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Brown Tumor with Multiple Lesions as a Manifestation of Tertiary Hyperparathyroidism: A Case Report and Literature Review

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Abstract **Case Report**

Brown tumor is an uncommon focal lytic bone lesion, which is considered as an end-stage lesion of abnormal bone metabolism, caused by long-standing increased parathyroid hormone levels. It is a rare manifestation of hyperparathyroidism that is classified into three types, of which tertiary is the rarest. It can be found in any part of the skeleton, and in some cases, occurs in multiple bones and can be easily misdiagnosed as a metastatic tumor. Therefore, although uncommon, it should be generally considered as a differential diagnosis with bone malignancy lesions, and particularly in patients with renal failure on long-term hemodialysis. In the present case report, a young patient with end stage renal disease presented with tertiary hyperparathyroidism revealed by multiple brown tumors of the pelvis and mandible. We recall through this observation the importance of clinical context, the complementary roles that different imaging modalities can play in different settings, and the relevance of measuring serum calcium and parathyroid hormone before the diagnosis of osteolytic bone lesions.

Keywords: metastatic tumor, skeleton, bone malignancy lesions, hemodialysis.

INTRODUCTION

Brown tumor, also called Von Recklinghausen's osteitis fibrosa, is a benign and non-neoplastic focal lytic bone lesion that occurs in the setting of uncontrolled primary, secondary or tertiary hyperparathyroidism [1, 2]. This lesion present in only 0.1% of all cases of hyperparathyroidism [3]. The name is a misnomer derived from the color of the tumor because of its vascularity, hemorrhage and hemosiderin deposit [2]. It can appear as solitary or multiple lesions that involve any skeletal structure, mainly found in extremities, sternum, clavicle, ribs, mandible and pelvis [1, 4]. However, axial spine involvement is considered exceedingly rare [5, 6]. The diagnosis is based on medical history, laboratory investigations, specific imaging features and mostly pathological examination which is the gold standard. However, due to it being rare, the radiological findings can easily be misdiagnosed with bone malignancy lesions and may lead to wrong diagnosis [7]. Treatment depends on tumor mass and varies from a conservative approach with supportive parathyroidectomy to extensive surgical resection with subsequent reconstruction [8]. Herein, we report the case of a young patient with end stage renal failure who presented with tertiary hyperparathyroidism revealed by multiple brown tumors of the pelvis and mandible.

CASE REPORT

This is a 20-year-old male with a history of end stage chronic renal disease on a single kidney, under hemodialysis at the rate of three sessions per week. He was admitted with a 6-month history of chronic inflammatory low-back and bilateral hip pain, with difficulty in gait and walking. Sacroiliac joints and lumbar spine magnetic resonance imaging (MRI) was performed and found diffuse bone signal anomaly of all pelvic bones with trabeculated appearance in T2 hypersignal and STIR, combined with multiple well-defined iliac, pelvic and sacral cystic lesions that were hyperintense in T2 weighted images. These lesions had lobulated contours, compartmentalized and comprising hematic levels for some (Figure 1). Meanwhile, during general clinical evaluation, the patient revealed the presence of a painless right-sided swelling of the mandible causing discomfort when chewing. The clinical examination found an endobuccal lesion, hard and fixed in relation to the deep plane. Computed tomography (CT) scan of the face has been requested. Non-contrast images showed a solitary expansile osteolytic tissue mass centered on the right body of the mandible, extended to the homolateral angle, heterogeneously enhanced after injection of iodinated contrast product (Figures 2). This lesion is

encompassing tooth roots of the 44 to 48 ones, associated with cortical thinning and blowing. The right inferior alveolar nerve canal was not noted to pass through the lesion. We also noted the presence of diffuse ground-glass appearance of the skull bones, mostly marked in the sphenoid bone, possibly associated with diffuse fibrous dysplasia (Figure 3). Blood analysis revealed mildly elevated serum calcium level at 129 mg/L, reduced phosphate at 17 mg/L and markedly raised parathyroid hormone level of 779 pg/mL. Therefore, parathyroid ultrasound and 99mTc-sestaMIBI (methoxy-isobutyl-isonitride) scintigraphy were performed. Ultrasound demonstrated the presence of a left lower polar extra-thyroidal tissue formation, hypoechoic and vascularized on color Doppler images. Scintigraphy exhibited focal retention below and behind the lower pole of the left thyroid lobe, in favor of pathological parathyroid tissue (Figure 4).

