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CASE

Brown tumor of the fibula: unusual presentation of an uncommon manifestation. Report of a case and review of the literature

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Abstract Brown tumors are erosive bony lesions caused by rapid osteoclastic activity and peritrabecular fibrosis due to hyperparathyroidism, resulting in a local destructive phenomenon. Although brown tumors are the most pathognomonic sign of hyperparathyroidism, they are very rarely observed at present as a result of early detection of hypercalcemia and elevated parathyroid hormone levels. The rare appearance of this entity in everyday practice is troublesome for both patients and physicians, because whenever it emerges, diagnosis could be mistaken for a giant cell tumor of the bone. However, clinical, biochemical, and radiologic findings can easily guide the diagnosis if one considers the full continuum of findings and their association with subject's medical history, instead of focusing only on bone lesion. In this report we present a case of brown tumor in the fibula with a short literature review, whose aggressive presentation and unawareness of the skeletal findings of hyperparathyroidism puzzled the caring doctors. This case illustrates the need for continuous vigilance of any physician, regardless of his specialty or his position in medical services structures.

Keywords Brown tumor · Hyperparathyroidism · Fibula · Bone mass

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Introduction

Since 1891 when Von Recklinghausen recognized the clinical spectrum of hyperparathyroidism he used the term "osteitis fibrosa cystica" has been used to describe the unique skeletal findings observed in hyperparathyroidism. Brown tumors (BTs) are a localized form of fibrous-cystic osteitis, appear as single or multiple well-defined lesions of the bone and are considered as the most pathognomonic skeletal changes that accompany this disease. Common sites of involvement are the facial bones, pelvis, ribs, and femurs. Other radiographic skeletal manifestations of hyperparathyroidism are 'salt and pepper' mottling of skull, loss of lamina dura in the mandible, subperiosteal erosions, and diffuse osteoporosis. It is important to mention that the skeletal changes caused by primary or secondary hyperparathyroidism are identical [1, 2].

Although from yhe last century BTs were classically associated with primary hyperparathyroidism, their appearance is very rare nowadays, because both primary and secondary hyperparathyroidism are diagnosed early, and proper treatment, either surgical or medical, is provided [3]. Occasionally, osteitis fibrosa cystica can be mistaken for a malignant lesion, even though BTs represent

a reactive cellular process rather than a true neoplasia [4]. This case is presented to emphasize the need for continuous alertness of the physicians to scarce nosologic entities, since a subject with clinical, biochemical, and radiographic findings suggestive of primary hyperparathyroidism associated with a brown tumor of the fibula was misdiagnosed, leading the patient to a plethora of painful and expensive diagnostic tests and the consulting doctors to diagnostic errors.

Case description

A 42-year-old woman presented to our clinic, accompanying her daughter suffering from PCOS, complained arthalgies of both knees expanding to the upper one-third of left calf and difficulties in rising from sitting position. Patient's symptoms started 6 months previously and gradually worsened. From her medical history, it is important to mention repeated attacks of nephrolithiasis for which she had undergone 5 sessions of lithotripsy the last 6 years. She reported that kidney stone analysis revealed calcium crystals.

On physical examination there were no significant findings, except for a palpable small goiter with smooth micro-nodular texture and bone pain under the pressure of left lower limb (at the region of tibia) and both knees. At the initial presentation the patient was carrying with her a radiograph of left knee which was considered as normal, although a careful examination revealed the presence of a cystic lesion in the left fibula (Fig. 1). Additionally, her routine biochemical testing was normal except the following: Serum calcium level was elevated at 11 mg/dl (nv: 8.4–10.1), with normal albumin levels at 3.9 g/dl (nv: 3–5), while phosphorus level was borderline low at 2.5 mg/dl (nv: 2.7–4.5). The running diagnosis of BT due to hyperparathyroidism was made, and the patient was recommended further testing to verify this condition. However, the patient lost her follow-up, and she presented several months later carrying a lot of tests, including computed tomography (CT), Magnetic resonance imaging (MRI), CT, bone scintigraphy, and biopsy of the affected region.

Analytically, CT depicted a lytic lesion in the proximal metaphysis of the fibula. The affected bone was expanded, the cortex was thinned, and cortical microfractures were observed. No sclerotic rim or periostal reaction was detected (Fig. 2). The imaging findings of the tumor on MRI (Fig. 3) were: (a) the lesion had an expansible character throughout its extent, (b) low-signal intensity on T_1W images and high-signal intensity on T_2W images, (c) after IV contrast administration the lesion showed homogeneous enhancement. The above findings are not specific and the possibility of a malignant tumor cannot be excluded. Surprisingly, the MRI revealed multiple cystic lesions in both lower extremities, a finding supporting the diagnosis of brown tumor. Bone scintigraphy with Technetium-99-MDP demonstrated a region with increased uptake of the

