A rare paraneoplastic syndrome causing weakness, pain and low serum phosphorous

Helena Hwang[1], M.D. and Jeffrey L. Elliott[2], M.D.

[1] Department of Pathology, [2] Department of Neurology, UT Southwestern Medical Center
5323 Harry Hines BLVD, Dallas, Tx 75390

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Introduction

Muscle pain is a common complaint often prompting neuromuscular referral. The differential for this clinical problem is broad, with causes ranging from inflammatory, toxic, metabolic, hereditary, or idiopathic. The presence of accompanying weakness, elevations in creatine kinase (CK) or abnormal EMG findings often triggers more extensive investigations into etiology. Here, we report an unusual case of musculoskeletal pain and weakness resulting from an FGF-23 related paraneoplastic syndrome and briefly review this rare but treatable condition that may be encountered within neuromuscular practice.

Case Report

A 25-year-old man was referred to neuromuscular clinic for evaluation of musculoskeletal pain, spasms and weakness. Symptoms had begun 4 years earlier with pain located primarily in low back, bilateral shoulders and hip but extending into arms and thighs. Pain was described as sharp, deep, becoming more constant over time, and accompanied by axial muscle spasms. Two years prior, he noted onset of bilateral leg weakness, more proximal then distal. He had difficulty lifting his legs at the hip and began to have frequent falls. He also developed weakness in both arms although to a lesser degree than his legs. He struggled lifting objects overhead, but hand movements/dexterity were largely unaffected. He lost muscle bulk throughout and experienced a 20-pound unintentional weight loss. He had developed chest pain over the past 2-3 months noting periods of dyspnea. He also began using a wheelchair for mobility due to pain, weakness and falls. He denied fasciculations, paresthesia, urinary incontinence, and bulbar or ocular symptoms.

His past medical history was notable for asthma, and a right inguinal lump which he was told was a lymph node. He was diagnosed with avascular necrosis of the head of the left hip 9 months earlier, after several episodes of acute weakness in the hip causing him to fall. He also had history of a foot fracture. He had been seen by his PCP and several orthopedists without establishing a clear diagnosis. Overall, there was no significant family or social history.

On exam, he had normal mental status and cranial nerves. His muscle bulk and tone were normal. There was proximal weakness in hip flexors and shoulder abductors, although proximal muscle testing was limited by pain. Distal muscle strength appeared normal. Sensory exam was normal and reflexes were preserved. Gait assessment was pain limited. On general physical exam, he had chest wall deformity with pectus excavatum. No scoliosis was noted.

Electrophysiological evaluation demonstrated normal motor and sensory nerve conductions in both upper and lower extremities. EMG exam found increased insertional activity in the deltoid with a rare fasciculation. Motor unit morphology and recruitment were unremarkable.

Table 1: Significant Laboratory Values

Lab	Result	Normal
CK	55 U/L	39-308 U/ml
PTH	50.8 pg/ml	15-65 pg/ml
TSH	1.3 mclU/ml	0.4-4.5 mcIU/ml
K	4.4 mmole/L	3.6-5.0 mmole/L
Ca	10 mg/dl	8.4-10.2 mg/dl
Magnesium	2.2 mg/dl	1.6-2.6 mg/dl
Vitamin d,25-OH Vitamin d 1,2 d-OH	50.4 ng/ml **13 pg/ml**	30-80 ng/ml 18-64 pg/ml
Alkaline phosphatase	**464 U/L- total** **358 IU/ml-bone**	40-129 U/L 12-43 IU/ml
P04	**1.2 mg/dl**	2.4-4.5 mg/dl
FGF-23	**7150 RU/ml**	<180 RU/ml

Significant laboratory evaluation is shown in Table 1. Glutamic decarboxylase (GAD) and Caspr2 antibodies in serum were negative. Aggressive Neutraphos supplementation was initiated, but normal phosphorous levels could not be achieved. A diagnosis of FGF-23 related osteomalacia and hypophosphatemia was made and a search for neoplasm began. Given the history of a right inguinal lymph node, the patient underwent abdominal/pelvis/hip imaging by CT and MRI modalities which

