Clinical Case Report

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Sinonasal hemangiopericytoma caused hypophosphatemic osteomalacia

A case report

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Abstract

Rationale: Tumor-induced osteomalacia (TIO) is a rare, paraneoplastic syndrome featured with fibroblast growth factor 23 (FGF23) secretion primarily by benign mesenchymal tumors and sometimes by malignancies. TIO diagnosis and treatment is often delayed because TIO usually has nonspecific generalized bone pain and weakness, and location of TIO tumor is quite challenging. Very few TIO caused by sinonasal hemangiopericytoma have been reported in the literature.

Patient concerns: A 40-year-old Chinese woman presented with diffuse bone pain for more than 1 year. Laboratory examination showed hypophosphatemia, hyperphosphaturia, hypocalcemia, an elevated serum alkaline phosphatase (ALP) level and bone-specific ALP level. Imaging studies revealed low bone mineral density (BMD) and multiple pseudofractures at the ribs. F-18 fluorodeoxyglucose positron emission tomography was negative in searching for tumors. Because no tumor was located, the patient was treated with oral phosphate, calcium, and alfacalcidol, and achieved great relief in her symptoms and improvement in BMD. Six years later, the patient had breast cancer surgery and received chemotherapy, and still had hypophosphatemia. During this time, nasopharyngo-fiberscope showed nasal mass in her left nasal cavity. Then she had her nasal polyps removed and surprisingly the serum phosphate became normal.

Diagnoses and interventions: The patient had the nasal mass resected, and pathological diagnosis of the nasal mass was sinonasal hemangiopericytoma. Immunohistochemical analysis was positive for FGF23. Thus the final diagnosis was osteomalacia induced by sinonasal hemangiopericytoma. Phosphate supplementation and alfacalcidol were discontinued.

Outcomes: The patient had normal serum phosphate after 6-month follow-up.

Lessons: By presenting this case, we hope to remind clinicians that in patients with osteomalacia with undetermined reason and intranasal polypoid mass, sinonasal hemangiopericytoma should be suspected.

Abbreviations: ALP = alkaline phosphatase, BMD = bone mineral density, CT = computed tomography, FDG = F-18 fluorodeoxyglucose, FGF23 = fibroblast growth factor 23, PET = positron emission tomography, PMT = phosphaturic mesenchymal tumor, TIO = tumor-induced osteomalacia, VAS = visual analog scale.

Keywords: fibroblast growth factor 23, osteomalacia, phosphate, tumor

1. Introduction

Tumor-induced osteomalacia (TIO) is a rare, paraneoplastic syndrome featured with fibroblast growth factor 23 (FGF23) secretion primarily by benign mesenchymal tumors and sometimes by malignancies.[1] Approximately 300 cases of TIO have been reported by single case reports or case series around the world.[2] As a phosphatonin, FGF23 affects bone mineralization by reducing phosphate resorption in the renal tubule and inhibiting 1α-hydroxylation of vitamin D, which ultimately leads to osteomalacia.[3] Patients with osteomalacia complain of progressive bone pain, muscle weakness, walking disability, and other symptoms. TIO diagnosis and treatment is often delayed because TIO usually has nonspecific generalized bone pain and weakness, and location of TIO tumor is quite challenging. In this article, we presented a case of TIO, caused by a very rare sinonasal hemangiopericytoma,[4] who was misdiagnosed with nasal polyps and had a negative F-18 fluorodeoxyglucose (FDG) uptake in the positron emission tomography (PET).

2. Case report

A 40-year-old Chinese woman presented with diffuse bone pain for more than 1 year. Pain firstly affected her spine, then gradually developed in the ribs, pelvis, sternum, and hips, and was aggravated during activity and weight bearing. She had mild nasal obstruction and occasional pus snot for a few months, and was otherwise healthy. On past medical history, the patient took dexamethasone and prednisone occasionally on her own, and

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was also given intravenous zoledronate once in a regional hospital because she was considered to have osteoporosis-related bony pain, yet had no relief of pain. Her family history is not remarkable. When admitted, she had difficulty in walking and other weight bearing activities. Physical examination showed diffuse bony tenderness, and a visual analog scale score of 8.

