

Brown tumors; a possible pitfall in diagnosing metastatic disease

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Abstract

Brown tumors (BT) are scarcely diagnosed and present a possible diagnostic pitfall in imaging modalities. Imaging modalities and especially positron emission tomography cannot differentiate between brown tumors and metastatic foci and only clinical diagnosis of hyperparathyroidism and histology will support the diagnosis. We describe the histology, clinical expression, significance and the differential diagnosis of BT. We also describe imaging characteristics and imaging techniques for identifying BT. Brown adipose tissue, unrelated to BT may also mimic metastatic disease in imaging modalities.

Introduction

Brown tumors (BT) are bone formations, that arise in settings of excess osteoclast activity, in cases of hyperparathyroidism. The pathophysiological mechanism that leads to their formation is linked to abnormalities that appear in hyperparathyroidism (HPT) such as excess parathyroid hormone (PTH) production in primary hyperparathyroidism (PPT), or phosphate retention, skeletal resistance to PTH, impaired degradation of PTH and altered feedback regulation of PTH by calcium in secondary hyperparathyroidism (SPT) [1]. Increased PTH production results in hypercalcemia due to increased calcium absorption in the gut, increased renal tubular resorption, and increased osteoclastic activity.

A frequent result of chronic renal failure (CRF) particularly in dialysis-dependent patients is SPT. Several factors contribute to HPT of CRF including bone resistance to PTH, increased phosphorus retention causing decreased malabsorption of calcium in the gut, and inhibition of 1,25(OH)₂D production by increased phosphorous [1]. The incidence of skeletal BT in patients with CRF ranges from 1.5% to 13% [6-11]. Opposing to their name, BT are not of neoplastic origin.

We shall describe the histology, clinical expression, significance and the differential diagnosis of BT.

Histology, morphology, bone transformation

Brown tumors consist of fibrous tissue, woven bone and supporting vasculature, but no matrix. Microscopically, there is increased resorption of trabeculae in a "tunneling" or "dissecting" pattern. Osteoclastic resorption leads to microfractures and microhemorrhages which progressively produce a small vacuum that becomes confluent with others to create macroscopically visible BT. The characteristic brown coloration results from hemosiderin-laden histiocytes and hemosi-

derin deposition into the osteolytic cysts [2] (Fig. 1). The osteoclasts consume the trabecular bone that osteoblasts lay down, and this front of reparative bone deposition followed by additional resorption can expand beyond the usual shape of the bone to the periosteum and cause bone pain. The involvement of BT in bones weakens them and results in pathological fractures [3].

Clinical and laboratory findings

Brown tumors or osteitis fibrosa cystica are now very rarely seen in cases of PPT because HPT is diagnosed and treated at early stages.

Primary HPT is caused by solitary parathyroid adenomas (85%), by parathyroid carcinomas (5%), or by glandular hyperplasia (10%) associated with multiple endocrine neoplasia (types I and II) [13]. Serum phosphate, alkaline phosphatase and urate are elevated.

Clinically, HPT presents as "stones, bones and groans", where "stones" refer to recurrent kidney and "groans" describe the gastrointestinal symptoms like vomiting, nausea, peptic ulcers and pancreatitis [14].

Radiologically, HPT presents as diffuse osteopenia as well as circumscribed lucent bone areas. Erosion of the tufts of the phalanges is an associated finding and is more pronounced on the radial than the ulnar [15]. Other areas of resorption include symphysis pubis, distal clavicle, vertebral bodies and

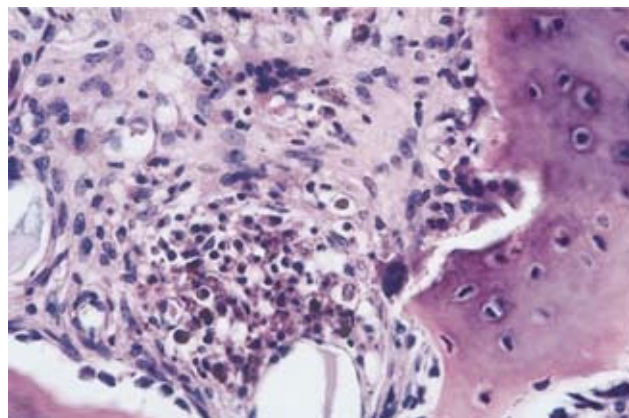


Figure 1. Photomicrograph of sections of a T-9 brown tumor. A salient feature of this lesion is the presence of hemosiderin deposits (brown pigment) and hemosiderin-laden histiocytes. Original magnification x 200 (H and E) [2].

