Chinese Medical Journal®

Consensus on clinical management of tumor-induced osteomalacia

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Tumor-induced osteomalacia (TIO) is a rare paraneoplastic syndrome caused by excessive fibroblast growth factor 23 (FGF23) production by a tumor, which often arises from a mesenchymal origin.[1-3] Most clinical symptoms of TIO are the consequences of prolonged FGF23-mediated hypophosphatemia as muscle weakness, bone pain, impaired mobility, and fractures.[4] Clinical diagnosis and management of TIO are challenging because knowledge about this condition is still restricted to a few specialized centers, leading to delay in diagnosis and appropriate treatment. The scope of the present consensus is to provide up-to-date guidance on the assessment and treatment of TIO. The writing committee consists of experts representing endocrinology, pathology, radiology, nuclear medicine, orthopedics, stomatology, and rhinology departments. From the evidence, especially high-quality evidence is limited or even non-existent for this rare disease; we provide recommendations based on expert's review on the limited data, as well as their experiences and opinions when data are unavailable. This process may be less systematic than the grade methodological framework; however, it is unrealistic to gather more reliable evidence without an international consensus to promote standard management of TIO. All participants signed a conflict of interest declaration, and the consensus was strictly supported by funding from academic or professional societies only, with no sponsorship from the pharmaceutical industry. The details of consensus on clinical management of TIO are shown in Supplementary Material, http://links.lww.com/CM9/A506.

Access this article online	
Quick Response Code:	Website: www.cmj.org
	DOI: 10.1097/CM9.0000000000001448

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Chinese Medical Journal 2021;Vol(No)
Received: 11-01-2021 **Edited by:** Li-Shao Guo

Diagnosis

The diagnosis of TIO is based on the association of clinical manifestations, biochemical findings, and the identification of the tumor (most importantly). Patients with symptoms, such as bone pain, weakness, and/or radiological signs of osteomalacia like obscure bone structure, concave changes of vertebrae, inward bending of the pelvic sidewall, and pseudofracture (Looser zone), should be suspected as TIO.[4-6] Suspected patients should have further tests. Decreased serum phosphate, tubular maximum reabsorption of phosphate/glomerular filtration rate, low or inappropriately normal 1,25-dihydroxyvitamin D (1,25 $(OH)_2D$) levels, and elevated alkaline phosphatase (ALP) accompanied with elevated FGF23 are typical laboratory findings. Besides, inherited disorders or other acquired causes of hypophosphatemic rickets/osteomalacia should be excluded at the very beginning of the diagnosis.[2]

If clinical features, laboratory findings, and radiological results hint a diagnose of TIO together, a stepwise approach to locate the causative tumor is widely recommended since tumors are usually small, slow-growing with unexpected locations over the whole body.[1,2] The first step is to screen the whole body for suspected lesions. This step comprises a thorough inquiry and physical examination, as well as functional imaging. The somatostatin receptor imaging method is recommended as a first-line imaging investigation, which comprises ^{68}Ga-DOTA-conjugated-somatostatin-receptor-targeting-peptides positron emission tomography/ computed tomography (CT) scan and octreoscan with single-photon emission computed tomography/ CT. Once the TIO tumors are suspected by functional imaging or physical examinations, the next step is to confirm the lesions by anatomical imaging. Based on different sites of suspected masses, techniques including radiography, magnetic resonance imaging (MRI), CT, or ultrasound may be used. When accessible, MRI and CT are recommended because of their advantage in high resolution. Selective venous sampling may be useful to confirm causative tumors in patients with multiple suspicious regions. For patients who fail to locate the tumor, we recommend to start medical therapy and repeat imaging studies within 1 to 2 years.

Pathology

The overwhelming majority of TIO-associated tumors are of mesenchymal origin. Despite its polymorphous histology, it is widely accepted that almost all TIO-associated mesenchymal tumors are caused by a single morphologically and genetically distinct neoplasm, known as phosphaturic mesenchymal tumor (PMT).[7] Most PMTs present as nonspecific soft tissue or bone masses and typically produce a characteristic "smudgy" matrix that calcifies in a peculiar "grungy" or flocculent fashion.

Management and Treatment

Surgery

We recommend that surgical treatment is the first-line therapy when feasible. From the surgical perspective, the optimal treatment for TIO involves the complete removal of the disease-causing tumor.[8] In most cases, this procedure can correct biochemical abnormalities and accelerate the process of bone remineralization. However, even a small amount of tumor tissue remains, the patient's symptoms continue to present or relapse easily. We recommend that non-remission and recurrent patients should repeat the diagnostic work-up to exclude other diseases and re-located causative tumor and receive reoperations when possible.[9]

Medical treatment

We recommend that inoperable patients should initiate medical therapy to alleviate symptoms, and biochemical tests should be monitored every 3 to 6 months. Burosumab or phosphate with active vitamin D should be the first consideration when accessible.

