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Case Report

Malignant transformation of phosphaturic mesenchymal tumor: a case report and literature review

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Abstract. Phosphaturic mesenchymal tumor, mixed connective tissue variant (PMT-MCT) causes tumor-induced osteomalacia (TIO). Most cases follow a benign clinical course, with rare occurrences of malignant transformation. We report a case of malignant PMT-MCT and review previous malignant cases to identify predictive factors for transformation. A 13-yr-old female, who presented with hypophosphatemic rickets, elevated serum intact fibroblast growth factor 23 (FGF23) levels, and a nodule in the back, received a diagnosis of TIO because of the benign PMT histopathology. After resection of the primary tumor, regular imaging analyses did not indicate any relapse. At 17 years of age, a tumor developed in the left leg and increased in size. The resected tumor showed a histopathology of pleomorphic sarcoma positive for the *TP53* mutation. Despite amputation of the affected leg, the patient died due to multiple metastases at 18 years of age. A literature review revealed that 14 out of 15 reported malignant PMT-MCT tumors occurred in adults, and found no predictive factors for malignant transformation and treatment outcome. Changes in size or number of the tumors along with intact FGF23 levels have been considered as the only sign of malignant transformation. This pediatric case report and literature review indicate the need for prolonged regular monitoring for PMT-MCT.

Key words: FGF23, tumor-induced osteomalacia, malignant phosphaturic mesenchymal tumor-mixed connective tissue variant (PMT-MCT)

Introduction

Phosphaturic mesenchymal tumor, mixed connective tissue variant (PMT-MCT) is a rare neoplasm arising from bones and soft tissues. It often presents with tumor-induced osteomalacia (TIO), a paraneoplastic syndrome. The tumor produces excessive amounts of fibroblast growth factor 23 (FGF23) that primarily acts on the proximal renal tubule to reduce phosphate reabsorption and 1α-hydroxylation of 25-hydroxyvitamin D (1). TIO is characterized by phosphaturia, hypophosphatemia, and osteomalacia, which mimics the clinical expression of hereditary hypophosphatemic rickets with either X-linked or autosomal dominant inheritance.

PMT-MCT usually occurs as a benign tumor in adults, and malignant onset or transformation is quite rare. Malignant PMT-MCT shows varied histopathological types, including sarcoma, which do not usually respond to chemo- and radiotherapy. Among the 15 patients with malignant PMT-MCT previously reported, only one was a pediatric case, aged 5 yr (2). The initial presentation of reported cases was TIO with or without a mass effect on the adjacent organ. Total resection of the tumor is currently the sole effective treatment for malignant PMT-MCT. There is no information about useful biomarkers for the progressive disease or alternative therapies for surgical intervention.

Herein, we report a case of a 13-yr-old girl with PMT-MCT that evolved to pleomorphic sarcoma harboring a *TP53* mutation after a 4-yr-treatment course for TIO. She died of multiple metastases after the removal of

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the primary lesion. Serum intact FGF23 levels showed no drastic changes after the resection of the primary tumor, which hampered the determination of the time of transformation. We present a case of transformed pediatric-onset PMT-MCT, and then discuss the prolonged management based on a literature review of malignant cases.

Case Report

An 8-yr-old Japanese girl visited an orthopedic clinic because of bilateral leg pain. Her perinatal history, growth, and development were unremarkable. She had no previous history of bone fractures and no family history of rickets, bone disease, or cancer predisposition. This patient received a tentative diagnosis of Osgood-Schlatter disease, and was subjected to observation without administration of any medication. At 11 yr of age, she suffered from fractures of the bilateral femora due to an accidental fall. An X-ray film of the limbs revealed irregular widening of the metaphyseal regions (**Fig. 1-A**), suggesting the presence of rickets. Blood tests at Fukuoka Children's Hospital revealed high levels of alkaline phosphatase (4820 U/L, reference range [rr]: 400–1450), normal levels of calcium (9.8 mg/dl, rr: 8.8–10.1), and severe hypophosphatemia (1.7 mg/dl, rr: 3.7–5.8), along with increased levels of serum intact FGF23 (132 pg/ml, rr: 16–69). No mutations were identified in the phosphate-regulating gene with homologies to endopeptidases on the X chromosome (*PHEX*). Phosphate salt and vitamin D analogs were orally administered to the patient under the diagnosis of late-onset hypophosphatemic rickets.

