Tumor-induced osteomalacia

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Abstract

Tumor-induced osteomalacia (TIO) is a rare and fascinating paraneoplastic syndrome in which patients present with bone pain, fractures, and muscle weakness. The cause is high blood levels of the recently identified phosphate and vitamin D-regulating hormone, fibroblast growth factor 23 (FGF23). In TIO, FGF23 is secreted by mesenchymal tumors that are usually benign, but are typically very small and difficult to locate. FGF23 acts primarily at the renal tubule and impairs phosphate reabsorption and 1α-hydroxylation of 25-hydroxyvitamin D, leading to hypophosphatemia and low levels of 1,25-dihydroxy vitamin D. A step-wise approach utilizing functional imaging (F-18 fluorodeoxyglucose positron emission tomography and octreotide scintigraphy) followed by anatomical imaging (computed tomography and/or magnetic resonance imaging), and, if needed, selective venous sampling with measurement of FGF23 is usually successful in locating the tumors. For tumors that cannot be located, medical treatment with phosphate supplements and active vitamin D (calcitriol or alphacalcidiol) is usually successful; however, the medical regimen can be cumbersome and associated with complications. This review summarizes the current understanding of the pathophysiology of the disease and provides guidance in evaluating and treating these patients. Novel imaging modalities and medical treatments, which hold promise for the future, are also reviewed.

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Introduction

Tumor-induced osteomalacia (TIO), also known as oncogenic osteomalacia, is a rare paraneoplastic syndrome of abnormal phosphate and vitamin D metabolism caused by typically small endocrine tumors that secrete the phosphaturic hormone, fibroblast growth factor 23 (FGF23; Drezner 2001, Folpe et al. 2004, Jan de Beur 2005). Biochemical hallmarks of the disorder are hypophosphatemia due to renal phosphate wasting, inappropriately normal or low 1,25-dihydroxy vitamin D, and elevated or inappropriately normal plasma FGF23. TIO is counted among the ranks of endocrine neoplasms that have a striking presentation and, when resected, a dramatic and satisfying resolution. Due to a lack of knowledge of the existence of the disease, the length of time from onset of symptoms until diagnosis is often long. As a result, patients frequently present with multiple fractures, height loss, and generalized debilitated status, reminiscent of how patients in the past would present with advanced primary hyperparathyroidism (Fig. 1). If the condition develops before growth plate closure, rickets is also present. There is also a group of patients with a TIO-like syndrome in which a tumor is never found. Whether or not this is due to the inability to find the tumor or this represents a separate syndrome is not known. In our series of 31 patients with TIO syndrome in which genetic causes of hypophosphatemia have been excluded, we have been able to find the tumor in 19 (61%) of them. Given that most of the patients referred to our center have already failed tumor localization at the referring institution at least once, the percent of patients in whom we have not been able to find the tumor is probably higher than is seen in patients being evaluated for the first time.

A TIO-like syndrome can also be seen in association with other diseases such as prostate cancer, oat cell cancer, hematologic malignancies, neurofibromatosis,
epidermal nevus syndrome, and polyostotic fibrous dysplasia of bone (FD; Saville et al. 1955, Dent & Gertner 1976, Taylor et al. 1984, Carey et al. 1986, Rao et al. 1987, Konishi et al. 1991, Nakahama et al. 1995, Ivker et al. 1997, Reese & Rosen 1997, Collins et al. 2001, Riminucci et al. 2003). In these cases, the primary disease is usually obvious, and as such it may be useful to refer to this as secondary TIO. In cases of secondary TIO, the goal is treatment of the underlying disease. However, when the underlying disease is not amenable to cure or adequate treatment, as is the case in FD, the medical treatment of the hypophosphatemic syndrome is the same as in cases of primary TIO.

Robert McCance is often credited with the first reported case of TIO. McCance (1947) reported a patient with manifestations of what was clearly TIO. The patient had pain, weakness, gait abnormalities, and low phosphorus levels. She was treated with high doses of vitamin D, but her symptoms did not completely resolve until a tumor in her femur was resected. Her cure, however, was attributed to the high-dose vitamin D therapy. She was diagnosed with resistance to vitamin D. During that period, vitamin D resistance was believed to be the mechanism of what would eventually come to be understood as FGF23-mediated phosphate wasting disorders (Albright et al. 1937).

The first person to clearly recognize that the disease was the result of a ‘rachitogenic’ substance was Andrea Prader. In 1959, he described an 11 ½-year-old girl who developed severe rickets over the course of a year (Prader et al. 1959). Evaluation showed decreased tubular phosphate reabsorption but otherwise normal studies of kidney function. A tumor, classified as a giant cell granuloma, was identified in a rib and resected with resultant healing of her rickets. Prader highlighted the association between the resection of the tumor and the cure of the rickets and posited that the granuloma was secreting a rachitogenic substance.


**Figure 1** Clinical effects of advanced tumor-induced osteomalacia (TIO). The patient in the gown in panel A is depicted standing next to his father. The patient was previously taller than his father, but this is no longer the case. Panel B demonstrates kyphosis and pectus carinatum, which resulted from multiple compression fractures due to osteomalacia. While these findings are the result of advanced osteomalacia, they are strikingly similar to those seen in advanced hyperparathyroidism, as demonstrated by the famous patient reported by Fuller Albright, Captain Martell, shown in panels C and D, who suffered from years of untreated hyperparathyroidism. (Photo of patient and father are reproduced with their permission. Material is reproduced with permission from Albright & Reifenstein (1948)).
The overall effect is to lower blood phosphate levels (Albright & Reifenstein 1948).

This review aims to provide insight into the pathophysiology and mechanism of TIO as well as guidance in evaluating and diagnosing this rare disease. Clinical presentation, diagnostic testing and therapeutic options are discussed with an emphasis on recent advances. Future areas of interest for research are also discussed.

Physiology and pathophysiology

Phosphate homeostasis

Phosphate is vital to normal physiologic functioning; it plays a role in intracellular signaling, membrane function, energy metabolism, and bone mineralization (Sommer et al. 2007, Renkema et al. 2008). Approximately, 65% of dietary phosphate is absorbed in the duodenum and jejunum (Mount & Yu 2008). Phosphate is predominantly stored in the skeleton with a small amount available in the extracellular fluid. This freely circulating phosphate is filtered by the glomerulus, and under normal physiologic conditions, 85–95% of filtered phosphate is reabsorbed. As renal phosphate load increases, phosphate reabsorption increases until a threshold is reached, at which point phosphate is excreted in the urine (Mount & Yu 2008). Renal phosphate excretion is the primary mode of phosphate clearance and regulation of phosphate balance. The majority of phosphate reabsorption takes place in the proximal renal tubule through type 2a and 2c Na-dependent phosphate cotransporters (NaPi-2a and NaPi-2c; Mount & Yu 2008, Bergwitz & Juppner 2010).