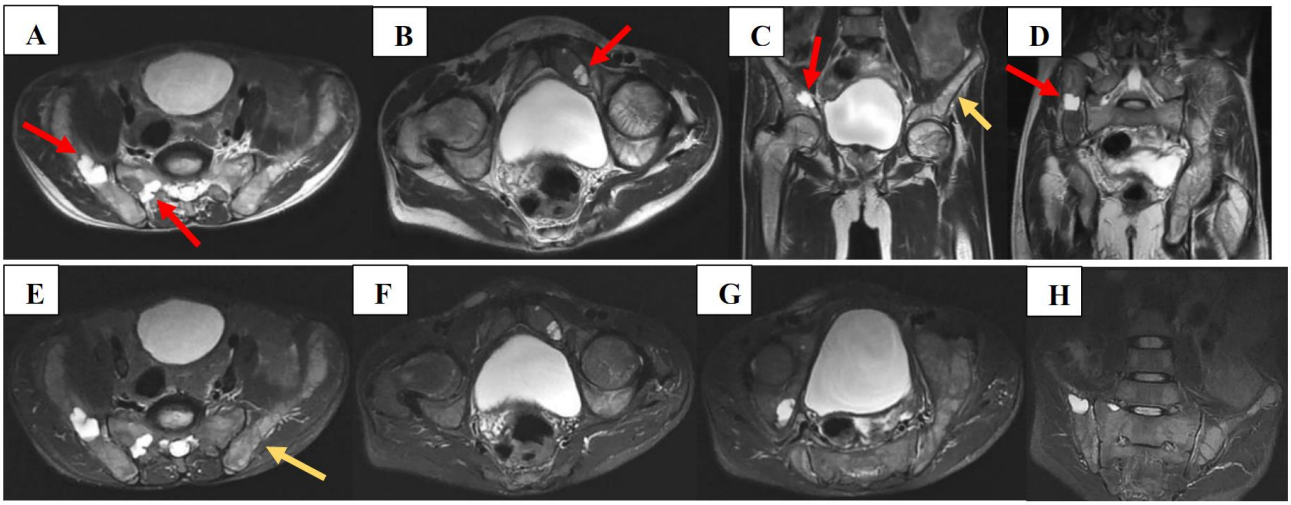

Figure 1: Axial and coronal MR images demonstrating diffuse bone signal anomaly of all pelvic bones with trabeculated appearance (yellow arrows) in T2 hypersignal (A, B, C, D) and STIR (E, F, G, H), combined with multiple well-defined iliac, pelvic and sacral cystic lesions (red arrows) that were hyperintense in T2-weighted images. Some had lobulated contours, compartmentalized and comprising hematic levels

