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Case Report

Phosphaturic mesenchymal tumour mixed connective tissue variant: report of three cases with unusual histological findings

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Abstract: Phosphaturic mesenchymal tumour mixed connective tissue variant (PMTMCT) is a rare tumour occurring in bone and soft tissue that usually behaves in a benign manner. Elaboration of biologically active substances by this tumour gives rise to a paraneoplastic syndrome known as oncogenic osteomalacia, manifesting clinically as bone pain, generalized weakness and pathological fractures. Recognition of PMTMCT and its associated syndrome is important, as resection of the tumour in most instances results in prompt resolution of symptoms. Previously reported cases of this tumour have emphasized the consistent presence of certain histological features that are considered prerequisite for making the diagnosis of PMTMCT. We describe three cases of PMTMCT, of which two first presented with progressive symptoms of osteomalacia and one remained clinically silent aside from the symptom of a palpable lump. Our cases highlight the wide-ranging histological patterns displayed by these tumours, and draw attention to certain microscopic findings that until now have been given little if any mention. Tentacular growth pattern and satellite nodules appear to be common findings in PMTMCTs, and can make complete surgical excision of these tumours challenging. The ability of this otherwise histologically benign tumour to permeate vascular spaces has to our knowledge never been described previously. One tumour lacked the characteristic calcifying matrix of PMTMCT, suggesting that in some tumours this defining feature may be focal if not entirely absent. PMTMCT shares features with and can resemble a variety of bone and soft tissue neoplasms, requiring the surgical pathologist to be familiar with this entity.

Keywords: Phosphaturic mesenchymal tumour, oncogenic osteomalacia, tumour induced osteomalacia, phosphaturia, matrix-producing tumours

Introduction

Awareness of oncogenic osteomalacia long predates the first description of a phosphaturic mesenchymal tumour mixed connective tissue variant (PMTMCT), the tumour most closely associated with this unusual paraneoplastic syndrome. The syndrome typically manifests as progressive generalized weakness and fatigue, bone pain and recurring pathological fractures in different locations, that can persist for months or years before the underlying tumour becomes clinically apparent [1-4]. Causative tumours, which show a predilection for the soft tissues of the distal extremities, the femur and the facial skeleton, but may occur in virtually any location, are often too small to be identified by clinical examination and likewise may elude detection by sensitive imaging modalities like MRI [3-7]. The biochemical derangements that characterize oncogenic osteomalacia consist of depressed levels of serum phosphate and 1,25-dihydroxyvitamin D_3, together with elevated levels of urine phosphate. This constellation of biochemical abnormalities is shared by two other hereditary forms of osteomalacia known as autosomal dominant hypophosphataemic rickets and X-linked hypophosphataemic rickets [1, 4, 8]. The common physiologic defect in these three conditions involves a impairment in renal tubular phosphate reabsorption and a downregulation of renal 1α-hydroxylase activity, while calcium metabolism remains essentially unaffected. Laboratory investigations thus will

show normal serum levels of 25-dihydroxyvitamin D_3 and calcium in most cases, distinguishing these conditions from more common forms of osteomalacia like primary vitamin D deficiency [1]. Impairment in bone mineralization in the face of inadequate serum phosphate levels leads to increased bone fragility, with attendant susceptibility to pathological fractures.

PMTMCT was first recognized as a distinct entity by Weidner and Santa Cruz in 1987, who described 17 cases of tumours causing osteomalacia, of which 10 showed unique histology including sheets of round to spindled mesenchymal cells with fibroblast-like differentiation, prominent vascularity and a cartilage-like matrix [9]. Cases reported prior to and in the years following this seminal publication often assigned descriptive diagnostic terms to these tumours. Alternatively, diagnoses given reflected particular histological findings observed in these tumours, many being labelled as hemangiopericytomas, giant cell tumours and sclerosing hemangiomas, the latter term having now fallen out of favour as a designation for a variant form of benign fibrous histiocytoma. A larger series that combined 27 newly reported cases with a detailed reappraisal of 109 previously published cases of mesenchymal tumours associated with oncogenic osteomalacia refined the diagnostic criteria of PMTMCT, emphasizing that despite the wide-ranging histomorphological patterns these tumours may show, several features are consistently present [10]. The cardinal histological features that hold the key to the diagnosis of PMTMCT, as outlined in this series, are a proliferation of bland spindle cells accompanied by a distinctive basophilic matrix containing flocculent calcifications. The authors of this series identified PMTMCT as the cause of oncogenic osteomalacia in the overwhelming majority of cases, with the caveat that other common bone and soft tissue tumours can also rarely give rise to this syndrome [10]. We present herein three cases of PMTMCT that in addition to reinforcing the diversity of its histologic appearances, illustrate a few seemingly common features of these tumours that have been given little attention, yet which raise important considerations pertaining to their surgical management. One of these tumours lacked the characteristic basophilic matrix, challenging the strict reliance on certain criteria to establish the diagnosis of PMTMCT and re-eliciting an observation originally made by Weidner and Santa Cruz that intra-osseous tumours as a whole show slightly different histomorphology [9].