For years, it has been recognized that phosphate concentrations are under the control of parathyroid hormone (PTH), 1,25-vitamin D, and the so-called ‘phosphatonin’ (Mount & Yu 2008, Bergwitz & Juppner 2010). While the primary role of PTH is thought to be the maintenance of serum calcium levels, it also plays an important role in phosphate regulation. In the process of mobilizing calcium from bone, PTH also mobilizes phosphate from bone. To help excrete this increased blood phosphate, PTH acts to inhibit renal phosphate reabsorption through endocytosis of NaPi-2a, thus increasing renal phosphate excretion. The overall effect is to lower blood phosphate levels (Renkema et al. 2008). 1,25-vitamin D is thought to play a role in phosphate regulation in both the gastrointestinal tract and in the kidney, but the mechanism is less understood. Increases in 1,25-vitamin D lead to an increase in phosphate absorption now the case with the primary hyperparathyroidism (Albright & Reifenstein 1948).
from the gastrointestinal tract. In the kidney, the role is more complex. With chronic administration of vitamin D, there is reduction of NaPi-2a and subsequent phosphaturia (Friedlaender et al. 2001). With acute administration of vitamin D metabolites, there is reduced renal phosphate excretion (Taketani et al. 1998). However, many of the effects of 1,25-vitamin D on phosphate metabolism were posited before the discovery of FGF23. It is now clear that FGF23 and PTH play much more important roles in phosphate homeostasis than 1,25-vitamin D.

**Fibroblast growth factor 23**

While Prader was the first to propose the idea of a circulating factor that could cause phosphate wasting, the first evidence that a circulating factor was responsible for the hypophosphatemia of phosphaturic disorders such as TIO was demonstrated in an elegant set of experiments by Meyer et al. By performing parabiosis experiments in hyp mice, the mouse model for X-linked hypophosphatemic rickets, Meyer et al. (1989) were able to demonstrate that a factor in the hyp mouse’s circulation could induce hypophosphatemia in wild-type (WT) mice. A similarly elegant set of experiments by Nesbitt et al. (1992), in which the transplantation of WT kidneys into hyp mice failed to correct hypophosphatemia, confirmed the etiology as a circulating factor and not a primary renal defect. The first evidence to support this concept in humans was the work by Miyauchi et al. (1988), in which a TIO tumor resected from a patient and transplanted into nude mice caused hypophosphatemia and the work that showed that the supernatant from cultured tumor cells could also cause hypophosphatemia in mice (Cai et al. 1994). This phosphaturic substance was termed ‘phosphatonin’ by Econs & Drezner (1994) because of its ability to lower blood phosphorus level.

The first identification of FGF23 as the putative phosphatonin was when mutations in FGF23 were identified by Econs and the autosomal-dominant hypophosphatemic rickets (ADHR) consortium as the cause of ADHR (ADHR Consortium 2000). FGF23 is a member of the FGF ligand superfamily and functions as an endocrine factor. It has a FGF-like amino terminus and a unique carboxy-terminus domain (ADHR Consortium 2000). Once identified as the cause of ADHR, elevations in serum FGF23 were soon found in TIO (White et al. 2001), X-linked hypophosphatemia (XLH; Jonsson et al. 2003), FD (Riminucci et al. 2003), ADHR (Imel et al. 2007) and autosomal-recessive hypophosphatemic rickets (ARHR; Feng et al. 2006). The first insight into the physiologic source of FGF23 was from the study of patients with FD, wherein it was found that dysplastic osteogenic cells are the source of FGF23 (Riminucci et al. 2003). Reasoning that if dysplastic osteogenic cells are the source of FGF23 in FD, we went on to show that normal bone cells are the physiologic source of FGF23 (Riminucci et al. 2003). Physiologic regulation of FGF23 secretion is still being defined, but probably involves serum phosphorus (Larsson et al. 2003, Ferrari et al. 2005, Nishida et al. 2006, Ito et al. 2007) and/or serum 1,25-vitamin D (Collins et al. 2005) are important in regulating the levels of FGF23.

FGF23 acts by binding to target cells via an FGF receptor (probably FGFR1), but signaling requires the co-receptor Klotho (Razzaque 2009). When FGF is activated, there is reduction of NaPi-2a transcription and less NaPi-2a on the basal cell surface of proximal tubule cells, which in turn leads to renal phosphate excretion (Shimada et al. 2004). At this point, it is not clear how this occurs, as Klotho expression has been clearly reported only in distal tubule cells so far (Farrow et al. 2009). There is a secreted form of Klotho, and it is possible that this circulating Klotho may play a role in FGF23 signaling (Kurosu et al. 2006).

There is evidence that the phosphaturic action of FGF23 is to some extent PTH-dependent. Subjects with hypoparathyroidism, who have very low or undetectable PTH levels, have high serum phosphorus in the setting of high serum FGF23, which is consistent with the need for PTH for the full phosphaturic effect of FGF23 (Gupta et al. 2004). This observation is further supported by the fact that in patients with TIO and XLH, medically induced hypoparathyroidism by cinacalcet results in increased renal phosphate reabsorption and an increase in serum phosphorus (Geller et al. 2007, Alon et al. 2008).

In addition to its action on NaPi-2a and NaPi-2c, FGF23 is also a regulatory hormone for 1,25-vitamin D (Shimada et al. 2004). Through downregulation of 1α-hydroxylase and up-regulation of 24-hydroxylase, it leads to a decrease in 1,25-dihydroxy vitamin.

Other compounds such as frizzled related protein-4, matrix extracellular phosphoglycoprotein, and FGF7 have also been suggested to be phosphatonin (De Beur et al. 2002, White et al. 2006). However, the preponderance of data to date suggests that FGF23 is the primary, if not the only, clinically relevant phosphatonin.

