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Case Report
Clinical Pathology

Maxillary tumour-induced osteomalacia

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Abstract. Tumour-induced osteomalacia (TIO) is a rare paraneoplastic form of renal phosphate wasting that results in severe hypophosphatemia, defective vitamin D metabolism, and osteomalacia. In the case reported here, maxillary TIO was not diagnosed for 6 years, although initial complaints were reported when the patient was 12 years old. Meanwhile she suffered from profound growth limitation, pain, weakness, and spontaneous multiple bone fractures, culminating in complete loss of ambulatory ability and severe limitation in daily activities. At age 18 years, she finally received an accurate diagnosis and definitive treatment was administered. She underwent a partial maxillectomy with complete removal of the tumour, resulting in a full cure. Shortly afterwards the patient regained the ability to walk, no longer needing the wheelchair to which she had been confined. This definitive diagnosis was based on three modalities: (1) fibroblast growth factor 23 analysis (high levels of the secreted hormone were found on the left side of the maxilla in the facial vein and pterygoid plexus, pinpointing the tumour location), (2) octreotide scan, and (3) ^{68}Ga-DOTA-NOC-PET/CT. TIO removal via partial maxillectomy led to a complete reversal of this patient's health condition, restoring her ability to walk and function. The importance of prompt employment of these diagnostic modalities and the high level of clinical suspicion required in such cases are clear.

Key words: tumour; osteomalacia; maxillofacial; maxilla; phosphate; alkaline phosphatase; FGF23.

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Oncogenic osteomalacia, which is also called tumour-induced osteomalacia (TIO), is a rare paraneoplastic syndrome of abnormal phosphate and vitamin metabolism. It is most often a small ectopic endocrine tumour producing the phosphaturic hormone fibroblast growth factor 23 (FGF23). FGF23 acts primarily at the renal tubule and impairs phosphate reabsorption and 1α-hydroxylation of 25-hydroxyvitamin D, leading to hypophosphatemia, low levels of 1,25-dihydroxy vitamin D, and increased serum alkaline phosphatase levels. Thus, TIO results in severe hypophosphatemia, a defect in vitamin D metabolism, and osteomalacia[1,2]. TIO is characterized by normal serum levels of calcium and parathyroid hormone and a low level of 1,25-dihydroxy vitamin D. TIO patients suffer from bone pain, spontaneous fractures, and muscle weakness[3,4]. In the maxillofacial region, tumours associated with paraneoplastic osteomalacia are usually benign phosphaturic mesenchymal tumours, although other types of tumour have also been reported[5]. However, there have been relatively few reports of such tumours in the jaw[6]. It is an accepted premise that complete excision of the tumour will rapidly improve hypophosphatemia and decrease serum levels of FGF23 to normal values[7].

FGF23 has been shown to be responsible for the development of several hypophosphatemic diseases, including X-linked hypophosphatemic rickets (XLHR) and TIO[8]. FGF23 is a circulating FGF produced by osteocytes and osteoblasts, and its excessive action causes several

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hypophosphatemic diseases, whereas deficient FGF23 activity results in hyperphosphatemic tumoural calcinosis[4].

This report describes the case of a young female whose maxillary TIO was not diagnosed for 6 years, who first presented with complaints at the age of 12 years. During this 6-year period she suffered from profound growth limitation, as well as pain, weakness, and spontaneous multiple bone fractures, culminating in complete loss of ambulatory ability and severe limitation in daily activities. The patient did not complain of anything in her oral cavity; there was certainly some degree of dental neglect, but no complaints of pain. An oral swelling was not large enough to arouse suspicion. Only when the patient was 18 years old was an accurate diagnosis finally made and definitive treatment administered. She underwent a partial maxillectomy with complete removal of the tumour, which resulted in a full cure. Shortly following removal of the maxillary tumour the patient regained the ability to walk, no longer needing the wheelchair to which she had been confined.