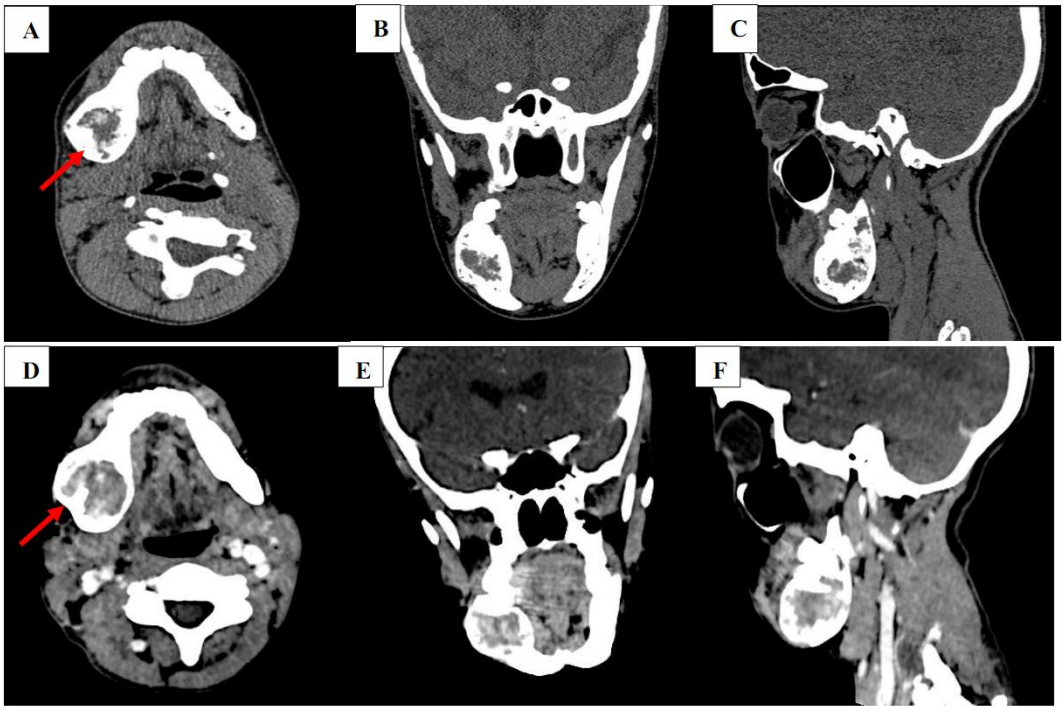

Figure 2: Non-contrast axial (A), coronal (B) and sagittal (C) CT images in parenchymal window showing a solitary expansile osteolytic tissue mass centered on the right body of the mandible and extended to the homolateral angle. Post-contrast axial (D), coronal (E) and sagittal (F) CT images showing heterogenous enhancement of the lesion

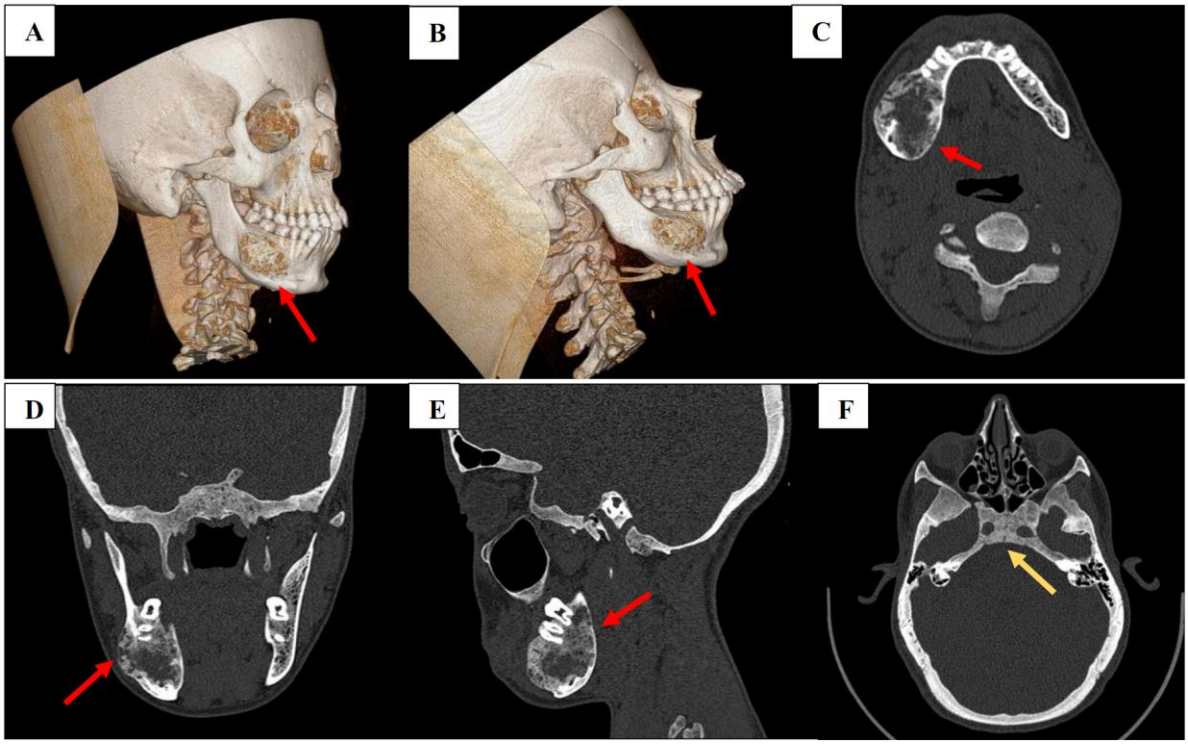

Figure 3: Three-dimensional reconstruction (A, B), axial (C), coronal (D) and sagittal (E) CT scan images in bone windows showing that the lesion is encompassing tooth roots of the 44 to 48 ones, associated with cortical thinning and blowing (red arrows). Also noting the diffuse ground-glass appearance (yellow arrow) mostly marked in the sphenoid bone (E)