**Histopathology**

Tumors associated with TIO have included a wide range of histopathological diagnoses, and despite the description and classification scheme proposed by
Weidner (1991) and Folpe et al. (2004), many clinicians and pathologists continue to be unaware of these tumors as a distinct entity. The prototypical phosphaturic mesenchymal tumor (mixed connective tissue variant) (PMTMCT) contains neoplastic cells that are spindled to stellate in shape, normochromatic with small nuclei and indistinct nucleoli. A spectrum of histopathological features is shown in Fig. 2A–F. The nuclear grade is low, and mitotic activity is usually absent or very low. The cells are typically embedded within a myxoid or myxochondroid matrix with ‘grungy’ calcification that can resemble chondroid or osteoid. Numerous osteoclast-like giant cells are a frequent finding, and mature fat and even lamellar bone may also be seen. A prominent feature of these tumors is an elaborate intrinsic microvasculature with an admixture of vessel size and vascular pattern (Folpe et al. 2004). The most common diagnosis for these tumors has been hemangiopericytoma, but it has also included hemangioma, sarcomas, ossifying fibromas, granulomas, giant cell tumors, and osteoblastomas (Weidner 1991, Drezner 2001, Folpe et al. 2004).

Weidner (1991) reviewed the literature of ~60 cases of TIO that had been described at that time. They were the first to propose a classification system based on the histological findings of their 16 cases of TIO, and designated the tumors as phosphaturic mesenchymal tumors. These were then subdivided into four categories: mixed connective tissue variant (PMTMCT), osteoblastoma-like variant, non-ossifying fibroma-like variant, and ossifying fibroma-like variant. The first group, PMTMCT, comprised neoplasias containing primitive stromal cells, prominent vessel, and osteoclast-like giant cells (Fig. 2D and F). Osseous metaplasia and poorly formed cartilage-like areas with dystrophic calcification were also present (Fig. 2B and E). They noted that these tumors usually occurred in soft tissue and were typically benign in behavior. The remaining three groups tended to occur in bone and were also typically benign in behavior. Folpe et al. (2004) reviewed the clinic-pathological features of 32 new cases and re-reviewed all of the previously published cases, and made the assertion that virtually all of the cases fell into the category of PMTMCT.

Antigen expression was first evaluated in two immunohistochemical studies by Weidner et al. In the first study, the immunostainings were negative for FVIII-related antigen, S-100, and cytokeratin (Weidner et al. 1985). The second study revealed only vimentin immunoreactivity in some cases within the tumor cells. All other antibodies (desmin, S-100 protein, leu-M 1, chromogranin, cytokeratin, neuron-specific enolase, leukocyte common antigen, and factor VIII-related antigen) were negative (Weidner et al. 1985). In their series, Folpe et al. (2004) performed a series of immunohistochemical stainings, including pan-cytokeratin, desmin, S-100, smooth muscle actin, CD34, and FGF23. With the exception of smooth muscle actin, which they found reactive in three cases, and FGF23, which was positive in about 70% of all the cases studied, all other markers were negative. In terms of FGF23 staining, it is the proliferating cells within the tumor that usually stain positive for FGF23 (Fig. 3A).

**Figure 2** TIO tumor histopathology. (A) This tumor area shows immature mesenchymal cells, with no particular differentiation. There are areas of edema and blood lacunae (arrow). (B) This proliferation is solid, with what seems to be abundant intercellular matrix (arrow). The nuclei are typical with some variation in shape and size. (C) Numerous and irregular vascular structures (arrows), as well as areas of solid proliferation, are seen in this tumor area. (D) This tumor is composed mostly of irregular vascular structures (arrows) embedded in a relatively soft matrix. Variations in size and shapes of the nuclei are evident. (E) Lattice-like areas with ossification (arrow). (F) This photomicrograph was taken from a lung metastasis. The area shows numerous very large osteoclastic-like giant cells (arrows). Note that even though the proliferation is biologically malignant, there are few or no histological signs of malignancy.
In terms of ultrastructural features, Stone et al. (1992) described features consistent with a neuroendocrine tumor in a PMTMC from a 33-year-old woman. Neurosecretory granules were also found in the case by Wilkins et al. (1995). However, immunostaining for typical markers of neurosecretory tumors, such as S-100, neuron-specific enolase, chromogranin and synaptophysin, were negative, as was staining for actin, cytokeratin, epithelial membrane antigen, and FVIII. The only positive finding was vimentin, confirming what had been already described by Weidner. An additional case communicated by Shelekhova et al. (2006) also showed similar neurosecretory granules.

While typically benign, malignant presentation and metastases can occur (Wyman et al. 1977, Rico et al. 1986, Harvey et al. 1992, Ogose et al. 2001, Uramoto et al. 2009). Two of the 19 tumors in our series went on to metastasize (Figs 2F and 3B), a feature that is hard to predict from the benign histological appearance. While metastases are rare, infiltration of surrounding connective tissue is typically present, which has significant implications for surgical management and emphasizes the importance for wide surgical margins to avoid persistence or recurrence – a point that cannot be emphasized enough in the management of TIO.

It seems to be that PMTMC constitute a single, albeit morphologically heterogeneous, histopathological entity. Regardless of tumor morphology, the hallmark of the diagnosis of a PMTMC is the association of the tumor with the clinical syndrome of TIO, which includes an elevation in plasma FGF23 and its disappearance after tumor resection. It is this heterogeneity that may account for their frequent misdiagnosis (Folpe et al. 2004).

To date, the immunohistochemical and electron microscopy findings have not shed light on the cell of origin of these neoplasias, but only served to confirm their mesenchymal origin. It is also quite possible that all of the tumors share a common origin: a primitive mesenchymal cell that itself has the ability to secrete the hormone and which can differentiate into several cell lineages.

To summarize, PMTMC constitute a group of tumors with a spectrum of histopathologic findings that include a background of spindle/stellate cells with low nuclear and mitotic activity. This is true even in cases of metastatic disease. Prominent vascularity is common and includes vessels of different sizes and patterns, consistent with the fact that they are most commonly classified as hemangiopericytomas. Osteoclast-like giant cells are frequently seen in these tumors and mature fat or lamellar bone can be present as well. FGF23 staining is positive and appears in the cytoplasm of the tumor cells. It is important to note that histopathologic diagnosis of malignant disease is difficult, as even in clinically proven metastatic disease the cellular features appear benign.

