Diagnostic Findings and Treatment in a 51-Year-Old Woman With Oncogenic Osteomalacia

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A 51-year-old woman presented with recurrent insufficiency fractures of the right midfoot, the left femoral condyle, and the ribs. Furthermore, she complained of unspecific muscle and joint tenderness as well as lower back pain that had evolved over the past few years.

Initial laboratory testing revealed hypophosphatemia and elevated alkaline phosphatase levels; vitamin D and PTH were within normal limits. Subsequent analyses showed elevated levels for fibroblast growth factor 23 (FGF-23) and urinary phosphorus loss at the upper normal limit.

Differential diagnoses included congenital forms of hypophosphatemic rickets and renal phosphate wasting, as well as (especially in a previously asymptomatic patient) oncogenic osteomalacia due to a phosphaturic mesenchymal tumor.

Although bone scintigraphy performed to localize an osseous tumor was negative, whole-body positron emission tomography (PET)/computed tomography (CT) using the radiolabeled somatostatin analog [^{68}Ga]DOTATATE revealed a suspicious lesion measuring approximately 20 mm in diameter within the right gluteal region (Figure 1, A–C). Magnetic resonance imaging (MRI) for further surgical planning confirmed the PET finding (Figure 1D) and illustrated markedly increased tumor blood supply (Figure 1E).

The patient underwent surgery. Macroscopy showed a sharply demarcated gray tumor without necrosis. Upon histological examination, the tumor was of medium cell density with a rich capillary supply and a characteristic deposition of a homogenous eosinophilic substance between the evenly spaced tumor cells (Figure 1, F and G). No signs of atypia, mitosis, or necrosis could be observed, thus leading to the final diagnosis of a phosphaturic mesenchymal tumor of mixed connective tissue type (PMTMCT) (1).

Postoperatively, musculoskeletal pain and tenderness relieved and biochemical parameters of disease burden (FGF-23, serum phosphorous) recovered subsequently (Figure 2).

Oncogenic osteomalacia (synonym, tumor-induced osteomalacia, or TIO) is a rare cause of hypophosphatemic rickets. Main symptoms include musculoskeletal tenderness, recurrent bone marrow edema, or insufficiency fractures associated with severe hypophosphatemia, hyperphosphaturia, elevated levels of FGF-23, and typically alkaline phosphatase (2, 3).

In most cases, hyperphosphaturia is caused by a benign mesenchymal tumor with unregulated secretion of phosphaturic factors/phosphatonins such as FGF-23 and secreted frizzled-related protein 4 (1, 2, 4). However, some reports indicate that this syndrome (as a paraneoplastic condition) is underdiagnosed in malignant tumors, eg, prostate, colon, and small-cell lung cancer (3).

Surgical removal of the tumor is the causative treatment that will stop phosphaturia and normalize bone metabolism (2, 4).

Because these tumors may be very small and indolent and occur at unusual anatomic sites, they are generally difficult to localize. Typical manifestations include the long bones (55% of cases) and the soft tissues (45%, including the skin)—with most lesions localized in the lower limbs (ie, femur and tibia) (5). Conventional x-ray, MRI, and CT scans are usually not sufficient for tumor identification and localization.

Because these tumors typically express somatostatin receptors, functional imaging with radiolabeled somatosta-

Abbreviations: CT, computed tomography; FGF-23, fibroblast growth factor 23; MRI, magnetic resonance imaging; PET, positron emission tomography.

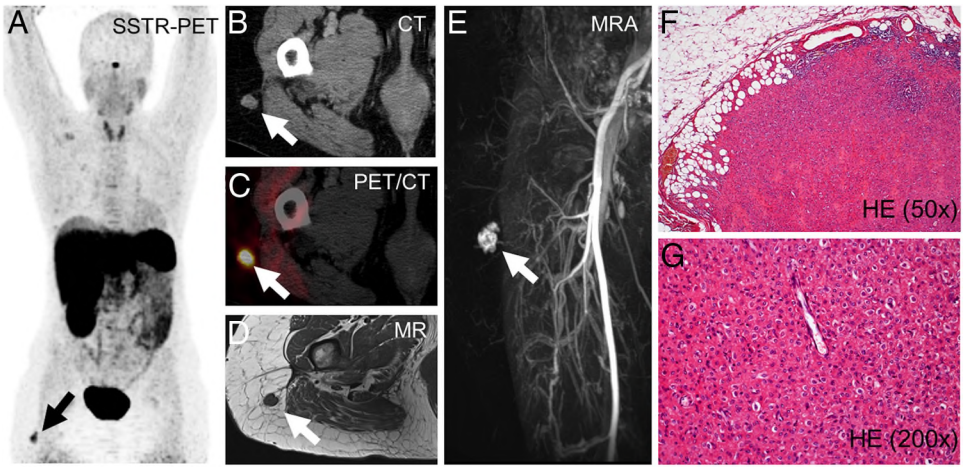

Figure 1. A, SSTR-PET (three-dimensional projection) showing focally increased uptake in the right gluteal region (arrow) and normal SSTR expression in the pituitary and the thyroid. B–D, CT scan (B), fused PET/CT scan (C), and T1-weighted MRI scan (D) depicting an SSTR-expressing soft-tissue tumor (arrows). E, Magnetic resonance angiography (MRA) illustrating intense blood supply of the tumor (arrow). F, Histological overview (×50; HE) showing medium cellularity. G, The detailed view (×200; HE) reveals evenly spaced tumor cells with pale cytoplasm and a characteristic eosinophilic matrix, no atypia, no mitotic figures, and no necrosis. SSTR, somatostatin receptor; HE, hematoxylin and eosin.

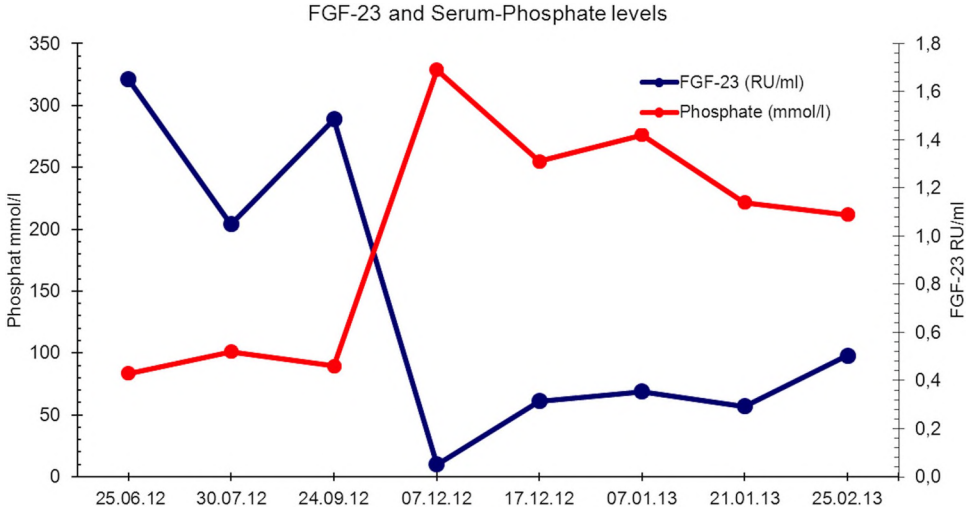

Figure 2. Immediate decline of serum FGF-23 levels after surgical removal of the tumor, accompanied by subsequent recovery of serum phosphate levels within normal ranges.

tin analogs (eg, 111-Indium octreotide scintigraphy or [^{68}Ga]DOTATATE-PET [preferably in combination with CT]) is a valuable diagnostic tool.

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