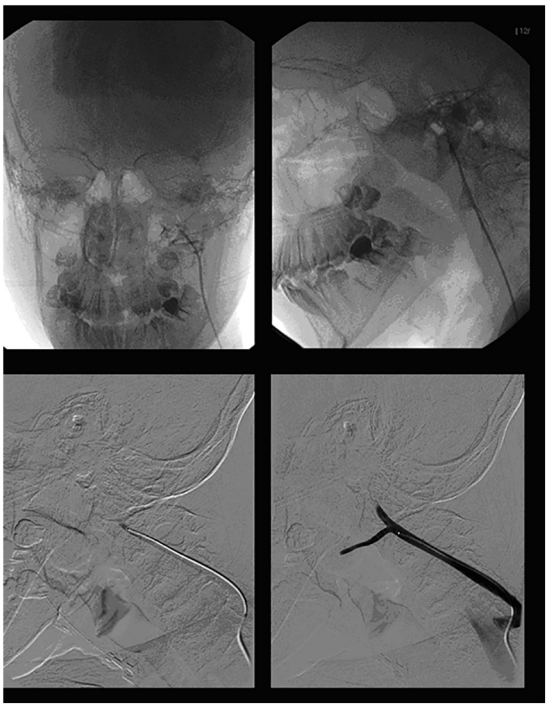

Fig. 2. Fibroblast growth factor 23 (FGF23) expression and venous sampling using selective catheterization. Venous sampling suggested a local increase in serum FGF23 in the left maxilla region, at the facial vein and pterygoid plexus, supporting the diagnosis of left maxillary tumour-induced osteomalacia (TIO).

Case report

A 12-year old female with heterozygosity for the factor V Leiden mutation but otherwise healthy was admitted for a medical examination due to complaints of growth inhibition, back and joint pain, and limping, as well as weakness, muscle ache, repeated falls, and a left wrist fracture. At that point, no definitive diagnosis was made. Two years later, at the age of 14 years, she suffered from recurrent left wrist fracture and was diagnosed with severe osteomalacia and hypophosphatemic rickets.

At the age of 15 years, her condition deteriorated further and she had bilateral hip fractures, bone pain, and severe weakness. At that point, the patient completely lost her ambulating capacity, had profound difficulties in daily living activities, and suffered from poor appetite and weight loss. Clinical examination revealed a left palatal bulge and a computed tomography (CT) scan and magnetic resonance imaging (MRI) showed a left palatal–paranasal mass. Laboratory indices revealed low 1,25-dihydroxy vitamin D and hypophosphatemia, suspicious for elevated FGF23. Genetic examinations were negative for the phosphate regulating endopeptidase homolog, X-linked (PHEX), dentin matrix protein 1 (DMP1), and ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1) genes. The therapy administered at that time included phosphate replacement therapy with calciless (dibasic sodium phosphate and

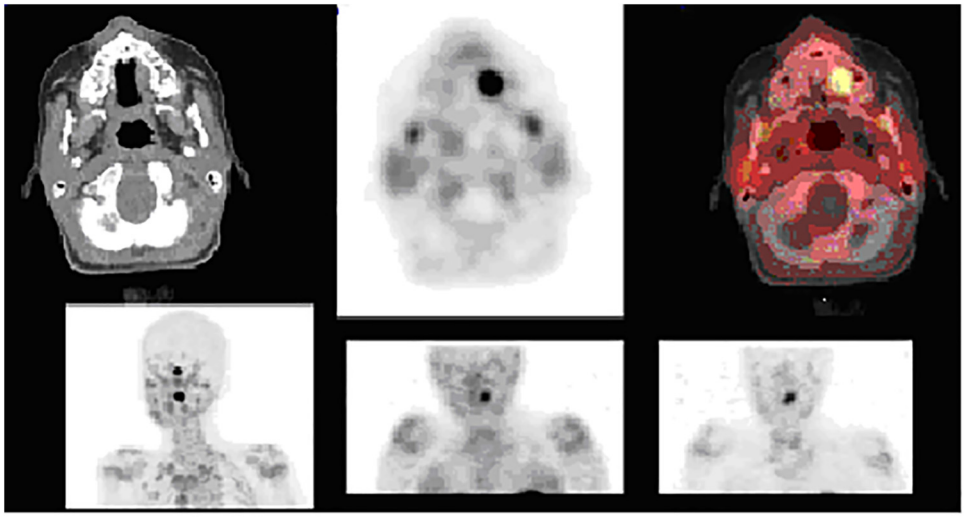

Fig. 1. ^{68}Ga-DOTA-NOC-PET/CT allowing exact tumour localization.