**Clinical evaluation**

A summary of our approach to the evaluation of these patients can be found in Fig. 4, and a summary of medical treatment recommendations can be found in Box 1. Patients with TIO often present with many years of symptoms before they are diagnosed. The symptoms, which lead to their evaluation, are non-specific, and often progressive. Common complaints are bone pain, muscle weakness, and multiple
fractures (Jan de Beur 2005). Pediatric patients can develop rickets and growth retardation (Jan de Beur 2005, Haeusler et al. 2010). These patients are often misdiagnosed with a variety of musculoskeletal ailments, rheumatologic diseases, and sometimes even psychiatric disorders (Teasell & Shapiro 2002, Lewiecki et al. 2008). Hypophosphatemia caused by impaired renal phosphate reabsorption is the biochemical hallmark of the disease. In many institutions, phosphate is no longer part of the routine chemistry panels, thus hypophosphatemia can often go unrecognized, further delaying diagnosis (Halperin et al. 2007).

**Differential diagnosis**

The differential diagnosis for hypophosphatemia should first be separated into genetic versus acquired causes. Genetic causes include XLH, ADHR, and ARHR, which are essentially biochemical phenocopies of TIO. In all of these genetic forms of hypophosphatemia, the plasma FGF23 is either directly elevated or inappropriately normal. XLH is almost invariably present in early childhood, while ADHR can present in either childhood or adulthood (Econs & McEnery 1997). Therefore, a detailed personal history to identify the age of onset, which can often be aided by...
review of the growth chart in the case of young patients, and a detailed family history, looking for family members with short stature and bowed legs, is especially important in children and young adults. Some genetic forms, especially XLH, are associated with dental findings, including enamel hypoplasia, dental abscesses, and caries; thus, a detailed dental history is important (Baroncelli et al. 2006). Generally, the younger the patient is at presentation, the more likely is a genetic cause. Additional genetic disorders that can present with hypophosphatemia and should be considered in the hypophosphatemic patient are hereditary hypophosphatemic rickets with hypercalciciuria (HHRH; Bergwitz et al. 2006), X-linked recessive hypophosphatemic rickets (XLHR)/Dent’s disease (Scheinman 1998), and the inherited renal Fanconi syndromes, Fanconi-Bickel syndrome (MIM ID 227810) (Santer et al. 1997) and Fanconi renal tubular syndrome (MIM ID 134600) (Lichter-Konecki et al. 2001). HHRH and XLHR differ from the other genetic causes of hypophosphatemia in that hypercalciuria due to increased 1,25-vitamin D accompanied by nephrocalcinosis and/or nephrolithiasis is a feature. Patients with XLHR also have proteinuria. Patients with the genetic Fanconi syndromes have a more generalized renal tubulopathy. This can include any combination of aminoaciduria, low molecular weight proteinuria, bicarbonaturia, calcium, and others. However, the most important fact that distinguishes these genetic syndromes of hypophosphatemia from TIO is that plasma FGF23 is high in TIO, but low in HHRH and Fanconi syndrome. FGF23 levels in XLHR have not been reported, but should be low as well. The genes for the genetic forms of hypophosphatemia, as well as various features, are detailed in Table 1.

In addition to the genetic causes of non-TIO hypophosphatemia, there are acquired causes. Most of the acquired forms of hypophosphatemia are the result of direct renal tubular damage by a drug or a toxin. Tubular damage usually results in a generalized tubulopathy, similar to what is seen in the genetic Fanconi-type tubulopathies mentioned above (Bonnardeaux & Bichet 2008). This type of tubulopathy can be seen as a result of burns (Nordstrom et al. 1977), heavy metal exposure (cadmium, lead and arsenic) (Omdahl & DeLuca 1971, Aranami et al. 2010), aminoglycoside antibiotics, certain chemotherapeutic agents, especially cisplatin, and the anti-retroviral drug, tenfovir, which is used in the treatment of HIV and hepatitis B (Davis et al. 1980, Izzedine et al. 2003, Earle et al. 2004). It can also occur in association with multiple myeloma and other dysproteinemias (Dash et al. 1997). 1,25-vitamin D levels are

### Table 1 Differential diagnosis of hypophosphatemia

<table>
<thead>
<tr>
<th>Disease</th>
<th>Gene</th>
<th>FGF23</th>
<th>Other findings</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic causes</td>
<td></td>
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</tr>
<tr>
<td>XLH</td>
<td>PHEX</td>
<td>Elevated</td>
<td>Childhood onset, rickets and dental caries</td>
<td>The HYP Consortium (1995)</td>
</tr>
<tr>
<td>ADHR</td>
<td>FGF23</td>
<td>Elevated</td>
<td>Variable age of onset, may spontaneously remit and recur</td>
<td>White et al. (2000)</td>
</tr>
<tr>
<td>ARHR</td>
<td>DMP-1, ENPP1</td>
<td>Elevated</td>
<td>May have consanguinity in parents</td>
<td>Feng et al. (2006)</td>
</tr>
<tr>
<td>HHRH</td>
<td>SLC34A3</td>
<td>Low</td>
<td>Increased 1,25-vitamin D, increased urinary calcium, low PTH, and nephrocalcinosis</td>
<td>Bergwitz et al. (2006)</td>
</tr>
<tr>
<td>XLRH/Dent’s</td>
<td>CLCN5</td>
<td>Unknown</td>
<td>Male predominance, hypercalciciuria, nephrocalcinosis, kidney stones, and renal failure</td>
<td>Pook et al. (1993)</td>
</tr>
<tr>
<td>Inherited Fanconi</td>
<td>Various</td>
<td>Low</td>
<td>Glucosuria, aminoaciduria, calcium, and proximal renal tubular acidosis</td>
<td>Chadha &amp; Alon (2009)</td>
</tr>
<tr>
<td>Acquired causes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIO</td>
<td>NA</td>
<td>Elevated</td>
<td>Variable age of onset, low 1,25-D, low TmP/GFR</td>
<td>Drezner (2001)</td>
</tr>
<tr>
<td>Acquired Fanconi</td>
<td>NA</td>
<td>Low</td>
<td>Glucosuria, aminoaciduria, proximal renal tubular acidosis, history of exposure to heavy metals, chemotherapeutic agents, etc. (see text)</td>
<td>Jan de Beur (2005) Izzedine et al. (2003)</td>
</tr>
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</table>

XLH, X-linked hypophosphatemic rickets; ADHR, autosomal-dominant hypophosphatemic rickets; ARHR, autosomal-recessive hypophosphatemic rickets; XLRH, X-linked recessive hypophosphatemic rickets; HHRH, hereditary hypophosphatemic rickets with hypercalciciuria; XLHR, X-linked recessive hypophosphatemic rickets; TIO, tumor-induced osteomalacia.
variable, and can be low, as seen in TIO. Unlike TIO, Fanconi-type syndromes tend to be associated with more severe proximal renal tubular defects and metabolic acidosis. Again, the key factor in discriminating these sorts of disorders from TIO is the plasma FGF23 level, which is low in cases of tubular damage, and high in TIO. Other disorders which can be associated with hypophosphatemia are hematologic malignancies, total parenteral nutrition, organ transplant, refeeding syndrome, correction of diabetic ketoacidosis, and dietary deficiency.