Case report

Case 1

A 34 year-old man with no significant medical history presented with a palpable lump in the sole of the right foot that was first detected one year earlier and had been slowly increasing in size. Prior to this, he had suffered worsening generalized bone pain over a three year period, causing gait unsteadiness and interfering with activities of daily living. A limited diagnostic work-up during this time, including serum biochemistry panel, revealed hypophosphataemia, for which treatment with oral phosphate supplements and vitamin D_3 nasal spray was initiated. His condition nevertheless deteriorated, to the point of being unable to tolerate weight-bearing for extended periods of time.

Laboratory investigations at the time of presentation to our hospital showed a serum phosphate level of 0.57 mmol/L (reference range 0.77-1.38 mmol/L), serum calcium level of 2.28 mmol/L (reference range 2.09-2.46 mmol/L) and 25-hydroxy-vitamin D level of 56.9 μg/L (reference range 10.1-40.3 μg/L). His biochemical profile was considered to be in keeping with oncogenic osteomalacia. An MRI scan of the right foot revealed a solid nodular tumour measuring 3 cm located within subcutaneous tissue on the plantar aspect of the foot, in addition to non-displaced stress fractures of the 1st and 4th metatarsal bones. A wide resection of the tumour was performed subsequently. Intraoperatively, the surgical margin was noted to be approximating the tumour, requiring additional excision of skin and subcutaneous tissue around the tumour.

Gross inspection of the tumour showed ill-defined borders and a relatively uniform, whitish-yellow cut surface with interspersed small foci of haemorrhage. Histologically, the tumour demonstrated irregular, infiltrative margins, characterized by elongated, tentacular projections into the surrounding fibroadipose tissue with serrated borders (**Figure 1A**). Large expanses of the tumour showed modest cellularity and consisted of a basophilic chondromyxoid matrix, alternating with sporadic areas of eosinophilic fibrous stroma. Rare small foci