Biochemical tests showed hypocalcemia (1.92 mmol/L; normal range, 2.10–2.70 mmol/L), hypophosphatemia (0.17 mmol/L; normal range, 0.81–1.45 mmol/L), an elevated intact parathyroid hormone level (15.26 pmol/L; normal range, 1.60–6.90 pmol/L), and a normal 25-hydroxy vitamin D (100.1 nmol/L; normal range, 47.7–144 nmol/L) and $1,25(OH)_2D$ level (46.82 pmol/L; normal range, 39–193 pmol/L). Studies of bone turnover markers showed an elevated alkaline phosphatase (ALP) level (210 IU/L; normal range: 47–138 IU/L), an elevated bone-specific ALP level (56.97 μg/L; normal range: 11.4–24.6 μg/L), and a decreased collagen type I C-telopeptide (0.242 ng/mL; normal range: 0.299–0.573 ng/mL). 24-Hour urine test revealed a lower limit of normal urinary calcium (2.50 mmol; normal range: 2.5–7.5 mmol), and a remarkably elevated urinary phosphate (31.65 mmol; normal range: 22–48 mmol) with regard to the extremely hypophosphatemia. Her blood gas, renal function, liver function, and hemogram were normal. Urinalysis showed normal specific gravity, a pH of 7.0, and no glycosuria or proteinuria.

Dual-energy x-ray absorptiometry revealed decreased bone mineral density (BMD) with a mean z score of −2.8 in lumbar spine (L1–4), −2.7 and −2.6 in femoral neck and total hip, respectively. Radiography of the spine, pelvis, and extremities showed multiple pseudofractures at the ribs, generalized osteopenia, thinning of the cortex of spine, and coarsened trabeculae. Osteomalacia was considered based on the radiographic features. Given her hyperphosphaturic hypophosphatemia and normal renal tubular function, TIO was highly suspected.

The tumor survey revealed a slightly elevated cancer antigen 153 (24.98 U/mL; normal range: <21 U/mL) and 199 (29.28 U/mL; normal range: <22 U/mL), and normal carcinoembryonic antigen, alpha-fetoprotein and cancer antigen 125. Serum and urine protein electrophoresis were normal. Abdominal ultrasonography showed renal cyst in the left kidney. PET-computed tomography revealed slight high diffuse F-18 FDG intake in the sternum, spine, and both sides of hip and iliac bone, slightly enlarged spleen, left nasal polyp, and left adnexa cyst. Nasopharyngo-fiberscope showed polypoid mass in the left nasal cavity. FGF23 testing was not available at that time.

The patient had a surgery to remove the nasal polypoid mass in another hospital after discharge, and the pathological findings showed hemorrhagic necrotic polyps. Because no tumor was located, oral phosphate, calcium, and alfacalcidol were prescribed. The patient took these drugs regularly, and symptoms were improved after 1 month. During the follow-up, her serum phosphate fluctuated between 0.35 and 0.62 mmol/L, and serum calcium remained normal. She was able to do daily activities and back to work. She had a dramatic increase of BMD in lumber (31%), femoral neck (22%), and total hip (18%) in 11 months.

Six years after discharge, the patient was diagnosed with breast cancer (T4N1M1, stage IV). Surgery was performed after 8 cycles of chemotherapy, followed by radiotherapy. Her nasal obstruction relapsed during this period, and nasopharyngo-fiberscope showed nasal mass in her left nasal cavity again. Computed tomography (CT) showed soft tissue mass in the left nasal passage, and bony lesions were not found. Surgery of the mass resection was done 2 months after the breast cancer surgery. Serum phosphate was 0.35 mmol/L the day before the nasal surgery yet was 1.24 mmol/L, 1 month after. Pathological diagnosis of the nasal mass was sinonasal hemangiopericytoma (Fig. 1). Immunohistochemical analysis was positive for FGF23 (Fig. 1). Phosphate supplementation and alfacalcidol were discontinued, and the patient had normal serum phosphate after 6-month follow-up. The patient has provided informed consent for publication of the case.

