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Review article

Tumor-induced osteomalacia

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ABSTRACT

Tumor-induced osteomalacia (TIO), also known as oncogenic osteomalacia, is a rare paraneoplastic syndrome characterized by hypophosphatemia resulting from decreased tubular phosphate reabsorption, with a low or inappropriately normal level of active vitamin D. The culprit tumors of TIO could produce fibroblast growth factor 23 which plays a role in regulating renal Pi handling and 25-hydroxyvitamin D 1α-hydroxylase activity. Chronic hypophosphatemia could eventually lead to inadequate bone mineralization, presenting as osteomalacia. The diagnosis should be considered when patients manifest as hypophosphatemia and osteomalacia, or rickets and needs to be differentiated from other disorders of phosphate metabolism, such as the inhereditary diseases like X-linked hypophosphataemic rickets, autosomal dominant hypophosphataemic rickets, autosomal recessive hypophosphataemic rickets and acquired diseases like vitamin D deficiency. Localization of responsible tumors could be rather difficult since the vast majority are very small and could be everywhere in the body. A combination of thorough physical examination, laboratory tests and imaging techniques should be applied and sometimes a venous sampling may come into handy. The technology of somatostatin-receptor functional scintigraphy markedly facilitates the localization of TIO tumor. Patients undergoing complete removal of the causative neoplasm generally have favorable prognoses while a few have been reported to suffer from recurrence and metastasis. For those undetectable or unresectable cases, phosphate supplements and active vitamin D should be administrated and curative intended radiotherapy or ablation is optional.

1. Introduction

Tumor-induced osteomalacia (TIO) is clinically featured by bone pain, proximal muscle weakness, height loss, and multiple fractures. The first case was described by McCance in 1947 [1], however the relationship between tumors and osteomalacia was not revealed until 1959 [2]. With the progress in radiological technology and better understanding of the disorder, more and more cases were reported in the past several decades, including both the newly diagnosed ones and corrections of misdiagnosed ones. TIO is sort of diseases apt to be misdiagnosed or undiagnosed [3,4]. In a retrospective study of 144 patients, the initial misdiagnosis rate was 95.1% with the most common misdiagnoses were intervertebral

disc herniation, spondyloarthritis and osteoporosis [3]. It could be attributed to the atypical clinical manifestations during the first consult, insensitive or inadequate auxiliary examinations and physicians' lack of knowledge of this disorder. In this review we will discuss the pathogenesis, molecular mechanism and clinical presentations of TIO. The methods to facilitate the localizations of the responsible tumors and their pathologic features will also be covered to better assist the diagnosis and management of the disease.

2. Epidemiology

About 500 cases of TIO have been reported worldwide till now whereas no population-based epidemiological study of has not been conducted [5–10]. On the basis of the published case reports, the average age of diagnosis is 40–45 years indicating that adults may be more vulnerable to this disease. Rare though more than ten children cases were described with the youngest being 9-month-old [11]. Hypophosphatemia could lead to severe damage to their

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physical growth if not managed well, thus emphasizing the importance of TIO differential diagnosis when related symptoms appear in younger population. No sex differences or ethnic differences have been observed.

3. Clinical description and evaluation

3.1. Clinical manifestations

Manifestations vary in TIO patients but typical symptoms generally include: pain, short hand, muscle weakness, and gait disturbance, which are similar to that described by McCance in 1947 firstly in a 15-year-old female [1]. Bone pain was the most commonly reported symptom and often started from lower limbs [3]. Height loss could also be observed in more than 50% of the patients [3,6]. Pathological fractures were most commonly reported to occur at vertebrae, ribs, femurs and the pelvic [3] and constituted a major cause of morbidity associated with TIO [12].

In a retrospective study of 144 cases, local lumps of 21 patients (14.6%) were proved to be responsible tumors [3] of TIO. For those whose tumors located in oral or maxillofacial region, a lump or obstructive symptom or bleeding resulting from the lump could be the only notable finding [13,14]. Physical examination is generally of limited value because the tumor is always small in size and difficult to detect. Thorough assessment should be conducted to avoid a missed diagnosis or misdiagnosis. It could be rather meaningful for patients to have new lumps or bumps [3,5,6]. Oral cavity is the place where should be given intensified attention to.