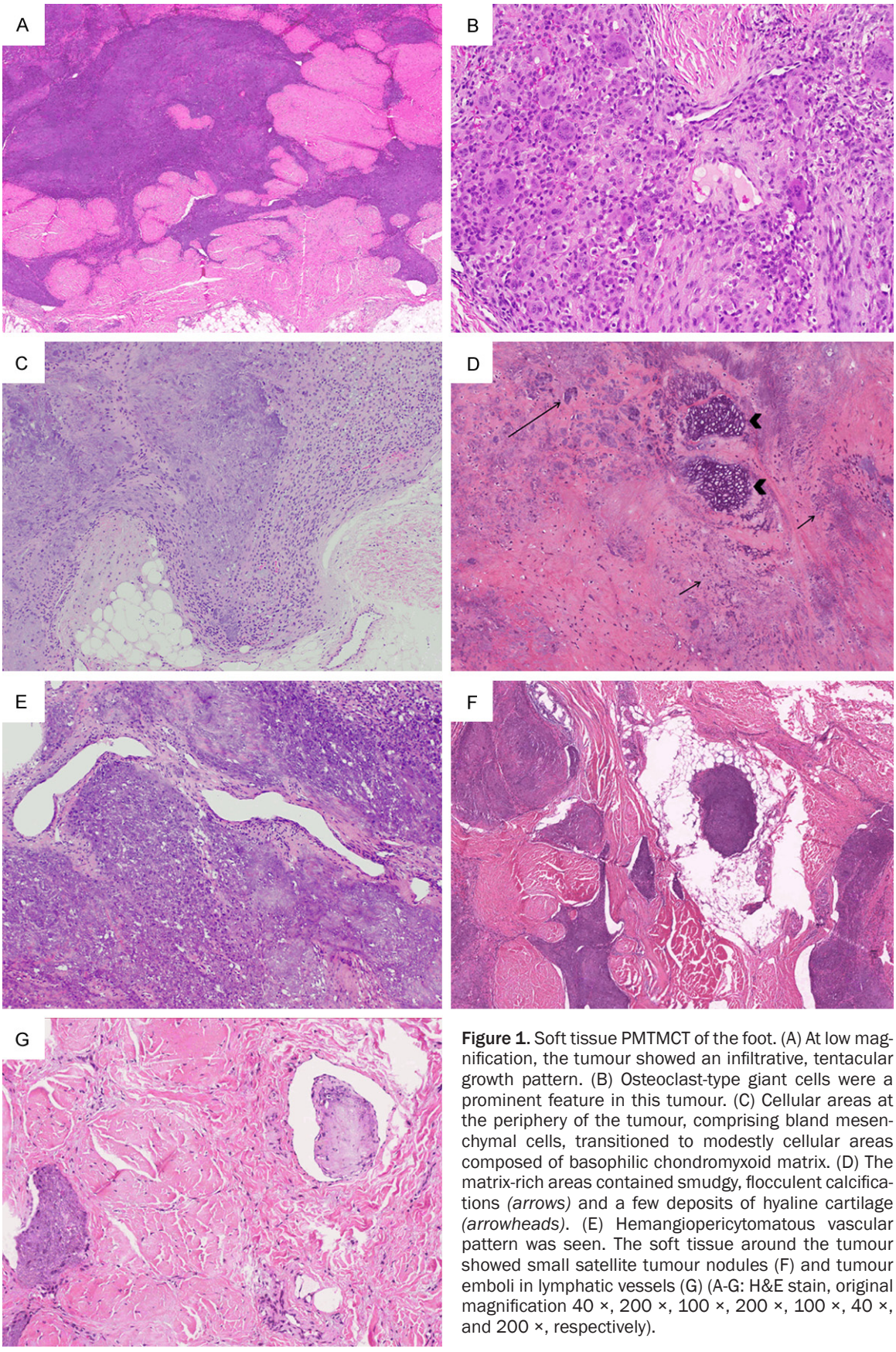

Figure 1. Soft tissue PMTMCT of the foot. (A) At low magnification, the tumour showed an infiltrative, tentacular growth pattern. (B) Osteoclast-type giant cells were a prominent feature in this tumour. (C) Cellular areas at the periphery of the tumour, comprising bland mesenchymal cells, transitioned to modestly cellular areas composed of basophilic chondromyxoid matrix. (D) The matrix-rich areas contained smudgy, flocculent calcifications *(arrows)* and a few deposits of hyaline cartilage *(arrowheads)*. (E) Hemangiopericytomatous vascular pattern was seen. The soft tissue around the tumour showed small satellite tumour nodules (F) and tumour emboli in lymphatic vessels (G) (A-G: H&E stain, original magnification 40 ×, 200 ×, 100 ×, 200 ×, 100 ×, 40 ×, and 200 ×, respectively).

of hyaline cartilage were encountered. The peripheral infiltrative front of the tumour in general showed increased cellularity, comprising a monotonous population of cells with ovoid to spindled nuclei and fine, evenly distributed nuclear chromatin. The tumour cells showed minimal nuclear atypia and anisonucleosis, and mitotic activity was not seen. Frequent osteoclast-type giant cells were present, also preferentially distributed towards the periphery amidst the tumour cells and sometimes coalescing to form small aggregates (**Figure 1B**). The cellular areas showed a seamless transition to hypocellular matrix-rich areas (**Figure 1C**). Calcifications were scattered throughout this basophilic matrix, showing a variably chunky, chalklike and smudgy, flocculent appearance (**Figure 1D**), the latter pattern of calcification supporting the diagnosis of PMTMCT. Prominent thin-walled blood vessels were occasionally seen throughout the tumour, some of these with ectatic, tortuous luminal outlines typifying a hemangiopericytomatous vascular pattern (**Figure 1E**). Immunohistochemical staining for D2-40 showed absent expression in the endothelial cells of tumour blood vessels. The fibroadipose tissue surrounding the tumour contained a number of small satellite tumour foci (**Figure 1F**), a feature that hasn't been emphasized previously. As well, multiple intravascular tumour emboli were identified in vessels in the vicinity of the tumour (**Figure 1G**). There was extensive involvement of the surgical margins by the tumour, including in the separately received piece of subcutaneous tissue obtained after the initial wide excision.

While the patient's serum phosphate level had initially normalized following resection of the tumour (0.95 mmol/L on postoperative day 1), biochemical investigations at follow-up 19 months later showed recurrent hypophophataemia (serum phosphate 0.40 mmol/L). A locally recurrent tumour was discovered, and surgical re-excision was performed. Histological examination of the recurrence showed identical features to those of the original tumour.

Case 2

A 37 year-old woman presented with a gradually enlarging mass in the left gluteal region that had reached approximately 8 cm in size. She was otherwise asymptomatic, and denied experiencing any form of musculoskeletal pain, weakness or excessive fatigue in the recent past. Radiological and laboratory investigations were likewise unrevealing, with no occult fractures detected or derangement of serum phosphate levels. An incisional biopsy of the mass was initially performed at another hospital, where a diagnosis of myxoid liposarcoma was rendered. Definitive resection of the tumour at our hospital showed a biopsy cavity measuring 6.5 cm in length and 2 cm in diameter, surrounded by a firm, whitish-tan lesion measuring 1 cm in thickness. A thick layer of fibromuscular tissue separated the tumour from the underlying pelvic bone.