**Approach to the diagnosis of TIO**

**Diagnosis confirmation**

TIO should be suspected in patients who present with consistent symptoms and with hypophosphatemia. If hypophosphatemia is present, the presence of renal phosphate wasting should be confirmed.

Two ways to evaluate urinary phosphate wasting are the calculation of percent tubular reabsorption of phosphate (%TRP) and tubular maximum for phosphate corrected for glomerular filtration rate (GFR) (TmP/GFR). Open access programs that calculate %TRP and/or TmP/GFR can be found on the Internet (by searching under these terms), but caution should be exercised to enter the proper units (traditional versus SI), as indicated by the site. TmP/GFR can be calculated only in the fasting state, but %TRP can be calculated at any time using the following formula:

$$100 \times \left(1 - \frac{\text{urine phosphate}}{\text{urine creatinine}}\right) \times \left(\frac{\text{serum creatinine}}{\text{serum phosphate}}\right)$$

When phosphate is normal, the normal range is between 85 and 95%.

The TmP/GFR is another measure of renal phosphate handling and is independent of plasma phosphate and renal function. TmP/GFR can be determined using a nomogram or algorithm (Kenny & Glen 1973, Walton & Bijvoet 1975). Use of the algorithm is less cumbersome and there is no clinically significant difference between the values obtained, making it the preferred method (Barth et al. 2000). The formula used to calculate TmP/GFR is dependent on the value of TRP and can be calculated using the formulas below:

If TRP is $\leq 0.86$ (86%), then TmP/GFR

$$= \text{TRP} \times \text{phosphate}.$$  

If TRP is $> 0.86$ (86%), then TmP/GFR

$$= 0.3 \times \frac{\text{TRP}(1 - 0.8 \times \text{TRP})}{\text{phosphate}} \times \text{phosphate}.$$  

In using these algorithms, it is important that units for urine creatinine, urine phosphate, serum creatinine, and serum phosphate are consistent.

The normal reference ranges for TmP/GFR are age- and gender-dependent, but have not been well defined in large patient populations. Reasonable age- and gender-dependent values are listed in Table 2, and are derived from data compiled by Stark et al. (1986), Alon & Hellerstein (1994) and Payne (1998).

TmP/GFR should be calculated from testing done in the fasting state, typically from second morning-void urine and blood samples taken at the same time. In the non-disease state, the values for TRP and TmP/GFR will be high when there is hypophosphatemia. In TIO, these values are abnormally low. It is important to note that the calculations of %TRP and TmP/GFR in patients with suspected TIO need to be done off of phosphate supplementation. Phosphate supplementation will elevate urinary phosphate in both subjects with and without TIO and can lead to falsely low determinations of %TRP and TmP/GFR in patients without the disease.

After confirming renal phosphate wasting as the etiology for hypophosphatemia, additional lab tests can be helpful in making the diagnosis of TIO. 1,25-vitamin D can be low or inappropriately normal. Calcium and PTH are usually normal, but PTH can be high reflecting secondary hyperparathyroidism, which is the normal response to low 1,25-vitamin D caused by elevated FGF23. Measurement of blood FGF23 is now commercially available and is essential for the diagnosis. Currently, only the less-sensitive C-terminus assay is widely available for commercial testing (Imel et al. 2006). It is important to note that this is only valid for plasma, not serum, samples. The most sensitive and specific assay for use in the diagnosis of TIO is the intact assay manufactured by Kainos (Imel et al. 2006), which at present is typically only used in research laboratories.

Once the diagnosis of an FGF23-dependent, phosphate wasting disorder is made, a thorough history can aid in excluding the genetic causes, such as XLH, ADHR, and ARHR. Genetic testing can also be done. Having narrowed the diagnosis to TIO, a careful physical examination should be performed, as the tumors that cause TIO can sometimes be found in the subcutaneous tissue (Fig. 5; Colt et al. 2005, Dewitt et al. 2007, Ogura et al. 2008). It is also prudent to ask the patient if she/he has noticed any new ‘lumps’ or ‘bumps’ as well as to examine the oral cavity, as tumors have been reports in the jaws (Yun et al. 2009).
Localizing studies: functional imaging

As tumors can arise in bone or soft tissue, occur from head to toe, and are typically very small in size, locating these tumors is often quite challenging. We have seen in our cohort of patients that tumors are found more commonly in bone than in soft tissue.

We advocate a stepwise approach, first performing functional tests. In our hands, F-18 fluorodeoxyglucose positron emission tomography, with computed tomography (FDG-PET/CT), has proven to be most sensitive for localizing TIO tumors (Dupond et al. 2005, Andreopoulou et al. 2010). However, while FDG-PET/CT may be very sensitive, it is also non-specific and identifies areas of metabolic activity that are not tumors. This is especially true in patients with many areas of active fracture healing (Fig. 6).

Another important functional imaging modality is 111Indium octreotide scintigraphy, ideally combined with single photon emission CT and CT (SPECT/CT). Somatostatin receptors have been found to be present on many TIO tumors (Duct et al. 2008) and 111Indium-octreotide has a high affinity for the somatostatin receptor, especially subtype 2 and to a lesser extent subtype 5. As with FDG PET/CT, emphasis should be placed on making sure these imaging tests cover the entire body, from head to toe, including the hands and feet. Standard PET/CT and octreotide often exclude portions of the extremities and may exclude portions of the head. Addition of co-registered CT to both FDG-PET and octreotide significantly increases the ability to localize tumors, and whenever possible it should be performed.