The therapeutic goal of conventional medical treatment is to alleviate clinical symptoms, increase the serum phosphate levels, normalize ALP, and maintain parathyroid hormone (PTH) in the normal range. Complete normalization of serum phosphate usually represents an overdose. We recommend a dose of 20 to 40 mg/kg daily (1–3 g/d for adults) of element phosphate and a dose of 20 to 30 ng/kg daily (0.5–1.5 μg/d for adults) of calcitriol. The equivalent dosage of alphacalcidol is 1.5 to 2 times that of calcitriol. Phosphate supplements should be divided into 4 to 6 doses/d and titrated to the target dose over several days to weeks. Renal function, serum calcium, phosphate, ALP, PTH, and 24-h urinary calcium should be monitored every 3 to 6 months to adjust the medical dosage to prevent complications including secondary or tertiary hyperparathyroidism, nephrolithiasis, and reduced renal function.

Burosumab, a fully human monoclonal antibody against FGF23, is the most promising drug in the near future. The recommended initial dosage of burosumab for TIO is 0.5 mg/kg once every 4 weeks; round dose to the nearest 10 mg; and maximum dosage 2 mg/kg (not to exceed 180 mg) for every 2 weeks. Dosage adjustment based on serum phosphate: evaluate fasting serum phosphate monthly, measured 2 weeks post-dose, for the first 3 months of treatment and as clinically necessary thereafter.

Radiofrequency ablation and cryoablation can be tried in patients with TIO who are neither willing nor qualified to undergo complete excision surgeries on tumors. The effectiveness of other treatments, such as FGF receptor inhibitor or cinacalcet, is still doubtful because the evidence is insufficient.

Monitoring

Upon the removal of the tumor completely, the serum phosphate levels are normalized in 5 days (2–10 days).[4] The serum $1,25(OH)_2D$ levels rise synchronously with the decrease of FGF23. For patients with complete tumor removal, biochemical parameters, especially serum phosphate, should be measured initially every 6 months and then at yearly intervals with a dual-energy X-ray absorptiometry examination. For patients who fail to locate the tumor and adopt a long-term medical treatment, the interval examinations for biochemical parameters

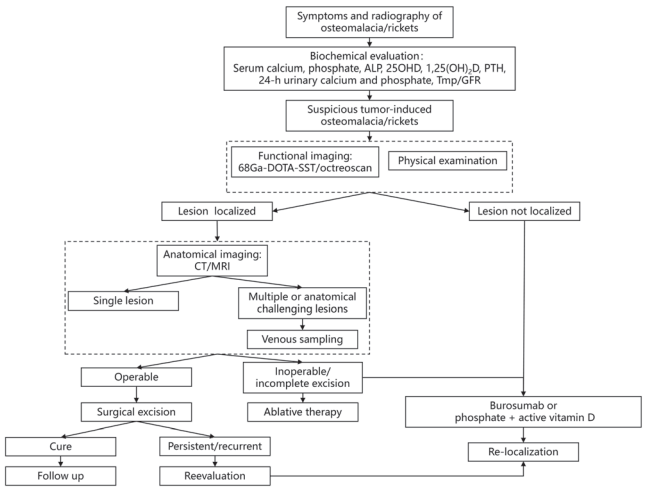

Figure 1: Diagnostic and management diagram of TIO. $1,25(OH)_2D$: 1,25-dihydroxyvitamin D; ALP: Alkaline phosphatase; ^{68}Ga-DOTA-SST: ^{68}Ga-DOTA-conjugated-somatostatin-receptor-targeting-peptides; GFR: Glomerular filtration rate; PTH: Parathyroid hormone; TmP: Tubular maximum reabsorption of phosphate; TIO: Tumor-induced osteomalacia.

should be shortened to every 3 to 6 months to adjust the drug doses and prevent the side effects.[10] The diagnostic and management diagram of TIO is shown in Figure 1.

Future Prospects

In terms of diagnosis, we need to propose some specific and easily-obtained criteria to help making suspicious diagnoses quickly in primary health care institutions. The mechanisms of tumorigenesis and FGF23 overproduction, detailed models and risk markers for stratifying severity, and refractory of TIO need to be further explored which would accurately benefit clinical management markedly. Prospective evidence of the effectiveness of novel drugs including burosumab, FGFR1 inhibitors would greatly expand treatment options of TIO in the future.

Acknowledgements

The authors deeply appreciate Prof. Seiji Fukumoto for his meticulous and insightful opinions in the process of revising the consensus. The authors thank Dr. Chen-Xi Jin, Dian-Yin Shi, Guo-Zhu Hou, Shu-Zhong Liu, Xiao-Lin Ni, and Zhen-Zhen Zhu for their indispensable contributions in developing the consensus.

Funding

This work was supported by grants from the CAMS Innovation Fund for Medical Science (No. 2016-I2M-3-003) and the National Natural Science Foundation of China (No. 81970757 and No. 81670714).

Conflicts of interest

None.

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How to cite this article: Jiang Y, Li X, Huo L, Liu Y, Lyu W, Zhou L, Yu W, Wu HW, Xing XP, Li M, Wang O, Chi Y, Jiajue RZ, Pei Y, Liu JM, Ba JM, Zhang Q, Sheng ZF, Zhang ZL, Zhao JJ, Minisola S, Xia WB; on behalf of Chinese Society of Osteoporosis and Bone Mineral Research and Chinese Society of Endocrinology. Consensus on clinical management of tumor-induced osteomalacia. Chin Med J 2021;00:00–00. doi: 10.1097/CM9.0000000000001448