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A case of phosphaturic mesenchymal tumor (mixed connective tissue variant) that developed in the subcutaneous tissue of a patient with oncogenic osteomalacia and produced fibroblast growth factor 23

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Sir, Oncogenic osteomalacia (OOM) is an extremely rare osteomalacia associated with tumors. It is characterized by a presence of a tumor, hypophosphatemia caused by renal phosphate wasting, and low serum concentration of 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) with clinical and histological evidence of osteomalacia. [1] Since removal of the tumor results in rapid resolution of the symptoms and signs of OOM, it is believed that a humoral phosphaturic factor derived from the tumor is responsible for these abnormalities. [1] In 2001 fibroblast growth factor 23 (FGF23) was identified as causative factor of OOM. [2] High level of FGF23 is detected in either the tumor [3,4] or serum from OOM patients. [5] It is considered that overproduction of FGF23 by tumors induces hypophosphatemia by inhibiting the re-absorption of phosphate in the kidney, although its exact molecular mechanism is not clear. It is hypothesized that FGF23 is also secreted by one or more normal tissues as a phosphate-regulating hormone since a low level of FGF23 is detected in healthy people. [6]

The majority of OOM-associated tumors have been diagnosed as benign mesenchymal tumors such as hemangiopericytoma, hemangioma, giant cell tumor, and osteoblastoma. [7,8] Several investigators, however, have described that OOM-associated mesenchymal tumors were in most cases histologically distinctive and unlike any other known mesenchymal tumors and have suggested that most OOM-associated tumors are of a single histopathologic type called phosphaturic mesenchymal tumor, mixed connective tissue variant (PMTMCT).

We report a case of PMTMCT that developed as a subcutaneous nodule on the back of an OOM patient. The patient was a 47-year-old man who presented with typical clinical and biochemical features of osteomalacia. Laboratory tests (Table 1) showed hypophosphatemia, hyperparathyroidism, and low $1,25(OH)_2D$. An increase in alkaline phosphatase was also noted. An elastic hard subcutaneous tumor of about 3 cm in diameter was noted in the right side of his lower back. The surface skin was erythematous and slightly dome-shaped. On the basis of these findings the patient was

diagnosed as having OOM. The tumor was surgically removed *en bloc*. After surgery, the patient's clinical abnormalities gradually improved and 10 weeks after surgery the pain was almost eradicated. The clinical response after the surgery is shown in Table 1. The levels of serum phosphate and $1,25(OH)_2D$ became normal immediately after surgery. FGF23 in serum sample of before and after surgery was assayed at the same time as described previously [9] (Table 1). In preoperative serum, FGF23 was elevated, whilst on the day following surgery, the FGF23 concentration fell to within the normal range.

The tumor was embedded in subcutaneous fat tissue. It was a well-circumscribed and encapsulated mass that measured 2.8 X 1.0 X 1.0 cm. The cut surface was gray white with partial areas of prominent hemorrhage. Histopathologically, a nodular lesion with a clear boundary was present in the subcutaneous area. The tumor cells were embedded at low density within an eosinophilic and distinctive smudgy matrix (Fig. 1A). They were rounded in shape with ovoid nuclei, scanty cytoplasm, and indistinct cellular boundaries. Neither cytological atypia nor atypical mitotic figures were seen. Slight calcification was observed in the matrix and intercellular spaces (Fig. 1A, arrow). Many foci of eosinophilic chondroid matrix was observed in the periphery of the tumor (Fig. 1B), in which some cells with vacuolated cytoplasm scattered (Fig. 1C, white arrows). A small number of osteoclast-like giant cells were also present in the matrix (Fig. 1C, black arrows). There were numerous blood vessels in the peripheral region of the tumor (Fig. 1D), especially where matrix deposition was absent. Many of these blood vessels were dilated and showed a large sinusoidal configuration. The major histological features of PMTMCT pointed out by Folpe *et al.* consist of (1) spindle- to stellate- or round-shaped tumor cells with normochromatic, small nuclei, and indistinct nucleoli, (2) myxoid to myxochondroid matrix, (3) calcification with osteoclast-like giant cells, (4) prominent blood formation whose patterns are similar to those from

hemangiopericytoma.[8] Our case showed all of these features and thus we diagnosed our case as PMTMCT associated with OOM. Immunohistochemically, the tumor cells showed reactivity for vimentin (data not shown). The tumor cells were not reactive with S-100, CD34, or EMA (data not shown). Tumor matrix contained variable amounts of mucus, which stained with alcian blue (data not shown). Blood vessels were not reactive with α-SMA. To determine whether the tumor expressed FGF23 protein, immunohistochemical analysis using anti-human FGF23 antibody was performed as described previously.[10] The majority of tumor cells were stained with FGF23 (Fig. 1E). No FGF23 expression was observed in the smudgy matrix.