3.2. Biochemical abnormalities

Biochemical findings play an important role in the diagnosis of TIO. The typical biochemical pattern includes low serum phosphate, normal to low calcium, normal parathyroid hormone (PTH), low or inappropriately normal 1,25-dihydroxy vitamin D $(1,25(OH)_2D)$, normal 25-hydroxyvitamin D (25(OH)D), elevated alkaline phosphatase and elevated fibroblast growth factor 23 (FGF-23) concentrations in serum as well as normal creatinine and increased phosphate excretion in urine with tubular maximum phosphate reabsorption per glomerular filtration rate (TMP/GFR) reduction.

Systemic FGF-23 levels is an essential indicator for the diagnosis and surveillance of TIO. It could be measured in 2 formats of enzyme-linked immunosorbent assays: a C-terminal assay measuring both full-length and cleaved C-terminal fragment of FGF-23 [15] and intact assays of FGF-23 (iFGF-23) [16] recognizing N-terminal and C-terminal potion of the processing sites of FGF-23 to detect only full-length uncleaved FGF-23. Though a higher sensitivity of iFGF-23 assay has been reported by Imel et al. [17] in TIO patients, some investigators preferred cFGF-23 assay for its stability. Whichever method is used [18–20], an elevated level of serum FGF-23 could be observed in the majority of TIO patients while the iFGF-23 levels ranged from 44.1 to 14 922.3 pg/mL as reported [16,21,22]. A rapid decrease was reported after successful removal of the offending tumor [6,9] in a number of literature, among which the shortest time interval was 2 h [21], which was exactly the half-life of FGF-23 in humans [23]. A case in 2004 reported an undetectable serum iFGF-23 level (<8 pg/mL) after the operation [24]. The detection limit of the measuring method used then was proposed as a possible explanation. Whether the physical production of FGF-23 was suppressed as a negative feedback to the pathogenic status in TIO patients needs to be clarified by further research. If the level persists or it increases again in the follow-up, it warns that an incomplete resection or a relapse exists.

As a part of the hypophosphatemia osteomalacia disease spectrum, TIO should be differentiated from others including both inherited forms and acquired ones. The former may include X-linked hypophosphatemic rickets (XLH), autosomal dominant hypophosphatemic rickets, and autosomal recessive hypophosphatemic rickets, while the latter consists of vitamin D deficiency, phosphorus deficiency and severe Fanconi syndrome. They may present with a rather similar phenotype to TIO. A positive family history would be a strong indicative of inherited hypophosphatemic disorders but a negative one cannot exclude the possibility. Levels of serum FGF-23 is of usefulness. In a cross-sectional study in Japan [22], hypophosphatemic patients with excess FGF-23 production (TIO and XLH) showed higher serum FGF-23 levels than those with other causes such as vitamin D deficiency and Fanconi syndrome, and there was no overlap between these two ranges. Due to the limitation of the amount of the samples, a combination of serum PTH, $1,25(OH)_2D$, 25(OH)D as well as urinary calcium and phosphorous should be taken into consideration in clinical practice for differential diagnosis [25]. Besides, when Fanconi syndrome is suspected, arterial blood gas, serum and urine levels of sodium, potassium, chloride, bicarbonate, and immunoglobulins in addition to urine levels of amino acids should also be measured [26].

3.3. Imaging performance

Adults with osteomalacia and children with rickets could demonstrate vertebral double concave deformation, pseudofractures and pelvis deformities in skeletal radiography and decreased bone mineral density in dual energy X-ray absorptiometry (DXA). Microstructural alternations in TIO patients assessed with high resolution peripheral quantitative computed tomography (HR-pQCT) have not been reported yet. Studies are urged to fill this knowledge gap. Given the outstanding performance of HR-pQCT in detecting delicate bone architecture changes, we could expect a higher detection rate and more individualized management of TIO. Pathogenic tumors of TIO are often small and exist within bone, making them difficult to detect with general radiological methods. Thus a stepwise procedure combining functional and anatomical tests is of value.

3.4. Tumor pathology

TIO had been perceived to be caused by a number of mesenchymal tumors such as hemangiopericytoma (HPC), osteosarcoma, giant cell tumor, and others [5] until Evans and Azzoparidi [27] raised in 1972 that TIO-associated tumors were morphologically distinctive and possibly represented a characteristic type. In 1987 Weidner and Santa Cruze [28] described them with the name phosphaturic mesenchymal tumors (PMT). Folpe et al. [5] brought up the idea that these tumors were a single histopathologic entity and expanded the notion as PMT mixed connective tissue variants. Features were "low cellularity, myxoid change, bland spindled cells, distinctive 'grungy' calcified matrix, fat, HPC-like vessels, microcysts, hemorrhage, osteoclasts, and an incomplete rim of membranous ossification" which were proved by subsequent studies. The World Health Organization defined PMT in 2013 Classification of Tumors of Soft Tissue and Bone as "morphologically distinctive neoplasms that produce tumor-induced osteomalacia in most affected patients, usually through production of fibroblast growth factor 23."