3. Discussion

We reported a rare case of hyperphosphaturic hypophosphatemic osteomalacia induced by FGF23-secreting sinonasal hemangiopericytoma, which was misdiagnosed with nasal polyps, and thus delayed diagnosis and definitive treatment. Immunohistochemical analysis of FGF23 was performed to confirm that osteomalacia was associated with synthesis of FGF23 by sinonasal hemangiopericytoma. By presenting this case, we hope to remind clinicians that in osteomalacia patients with unknown reason and intranasal polypoid mass, sinonasal hemangiopericytoma should be suspected.

Approximately 70% of tumors leading to TIO were histologically classified as phosphaturic mesenchymal tumor (PMT), and other histological entities were giant cell tumor, osteosarcoma, hemangioma, hemangiopericytoma, and so on.[3] Among them, hemangiopericytoma is one of the most common type,[5] as a study showed that 37 of 105 cases of non–PMT-induced TIO were hemangiopericytoma.[2] The majority of tumors causing TIO were of soft tissue origin, with very few located in nasal sinus. As by far the biggest case series of TIO showed, only 4 cases among 39 patients with TIO were found to have tumor in nasal sinus.[2]

Sinonasal hemangiopericytoma, also known as glomangiopericytoma, is very rare, accounting for <0.5% of sinonasal tumors,[6] and 5% of hemangiopericytoma at any site.[7] Till now, 12 cases of TIO caused by sinonasal hemangiopericytoma have been reported by single case reports, although there might be more reported in case series which were hard to verify the diagnosis. The clinical features of all the cases of TIO caused by sinonasal hemangiopericytoma reported by far are summarized in Table 1.[8–19] To be noticed, sinonasal hemangiopericytoma were unilateral in all cases except one with a mass in right nasal cavity extending into the left one,[8] and 8 cases were in the left side.[9–16] Six cases had regional bony resorption by CT.[8–14] Time for diagnosis was from 2 to 6 years since disease onset. One case reported severe bleeding,[17] and another an amount of bleeding of approximately 300 mL during resection of the sinonasal hemangiopericytoma.[10]

Serum FGF23 measurement is critical to TIO diagnosis, and FGF23 levels are elevated in most patients with TIO. Although FGF23 level was not measured in our case, FGF23 immunohistochemical analysis was performed as a surrogate. As far as we know, only 1 study has tested FGF23 protein expression by immunohistochemical analysis in TIO causative tumors in previous literature, which found FGF23 protein expression in 17 of 20 TIO cases.[20]

Mesenchymal tumors that induce TIO are usually small, slowly growing, and difficult to locate, which makes the diagnosis of TIO quite challenging, as was shown that it took 2 to 6 years to reach the diagnosis since disease onset, and 7 years in our case. Imaging is necessary for almost every patient with TIO to locate tumor. A step-wise approach is suggested which starts with functional imaging, such as 18FDG-PET-CT, octreotide SPECT-