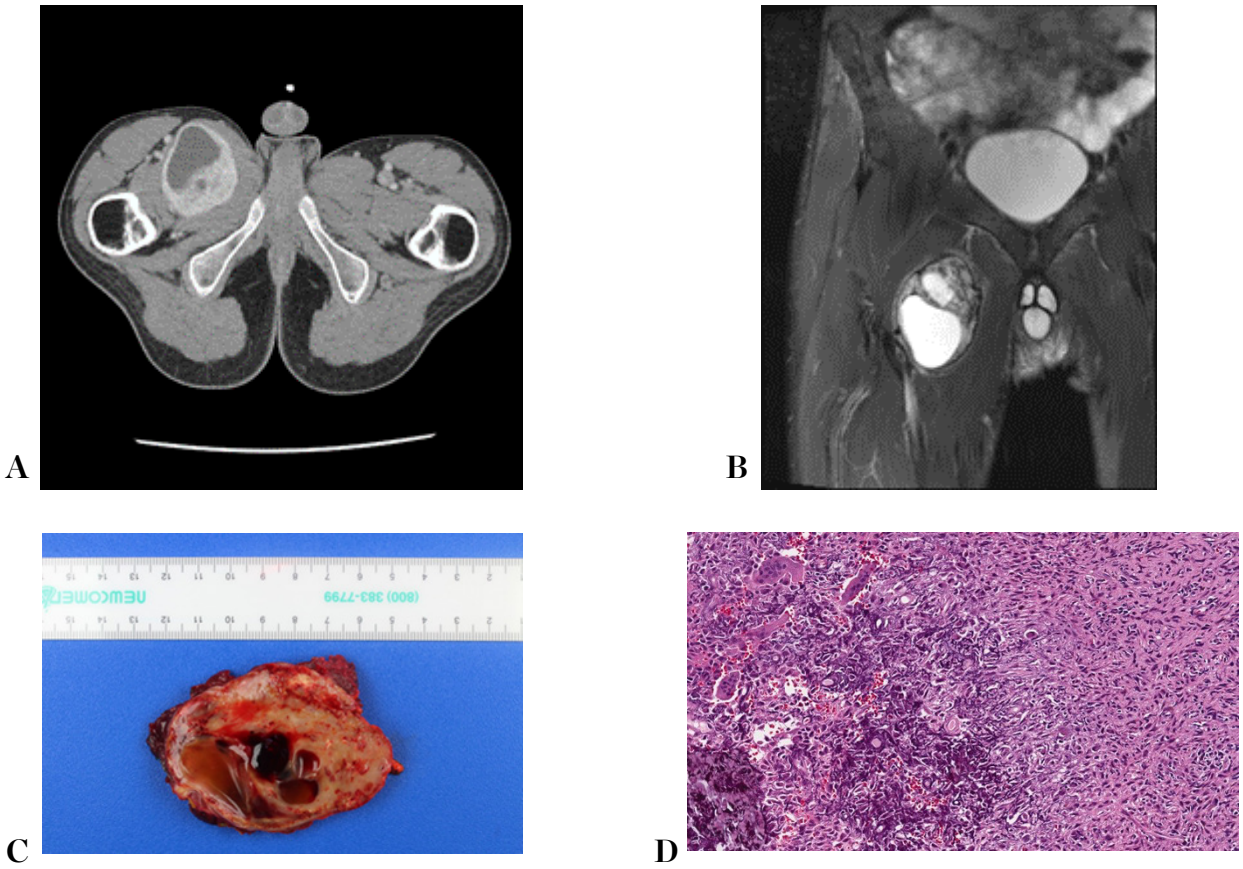

Figure 1. A) Contrasted CT scan of the pelvis showing a 5.5 x 7.4 cm mass anteriorly centered at right adductor brevis muscle. B) T2 fat suppressed MR image of pelvis/thigh. C) Gross photograph of phosphaturic mesenchymal tumor showing mass with cystic change and hemorrhage. D) Tumor consists of spindled cells with areas of calcification. Osteoclast-like giant cells are also present.