PMT could be seen in wherever the soft tissue and bone tissue is theoretically. The most common sites include extremities and acral sites but soft tissue organs like the liver or heart have not been reported to be involved yet [3,5,6,14,29]. Rarely PMTs present as multifocal disease [30–33].

PMTs are characterized by prominent vascularity and aggregation of bland spindle-shaped to stellate-shaped cells which could produce "groungy" calcified matrix [5,6,27,28]. Osteoclast-like giant cells could often be seen in it [5,6,27,28]. However, individual PMT has shown great diversity in cellularity, vascularity and matrix composition. The broad morphological spectrum obviously accounted for the misdiagnoses in the past and demonstrates the limited value of traditional immunohistochemical tests in the diagnosis of PMT.

Similar to other mesenchymal tumors, PMTs also express somatostatin receptors [34,35], which enables us to locate them with the use of somatostatin-receptor (SSTR) imaging. But it is not specific to make a pathological diagnosis by detecting SSTR on PMTs.

FGF-23 is a typical marker of PMTs. Most PMTs express FGF-23 both at mRNA [36,37] and protein level [5]. TIO is thought to arise from the overproduction of FGF-23 [38] which plays a role in inhibiting renal reabsorption of phosphate [39] and synthesis of active vitamin D [40,41]. The diagnostic significance of FGF-23 has been gradually recognized considering the difficulty in making a diagnosis merely in histopathological method due to the broad morphological spectrum of PMTs. The specificity of FGF-23 detection is more depended on the methods since non-PMT bone tumors could express FGF-23 mRNA as well [42,43]. Assays having been reported are reverse transcription-polymerase chain reaction (RT-PCR) to detect FGF-23 mRNA [5,43], immunohistochemical staining [44] and RNA scope Chromogenic *in situ* Hybridization (CISH) [36]. RT-PCR is a method with high sensitivity but low specificity and even a very low level of FGF-23 mRNA expression in non-PMT bone tumors could be detected, making it difficult to distinguish with chondromyxoid fibroma, myxoid liposarcoma and aneurysmal bone cyst [44]. Immunohistochemical staining, showed a sensitivity of more than 70% and 100% specificity for PMTs in studies of the Shiba et al. [44] and Yamada et al. [37], respectively. The definition for "positive staining" is crucial in these studies. Folpe and his colleagues had reported a much lower specificity since they scored diffuse cytoplasmic staining as positive which was abandoned in the research of Shiba et al. [44]. Antibodies remain another concern. Commercially available FGF-23 antibodies are generally not specific and reliable enough to diagnose PMT. The RNA scope CISH is a preferred technique with better specificity and sensitivity (100% and 96% respectively as reported). The RNA scope methodology limits nonspecific signals and CISH allows preservation of tissue architecture and direct visualization of reactivity in the neoplastic cells. It matters a lot in distinguishing the real positive FGF-23 neoplastic cells from normal osteocytes and osteoblasts which cannot be obtained by using conventional PCR-based techniques.

Several studies have shown that mesenchymal tumors with morphological features of PMT and demonstrable levels of FGF-23 but without known TIO could occur [29,37]. Some referred to them as "non-phosphaturic" variant of PMT. The possible explanations are: (1) The responsible tumors were found in the primary stage of the disease before any clinical manifestations of osteomalacia; (2) The levels of FGF-23 were elevated but not enough to cause clinical syndrome. RT-PCR may come into play in view of its highly proved sensitivity to test the little expression of FGF-23 mRNA in PMTs without TIO.

Besides FGF-23, expressions of fibroblast growth factor receptor 1 (FGFR1) and other matrix-associated proteins have been demonstrated such as dentin matrix acidic protein 1, matrix extracellular phosphoglycoprotein (MEPE), and secreted frizzled-related protein 4 [45—48]. But their exact effects in TIO have not been found out. Cases with typical PMTs, severe osteomalacia but normal systemic FGF-23 levels were described [49,50]. The CISH

study showed a TIO patient with a FGF-23 mRNA negative PMT as well. It indicates that some other phosphatonins secreted by PMTs may play a role in the development of TIO.