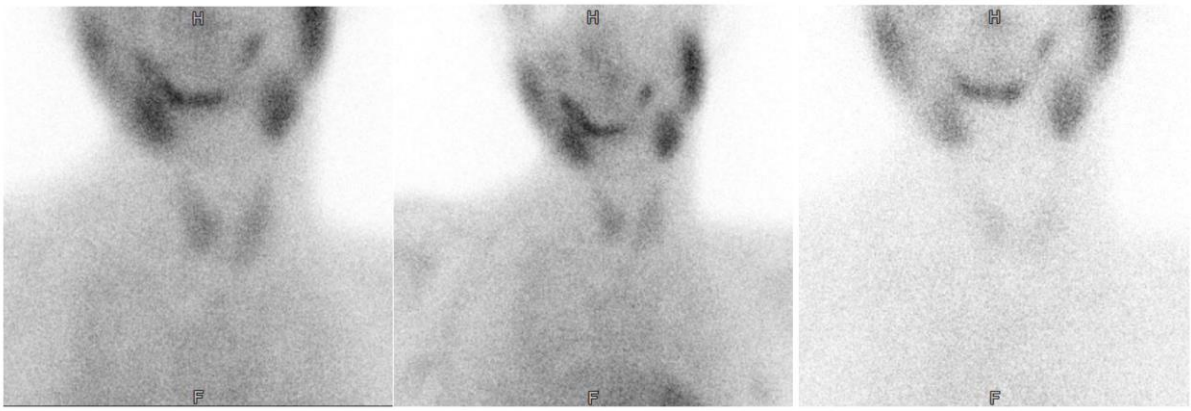

Figure 4: ^{99m}Tc-sestaMIBI parathyroid scintigraphy exhibiting focal retention below and behind the lower pole of the left thyroid lobe, in favor of pathological parathyroid tissue

Clinical setting characterized by renal failure responsible for hyperparathyroidism, biochemical and imaging findings strongly supported the diagnosis of brown tumor. Also, the tumor biopsy of the right mandibular lesion identified fibrillar connective tissue with intense proliferation of multinucleated giant cells, vascular neoformation, inflammatory cell infiltrate, and focal hemorrhage. Microscopically, the lesion consisted of plump fibroblasts and numerous osteoclast-like giant cells surrounded by reactive bone formation. Furthermore, focal deposits of hemosiderin and small blood vessels were found. Subsequently, our patient required total excision of the parathyroid gland that was histologically examined in the trans-operative period, which showed parathyroid glands increased in volume, with chief cells, oxyphil cells, regular clear cells supported by a fibro-adipose stroma. No histologic evidence of malignancy was found. The histological features were compatible with parathyroid hyperplasia. Postoperatively, blood parameters improved and regression of the mandibular swelling was noticed months later. To best of the author's knowledge, most of the cases published up to date are females and presented mainly in the form of case reports describing a single affected site. This patient had rare features including his sex, multiple brown tumors involving pelvis and mandible, as a result of tertiary hyperparathyroidism.

DISCUSSION

Brown tumor is a rare focal giant-cell lesion secondary to disrupted bone remodeling. Patients typically range from 16 to 69 years of age with a certain predominance among females [9, 10]. It arises as a direct result of the effect of extremely elevated parathyroid hormone levels for a prolonged period of time on bone tissue in some patients with hyperparathyroidism [5, 11]. The increasing parathyroid hormone level will improve osteoclastic cell activity which can cause a series of changes, such as the decreasing of bone trabeculae, the proliferation of fibrous tissue, hemorrhage, and deposition of hemosiderin [1], giving the tumor its appearance being a brownish mass [12]. Hyperparathyroidism occurs in three significant forms as primary, secondary and tertiary. Primary hyperparathyroidism is associated with parathyroid adenoma (80% of cases), gland hyperplasia (15 to 20%), and in rare cases carcinoma [13]. In contrast, secondary hyperparathyroidism is a common complication of late-stage renal diseases in response to low serum levels of calcium and vitamin D [8]. Tertiary hyperparathyroidism, which is rarer, is a consequence of long-lasting secondary hyperparathyroidism which, due to renal failure, develops an autonomous functioning of the parathyroid with hypersecretion of parathyroid hormone. Some authors also defend the existence of a quaternary type, where the autonomic hyperplasia of tertiary hyperparathyroidism progresses to adenomas formation [13, 14]. Brown tumors can affect the entire skeleton, more often in long bones such as femur, ribs, pelvis and clavicle [15]. The diagnosis is based on a bundle of arguments including clinical history, biological assessment, imaging characteristics and histopathological findings [16]. These benign and reactive lesions exhibit slow growth, and their clinical presentation depends on size and anatomical location. The symptoms can vary from totally asymptomatic to painful cases with swollen masses, responsible in the face for facial deformation with discomfort, impaired mastication, mobility or even dental loss [14, 15].