More recently, 68Ga-DOTANOC PET/CT has been explored as a means of finding TIO tumors (Hesse et al. 2007a, von Falck et al. 2008). This scan combines the specificity of octreotide scanning with the sensitivity of PET/CT. It utilizes a modified octreotide molecule (DOTANOC) that has increased affinity for both somatostatin receptor 2 and 5 (Wild et al. 2003, 2005). Labeling this compound with the positron emitter 68Ga results in a PET compound that may be more specific than FDG. However, studies comparing 68Ga-DOTANOC PET/CT with standard octreotide SPECT/CT in the diagnosis of TIO have not been done.

Table 2: Normal ranges for tubular maximum for phosphate corrected for GFR

<table>
<thead>
<tr>
<th>Age</th>
<th>Male mg/dl (mmol/l)</th>
<th>Female mg/dl (mmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newborn</td>
<td>5.7–8.1 (1.27–2.59)</td>
<td>5.7–8.1 (1.27–2.59)</td>
</tr>
<tr>
<td>1 month–2 years</td>
<td>3.6–5.4 (1.15–1.73)</td>
<td>3.6–5.4 (1.15–1.73)</td>
</tr>
<tr>
<td>2–12 years</td>
<td>3.8–5.0 (1.22–1.60)</td>
<td>3.8–5.0 (1.22–1.60)</td>
</tr>
<tr>
<td>12–16 years</td>
<td>3.4–4.6 (1.09–1.47)</td>
<td>3.4–4.6 (1.09–1.47)</td>
</tr>
<tr>
<td>16–25 years</td>
<td>3.33–5.9 (1.07–1.89)</td>
<td>3.18–6.41 (1.02–2.05)</td>
</tr>
<tr>
<td>25–45 years</td>
<td>3.09–4.18 (0.99–1.34)</td>
<td>2.97–4.45 (0.95–1.42)</td>
</tr>
<tr>
<td>45–65 years</td>
<td>2.78–4.18 (0.89–1.34)</td>
<td>2.72–4.39 (0.87–1.40)</td>
</tr>
<tr>
<td>65–75 years</td>
<td>2.47–4.18 (0.79–1.34)</td>
<td>2.47–4.18 (0.79–1.34)</td>
</tr>
</tbody>
</table>


Figure 5: Subcutaneous TIO tumor detectable on physical examination. Physical examination of a patient with TIO (the same patient shown in Fig. 1) revealed a subcutaneous nodule (A). This nodule was implicated as the culprit tumor by the fact that it was detected on functional imaging, FDG-PET (B). The lesion was visualized on CT scan, which also suggested intraskeletal calcification (C, arrow). On the low-power view, it can be seen that the tumor was completely contained in the subcutaneous tissue (D), and on a high-power view, it was revealed that the calcification in the lesion was actually ossification and contained areas of lamellar bone (E). TIO resolved after excision.
201Thallium and 99Technetium MIBI scintigraphy have been used in TIO (Kimizuka et al. 2004, Hodgson et al. 2006), but we have not found them to add anything to FDG-PET or octreotide scanning. 99Tc-MDP bone scintigraphy (bone scans) has not proven to be a useful study in localization of TIO tumors (Lee et al. 1995, Garcia & Spencer 2002). It often reveals multiple foci of uptake at areas of fracture and may actually misdirect the effort to localize the tumor. Of interest, though, is that 99Tc-MDP bone scans often show uptake at the costochondral junctions (a sort of adult rachitic rosary) and areas of the bone in skeletally mature adults where the growth plates were previously located (Fig. 7). This finding should suggest the diagnosis of TIO, and may represent a sort of ‘pseudo-reactivation’ of growth plates in the adult skeleton. The pathophysiology underlying this interesting and frequently observed phenomenon is unclear at this time. Importantly, this finding should not be misinterpreted as evidence of metastatic tumor, as it sometimes is.

Localizing studies: anatomical imaging

Once suspicious lesions have been identified with functional imaging, one should proceed to anatomical imaging to confirm the location of the tumor. Anatomic imaging studies include X-rays, CT, and/or magnetic resonance imaging (MRI) scans. Some investigators advocate total body MRI as an initial imaging study. However, we have not found this approach to be fruitful. It should also be noted that there are ‘blind’ spots on both FDG-PET and octreoscan; brain uptake on FDG-PET may obscure intracranial tumors, and liver and spleen uptake of octreotide may obscure potential lesions in these regions. Therefore, anatomical imaging of these areas may be indicated if a tumor has not been identified.

Venous sampling

Usually, the combination of functional and anatomical imaging is successful in localizing the FGF23-secreting tumor. However, there are certain circumstances in which more certainty and testing are indicated. Often, more than one lesion is found on functional imaging, particularly FGD-PET, each with a reasonable degree of suspicion or the suspicious lesion is located in an area where the indicated operation is associated with a high level of potential morbidity. In these cases, additional certainty and testing are indicated. Of particular utility is selective venous sampling with measurement of FGF23 (Andreopoulou et al. 2010b). Examples of the utility of venous sampling in distinguishing between multiple sites and difficult sites are shown in Fig. 8.

Figure 6 Multiple imaging modalities may be needed to localize TIO tumors. In this patient, FDG PET/CT revealed multiple areas of increased uptake (A). Octreotide scan only demonstrated a single lesion (B–D). MRI revealed a tumor in the area identified on functional imaging (E). TIO resolved after excision of the lesion.
Venous sampling has been attempted in localizing tumors in the absence of any suspicious lesions identified on either functional or anatomical imaging, the so called ‘blind sampling’. In a trial designed to test this, we were unable to localize tumors by venous sampling without a ‘target’ lesion suggested by anatomical or functional imaging, and concluded this was not a useful approach (Andreopoulos et al. 2010b). Van Boekel et al. (2008) advocated a two-step approach to venous sampling. They suggested that if a suspected tumor cannot be localized by imaging, whole body venous sampling can be performed with assessment of the average values for samples from different anatomical regions. If the average values in samples from a region appear to be higher, more detailed sampling is performed in the smaller branches of the veins in that region. In the one patient studied by this approach, it appeared to suggest a particular region. However, in retrospect, the tumor was evident on an MRI that had been performed prior to venous sampling, so the utility of this approach is not clear.