The overwhelming majority of PMTs are benign but a few cases have been reported [5,51,52] to be caused by malignancy. The malignant PMTs showed features such as high cellularity, evident nuclear atypia and necrosis [5,37]. Recurrence and metastasis could be seen even after surgical resections and lungs as well as bones are the most frequent involved metastatic sites [5,10,53]. Distant lung metastasis has also been reported to be witnessed with a histologically benign PMT [53,54]. PMTs can present as paraneoplastic syndrome of carcinoma as well, relative reports involving ovarian cancer [55], prostate cancer [56], colon cancer [57] and lung cancer [58].

3.5. Pathophysiology

Phosphate is vital in normal physiological functioning, playing a critical role in intracellular signaling, membrane function, energy metabolism and bone mineralization [59]. Acute reductions of phosphate in serum could result in myopathy, dysfunction of heart [60], neutrophils and platelets and red cell membrane fragility [61] while chronic phosphate insufficiency leads to defective bone mineralization, osteomalacia and rickets if the condition grows before growth plate closure [62].

Systemic phosphate homeostasis is regulated by the cooperation of intestinal uptake, retention and release of bone and renal reabsorption. There are sodium-dependent [63] and independent pathway [64] for intestinal phosphate absorption, and the relative significances of them are different depending on phosphate intake. After being absorbed alongside the whole intestine with small intestine accounting for a larger part, most phosphate is stored in bone. A small portion circulating in extracelluar fluid is filtered by glomerulus and then gets reabsorbed through type II sodium dependent phosphate transporters Na-Pi 2a and Na-Pi 2c in proximal renal tubule prevailingly in a physiological state [65]. PTH, FGF-23, and $1,25(OH)_2D$ are three main hormones functioning in the regulatory work of phosphate homeostasis.

Phosphatonins were found in 1994 from tumor cell cultures of a TIO patient by Cai et al. [66] and were named for their role in the regulation of renal phosphate wasting the same year by Econs and Drezner [67]. Such phosphatonins as FGF-23, FGF-7, MEPE, and sFRP-4 were discovered by subsequent work [39,59,68,69].

As a typical example of phosphatonins, FGF-23 has been demonstrated to be overexpressed in most PMTs and been studied from various aspects. It is regarded as the key factor in the pathogenesis of TIO [38] whereas the exact function of other phosphatonins have not been identified because they merely expressed in several TIO patients in an unknown pattern. Produced by bone, FGF-23 works by binding to Klotho-FGF receptor complex (Fig. 1) [70]. It reduces the expression levels of Na-Pi 2a and Na-Pi 2c (Fig. 1) [40], resulting in inhibiting phosphate reabsorption of proximal tubular. It suppresses the expression of 25-hydroxyvitamin D-1α-hydroxylase but enhances the expression of 25-hydroxyvitamin D-24-hydroxylase [40] leading to decreasing serum $1,25(OH)_2D$ thus generally inhibits the phosphate absorption work of intestine [40]. Given the above, the overproduction of FGF-23 from PMTs enhances phosphate wasting both in kidney and intestine and causes chronic hypophosphatemia which eventually contributes to an osteomalacia or rickets.