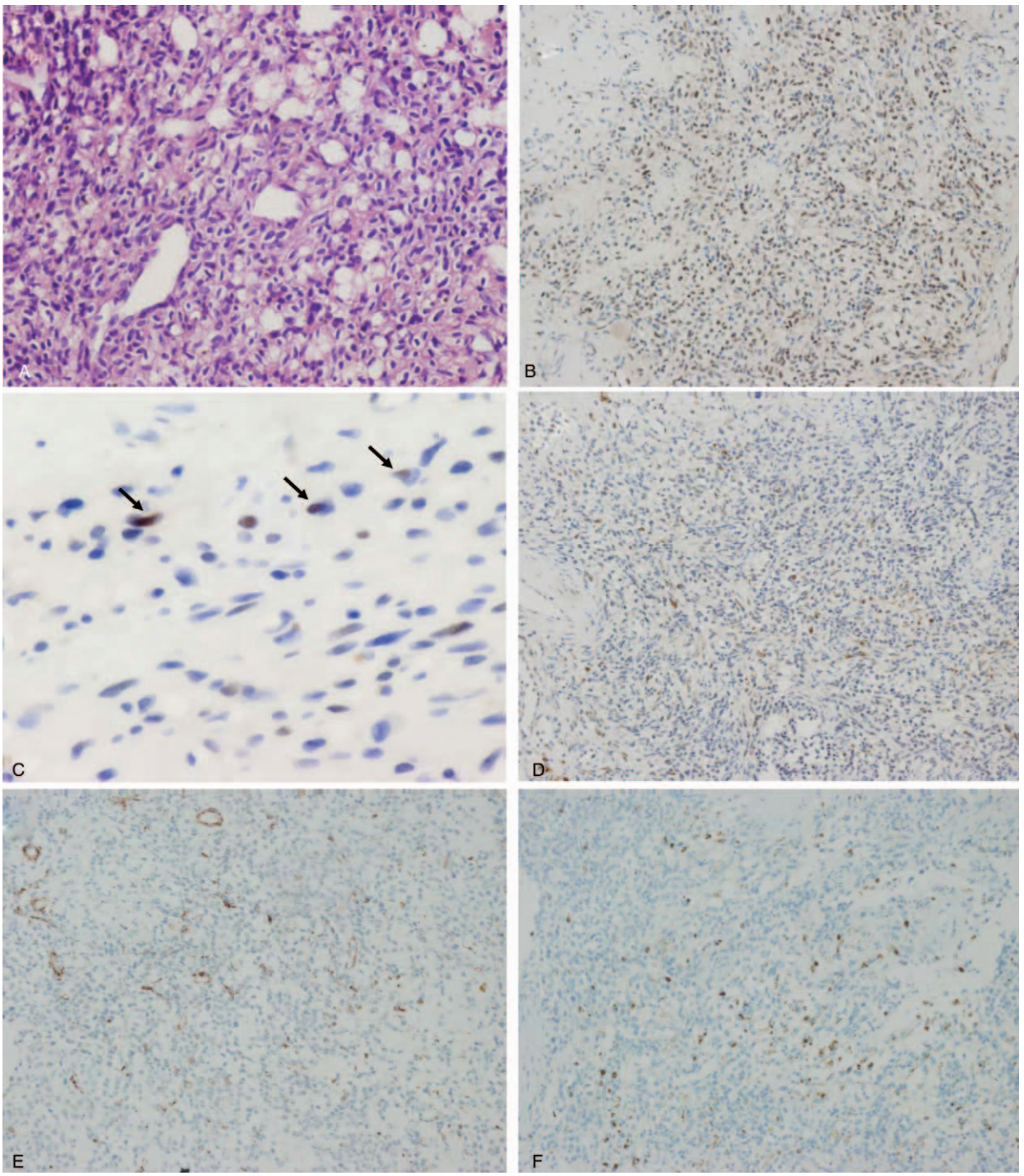

Figure 1. Morphological and immunohistochemical findings of the tumor. The tumor displays abundant blood vessels and sheet-like arrangement of uniform spindle cells (A). The tumor has diffuse express of cyclin D1 (B), focal expression of FGF23, STAT-6, and smooth muscle actin (C, D, and E), and 5% of tumor cells are Ki-67 positive (F).

CT, and DOTA-CT, followed by anatomical imaging, such as CT and magnetic resonance imaging.[1] Octreotide or DOTA scan are preferred if available, otherwise PET-CT can be performed as in our case. Study showed that PET-CT had a sensitivity of 71.4% to locate causative tumors.[21] Its sensitivity and specificity is inferior to DOTA scan in studies with small sample size,[22,23] and similar or even inferior to that of octreoscan.[21,22] In addition, PET-CT and somatostatin analog imaging can be complementary since some tumors may not be seen with somatostatin analog imaging yet were located by PET-CT. Our case showed that the causative tumor revealed a negative FDG uptake, which may be explained by low aggressiveness of the tumor.

