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Commentary

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Tumor-induced osteomalacia (TIO)[2] is a rare condition, well described in the literature. It is typically caused by tumors of mesenchymal origin that overexpress the phosphatonin fibroblast growth factor 23 (FGF-23). Patients present with bone pain, muscle weakness, and recurrent fractures. TIO has an insidious onset, and patients may have significant bone demineralization when they seek care. Hypophosphatemia is the hallmark of the disease. Laboratory data also show normal serum calcium and PTH, low or normal 25-hydroxyvitamin D, and low 1,25-dihydroxyvitamin D concentrations. Serum alkaline phosphate is high. Urine calcium is low but urine phosphate is high. Renal phosphate wasting can be assessed by calculating a random percent tubular reabsorption of phosphate or a fasting tubular maximum for phosphate corrected for glomerular filtration rate *(1)*. Inappropriately normal or increased plasma FGF-23 concentrations are present. Genetic causes of hypophosphatemia (X-linked, autosomal dominant, and autosomal recessive hypophosphatemic rickets) have similar biochemical profiles. These causes can be distinguished from TIO by detailed history including age of onset, physical findings (such as changes in dentition), and genetic testing. Acquired causes such as heavy metal poisoning or acquired Fanconi syndrome will have findings of renal tubular damage *(1, 2)*.

These tumors may be small, in obscure places, and difficult to localize. Patients should undergo a complete physical examination and extensive head-to-toe radiologic evaluation to locate these tumors. Functional studies include indium-111–labeled octreotide scan and fluorodeoxyglucose positron emission tomography (FDG-PET) *(1, 3)*. Coregistered computed tomography (CT) with PET or octreotide scan greatly improves localization success rates. Whereas CT scans and MRI may be helpful, dual-energy x-ray absorptiometry (DXA) and bone scans usually are not. Selective venous sampling is sometimes used to identify the offending lesion in patients with multiple tumoral growths or intracranial lesions *(1, 4)*.

Medical management includes replacement of phosphate and calcitriol. Octreotide therapy may mitigate symptoms *(5)*. Resection of tumor is curative.

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[2] Nonstandard abbreviations: TIO, tumor-induced osteomalacia; FGF-23, fibroblast growth factor 23; FDG-PET, fluorodeoxyglucose positron emission tomography; CT, computed tomography; DXA, dual-energy x-ray absorptiometry.

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Commentary

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With more than 20 family members, fibroblast growth factors (FGFs)[4] generally influence cell division and survival involving the differentiation and development of tissues, healing, and neoplasia. FGFs bind to FGF receptors (FGFRs) in contrast to fibroblast homologous factors (FHFs) that share structural homology with FGFs but do not bind to FGFRs. There are 4 receptors for FGF—FGFR1, FGFR2, FGFR3, and FGFR4—that vary as to which ligands they bind and their tissue distribution. The typical FGFR is composed of 3 immunoglobulin-like domains constituting the extracellular domain, a single hydrophobic membrane-spanning domain, and a cytoplasmic domain with tyrosine kinase activity.

FGF19, FGF21, and FGF23 (the endocrine FGFs) constitute 1 of the 7 subfamilies of FGFs based on their amino acid sequence similarity and their apparent evolution. The 5 paracrine FGF families are the FGF1/2 subfamily, the FGF4/5/6 subfamily, the FGF3/7/10/22 subfamily, the FGF9/16/20 subfamily, and the FGF8/17/19 subfamily. The single intracrine FGF subfamily is the FGF11/12/13/14 subfamily.

In the endocrine FGF subfamily (FGF19, FGF21, and FGF23), by binding to FGFR4, FGF19 is involved in inner ear development and regulating bile acid synthesis. FGF21 increases glucose transport into adipose cells by inducing solute carrier family 2 (facilitated glucose transporter), member 1 (SLC2A1), the glucose transporter 1 (GLUT1) facilitative glucose transporter. FGF21 binds to FGFR1c, FGFR2c, or FGFR3c. FGF21 agonists are under consideration as antidiabetic agents. The hypophosphatemic action of FGF23 is mediated by its binding to FGFR1, and to a lesser degree, FGFR4. Whereas FGF19 and FGF21 signaling involves klotho-β, FGF23 interacts with its receptor via klotho.

The discovery of FGF23 and its action clearly explains tumor-induced osteomalacia. Understanding FGF23 and its metabolism and signaling is providing novel insights into our understanding of inherited causes of hypophosphatemia. Recognizing the complexity of the FGF family and the FGFR receptors, there is much to learn that will likely be relevant to clinical care and laboratory medicine.

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[4] Nonstandard abbreviations: FGF, fibroblast growth factor; FGFR, FGF receptor; FHF, fibroblast homologous factor; SLC2A1, solute carrier family 2 (facilitated glucose transporter), member 1; GLUT1, glucose transporter 1.

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