showed an enhancing mass with apparent areas of cystic change centered at the adductor brevis muscle of the right thigh (Figure 1A-1B). Tissue from a CT-guided biopsy revealed a phosphaturic mesenchymal tumor. The tumor was surgically excised, but the right obturator nerve was sacrificed due to the large portion of tumor involving the adductor muscles. Final pathology confirmed a phosphaturic mesenchymal tumor (Figure 1C-1D) with surrounding lymph nodes and adjacent muscle, free of tumor. Within 6 days of tumor resection, serum phosphorous normalized at 3.5 mg/dl and remained stable thereafter. Proximal weakness also improved. At 1 month follow-up, patient had noted improved strength and function with reduced pain as well.

Discussion

Tumor induced or oncogenic osteomalacia (TIO) is a rare paraneoplastic disorder characterized by the triad of muscle weakness, musculoskeletal pain and bony fractures in the setting of persistent low serum phosphate.[1] The syndrome has been reported in wide range of ages, from childhood well into adulthood (mean age in early 5th decade) with no male/female predilection.[2,3] It results from production of FGF-23, a key hormonal regulator of phosphate and vitamin D metabolism by phosphaturic mesenychmal tumors (PMTs), a usually benign spindle shaped cell neoplasm derived from skeletal stem cells.[4,5] Rarely, paraneoplastic TIO phenotypes with FGF-23 expression have also been reported with small cell carcinoma of the lung, breast cancer and ovarian neoplasms.[6-8] FGF-23, one of three sub-members of the fibroblast growth factor metabolic subclass, acts primarily by suppressing expression of NPT2a and NPT2c sodium-phosphate cotransporters in the renal proximal tubule serving to decrease phosphate reabsorption and promote wasting.[4] In addition, FGF-23 may impair hydroxy vitamin d synthesis which is necessary for optimum phosphate absorption from the small intestine.[9] The prolonged low serum phosphate and vitamin d abnormalities result in significant osteomalacia which accounts for the clinically observed bony pain and multiple fractures seen with TIO.

As FGF-23 is not recognized to have direct effects on skeletal muscle function, the proximal weakness associated with TIO derives in part from the effects of seriously low and prolonged hypophosphatemia on skeletal muscle.[10] Low serum phosphate can lead to muscle breakdown

and rhabdomyolysis as levels of phosphate critical for adequate ATP production are compromised.[11,12] In animal models, prolonged hypophosphatemia can directly lead to a myopathy that itself may also increase the probability of rhabdomyolysis.[10] Intramuscular inorganic phosphate levels are also critical for myofibrillar performance and maintaining adequate Ca2+ release from the sarcoplasmic reticulum (SR) for muscle fiber contraction. Such alterations can produce skeletal muscle weakness as well as enhanced muscle fatigue.[13] The significant weight loss or as yet other unknown factors secreted by the tumor might also contribute to the proximal weakness observed in TIO.

Primary treatment for TIO-related musculoskeletal pain, weakness and hypophosphatemia consists of recognizing the disorder, then identifying and resecting the tumor. In the rare cases where complete tumor excision is not possible, adjunctive radiation therapy and potential use of anti-FGF 23 monoclonal antibodies (burosamab, Crysvita) may be considered.[14] Although rarely encountered in neuromuscular practice, TIO diagnosis should not be missed, as it is a treatable and reversible paraneoplastic syndrome. This case emphasizes the importance of assessing routine comprehensive metabolic panels in cases of musculoskeletal pain or weakness, as it was the abnormal alkaline phosphatase and serum phosphorous levels which initiated the proper course in making this rare diagnosis.

Corresponding Author
Dr Jeffrey L. Elliott
E-mail: jeffrey.elliott@utsouthwestern.edu
Phone: 214-648-8816
Fax: 214-648-5080

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