Histological examination revealed a tumour with largely well-defined borders, on the one hand showing knobby, bosselated contours (**Figure 2A**), and in other places having sharp, serrated edges. Separate satellite tumour nodules were seen in the surrounding fibroconnective tissue (**Figure 2B**). Cellularity varied across different regions of the tumour. Some areas had an appearance reminiscent of a chondromyxoid fibroma, showing a sparse and haphazard distribution of bland spindle and stellate cells in a chondromyxoid stroma. An abrupt transition was then seen to cellular areas consisting of patternless sheets of spindle cells lacking significant nuclear atypia in an eosinophilic, fibrous background (**Figure 2C**). The presence of scattered osteoclast-type giant cells in these cellular areas lent further support to the consideration of chondromyxoid fibroma. The cellular areas were, however, randomly placed, and lobular architecture was not observed. Other features included groups of closely spaced microcysts, some of which contained blood (**Figure 2D**), as well as rare foci of hyaline cartilage and osteoid. An additional notable finding within the less cellular chondromyxoid areas was the presence of calcifications showing a smudgy appearance (**Figure 2E**). Despite certain features evoking a chondromyxoid fibroma, the location of the tumour in fibroconnective tissue without any association with bone, its irregular borders, and the absence of lobular architecture and a peripheral sclerotic rim all argued against this diagnosis. On the other hand, the smudgy pattern of calcification together with the findings of a patternless spindle cell proliferation, microcystic

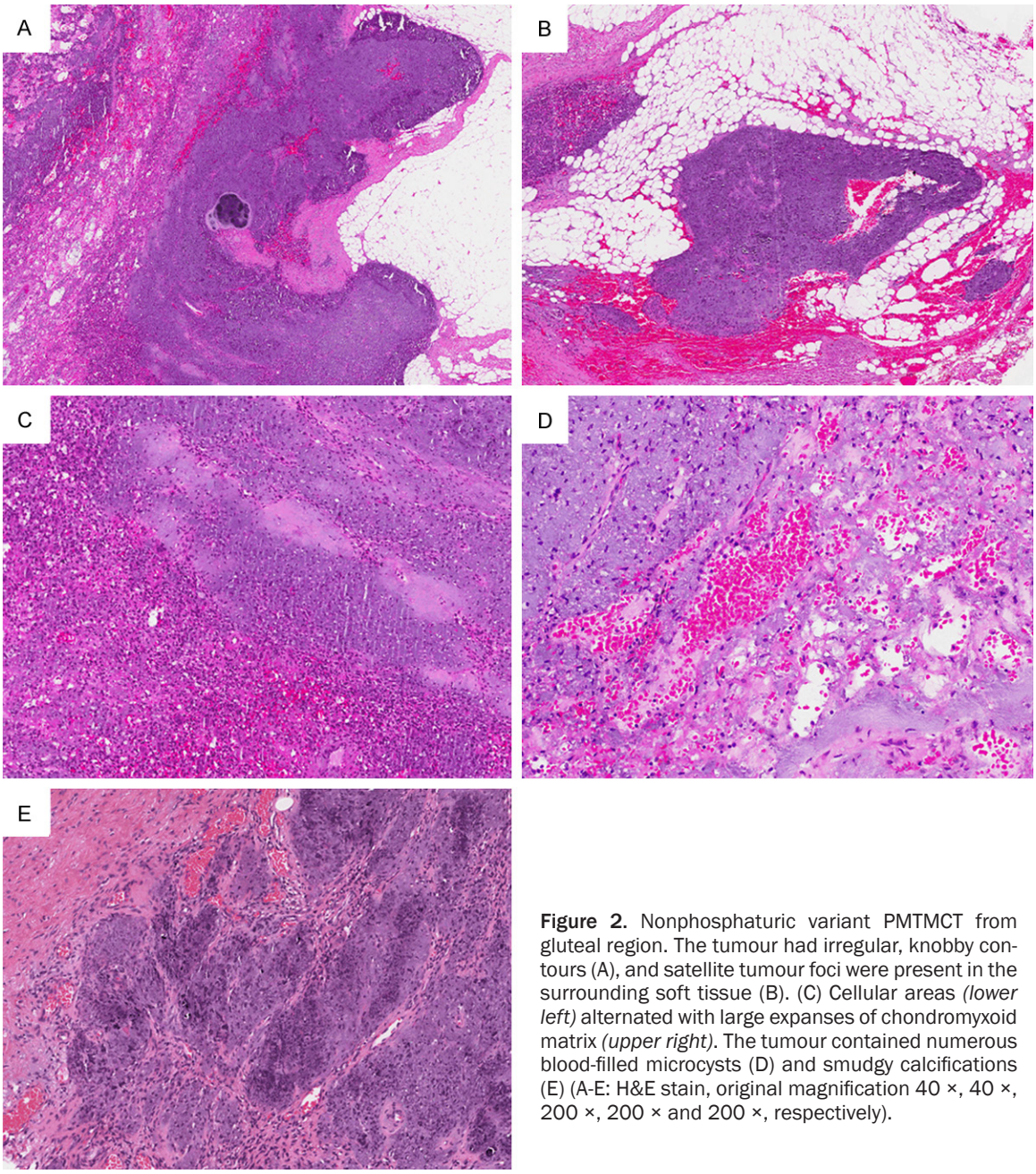

Figure 2. Nonphosphaturic variant PMTMCT from gluteal region. The tumour had irregular, knobby contours (A), and satellite tumour foci were present in the surrounding soft tissue (B). (C) Cellular areas *(lower left)* alternated with large expanses of chondromyxoid matrix *(upper right)*. The tumour contained numerous blood-filled microcysts (D) and smudgy calcifications (E) (A-E: H&E stain, original magnification 40 ×, 40 ×, 200 ×, 200 × and 200 ×, respectively).

spaces and osteoclast-type giant cells favoured the diagnosis of PMTMCT. In this case, the tumour represented a nonphosphaturic variant without the accompanying syndrome of osteomalacia.

