normal.

Considering multiple bone lesions, and the patient's longstanding smoking history, a metastatic disorder was suspected, but a CT scan of the chest, abdomen, and pelvis did not reveal evidence of an occult malignancy. Interestingly, CT chest showed fatty atrophy of the chest wall muscles (figure, C). PET scan showed only increased uptake in the vertebral lesions. No unifying diagnosis could be made, and he was referred to our neuromuscular clinic, where he was seen about 4 months later. In the interim, his weakness continued to progress, and he started to fall frequently.

Questions for consideration:

1. Can there be a connection between the patient's bone lesions and his weakness?
2. What is your differential and how would you proceed?

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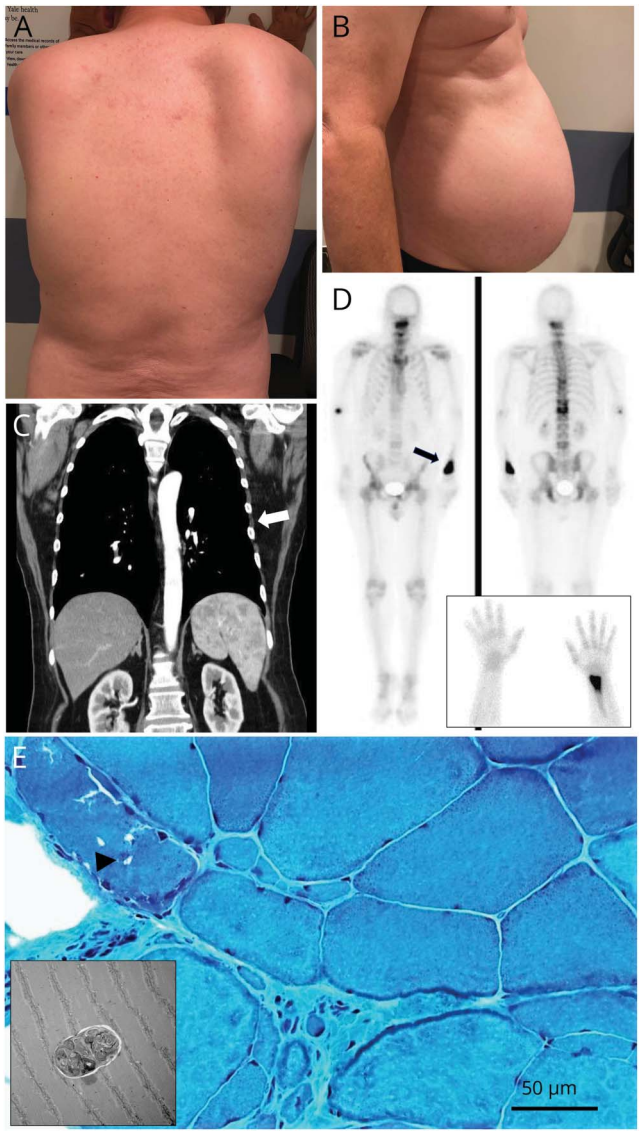
Figure Key clinical features and diagnostic findings



(A) Right scapular winging, (B) protruding abdomen, (C) muscle atrophy of chest wall muscles (white block arrow) on CT chest, (D) bone scan showing inhomogeneous sclerotic and lytic lesion involving the distal left radius (black block arrow, and the inset figure), and several foci of increased activity in the cervical and thoracic spine, (E) Gomori trichrome stain showing fiber size variability and rimmed vacuole (black arrowhead), inset showing electron microscopy image of a rimmed vacuole with inclusions.

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Section 2

On our examination, there was right-sided scapular winging (figure, A), mild atrophy of shoulder girdle muscles, and a protruding abdomen (figure, B). In addition, there was substantial proximal > distal muscle weakness (deltoid: 3/5; iliopsoas: 3+/5; biceps, triceps, wrist flexor, finger extensor, quadriceps, and ankle dorsiflexion: ranged 4 to 4+/5 on Medical Research Council scale). Grip strength was reduced (16 kg-force on right and 17 kg-force left, normal range 28–59 kg-force). Cranial nerves, reflexes, and sensory modalities were intact. There were no cerebellar signs. The patient had a waddling gait.

Weakness in the presence of multiple sclerotic bone lesions can raise suspicion for paraproteinemias, such as multiple myeloma and POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes) syndrome, or a metastatic bone disorder.[1,2] However, there was no firm evidence in support of these etiologies based on the initial workup. Subsequent biopsy of the left radial lesion revealed Paget disease of bone (PDB).