As for the spine, it includes pain, radiculopathy, myelopathy and myeloradiculopathy according to their locations [17]. Radiographic features are compatible with bone resorption caused by activated osteoclasts. Well-defined monogeodic or multilocular radiolucent images and generalized osteoporosis can be observed. Cortical bone can be expanded or ruptured, but most times it is not infiltrated by the lesion [13, 18]. Special feature of maxillomandibular location includes dental changes such as abnormally narrow pulp chambers, resorption of the lamina dura around the roots of teeth, and demineralization of the marrow bones of the jaws causing a characteristic “ground glass” appearance [13, 14]. On CT imaging, they appear as hyperdensity well-demarcated expansile lytic lesions with various amounts of bone destruction. The bone cortex may be destroyed and thinned. The tumor is rich in vascularity and can be strongly enhanced in the enhanced CT scan. The MRI appearance depends on the relative proportion of its components. The lesions, therefore, may be solid, cystic, or mixed. Solid components are intermediate to low intensity on T1- and T2-weighted images, while the cystic components are hyperintense on T2-weighted images and may have fluid-fluid levels. The solid component and septa can be intensely enhanced after contrast injection [1]. According to the analysis of the literature review, the histopathological characteristics of brown tumors are numerous multinucleated osteoclastic giant cells, increased osteoclastic activity, bone trabeculae reduced in number, and the remaining ones appearing thinned, proliferating fibrous tissue, and the vascular stroma, hemorrhagic infiltrates and hemosiderin deposits [1, 18, 19]. These characteristics are very similar histologically to other giant cell lesions, such as true giant cell tumors, reparative giant cell granuloma and aneurysmal bone cysts, making differential diagnosis extremely difficult [1, 5, 16, 20].

Hence the need to take into consideration the clinical history and the results of the biological examinations, especially the hormonal status, the demonstration of a disturbance of the phosphocalcic balance makes suspect a hyperparathyroidism, the increase in the level of the parathyroid hormone makes it possible to establish the diagnosis [15]. Apart from biochemical investigations for hyperparathyroidism, further correlation with both cervical ultrasound and 99mTc-sestaMIBI scintigraphy should be used to confirm the location of the active parathyroid gland [12, 21]. It is logical to consider that the primary treatment of brown tumors is the management of underlying medical disorders caused by hyperparathyroidism [1, 2, 15]. Controversies on the use of surgery and conservative treatment for brown tumors still exist [7]. Some authors recommend only the treatment of the endocrine and/or renal disturbance to allow the progressive sclerosis of the compromised bone. Parathyroidectomy is the ultimate choice to prompts remineralization of the bone [5, 22]. Surgical excision would be indicated only when the lesion does not respond to hyperparathyroidism treatment or in case of significant functional compromise, because the resolution of the lesion can take months to years [2, 7, 13, 15]. Actually, each case should be carefully evaluated, and treatment decision should take into account factors such as anatomic site, clinical behavior, lesion extent and also factors related to the patient such as age and systemic condition [13]. In our patient, brown tumor showed significant reduction after parathyroidectomy, even though there was residual lesion within the mandible. Without appropriate treatment, the brown tumor can cause bone destruction, fractures, and if localized in the spine, cord compression can occur with severe neurological deficits requiring emergent operative decompression [5, 9].

CONCLUSION

In summary, brown tumor is a rare bony disorder as a consequence of hyperparathyroidism.

Diagnosis can be easily overlooked since their appearance can mimic more serious diseases, such as malignancy. Clinically both may be characterized by skeletal pain, biochemically by a high level of serum calcium due to a high turnover of bone, radiologically by osteolytic lesions, and pathologically by the presence of giant cells. Differentiation is possible with brown tumors never penetrating bone cortex, while they biochemically differ from osteolytic cancer metastases in a high level of parathyroid hormone concurrent with a high serum calcium. This observation highlights the importance of imaging which, knowing the clinical and biological context, leads to a positive diagnosis, sparing patients from excessive investigations and unnecessary interventions.

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