At 13 yr of age, the patient was referred to Kyushu University Hospital for the examination of a small non-tender tumor in her upper back noticed by the

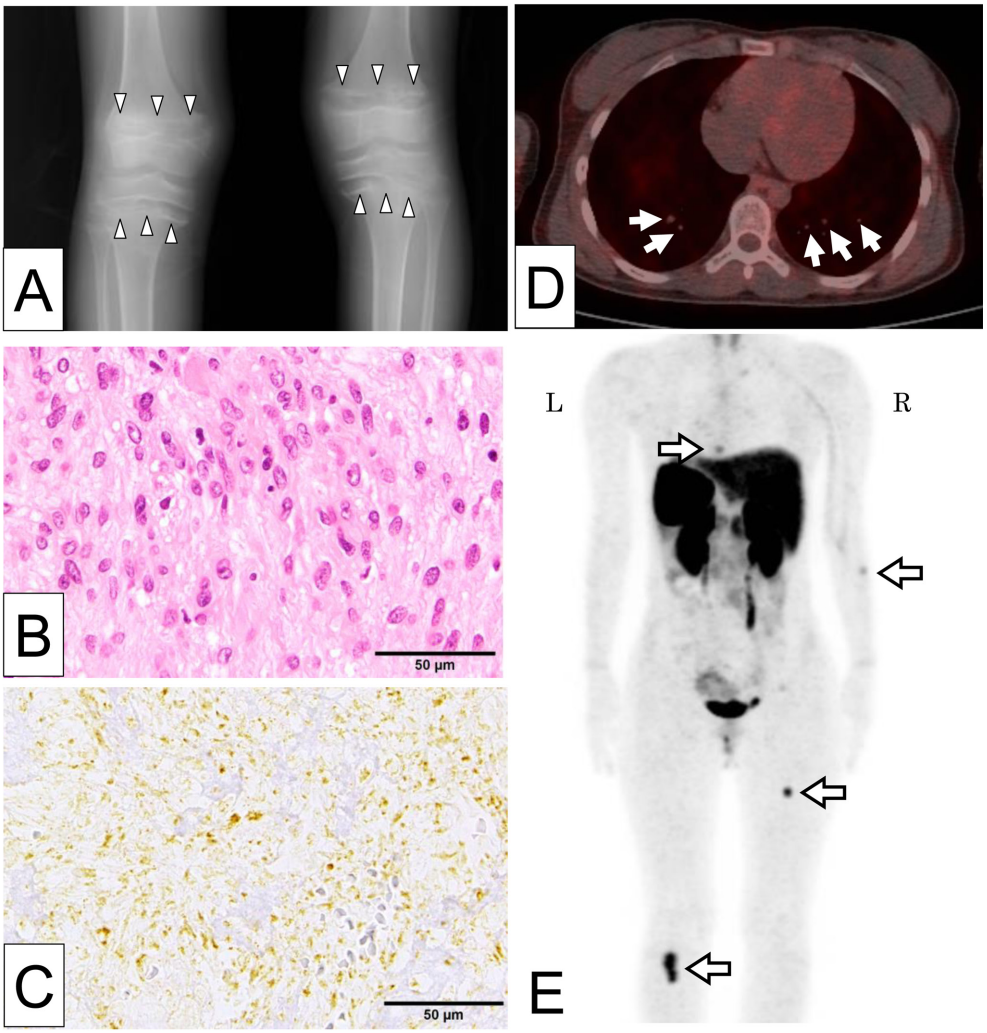

Fig. 1. (A) Plain X-ray images of bilateral knee joints of the patient at 11 yr of age: arrow heads indicate the rachitic changes. (B) Hematoxylin-eosin staining of the primary tumor: The histopathology of the tumor shows proliferation of spindle to oval-shaped cells with mild nuclear atypia and eosinophilic cytoplasm arranged in fascicular pattern with an absence of mitosis. (C) Immunohistochemical staining of fibroblast growth factor 23 (FGF23) shows immunopositive reactivity of the tumor cells for FGF23. (D, E) ^{68}Ga-DOTATOC-PET CT imaging revealed multiple tumors in the lung fields, right forearm, right thigh and left tibia (arrows).