Case 3

A 54 year-old woman with previous history of hypertension, diabetes mellitus and hyperlipidaemia first presented to another hospital with pain in the lower back and hips of three years' duration. Plain radiographs of the lumbar spine disclosed compression fractures of the T9, L1 and L2 vertebral bodies, and dual-energy x-ray absorptiometry (DXA) scan showed a bone mineral density within the osteoporotic range. She was meanwhile found to have Cushing's syndrome, allegedly resulting from longstanding use of steroid-containing traditional Chinese medicine. First-line treatment tailored to reversing her osteoporosis and the underlying Cushing's syndrome consisted of parenteral bisphosphonates, calcitonin, and withdrawal of

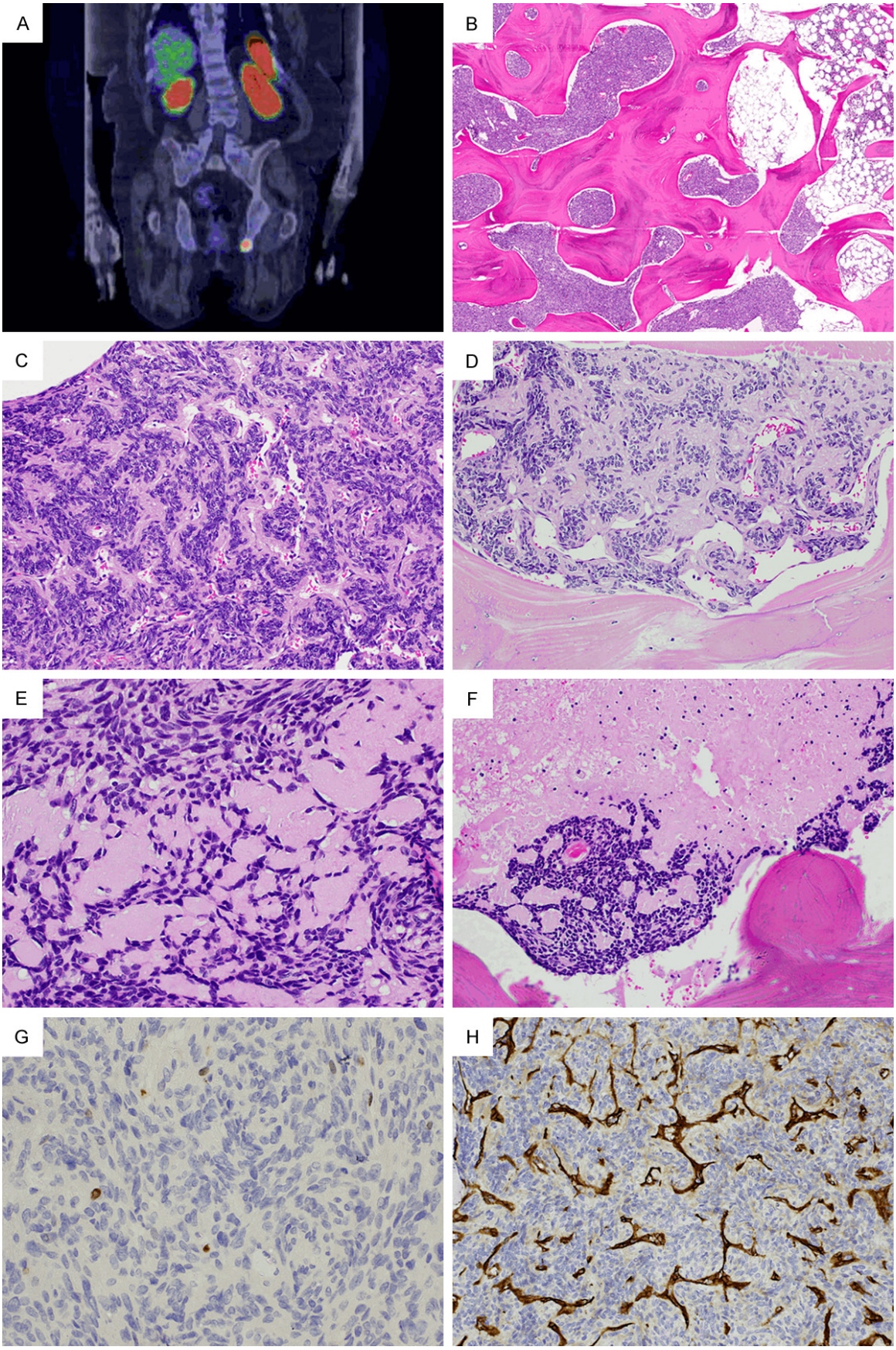
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Figure 3. Intra-osseous PMTMCT in pelvic bone. (A) Coronal PETCT fusion sections of the body showed focal uptake of Ga-68 DOTA-TATE in the left ischium. Low power histological examination showed infiltration of marrow spaces by the tumour without destruction of bone trabeculae (B). The tumour had a prominent vasculature, consisting of slender serpentine capillaries with perivascular cellular condensation (C) and larger hemangiopericytomatous blood vessels (D). There was focal deposition of osteoid matrix by the tumour cells (E), and areas of necrosis were present (F) (C-G: H&E stain, original magnification 40 ×, 200 ×, 200 ×, 400 ×, and 200 ×, respectively). The tumour cells showed a low proliferation rate (< 1%) by Ki-67 immunohistochemistry (G), and lacked immunoreactivity for CD34 (H) (H&I: immunoperoxidase stains, original magnification 400 × and 200 ×, respectively).