The identifications of FN1 (encoding gene of fibronectin [FN])-FGFR1 (encoding gene of FGFR1) [71,72] translocations and FN1-FGF1 (encoding gene of FGF1) translocations [72] in a series of PMTs are possibly the milestone pathophysiological findings in the research of TIO. According to the published data, FN1-FGFR1 fusion
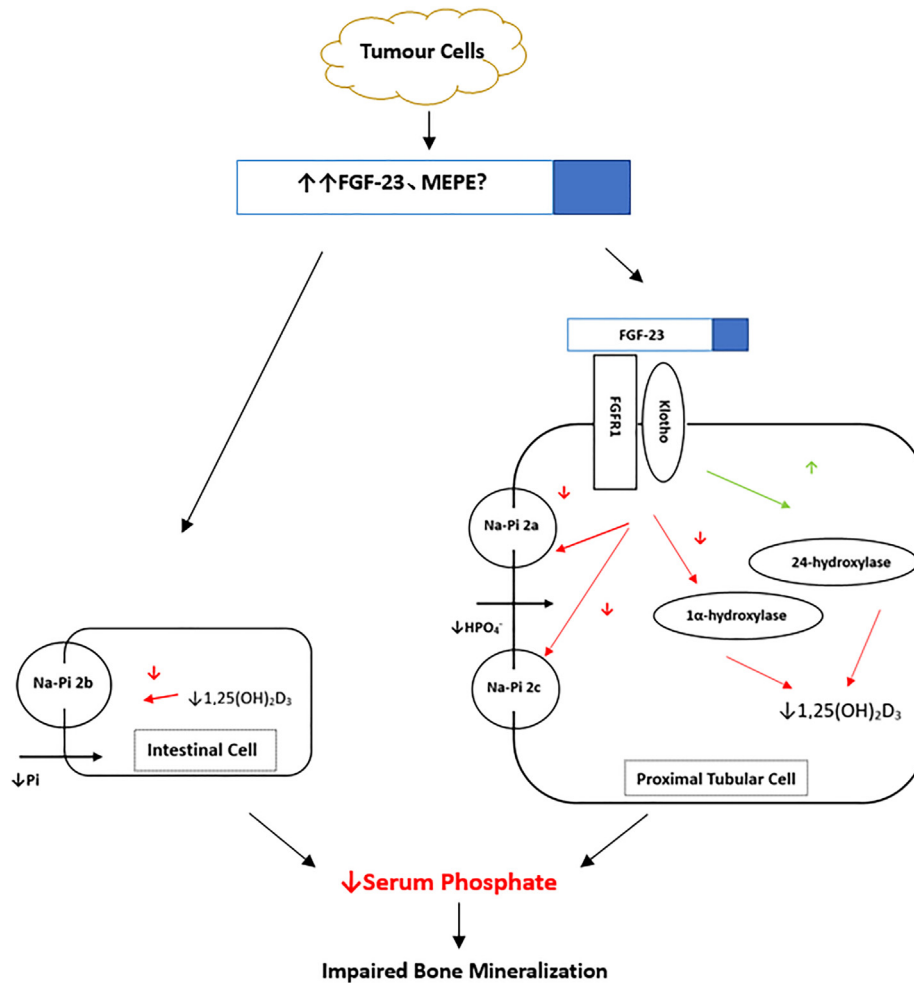
Fig. 1. Mechanism of tumor-induced osteomalacia. FGF-23, fibroblast growth factor 23; MEPE, matrix extracellular phosphoglycoprotein.

genes have been showed in 42% (21/50) PMTs [72] which supports the idea that PMTs are a single histopathological entity with a broad spectrum of morphological features [5]. The chimeric genes encode correlated chimeric proteins, which are supposed to preserve the ligand-binding domain of FGFR1. The activation of the domain causes abnormally increased FGFR1 signaling and FGF-23 over-expression which consequently further enhances the activation of the fusion receptor, forming an autocrine/paracrine circulation to lead to tumorigenesis. Another interesting finding is there showing minimal expression of Klotho which is obligatory for FGF23-FGFR1 binding in PMTs having FN1-FGFR1 translocations [71]. It may be explained by the invigorating effect the fusion proteins exerted on their binding affinity to FGF-23 [71,72].

FN1-FGF1 fusion genes were demonstrated in 6% (3 of 50) PMTs [72], all originating from PMTs without FN1-FGFR1 infusion. It is hypothesized that FN1-FGF1 and FN1-FGFR1 infusions might be exclusive mutually. Since FGF1 is crucial for all FGFRs [73,74] and the fusion protein contains almost the entire FGF1, the correlated infusion protein was expected to work like normal FGF1 and to play a role in the activation of FGFR1 signaling to form a circulation.

Hypoxia-inducible factor-1α (HIF-1α) is another new finding which was shown to be coexpressed in tumors from 2 TIO patients [75]. The treatment with HIF-1α inhibitors has demonstrated decreasing effects in the accumulation of HIF-1α and FGF-23 as well as the activity of FGF-23 promoter luciferase *in vitro*. It is indicative of the direct transcriptional activator role HIF-1α plays in the

activity of FGF-23. In spite of the limited cases, these results suggest that the upregulation of HIF-1α in PMTs contributes to the excessive activity of FGF-23 in TIO is worthy of further explorement.