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patient herself. During the visit, the well-nourished girl with a slightly short stature (143.9 cm, −2.2 SD) and normal weight (38.1 kg, obesity index: −4.8%), had an elastic-hard lump, less than 1 cm in diameter, on the left upper back. Blood tests revealed high levels of alkaline phosphatase (1426 U/L, rr: 220–1250), normal levels of calcium (10.0 mg/dl, rr: 8.7–10.3), and hypophosphatemia (2.3 mg/dl, rr: 3.5–5.8). Serum intact FGF23 levels increased to 685 pg/ml in the blood sample obtained from the right upper extremity, and 616 pg/ml in the blood sample obtained from the left upper extremity (each rr: 16–69), and percent tubular reabsorption of phosphate (%TRP) decreased to 79.9%. Computed tomography (CT) scan of the whole body detected a small mass in the left trapezius muscle. Under the diagnosis of TIO, the tumor was completely resected. Histopathological evaluation of the tumor showed proliferation of spindle-shaped or oval-shaped cells with mild nuclear atypia and eosinophilic cytoplasm arranged in fascicular or sheet-like pattern, accompanied by cystic degeneration and hyalinization. There was no calcification, osteoid formation or cartilaginous tissue and mitotic figures were not evident. The tumor cells were immunohistochemically positive for FGF23 (**Fig. 1-B, C**). Based on these findings, the patient received the diagnosis of TIO associated with a single lesion of non-malignant PMT-MCT.

Tumor resection, however, failed to normalize the levels of alkaline phosphatase, phosphorus, or serum intact FGF23 (**Fig. 2**). Four months after the intervention, non-tender massive lesions emerged in the right thigh, left tibia, and right forearm. Chest X-ray revealed multiple small nodules in the lung all positive for ^{68}Ga-DOTATOC-PET CT (**Fig. 1-D, E**). The mass lesions in the right thigh and left tibia were resected, followed by open biopsy for some of the pulmonary lesions. All biopsied sample specimens showed a histopathology of PMT-MCT, identical to that of the primary tumor. The immunohistochemical staining of FGF23 in the lesions of the right thigh, the left tibia and the lungs were all positive. The patient refused to resect the right forearm lesion due to apprehensions about limited movement of the arm post-surgery. Serum intact FGF23 levels were found to have increased to 3,100 pg/ml (**Fig. 2**), suggesting an effect of the residual tumors.

By the age of 17, follow ups had stopped completely due to the patient's refusal to visit the hospital. Eight months after the last hospital visit, her left leg began to swell and grew in size gradually. Two months after the beginning of swelling of the leg, the patient was