Considering the patient's proximal weakness, the differential is broad, encompassing myopathic and nonmyopathic etiologies. The inflammatory myopathies, dermatomyositis (DM) and polymyositis, should be highly considered given the proximal distribution of weakness, although normal muscle enzymes and negative autoantibodies make these diagnoses less likely. Moreover, he did not have any skin lesions typical for DM. Inclusion body myositis (IBM) should similarly be considered; however, quadriceps greater than hip flexors weakness and early involvement of distal muscles, for example, finger flexors and ankle dorsiflexors, would be expected. Genetic myopathies, such as limb-girdle muscular dystrophy and facioscapulohumeral muscular dystrophy, are enticing possibilities given shoulder girdle muscle weakness and scapular winging. However, lack of facial involvement and early leg involvement would be atypical for the latter and both typically present earlier in life. The origin of the weakness could also be nonmyopathic. Lambert-Eaton myasthenic syndrome may present with proximal weakness but the patient lacked fatigability or autonomic symptoms. Painless progressive weakness may raise concern for possible motor neuron disease but there were no upper or lower motor neuron signs. As discussed earlier, intact reflexes and absent sensory symptoms made CIDP unlikely. However, none of these conditions would explain the concurrent PDB.

To evaluate the etiology of the patient's weakness, an EMG was performed. His EMG revealed shorter amplitude and mildly polyphasic motor unit action potentials in deltoid and early recruitment in deltoid, biceps, iliopsoas, and vastus lateralis. There was no spontaneous activity or firm electrodiagnostic findings suggestive of muscle membrane irritability, which is commonly present in inflammatory myopathies.

These findings essentially suggested a myopathic picture and a biopsy of the patient's right quadriceps was performed. This demonstrated variability in myofiber size and increased internalized nuclei. Few rimmed vacuoles were also noted. Electron microscopy (EM) showed inclusions in these vacuoles (figure, E).

Question for consideration:

1. What clinical disease spectrum would be consistent with the patient's clinical presentation?

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Section 3

Rimmed vacuoles are a nonspecific finding in many myopathies, including sporadic IBM (sIBM) and myofibrillar myopathy (MFM). As noted previously, the patient's pattern of muscle involvement was not typical for sIBM. There was no amorphous or granular material on muscle histology and EM did not show myofibrillar degeneration to support MFM. Interestingly, rimmed vacuoles can also be found in a rare inherited spectrum of disorders known as inclusion body myopathy associated with Paget disease and frontotemporal dementia (IBMPFD). Knowing our patient was recently diagnosed with PDB, there was thus high clinical suspicion for this disorder.[3–5]

IBMPFD is a unique clinical syndrome with heterogeneous clinical presentation.[3] Myopathy is found in 80%–90% of patients and is an isolated finding in 30% of patients. Although weakness is commonly proximal, distal muscle groups may be involved. Serum CK is typically normal or slightly elevated and EMG is myopathic, although occasional neurogenic features have been reported. Muscle biopsy often shows nonspecific changes including atrophy, variation in muscle fiber size, rimmed vacuoles, and inclusions with valosin-containing protein (VCP), ubiquitin, or TDP-43 reactivity.

About 50% of patients develop PDB, often a decade earlier than the typical presentation, and nearly 30% of patients with IBMPFD will develop frontotemporal dementia (FTD), usually the behavioral variant. The latter typically appears late in the disease course; therefore, patients should receive baseline neuropsychological testing. In our patient, neurocognitive testing revealed nonamnestic mild cognitive impairment. The pattern of deficits suggested frontal and parietal lobe involvement with mild impairment of executive functioning.

The complete triad associated with IBMPFD manifests in only 12% of individuals and additional associated features have also been reported. These include hepatic steatosis, cataracts, dilated cardiomyopathy, sphincter disturbances, sensorimotor axonal neuropathy, and cerebellar signs.[4]

Question for consideration:

1. How would you confirm the diagnosis?

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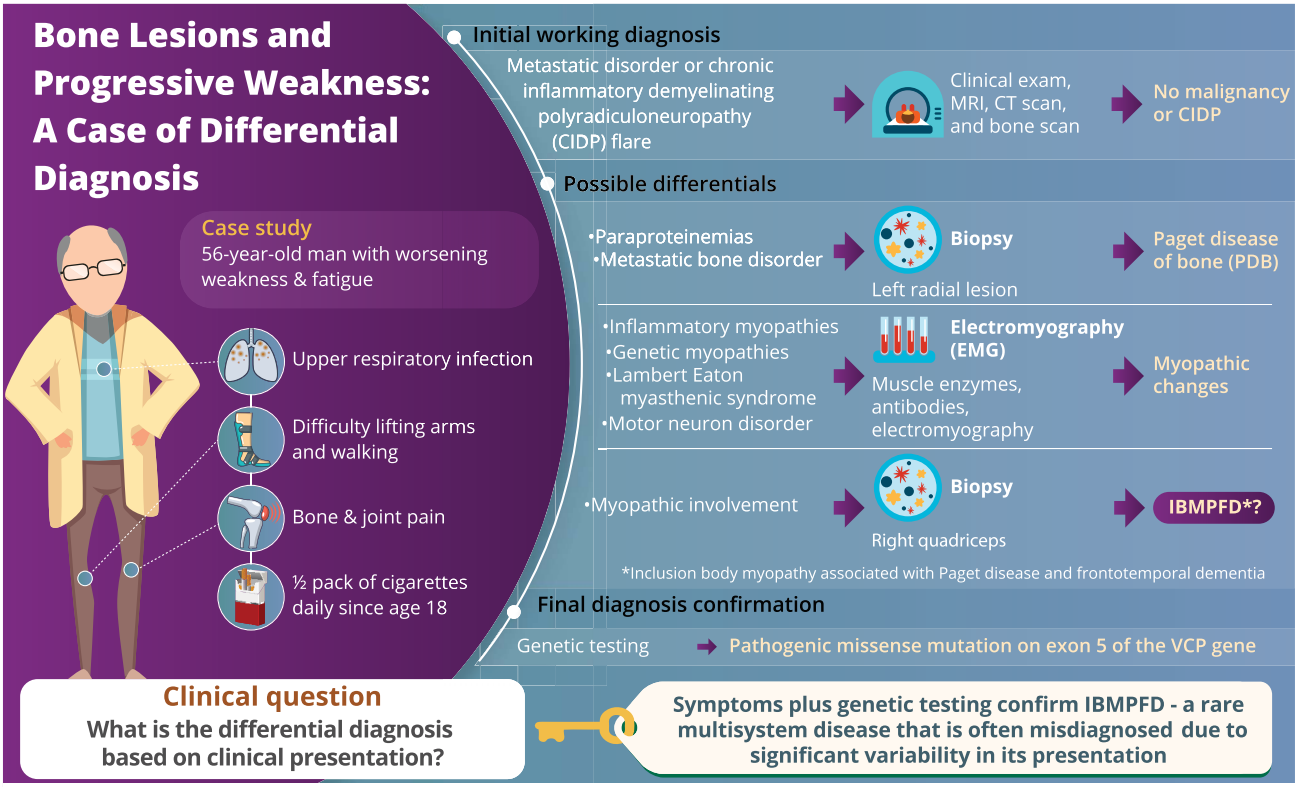

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Section 4

IBMPFD is an autosomal dominant disorder with variable penetrance secondary to *VCP* gene mutation located at 9p13.3.[3] Genetic testing is essential to confirm the diagnosis. Our patient had a pathogenic missense mutation on exon 5 of the *VCP* gene representing a heterozygous G > A nucleotide change that results in substitution of arginine for histidine, which confirmed his diagnosis.

VCP is involved in DNA repair, apoptosis, cell cycle control, and protein degradation. About 45 different mutations have been described in IBMPFD.[5] These mutations may disrupt VCP's normal roles in protein homeostasis, resulting in abnormal protein aggregation seen pathologically in IBMPFD.[6]

Recently, mutations in non-VCP proteins (SQSTM1, HNRPNA2B1, and HNRNPA1) have been associated with IBMPFD. As case descriptions of IBMPFD expand beyond the classical triad and other genes are implicated, multisystem proteinopathy has been proposed as a more appropriate classification.[7] This terminology emphasizes the multiple systems and pathology shared among these disorders while allowing for heterogeneity in genetic and phenotypical presentation.

Discussion

IBMPFD is a rare multisystem disease that is often misdiagnosed due to substantial variability in its presentation. No treatments exist to modify or prevent its progression. Physical and occupational therapy and assistive devices can promote functionality. Bisphosphonates may improve bone pain in patients with PDB, despite no convincing evidence that treatment alters disease course.[8] Selective serotonin reuptake inhibitors may be beneficial for behavioral symptom management in those patients with FTD.[9] In later stages, patients may present with respiratory or cardiac failure; some patients may eventually require assisted ventilation. EKG, echocardiogram, and regular pulmonary function tests are recommended.

This case represents the diagnostic challenges associated with IBMPFD. To make a unifying diagnosis for this heterogeneous multisystem disorder may not be straightforward and requires high clinical suspicion. This should be in the differential when evaluating patients with myopathy and concurrent bone disease. Early recognition may help to better manage associated complications and improve quality of life.

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Disclosure

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Anita Huttner, MD	Yale School of Medicine	Author	Analysis and interpretation of data, revising of manuscript
Richard J. Nowak, MD, MS	Yale School of Medicine	Author	Analysis and interpretation of data, revising of manuscript
Bhaskar Roy, MD	Yale School of Medicine	Author	Study concept and design, analysis and interpretation of data, revising of manuscript

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