traditional Chinese medicine. However, laboratory investigations at the same time also revealed markedly depressed levels of serum 1,25-hydroxy-vitamin D and phosphate, the latter failing to normalize after several cycles of intravenous phosphate replacement. She was therefore started simultaneously on oral phosphate and vitamin D supplements, and a phosphorus-rich diet was implemented. Her pain progressively worsened over the next two years, with follow-up radiographs showing interval development of fractures in the superior pubic rami and femoral necks, bilaterally, and the right radial neck. A repeat serum biochemistry panel before the patient was referred to our hospital showed persistent hypophosphataemia (serum phosphate 0.37 mmol/L; reference range 0.77-1.38 mmol/L), and normal serum levels of calcium (2.33 mmol/L; reference range 2.09-2.46 mmol/L) and 25-hydroxy-vitamin D (21.3 μg/L; reference range 10.1-40.3 μg/L). At that point, a whole-body FDG-PET/CT scan was performed, whereupon a discrete focus of increased radiotracer uptake was detected in the left ischial tuberosity (**Figure 3A**). This finding was corroborated by an MRI scan of the pelvis, showing a hyperintense lesion in T2-weighted sequences measuring 1.5 × 1.2 cm. The patient underwent wide resection of a segment of bone incorporating the ischial tuberosity and ischiopubic ramus, measuring 8 × 3.5 × 2.5 cm.

Gross examination revealed a whitish tumour with irregular borders, measuring 1.5 cm in largest dimension. Histological sections showed an intramedullary tumour, permeating the marrow spaces while leaving surrounding bone trabeculae undisturbed (**Figure 3B**). It comprised a single population of spindle cells that very focally were organized in streaming fascicles, but for the most part showed a patternless arrangement. The cells exhibited a mild to moderate degree of nuclear atypia and anisonucleosis, with nuclei often having a coarsely clumped chromatin pattern. A network of serpentine capillaries was present multifocally, around which condensations of tumour cells showing marked nuclear overlapping were seen (**Figure 3C**). A secondary vascular pattern consisted of slightly larger 'hemangiopericytomatous' blood vessels with tortuous luminal outlines (**Figure 3D**). There was deposition of an eosinophilic, osteoid-like matrix by the tumour cells in several foci (**Figure 3E**). Basophilic chondromyxoid stroma, calcifications and osteoclast-type giant cells were all notably absent. The tumour contained a few areas of necrosis (**Figure 3F**), but mitotic figures were hardly seen and Ki-67 immunohistochemistry disclosed a very low (< 1%) proliferative index (**Figure 3G**). The tumour cells showed complete absence of CD34 immunoreactivity, with strong positive control staining seen in the endothelium of the tumour vasculature (**Figure 3H**). Immunostaining for smooth muscle actin, S100 and pan-cytokeratins (MNF116) was also negative in the tumour cells, and intratumoural blood vessels lacked D2-40 immunoreactivity. While the cytomorphology, patternless cellular disposition and perivascular condensation of tumour cells would all be considered typical of a solitary fibrous tumour, the infiltrative margins of this tumour, together with the absent expression of CD34 by the tumour cells and absence of collagenous stroma negated this diagnosis. The consideration of osteosarcoma was also raised in view of the focal production of osteoid-like matrix. However, the tumour's non-destructive growth pattern with complete preservation of native bone, its unusual cytoarchitecture, low proliferation index and virtual absence of mitotic activity did not fit this diagnosis either. In the absence of any suitable alternative diagnosis, the histological findings were most consistent with PMTMCT.

Transient normalization of the patient's serum phosphate levels was achieved in the early postoperative period. However, the patient was again found to have hypophosphataemia at 16 month follow-up (serum phosphate 0.59 mmol/L).