An additional approach that can be used for confirmation that a suspicious lesion identified on functional or anatomical imaging is the culprit tumor is aspiration of the lesion. Elevated FGF23 in the aspirate is diagnostic of a culprit lesion. Inspection of cells in the aspirate may reveal cellular morphology consistent with that of a phosphaturic mesenchymal tumor, further supporting that the aspirated lesion represents the culprit lesion (Sciubba et al. 2009).

Despite all of the advances in imaging that are available today, tumor localization may not be successful. If this is the case, imaging studies should be repeated in hopes that a tumor may be more evident with time. This can be done every 1–2 years.

**Treatment**

**Surgical resection**

The treatment of choice for TIO is resection of the tumor with a wide margin to insure complete resection. Resection with a wide surgical margin is of utmost importance, as recurrences of these tumors have been reported (Clinic et al. 2000, Ogose et al. 2001, Uramoto et al. 2009). Tumor resection is almost always curative, and following complete resection of the tumor, there is relatively rapid improvement. FGF23 has a half-life of ~45 min and disappears rapidly from the circulation (Khosravi et al. 2007). The majority of patients demonstrate surgical cure, as evidenced by the return of serum phosphate to normal, by post-operative day 5. Some patients may take as long as 10 days and, in children, we have seen phosphate return to normal in as few as 2 days. In fact, it is return of serum phosphorus to normal after tumor resection that confirms the diagnosis of TIO. Most patients feel better within days to weeks of tumor removal. Bone healing starts immediately, but depending on the severity of the disease, it may take up to a year or more for significant clinical improvement.

Late recurrence due to metastatic disease is rare but possible. This probably occurs in <5% of the patients with TIO (Ogose et al. 2001, Folpe et al. 2004). Lung is a common site for metastasis (Fig. 3), and as such should be closely evaluated when there is a late recurrence without evidence of local disease. The lesions can be quite small and difficult to visualize. Therefore, high-resolution CT is recommended as the imaging modality of choice. More advanced disease may present with a miliary pattern. The course after metastasis is quite variable, and survival of up to 30 years has been reported (Harvey et al. 1992). In our series of 31 cases of TIO, we have seen two cases of recurrence due to tumor metastasis in the lung (Fig. 3). There is no chemotherapeutic regimen with any demonstrated efficacy in treating metastatic TIO.
Radiofrequency ablation (RFA) has also been reported as a possible treatment modality (Hesse et al. 2007). Hesse et al. reported use of RFA in a 40-year-old woman with TIO, in whom the tumor was located in the femoral head. In order to preserve the hip joint, CT-guided RFA was performed in two rounds of treatment. The patient showed complete biochemical and symptomatic recovery within weeks, and had unremarkable follow-up at 1 year. While this is promising, long-term follow-up and effectiveness in other cases remains to be seen. Again, the need for a wide margin is advocated to avoid recurrence or metastasis.

**Figure 8** Utility of selective venous sampling in TIO. Selective venous sampling is useful in distinguishing between multiple suspect lesions, as in this patient who had uptake at both the region of the acetabulum (A) and patella (B). Elevated FGF23 in the veins draining the acetabular region (C) identified the lesion in this region as the causative lesion. Selective venous sampling is also useful in identifying lesions in places difficult to image or to approach surgically. The brain shows generalized increased uptake on FDG PET/CT (D) making identification of a lesion in this area difficult. A lesion was seen on octreotide scan (E) and MRI (F). It was felt that this could be a TIO tumor or a meningioma, which are also octreotide positive. Venous sampling (G) demonstrated elevated FGF23 (H), confirming that the lesion was the FGF23-secreting tumor. This material is reproduced from Andreopoulou et al. 2010b with permission of John Wiley & Sons, Inc. r, right; l, left; pop, popliteal; sfv, superficial femoral vein; fem, femoral; prox, proximal; comm, common; int, internal; isch, ischial; mid, middle.
Medical treatment

When the tumor cannot be localized or is not surgically resectable, medical therapy with phosphate supplementation and calcitriol or alfacalcidiol is used. The treatment regimen that follows is essentially the same as that used in non-TIO causes of hypophosphatemia. When initiating treatment, it is prudent to check weekly labs to guide titration of medications until treatment targets are reached.

Phosphorus supplementation is the mainstay of treatment. However, since phosphorus is rapidly absorbed and cleared, multiple doses throughout the day are necessary (at least 3–4 times per day) in an attempt to try and get the serum phosphorus to the lower end of the age-appropriate normal range. Treatment to the lower end of the age-appropriate range has been shown by bone biopsy to improve bone disease. Whether treatment to targets below the normal range is effective remains unclear. GI upset and diarrhea may develop as a result of phosphate supplementation. GI side effects can sometimes be alleviated with divided dosing and administration with food; however, they should not be provided with calcium-rich foods. GI side effects can also sometimes be avoided by using concentrated oral preparations that were developed for treatment of constipation or for bowel preparation prior to endoscopy. Various phosphorus supplement preparations are listed in Table 3. Secondary hyperparathyroidism can be seen on presentation, due to suppression of 1,25-vitamin D by FGF23, or it can develop as a result of phosphorus supplementation. Active vitamin D (calcitriol or alfacalcidiol) is used to prevent or treat secondary hyperparathyroidism. The dose is titrated to keep the PTH in the normal range. In the early phases of the treatment of severe bone disease, additional calcium supplementation may be necessary to provide mineral ion substrate to heal the bone. Addition of calcium supplements or increases in calcitriol and/or alfacalcidiol are indicated for difficult to suppress PTH, very low urinary calcium, or hypocalcemia. As bone healing progresses, the regimen needs to be modified. Calcium supplementation and/or active vitamin D treatment usually need to be decreased. One consequence of over-treatment with active vitamin D is the development of hypercalcuiuria and the risk for nephrocalcinosis/nephrolithiasis. While on chronic treatment, periodic measurement of urine calcium should be performed. Prolonged phosphorus supplementation can lead to the development of tertiary hyperparathyroidism. This may require partial parathyreoidectomy, or treatment with the calcium-sensing receptor agonist, cinacalcet.