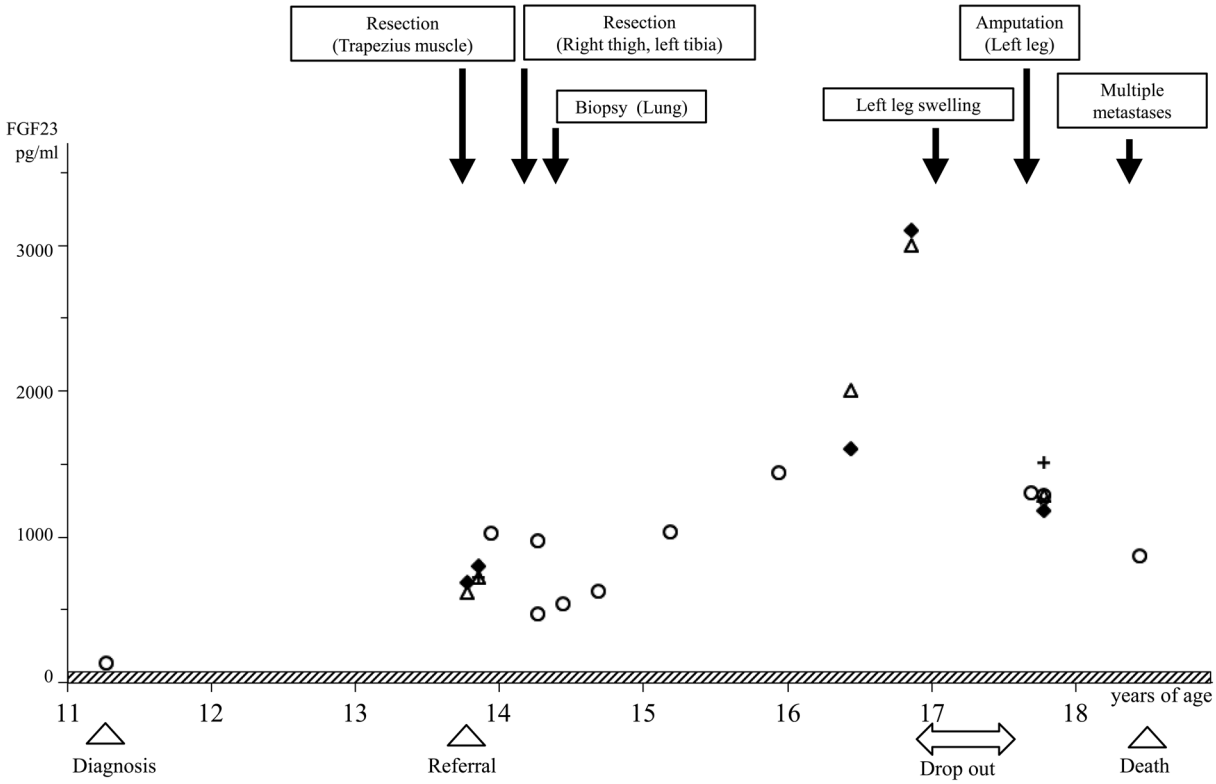

Fig. 2. Sequential levels of serum fibroblast growth factor 23 (FGF23) levels during the observation. FGF23 levels were plotted from the sampled sites of upper extremity (○), right upper extremity (◆), left upper extremity (△), right lower extremity (×), and left lower extremity (+). Serum FGF23 levels increased to 3100 pg/ml despite the resection of lesions in the trapezius muscle, right thigh and left tibia, and decreased to 1180 pg/ml prior to amputation of her left leg. Values higher than 800 pg/ml were measured after dilution of the samples; hatched area indicates the standard range of FGF23 in healthy subjects (16–69 pg/ml). Surgical intervention has been indicated in the upper panel of the figure, and clinical events have been shown below the horizontal axis.

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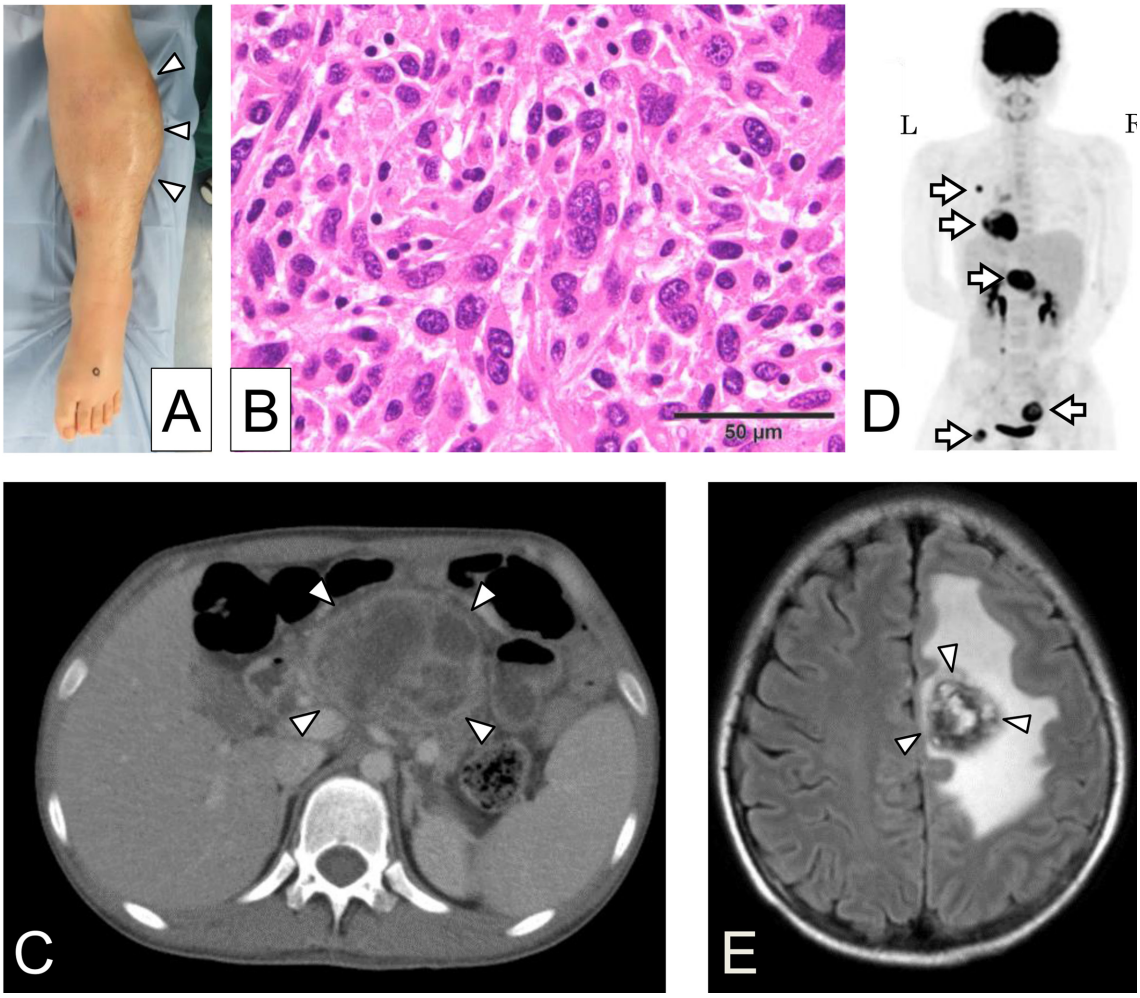