For TIO treatment, surgery of complete tumor resection is the first option.[24] Bleeding during surgery should be concerned that 1 case reported severe bleeding,[17] and another an amount of bleeding of approximately 300 mL during surgery.[10] For those causative tumors were not located, or complete resection were

Table 1

A summary of reported cases of tumor-induced osteomalacia caused by sinonasal hemangiopericytoma.

Study	Age, y	Ethnicity/ country	Sex	Imaging	Bony destruction	Serum FGF-23	Tumor site	Time for diagnosis	Treatment	Bleeding during surgery	Outcome
Lee et al, 1995[8]	66	US	Female	CT, MRI	Yes	ND	Right nasal cavity and extending to left nasal cavity	3 y	Resection	NR	Stable within 10-mo follow-up
Jamal et al, 2013[9]	55	Caucasian	Male	Octreotide scanning, CT	Yes	Elevated	Left nasal sinus	3 y	Radiation and resection	NR	Cured during 2 y follow-up
Burnand, 2012[10]	54	UK	Male	Octreotide, CT, MRI	Yes	Elevated	Left nasal sinus	6 y	Resection	NR	Stable during 6 wk
Chang et al, 2012[11]	37	Brazilian	Male	CT, MRI	Yes	ND	Left nasal sinus	NR	Resection	NR	NR
Cho et al, 2013[12]	47	Korean	Female	CT	Yes	ND	Left nasal sinus	3 y	resection	300 ml	Improve after 1 mo
Fuentealba et al, 2003[13]	63	Caucasian	Female	CT, MRI	Yes	ND	Left maxillary sinus	5 y	Partial resection, complete resection, and radiation	NR	Relapse 3 mo after partial resection
Ray et al, 2015[14]	35	Indian	Male	CT, MRI	NR	Elevated	Left nasal cavity	2 y	resection	NR	Improve after 4 wk
Reiss et al, 2013[15]	55	Canadian	Male	Octreotide, CT	ND	Elevated	Left nasal sinus	3 y	Partial resection	NR	NR
Ghosh et al, 2009[16]	48	Indian	Male	CT, MRI	NR	ND	Left nasal cavity	4 y	Resection	NR	Stable during 3 mo
Lee et al, 2014[17]	60	Korean	Female	CT	NR	ND	Right maxillary sinus	6 y	Partial resection	Severe bleeding	Stable during 10 mo
Brandwein-Gensler and Siegal, 2012[18]	66	UK	Female	CT	NR	ND	Right nasal cavity	NR	Resection	NR	Stable during 25 mo
Beech et al, 2007[19]	42	UK	Male	MRI	NR	NR	Right ethmoid sinus	4 y	Resection	NR	Improve within 1 mo follow-up

CT = computed tomography, MRI = magnetic resonance imaging, ND = not detected, NR = not reported.

impossible, medical treatment should be initiated. Phosphorus and active vitamin D supplementation is commonly used for TIO treatment.[24] Because the majority of causative tumors are of borderline or low-grade malignancy, patients may have long survival by medical treatment without tumor resection. It is notable that chemotherapy is not recommended for patients with TIO, as was shown in our case that chemotherapy for breast cancer did not increase serum phosphorus of this patient.

4. Summary

To conclude, sinonasal hemangiopericytoma is a very rare causative tumor of TIO. A step-wise approach is recommended to locate tumors associated with TIO, which starts with functional imaging followed by anatomical imaging. Serum FGF23 measurement is critical of TIO diagnosis, and immunohistochemistry of FGF23 is positive for the majority of causative tumors. Surgery is the first option of TIO treatment, and medical treatment is indicated for patients when surgery is not possible. By presenting this case, we hope to remind clinicians that in osteomalacia patients with intranasal polypoid mass, sinonasal hemangiopericytoma should be suspected.

Author contributions

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