4. Update of tumor localization for TIO

A stepwise method combining functional and anatomical imaging is recommended for the localization of TIO. Commonly, the entire body [76] functional imaging tests should be conducted first, which include SSTR imaging − Technetium [99]m octreotide with single photon emission computed tomography (octreo-SPECT), ^{111}In-octreotide with SPECT [77] and positron emission tomography/computed tomography (PET/CT) using ^{68}Ga-radiolabeled DOTA-conjugated peptide including DOTATOC [78], DOTANOC [79] and DOTATATE [80]-Technetium [99]m sestamibi scintigraphy and F-[18]fluorodeoxyglucose PET/CT ([18]FDG-PET/CT). TIO associated tumors express a series of somatostatin receptors (SSTRs) [34,35], making it practical to better locate the tumors with the use of SSTR imaging according to cases available now. [68]Ga DOTATATE PET/CT has been demonstrated to be superior to octreo-SPECT [81] and the possible reasons are: (1) ^{68}Ga DOTATATE has a higher affinity for SSTR type 2 and type 5 than octreotide [82]; (2) PET has a better spatial resolution than SPECT; thus being recommended by some to be the first option for PMT localization. In a retrospective study conducted in Peking Union Medical College Hospital, ^{68}Ga DOTATATE PET/CT was proved to have a 97.7% (42 of 43) overall accuracy

[83], a much higher rate than other established radiological detection modalities. Given that ^{68}Ga DOTANOC has an affinity for SSTR type 2, type 3, and type 5, it could be anticipated that ^{68}Ga DOTATATE shows a prominent sensitivity in TIO tumor localization as it has shown in locating neuroendocrine tumors. Technetium [99]m sestamibi scintigraphy and [18]FDG-PET/CT are both based on the metabolic activity of neoplastic tissue and showed not as good overall sensitivity and specificity as SSTR imaging did [80]. [18]FDG-PET/CT may sometimes reveal the tumor sites negative on SSTR imaging whereas sestamibi scintigraphy was probably the least accurate one and was gradually deprecated [84].

Once lesions are indicated on functional imaging, anatomical imaging tests ought to be done to confirm them. Radiography, ultrasound, CT and MRI are options. Generally, CT and MRI are of advantage because of their high resolution but there are few studies concerning the features of PMTs on CT or MRI.

5. Venous sampling

Venous sampling with measurement of FGF-23 is based on the assumption that the responsible tumor is the major or only source of FGF-23 in the patient [24]. It is utilized to identify the exact focus when there are more than one suspicious site of responsible tumors on image or when the imaging tests show no positive hints. A study of 14 cases with selective venous samplings has reported a sensitivity of 0.87 (95% confidence interval [CI], 0.47–0.99) and a specificity of 0.71 (95% CI, 0.29–0.96) [85]. A 2-staged venous sampling without positive imaging indications was conducted in a European case and the responsible tumor was finally located [86]. Though a blind venous sampling is advocated, the majority of venous samplings up to present have been performed on the basis of positive imaging tests, either functional or anatomical possibly because of concerns for the potential injuries occurred in the inserting of a catheter into a vein.

Despite all the advances in the investigations for diagnosis today, there are a portion of results being negative. Imaging should be repeated every 1–2 years in hopes that tumors may get evident to locate over time.

6. Clinical management and current treatments and response

6.1. Surgical treatment

Surgical removal is the best treatment for TIO patients whose pathogenic tumors could be located. Statistics from our hospital showed that total hip and lumbar spine bone mineral density of patients after surgeries were increased by 30.9% and 49.3%, repsectively while in the drug therapy group the increase were 12.9% and 8.7% after a 6-month follow-up. It reflected a far better outcome with complete excision. Since PMTs mostly locate in bone and soft tissue and complete resection may lead to articular or limb dysfunction, tumor curettage is another surgical choice and was suggested to be done with at least 5 mm from tumor margins. A retrospective study comparing the outcome of 40 TIO patients with extremity tumors receiving resections or curettages showed that tumor resections result in a lower rate of recurrence [7]. If curettage is incomplete or a recurrence is observed, a secondary excision ought to be considered. Serum phosphate and FGF-23 returned to normal over time in most cases after surgeries. Clinical complaints got alleviated, too [6–8,12,84,87]. For whose serum phosphate was low and FGF-23 was high still, residual should be alerted for. In this aspect, changes of FGF-23 appear to be more sensitive than serum phosphate [12,87] and more studies are needed to identify it.

6.2. Radiotherapy and ablation

Ablative therapy is less invasive compared to surgery and causes fewer side effects compared to current medical treatments like phosphorus and calcitriol supplementation. It is a process using heat (microwave, ultrasound, laser, or radiofrequency), cold (cryoablation) or chemical agents (percutaneous ethanol instillation) to destroy tissues, performed under the guidance of multimodality imaging such as ultrasound and CT augmented by fusion of MRI, [18]FDG-PET/CT or ^{68}Ga DOTATATE PET/CT with hollow needles. Ablation occurs through the mechanisms of direct cell injury, interrupting the blood supply and induction of apoptosis at least. It is used when the patients are not willing or qualified to undergo surgeries or added as an adjuvant therapy when the margins of tumors cannot be guaranteed to avoid recurrence [88]. Present case reports demonstrated prominent curative effects with biochemical resolution and clinical improvement after ablation of the tumor using radiofrequency, cold and ethanol [88–91] while long-term efficacy remains to be seen for the lack of follow-up data. The main adverse reaction is pain caused by frictional heating by radiofrequency ablation however similar reactions have not been reported in cases with other tools.