Fig. 3. (A) The swollen left leg (arrow head) shows (B) histopathology of the tumor in the leg at 17 yr of age. Tumor shows a diffuse sheet-like growth pattern with oval to spindle-shaped or polygonal cells possessing hyperchromatic and pleomorphic nuclei and occasional multinucleated giant cells. Numerous mitotic figures have been identified. (C) CT scan image of the abdomen shows a large mass at the head of pancreas (arrow heads). (D) PET CT scan image of body shows multiple positive lesions in the left lung, head of pancreas, right ovary and left inguinal lymph nodes (arrows). (E) CT scan image of the brain shows a mass measuring 35 mm × 29 mm, suggesting intracranial metastasis (arrow heads).

re-hospitalized due to difficulty in walking (**Fig. 3-A**). Magnetic resonance imaging (MRI) of the leg revealed a large tumor measuring 14.5 cm × 9 cm × 8.5 cm. The histopathology of the resected tumor showed a proliferation of spindle-shaped, oval-shaped and polygonal cells having hyperchromatic and pleomorphic nuclei arranged in a haphazard pattern. They were accompanied by bizarre giant cells, multinucleated osteoclast-like giant cells, osseous formations, hemosiderin deposition and massive necrosis with florid mitotic findings (**Fig. 3-B**) indicating pleomorphic sarcoma. Although the tumor cells were immunohistochemically negative for FGF23, they were positive for FGF23 mRNA assessed by real-time polymerase chain reaction (RT-PCR). The immunohistochemical staining of the tumor cells was diffusely positive for p53. Direct sequencing of the tumor-derived DNA showed a mutation in *TP53* gene; p.R249S (c747G>T). This findings of FGF23, p53 and *TP53* in tumors have previously been reported by Yamada *et al.* (3). The germline mutation of *TP53* was not tested. The left leg of the patient was amputated following which other lesions were found to be limited to the lungs.

The patient was put under close observation and oral supplementation of phosphate salt and vitamin D analogs for hypophosphatemia were restarted. Six months after amputation, the patient complained of abdominal pain. A CT scan was performed, which detected a mass at the head of the pancreas (**Fig. 3-C**). PET CT showed an increased number of lung lesions as well as new lesions emerging in the inguinal lymph nodes and the right ovary (**Fig. 3-D**). The patient underwent two courses of palliative chemotherapy with adriamycin (30 mg/m^2: day 1–2) and ifosfamide (2 g/m^2: day 1–5). One month later, the patient was brought into the emergency room because of convulsions, and the CT scan revealed a brain metastasis measuring 35 mm × 29 mm (**Fig. 3-E**). The patient died of the progressive nature of the disease at 18 years of age.