The treatment regimen is to give 15–60 mg/kg per day of elemental phosphorus (typically 1–3 g/day) divided into 4–6 doses. Various formulations with varying amounts of phosphorus are available (Table 3). Calcitriol or alfacalcidiol is given at 15–60 ng/kg per day, with a typical starting dose of 1.5 μg/day in an adult. A new treatment approach that holds promise, but needs additional study for confirmation of efficacy and establishment of safety, is cinacalcet, an agonist of the calcium-sensing receptor that lowers blood PTH levels (Geller et al. 2007). The use of cinacalcet was advocated on the basis of evidence that FGF23 action was PTH-dependent. Gupta et al. (2004) found that both FGF23 and serum phosphorus were high in the blood of patients with hypoparathyroidism, indicating that in the absence of PTH, FGF23 was unable to adequately lower blood phosphorus level. This led to the notion that medically induced hypoparathyroidism may be a potential treatment for TIO (Geller et al. 2007). In this paper, we were able to show that cinacalcet increased %TRP and serum phosphorus, allowed for a decrease in phosphate supplementation, and led to bone healing, as assessed by iliac crest bone biopsy. However, hypercalciuria developed, necessitating the addition of a thiazide diuretic to lower urinary calcium. Similarly, cinacalcet has shown promise in treating patients with XLH, which is also a disorder of excess FGF23 (Alon et al. 2008, Yavropoulou et al. 2010). In patients with TIO treated with cinacalcet, urinary calcium must be monitored carefully to avoid nephrocalcinosis and/or nephrolithiasis.

A previously advocated treatment for TIO was the somatostatin analog, octreotide (Seufert et al. 2001). This appeared to be a logical treatment, given the presence of somatostatin receptors on the cell surface of TIO tumors and the ability to detect the tumors with radiolabeled octreotide. However, most clinicians have not been able to reproduce the success that Seufert

Table 3 Phosphorus supplements

<table>
<thead>
<tr>
<th>Phosphorus source</th>
<th>Amount of elemental phosphorus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutra-Phos</td>
<td>8 mmol (248 mg) per capsule/packet</td>
</tr>
<tr>
<td>Neutro-Phos K</td>
<td>8 mmol (248 mg) per capsule/packet</td>
</tr>
<tr>
<td>K-Phos Neutral</td>
<td>8 mmol (248 mg) per tablet</td>
</tr>
<tr>
<td>K Phos Original</td>
<td>3.68 mmol (114 mg) per tablet</td>
</tr>
<tr>
<td>Fleet’s Phospho Soda</td>
<td>4.15 mmol (128.65 mg) per ml</td>
</tr>
<tr>
<td>Joulies Solution</td>
<td>Varies depending on compounding pharmacy</td>
</tr>
</tbody>
</table>

et al. had in the single patient they reported. Paglia et al. (2002) reported their lack of success in a single patient, and we saw no effect in five patients and have abandoned further attempts (unpublished data).

Few reports are available on the role of external beam radiation or chemotherapy in the treatment of these patients. In the few reports that mention radiation therapy, there does not appear to be any clear benefit (Fuentealba et al. 2003, Uramoto et al. 2009). Chemotherapy regimens that have been reported include the combination of cisplatin, doxorubicin, and methotrexate (Terek & Nielsen 2001) as well as the use of dasatinib (Peters et al. 2010). In the first case, chemotherapy was pursued as the first option as the patient was felt to have an osteosarcoma. Following treatment, the patient’s phosphate normalized (Terek & Nielsen 2001). In the second case, the patient had recurrent disease that could not be completely resected. Due to strongly positive immunohistochemical staining of platelet-derived growth factor receptor, the patient was started on dasatinib and has been stable on this therapy (Peters et al. 2010). Given the limited evidence for either radiation or chemotherapy, their roles in treating these patients are not known at this time. Given the slowly proliferating nature of these tumors, we would expect that these treatments would have little efficacy.

Medical treatment: monitoring

A baseline ultrasound should be obtained, and blood and urine studies should be monitored approximately every 3 months. For urine tests, checking the second morning void for calcium and creatinine is suggested to assess for hypercalciuria. If the calcium/creatinine is ≥0.2, urinalysis should be done to check for the presence of blood in the urine. If this is present, calcitriol should be decreased and a 24h urine for calcium and creatinine should be checked with a goal of obtaining normal urinary calcium/creatinine ratio. If this remains elevated, calcitriol should be decreased further. If calcium/creatinine is <0.2 and the serum phosphorus and PTH are within targets, the current regimen can be maintained. A summary of medical therapy and monitoring is provided in Box 1.

Future directions

Treatment with calcitonin has also been explored as a method to suppress FGF23 (van Boekel et al. 2008). A single s.c. injection of calcitonin was able to suppress FGF23 levels by 44.6% at 9 h post-injection. Long-term treatment, however, was not pursued as focus was given to localization of the tumor. We were unable to replicate these findings in a single patient in whom we attempted this treatment (unpublished data). Whether calcitonin is truly an effective treatment awaits further investigation.

Future treatment will likely be guided by a better understanding of the biology of FGF23 and the nature of these tumors. Recent investigations have led to a rudimentary understanding of FGF23 synthesis, post-translational modification, and signaling. While elucidation of the transcriptional and translational regulation of FGF23 is still lacking, it has become evident that posttranslational glycosylation by UDP-N-acetyl-alpha-D-galactosaminyltransferase 3 (GalNAc-T3) is essential for the secretion of biologically active FGF23 (Topaz et al. 2004, Benet-Pages et al. 2005, Frishberg et al. 2005, Dumitrescu et al. 2009). The fact that patients null for GalNAc-T3 have a phenotype that is completely confined to abnormalities in mineral metabolism suggests that GalNAc-T3 may eventually be a therapeutic target for diseases of FGF23 excess, such as TIO. A promising therapeutic currently in clinical trials are monoclonal antibodies that target the FGF23–FGFR1 interaction (Aono et al. 2009, 2010). A monoclonal antibody that disrupts the interaction of FGF23 with the FGFR appears to be the mechanism of action with this approach.

Conclusion

TIO is a fascinating paraneoplastic syndrome caused by unregulated over-secretion of the recently identified phosphate and vitamin D regulating hormone, FGF23. It is a debilitating disease that is cured with excision of the tumors. The benign-appearing histopathology typically seen in these tumors can be misleading, as even clinically proven metastatic disease can have benign cellular features. While the tumors can be difficult to locate, a step-wise approach that involves functional imaging, followed by anatomical imaging, and, if necessary, selective venous sampling or aspiration for confirmation is usually successful. Excision with wide margins is important to avoid late recurrence. When tumors cannot be identified, medical treatment can be successful though periodic surveillance is necessary.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.
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