6.3. Medical treatment

When tumors cannot be located or a complete excision cannot be performed, it is necessary to manage TIO patients with medicine. If the low serum phosphate and symptoms of osteomalacia persist after surgery, replacement therapy is suggested [92]. The basic medications for TIO include phosphate and active vitamin D (calcitriol or alphacalcidiol) supplements [93]. In our experience, the general dose of calcitriol or alphacalcidiol is 0.5–1.0 μg/d, while for phosphate the dose is 1- to 4-g elemental phosphorus divided into 4–6 times per day. Patients are suggested to take biochemical examinations every 3–6 months and a DXA every year. The therapeutic goals are to increase the serum phosphate to the lower limit of normal range to alleviate clinical symptoms and to control serum ALP levels. Side effects of these therapies involve nephrolithiasis, nephrocalcinosis, impaired renal function and secondary/tertiary hyperparathyroidism [92,94,95], thus necessitates close follow-up. The baseline renal ultrasound, serum calcium, serum phosphate, PTH, urinary calcium and creatinine need to be kept. Biochemical tests should be performed every 3 months and therapy must be adjusted according to the results.

Cinacalcet is a kind of calcimimetic and was proposed to be used in patients who are intolerable of phosphate and 1,25(OH)2D supplementation [96]. Decreases in serum PTH and sustained increases in tubular resorption of phosphate were observed [96]. However both 2 patients receiving cinacalcet developed evident hypercalciuria [96].

Efficacy of somatostatin receptor-based therapy with octreotide is controversial. Different reports reported quite opposite results. The phosphate levels were normalized in a 50-year-old man with a PMT in 2001 [97] while in another case series no significant changes in blood indexes had been found [98]. Two possible explanations were proposed. First, the levels of SSTRs in culprit tumors are insufficient for their agonists to normalize the blood indexes even merely the serum phosphate, 2 different pathogenic tumors of TIO may be regulated by different intercellular pathways [99]. The application of octreotide therapy in malignant TIO tumors and a combination with radionuclide [100] may shed lights on the future utility of it.

Considering the role of FGF-23 in the pathogenesis of TIO, inhibiting FGF-23 actions provides new sights into treatment, which might be realized by FGF-23 antibodies, FGF receptor

inhibitor and suppresser of the downstream signaling from Klotho-FGF receptor complex [101].

Compared to other 2 potent treatments, FGF-23 antibodies have been better studied. Firstly used in adult patients with XLH, the randomized trial of KRN23 (a kind of FGF-23 antibody) showed a positive effect on serum phosphate and favorable safety profile [102—104]. The advance in treatment of XLH will likely benefit other FGF-23-mediated hypophosphatemic disorders. A phase 2 study in TIO patients is under way.

Moreover, the inhibition of FGF receptor has shown its efficacy in suppressing FGF-23 activity [105]. The pan FGF receptor inhibitor NVP-BGJ398 was demonstrated to elevate serum phosphate levels, improve bone formation, correct growth plate organization and ameliorate mineralization in Hyp mice. The recent identification of the causative fusion protein of FN-FGFR1 resulting from the FN1-

FGFR1 translocations [71,72] further evidenced such potential. PD0325901, the inhibitor of mitogen-activated protein kinase (MAPK), which is one of the downstream signals activated by FGFR has showed the capacity to increase serum phosphate and 1,25(OH)$_2$D in Hyp mice [106], too. Even the effect of FGFR inhibitor and downstream signaling suppressor have not been proved in TIO or other FGF-23 related hypophosphatemic disorders, they offer new sights for our clinical practice in inoperable TIO patients.