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Literature Review of Malignant PMT-MCT

Available data of nine patients with malignant PMT-MCT, out of the 15 reported cases has been summarized in **Table 1**. Patients included five males and 10 females of ages ranging from 5 to 62 yr with the median age of 35 yr. The first sign of primary tumor was TIO in 6 out of 9 (67%) patients and the malignant tumors involved the larynx, tongue, liver, pelvis, and extremities. Six of the 9 (67%) patients died of the disease. The duration of time between the onset and the malignant transformation ranged widely from the time of the first presentation to more than 20 yr later. Serum intact FGF23 levels did not predict the transformation or the treatment outcome. To the best of our knowledge, our case presented here is the first case of malignant PMT-MCT examined for mutations in the *TP53* gene.

Discussion

We presented the course of treatment for the second youngest case of malignant PMT-MCT. The literature review of all the 15 reported patients neither indicated any effective therapy after surgical intervention, nor any useful markers predicting the transformation and outcome. Continuous monitoring of intact FGF23 levels and rapid growth in size and numbers of tumors may be the current recommended measure for early diagnosis of malignant transformation.

PMT-MCT was first introduced by Weidner and Santa Cruz in 1987, as a concept to unify the heterogeneous tumors of bone and soft tissues associated with phosphate wasting and osteomalacia (4). The pathophysiologic mechanism of phosphate wasting accounts for the overexpression of tumor-inducing FGF23 which results in decreased reabsorption of phosphate in the renal tubules and hyperphosphaturia. The diagnosis of PMT-MCT is challenging because the rare functional tumor is too small to be identified as a primary lesion by conventional radiological methods. Compared to a CT scan or MRI, ^{68}Ga-DOTATOC PET/CT scan of the whole body has reportedly been more useful to localize the involvement of PMT-MCT. However, the availability of institutions providing this facility is limited in Japan (5). Surgical resection is the most effective treatment for PMT-MCT, resulting in normalization of the serum phosphorus levels as well as improvement in all other symptoms within a span of few days to a few weeks after resection (1). The majority of PMT-MCT occurs in adults as a benign tumor. To the best of our knowledge, 15 cases with malignant PMT-MCT have been reported till date (**Table 1**) (2, 6–14). Of these, one patient was detected to have a malignant tumor during diagnosis and had the longest period of 22 yr until transformation. Benign PMT-MCT is usually less than 5 cm in diameter (13), although larger benign tumors have also been detected (15). Uchihashi *et al.* (11) reported a malignant tumor about 2.5 cm in diameter. Although multiple metastases are the hallmark of transformation (**Table 1**), multiple benign tumors have also been reported (3). During the prolonged course of treatment of the case study patient, multiple lesions did not always indicate the time-point of transformation. Endo *et al.* (16) reported that serum FGF23 levels in patients presenting with benign TIO varied between 44.0 and 18286.4 pg/ml (mean ± SD, 1304.1 ± 3660.3). A retrospective analysis of 144 cases revealed that the median FGF23 level of benign PMT-MCT was 302.9 pg/ml (range, 42.6 to 706.5) (17). Comparatively, an adult female patient showed 121 pg/ml of serum FGF23 on diagnosis of malignant PMT-MCT (9). The current literature review found no effective measures to predict transformation during diagnosis or at the initial stages of PMT-MCT. The patient of the case study showed sustained levels of intact FGF23 after the first resection of the primary tumor. Although multiple tumors did not indicate transformation, the rapid growth of the tumor in the leg led to the diagnosis of sarcoma. Considering that the period varied from presentation to transformation, longitudinal observations are essential to detect the early stages of transformation.

The first treatment goal of PMT-MCT is a complete resection of the tumor because there are no other effective therapies for malignant PMT-MCT. Seijas *et al.* (10) reported that six cycles of adriamycin arrested metastasis for two years. Sidell *et al.* (6) used doxorubicin, docetaxel, and gemcitabine for the chemotherapy of malignant PMT of the larynx. Morimoto *et al.* (9) proposed a combination chemotherapy consisting of adriamycin, ifosfamide, gemcitabine, and docetaxel in two cases. All 5 reported patients (6, 9, 10 and this case), were diagnosed with malignant PMT-MCT and received chemotherapy. However, only one patient out of the five survived (6). The survivor had been diagnosed with malignant PMT-MCT of the larynx. Because of the limited response to chemotherapy, she later underwent a total laryngectomy and survived. This review showed the lack of any significant relationship between the outcomes resulting from each treatment ($p = 0.4533$ for resection, $p = 0.3428$ for radiotherapy and $p = 0.3428$ for chemotherapy; Statistical analysis was performed by chi-square test). The effects of two courses of adriamycin and ifosfamide administered to the case study patient appeared to be negligible. The need for molecular targets to search for the rare transformation of PMT-MCT is thus emphasized.