Discussion

Insights gained from research on phosphate metabolism have advanced our understanding of the pathobiology of oncogenic osteomalacia. It is now well-established that the hypophosphataemia underlying this syndrome is directly linked to substances elaborated by the causative tumours called phosphatonins, among which fibroblast growth factor 23 (FGF23) has been studied most extensively [11]. The principal site of FGF23 activity is the distal convoluted tubule of the kidney, where in concert with its co-factor Klotho it downregulates expression of both the sodium-phosphate contransporter 2a and renal 1α-hydroxylase, resulting in impaired phosphate reuptake in the proximal renal tubules and decreased production of the bioactive form of Vitamin D respectively [2, 12]. Under normal circumstances, FGF23 is produced by osteocytes and cells of osteoblastic lineage [12]. The autonomous production and secretion of FGF23 by PMTMCTs has been confirmed by various methods [11, 13]. Elevated circulating levels of FGF23 have been detected by serum ELISA assay in patients with oncogenic osteomalacia, which fall to within normal range upon tumour resection [2, 4, 5, 8]. In one instance, combining selective venous blood sampling with the serum ELISA technique helped localize a tumour [14]. Immunohistochemistry and in situ hybridization have both been used previously to reveal FGF23 expression in PMTMCTs at the tissue level [15, 16]. However, FG23 expression in PMTMCTs has thus far been demonstrated most compellingly by RT-PCR [16, 17]. In one study, positive detection of FGF23 by RT-PCR was shown in 25 out of 29 histologically confirmed PMTMCTs, whereas only 3 out of 23 control specimens encompassing a varied assortment of soft tissue neoplasms, carcinomas and non-neoplastic lesions expressed FGF23 [17]. The absence of FGF23 expression in a small subset of PMTMCTs suggests the existence of other secreted factors that promote phosphate wasting. Evidence has emerged supporting an important role of matrix extracellular phosphoglycoprotein (MEPE), another phosphatonin that like FGF23 has been shown to be expressed in a majority of tumours associated with oncogenic osteomalacia [16]. Although the biologic functions of MEPE are incompletely defined, some findings indicate that it positively modulates expression and activity of FGF23. Specifically, an MEPE breakdown product known as acidic serine-aspartate-rich motif (ASARM) peptide binds to the PHEX protein, preventing the latter from blocking FGF23 gene expression [12]. PMTMCTs have been reported in patients without overt manifestations of osteomalacia or biochemical findings of hypophosphataemia and phosphaturia [18, 19], and one of the cases we have described represents this rare occurrence. It is speculated that in these so-called non-phosphaturic variants, tumours either produce insufficient amounts of FGF23 required to induce phosphaturia or secrete a biologically inert FGF23 protein. Another discovery of clinical relevance in PMTMCTs is their expression of the highly responsive subgroup of somatostatin receptors, justifying the use of octreotide as a therapeutic adjunct and the utility of octreotide scintigraphy as a diagnostic modality, which has been successful in uncovering small-sized tumours where CT or MR imaging have failed [2, 20]. In one report, a preoperative trial of octreotide brought about a transient normalization of serum phosphate levels in a patient who subsequently underwent resection of a 5.5 cm intramuscular tumour in the thigh that was diagnosed histologically as a hemangiopericytoma [21]. Given that PMTMCTs can show histological features classically attributed to hemangiopericytomas, and that CD34 immunoreactivity typically seen in hemangiopericytomas was reported as absent, it is possible that this tumour instead represented PMTMCT.

The difficulty in histopathological diagnosis of PMTMCTs arises in part from their resemblance to other tumours of mesenchymal origin. This is compounded by the lack of a specific immunohistochemical stain that can confirm the diagnosis of PMTMCT and the fact that other types of tumours giving rise to oncogenic osteomalacia have been described, including solitary fibrous tumour, osteosarcoma and sinonasal-type hemangiopericytoma/glomangiopericytoma [10]. The patternless spindle cell proliferation and hemangiopericytomatous vasculature observed in two of our cases bring into consideration a solitary fibrous tumour, and explain why historically many PMTMCTs were mislabelled as hemangiopericytomas. The tumour stroma can assume a variety of appearances, but in many cases consists of a chondroid or

chondromyxoid matrix that would lead one to consider differential diagnoses of enchondroma and mixed tumour of soft tissue, particularly when the characteristic "grungy" calcifications are not forthcoming. Osteoclast-type giant cells are frequently present and numerous within PMTMCTs, as two of our cases showed, but are by no means a universal feature. It is postulated that the giant cells are recruited into the tumour in response to the presence of calcifications [10], and so one would expect the unique calcifying matrix to be seen in such cases. Nevertheless, giant cell tumours of bone, giant cell reparative granulomas and brown tumours of hyperparathyroidism can show overlapping morphological features, and attention to clinical history and radiological findings in these instances is critical in arriving at the correct diagnosis. The idea put forth by Weidner and Santa Cruz of variant forms of phosphaturic mesenchymal tumour occurring in bone has largely been forgotten after Folpe et al. failed to identify any cases in their series of 27 tumours that matched these morphological patterns [10]. One of our cases, an intraosseous phosphaturic mesenchymal tumour in pelvic bone, did not show the basophilic calcifying matrix considered prerequisite for the diagnosis of PMTMCT. Although the histological appearance of this tumour does not correspond to the ossifying fibroma-like or non-ossifying fibroma-like variants described by Weidner and Cote, it does highlight the often unusual and distinct microscopic features of phosphaturic mesenchymal tumours arising in intraosseous locations. Knowing that PMTMCTs may not always be associated with the syndrome of oncogenic osteomalacia, and that their cellular composition, vascular patterns and stroma can be highly variable, it may be best to regard them as tumours which recapitulate features of a broad range of bone and soft tissue neoplasms. The surgical pathologist should therefore be familiar with this entity, albeit rare, and consider it among differential diagnoses in various situations, notably when faced with spindle cell tumours, giant cell-rich tumours or tumours containing chondroid and osteoid matrix.