As a rare paraneoplastic syndrome, TIO is mostly a devitalizing but curable disease. Not only physicians but also pathologists and radiologists should have a comprehensive image of it so that the diagnosis rates particularly the early metaphase diagnosis rates and the cure rates could be increased. Here we offer a flowchart (Fig. 2) of TIO diagnosis and treatment for reference. We have strong reason to believe that our improving understanding of the
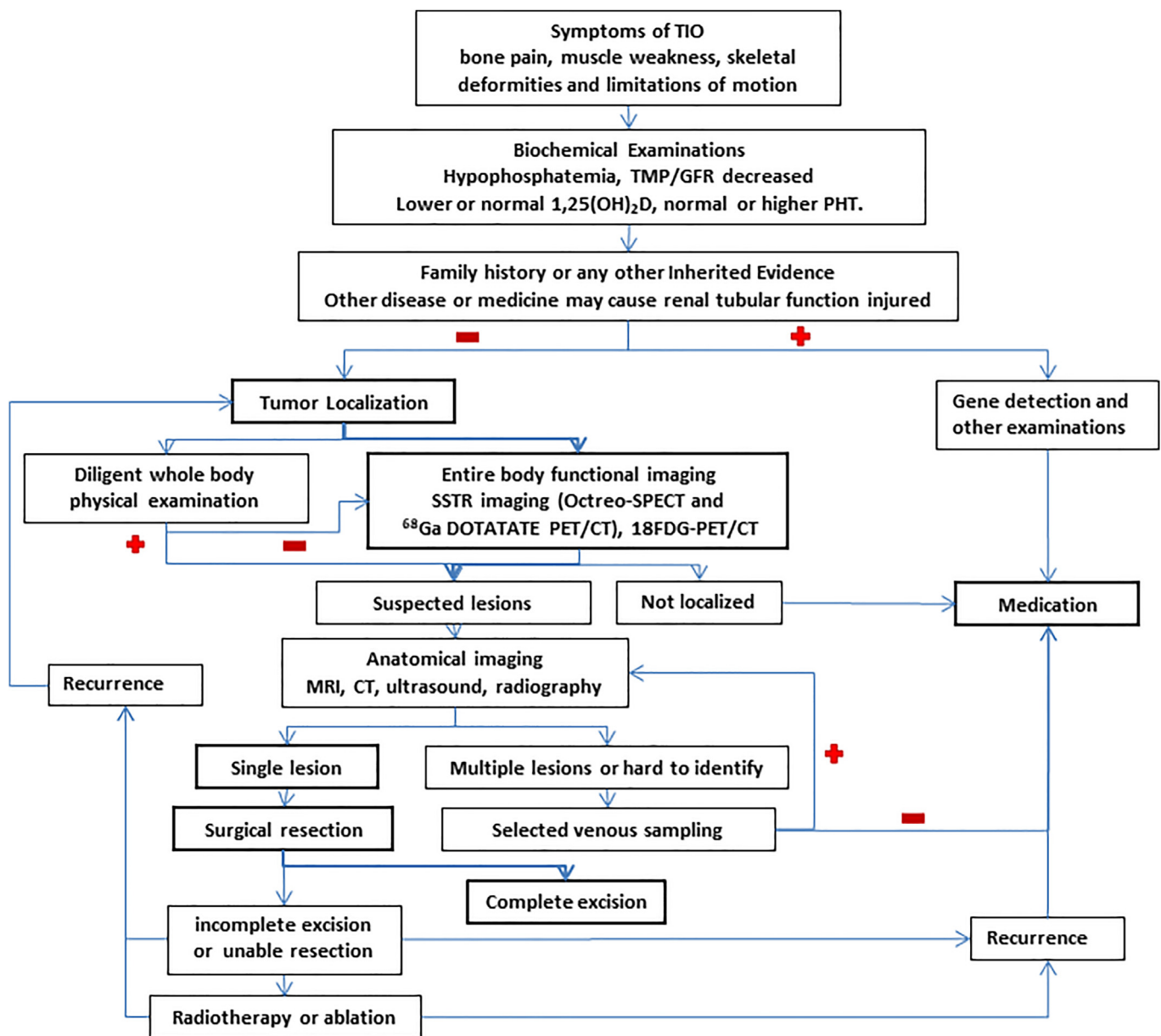

Fig. 2. Flow chart of tumor-induced osteomalacia diagnosis and treatment. TIO, tumor-induced osteomalacia; TMP/GFR, tubular maximum phosphate reabsorption per glomerular filtration rate; PTH, parathyroid hormone; SPECT, single photon emission computed tomography; PET/CT, positron emission tomography/computed tomography; MRI, magnetic resonance imaging; CT, computed tomography.

pathology and molecular pathogenesis behind it will hold great promises for new diagnostic and treatment modalities though more research and trials are to be done.

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

Acknowledgments

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