PMT-MCTs are microscopically characterized by a hypocellular to moderately cellular proliferation of bland, spindled or stellate cells, which produce an unusual smudgy basophilic matrix (4). The pathological diagnosis of a growing tumor in the left leg of the case study patient at the age of 17 was pleomorphic sarcoma, possessing no definitive component of typical PMT-MCT histology. It was assumed to be a malignant transformation of PMT-MCT, based on the progressive increase in circulating levels of intact FGF23 and the detection of FGF23 mRNA in the tumor cells. The diffuse positivity of p53 in immunohistochemical staining and the *TP53* mutation identified in the patient suggested a contribution of the

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Table 1. Data for malignant Phosphaturic mesenchymal tumor-mixed connective tissue variant (PMT-MCT) cases

Case	Age (yr/sex)	Clinical presentation			Site of tumors	
		Initial symptom	Time to malignant transformation	Clinical incidence at malignant transformation	Primary lesion	Malignant lesion
1	24/F	Airway obstruction	1 mo	Growth of tumor	Larynx	Larynx
2	41/F	Osteomalacia	9 yr	Increase in number of tumors	Right leg	Inguinal lymph node, right leg, left leg, right femur, lung
3	48/M	Oral bleeding	0 mo (primary lesion was malignant)	–	Tongue	Tongue, oral floor
4	13/F	Osteomalacia	4 yr	Growth of tumor	Trapezius muscle, left tibia, lung, right thigh	Right thigh, pancreas, inguinal lymph nodes, right oval, brain
5	25/M	Osteomalacia	8 yr	FGF23 elevation	Pelvis	Pelvis, lung, left elbow, bone, liver
6	27/F	Osteomalacia	6 yr	Increase in number of tumors	Liver	Liver, lung, ribs, right iliac wing, spinal bones, breast, pelvis, femurs
7	30/F	Mass in foot	3 yr	Increase in number of tumors, pain	Right foot	Toe, lung
8	35/F	Osteomalacia	N. A.	Increase in number of tumors	Pelvis	Pelvis, lung, bones
9	45/F	Osteomalacia	22 yr	Increase in number of tumors	Right fibia	Right fibia, inguinal lymph nodes, right lower extremity, pelvis

Case	Size of tumor (cm)	FGF23 (pg/ml)	Treatment of malignant PMT-MCT			Outcome	Reference
			Resection	Radioitherapy	Chemotherapy		
1	N. A.	N. A.	+	–	ADR, DTX, GEM	Alive	Sidell, 2011 (6)
2	6.4 × 4.9	N. A.	+	–	–	Alive	Oiu, 2017 (7)
3	3 × 5	N. A.	+	+	–	Alive	Uramoto, 2009 (8)
4	14.5 × 9 × 8.5	3100	+	–	ADR, IFO	Dead	The present case
5	Large	3319	+	+	ADR, IFO	Dead	Morimoto, 2014 (9)
6	N. A.	N. A.	+	+	ADR, imatinib	Dead	Seijas, 2009 (10)
7	2.5	N. A.	+	–	–	Dead	Uchihashi, 2013 (11)
8	N. A.	121	+	+	ADR, IFO, GEM, DTX	Dead	Morimoto, 2014 (9)
9	8 × 5	N. A.	+	+	–	Dead	Ogose, 2001 (12)

There were seven other cases without detailed information (2), (13), (14). Age indicates the age at the time of first visit. ADR, adriamycin; CDDP, cisplatin; DTX, docetaxel; FGF23, fibroblast growth factor 23; GEM, gemcitabin; IFO, ifosfamide; N.A., not available.

TP53 mutation to the transformation of PMT-MCT (3).

In conclusion, the rare transformation of PMT-MCT is difficult to diagnose and the disease progression is almost impossible to control. Changes in the size or the number of tumors, in conjunction with FGF23 levels, are currently considered biomarkers of this malignant transformation, and are recommended to be monitored for pediatric patients beyond transitional care. Further

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long-term studies for cumulative cases are needed to determine the effective predictors of the disease transformation and its therapeutic management.

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