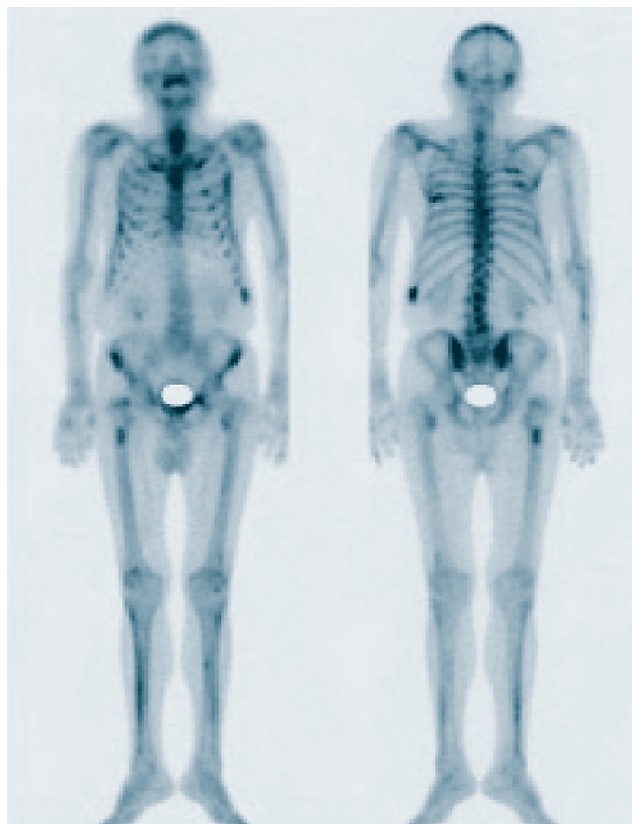


Figure 2. Whole-body scan with ^{99m}Tc -MDP. Increased radiotracer activity accumulation is shown on the back part of the 5th-6th right and 7th left ribs, on the lateral view of the 11th left rib, on the left trochanter minor and the mid portion of the left tibia diagnosed as BT [16].

lamina dura of the teeth. The calvaria may have a granular appearance called “salt and pepper” skull. Increased “patchy” activity in the scan is shown on the flat bones. The BT lesions occur most often in the pelvis, ribs, extremities and the mandible [16]. Lytic lesions are more often found in women than in men and have increased incidence with age. These findings are more intense than in SPT [17].

On the technetium-99m methyl diphosphonate (^{99m}Tc -MDP) bone scan or on fluorine 18-fluorodeoxyglucose scan (^{18}F -FDG) or on X-rays, the multifocal involvement of BT in the skeleton may be mistaken for metastatic disease [18]. However, the clinical history of either PPT or of CRF in SPT, usually establishes the diagnosis [18].

Discussion

Brown tumors appear as “hot” lesions by all radiotracers that diagnose metastatic disease. False-positive scans, mimicking multiple metastatic foci are shown by various radiopharmaceuticals like ^{99m}Tc -MDP (Fig. 2), ^{99m}Tc -methoxy-isobutyl-isonitrile (^{99m}Tc -sestamibi) [16], thallous-201 chloride ($^{201}\text{TlCl}$) [19] and even ^{18}F -FDG [20-23].

Brown tumors do not relate with brown adipose tissue (BAT), with which they only share the first part of their name. Brown adipose tissue induces thermoregulation, especially in

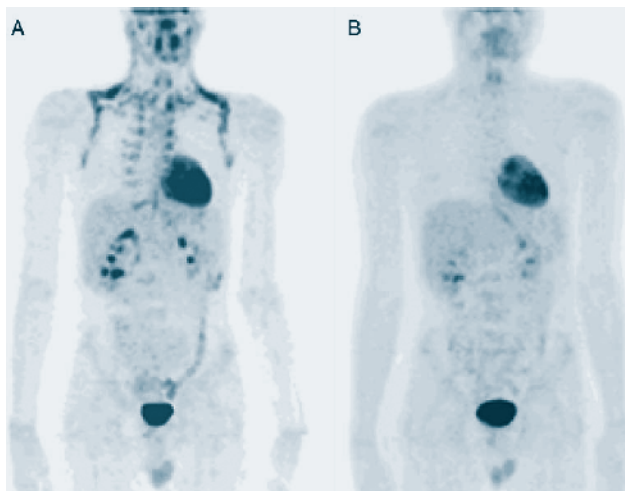


Figure 3. On the ^{18}F -FDG PET-CT scan at cold environment, 24°C (A) one can see multiple unilateral BAT mimicking metastases while the same scan in the same patient performed at warm environment (B) is clear.

children, through a non-shivering pathway. The interest about BAT has been brought up by the fact that on positron emission tomography (PET) scanning of adults, BAT deposits have been identified in the upper chest and neck, although at first it was considered that BAT was only found in childhood [12]. Sometimes, BAT can mimic metastasis disease [21-23]. Brown adipose tissue becomes more visible in PET scan images under exposure to cold, while at a warm environment (24°C or more) they may not be seen at all (Fig. 2) [4, 5].

In conclusion, the scintigraphic image only if supported by the clinical and laboratory findings can distinguish between metastatic disease and BT.

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Editorial Note

The present and future of our Journal

As we entered the thirteenth year of publication, the Hellenic Journal of Nuclear Medicine is gaining reputation in the international nuclear medicine community. Our new page in www.nuclmed.gr assisted many colleagues in finding useful references either by subject key word or by author's name. Every month since August 2009, more than 500 colleagues from 40 different countries visit our site. The United States are the principal visitor from countries outside Europe. Subscriptions can much easier be paid now through PayPal (go to www.nuclmed.gr, to Subscription: Individuals, non members or members, Pay now etc).

The Journal will have an Impact Factor by the end of 2009 which will be announced by ISI Tompson, later.

For 2009, 260 papers have been submitted while the published papers after peer's review were 75. The number of papers printed in the Journal increased by 60% while subscription rates remained the same.

We would like to thank our Editorial Board Members and our Advisors for supporting the Journal by submitting original papers and by reviewing the papers submitted.

The future has its roots in the past and is growing through the soil of the present.

The Editor