The tumour that seems to generate the greatest diagnostic confusion with PMTMCT is chondromyxoid fibroma (CMF). One of the cases we presented contained areas that were morphologically indistinguishable from CMF. However, because this tumour arose in soft tissue and didn't exhibit the multilobulated pattern or gradient of cellularity from center to periphery that one expects to find in CMF [22], this diagnosis was rejected. A recent study found positive FGF23 expression in 2 out of 7 cases of chondromxyoid fibroma tested with RT-PCR, both of which did not give rise to osteomalacia [23]. This finding, together with the similar histomorphology shared by PMTMCT and CMF, suggests that these may be biologically related tumours, the latter having a tendency to occur in the metaphyses of long bones and being seldom associated with oncogenic osteomalacia.

At present, immunohistochemistry has limited application in the diagnosis of PMTMCT. As mentioned earlier, FGF23 has been detected in PMTMCTs by immunohistochemistry in the experimental setting, although this practice has yet to gain wide acceptance and a validated commercially available antibody to this marker is lacking. Moreover, difficulty in interpretation of staining pattern would be expected, given that FGF23 is secreted by the tumour cells. The observation in previous studies that the vasculature of PMTMCTs shows a lymphatic phenotype offers a potential role for immunohistochemistry in the diagnosis of these tumours [4, 24]. Expression of the lymphatic endothelial markers LYVE-1 and D2-40 (podoplanin) in the vessels of PMTMCTs appears to be a relatively unique feature of these tumours, which can reliably differentiate them from histologically similar lesions like solitary fibrous tumour [24]. The absence of D2-40 staining in both tumours on which we tested this immunohistochemical marker suggests that its sensitivity needs to be investigated further before it can be put to routine use in the diagnosis of PMTMCT. Building on earlier findings of somatostatin receptor expression in PMTMCTs, there have been recent reports of a novel immunohistochemical marker SSTR2A (somatostatin receptor 2A) staining the neoplastic cells in these tumours with a high degree of sensitivity [25, 26] Despite suboptimal specificity, this marker appears promising as a complementary test for confirming the diagnosis of PMTMCT in the presence of suggestive histological features, particularly when dealing with small tissue samples.

Malignant variants of PMTMCT showing nuclear pleomorphism, mitotic activity and distant

metastases have been described, but are rare [10]. One of our cases showed a degree of nuclear atypia along with focal areas of necrosis. However, the virtual absence of mitotic activity throughout this tumour and negligible proliferation index revealed by Ki-67 immunohistochemistry were more in keeping with a benign tumour. A case was reported previously of an intra-osseous tumour in the mandible causing oncogenic osteomalacia, which recurred locally on multiple occasions and then metastasized to the lungs [6]. The diagnosis rendered of ameloblastic fibrosarcoma was based on the presence of islands of ameloblastic epithelium in the original tumour, although the histology of the later recurrences and metastatic tumour consisted solely of mesenchymal elements. Metastatic spread is unusual for a spindle cell tumour that, as the authors remarked, lacked malignant features such as cytological atypia, mitoses and necrosis. Park et al. likewise reported a case of a PMTMCT of the femur in which the patient was disease free 28 years after initial diagnosis, despite the development of lung metastases on three occasions during the follow-up period requiring pulmonary metastasectomies [27]. We have identified in one of our cases that similarly showed benign cytomorphology presence of tumour emboli in extra-tumoural lymphovascular channels. It is possible that in otherwise benign PMTMCTs, foci of tumour may penetrate vascular spaces in a manner similar to that described in giant cell tumours of bone, with subsequent risk of metastatic spread. While this is to our knowledge a novel finding, pathologists should be aware of this phenomenon and pay attention to the presence of lymphovascular invasion in benign PMTMCTs, as it may forecast future recurrence with attendant return of symptoms.

A distinctive characteristic of PMTMCTs that has received little if any recognition previously, but which was observed in two of our cases, was the seeding of small satellite tumour nodules into the adjacent fibroconnective tissue. One of these cases also showed an exaggerated tentacular pattern of growth, with markedly irregular borders histologically, which extended to involve the surgical resection margin. Not surprisingly, local tumour recurrence ensued within two years of the first operation. Macroscopic appearance of these tumours may therefore be misleading, potentially underestimating their true extent. Surgeons should be cognizant of these architectural features of PMTMCTs, and the challenges they present in terms of obtaining clear surgical margins. Complete excision of these tumours is paramount, as small foci of residual tumour left behind can result in persistence of osteomalacia. As such, a more liberal approach to surgical resection of PMTMCTs is advocated in order to achieve negative margins and clinical remission.

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Disclosure of conflict of interest

None.

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