Our case supports the involvement of FGF23 produced from PMTMCT in the pathogenesis of OOM. Identification of the origin of the tumor cells and the mechanism of high expression of FGF23 in the tumor cells are necessary for understanding the pathophysiology of PMTMCT.

Acknowledgement

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with serum phosphate level in isolated fibrous dysplasia. *Life Sci* 2006; **78:** 2295-301.

Figure legends

Figure 1. Histopathological findings (A – D) and immunohistochemical analysis of FGF23-producing cells in tumor tissues (E, F). (A) Typical tumor cells (haematoxylin and eosin; original magnification X 400). (B) Many foci of eosinophilic chondroid matrix in the periphery of the tumor (haematoxylin and eosin; original magnification X 100). (C) Magnified image of (B) (haematoxylin and eosin; original magnification X 400). (D) Prominent hemorrhage and vascular structures (haematoxylin and eosin; original magnification X 40). (E) Deparaffinized sections of isolated tumor were immunohistochemically examined using anti-human FGF23 antibody as described previously.[10] FGF23 immunoreactivity was present in tumor cells (original magnification X 100). (F) Sections treated without first antibody were used as negative controls (original magnification X 100).

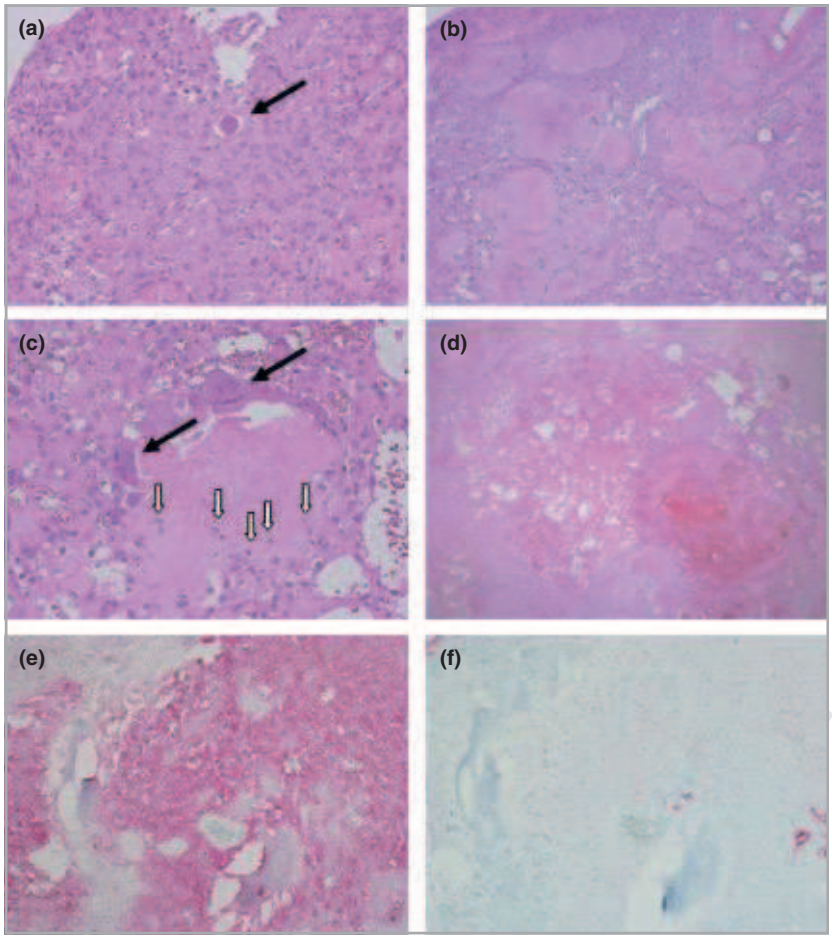

Table 1 Laboratory findings before and after resection

		After resection					
	Before resection	Day 1	Day 2	Day 5	Day 7	Day 14	Normal range
Phosphate (mg dL^{-1})	1·2	1·6	1·9	2·7	2·9	3·8	1·4–4·5
Calcium (mg dL^{-1})	8·8	8·4	9·0	9·4	8·9	8·6	8·4–9·9
Parathyroid hormone (pg mL^{-1})	98	ND	ND	ND	88	ND	10–65
1,25-dihydroxyvitamin D_3 (pg mL^{-1})	8	ND	ND	ND	129	ND	20–60
25-hydroxyvitamin D_3 (ng mL^{-1})	11·5	ND	ND	12·9	ND	ND	9·0–33·9
Alkaline phosphatase (IU L^{-1})	832	646	656	712	679	679	109–321
Fibroblast growth factor 23 (pg mL^{-1})	220	30	21	36	35	37	10–50

ND, not determined.