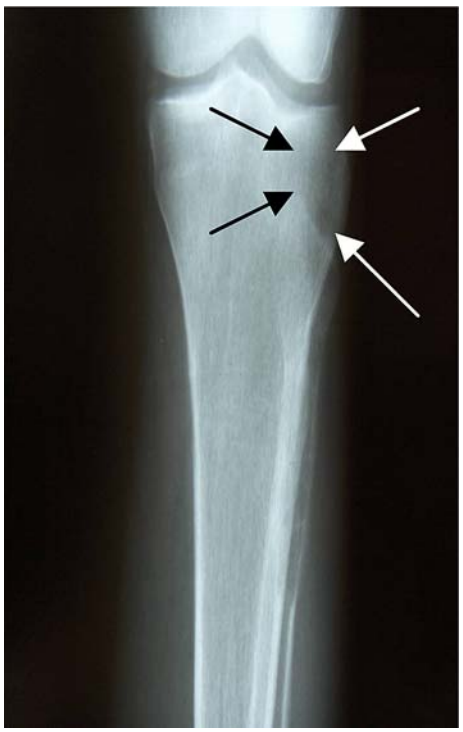

Fig. 1 Skeletal x-ray shows an osteolytic lesion without clear margin highlighted by arrows, in the upper third of the left fibula

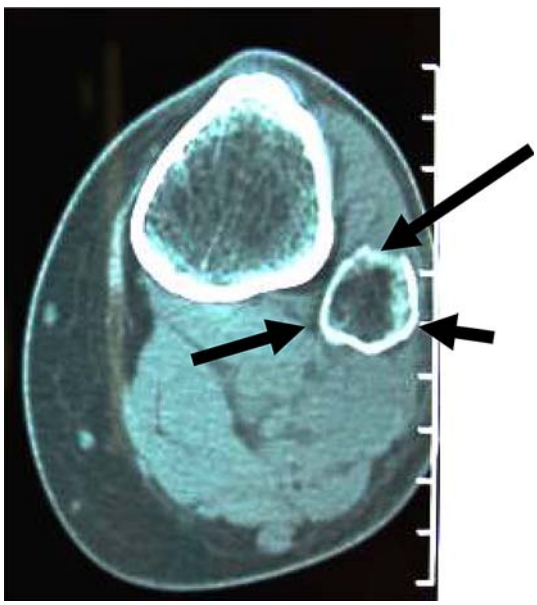

Fig. 2 Axial CT scan through the left extremity demonstrating an expansible soft-tissue mass indicated by arrows in the fibula

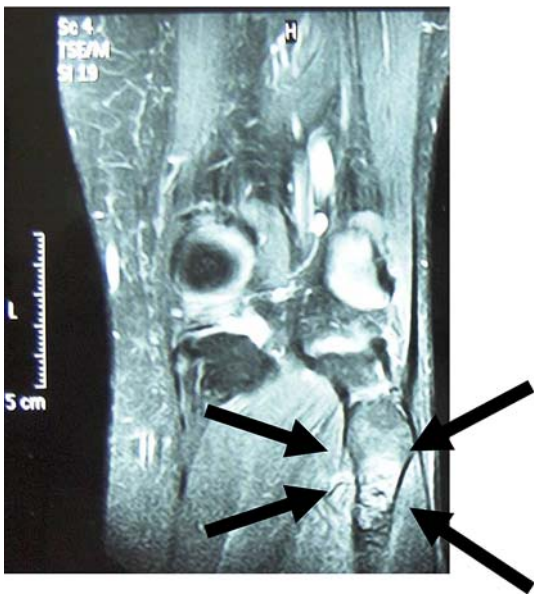

Fig. 3 Coronal T_2W MR image through left lower extremity shows the high-signal intensity of the tumor (4.4 cm) indicated by arrows at fibula

isotope to the upper one-third of left fibula in agreement with radiographic findings (Fig. 4).

Furthermore, the patient underwent bone biopsy which revealed the presence of a BT (Fig. 5) in the left fibula, and she came back to our endocrine clinic for further guidance and assistance. Laboratory testing confirmed the diagnosis

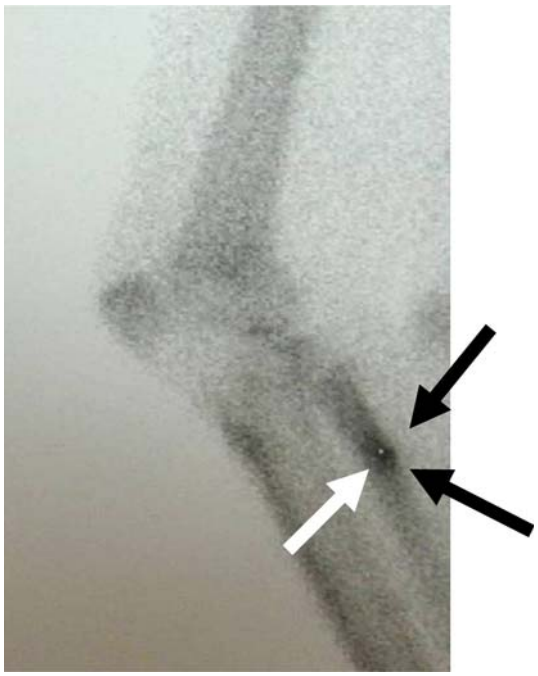

Fig. 4 Technetium-99m-MDP study of the lower extremities. Anterior images demonstrated markedly increased flow to the upper one-third of the left fibula highlighted by arrows

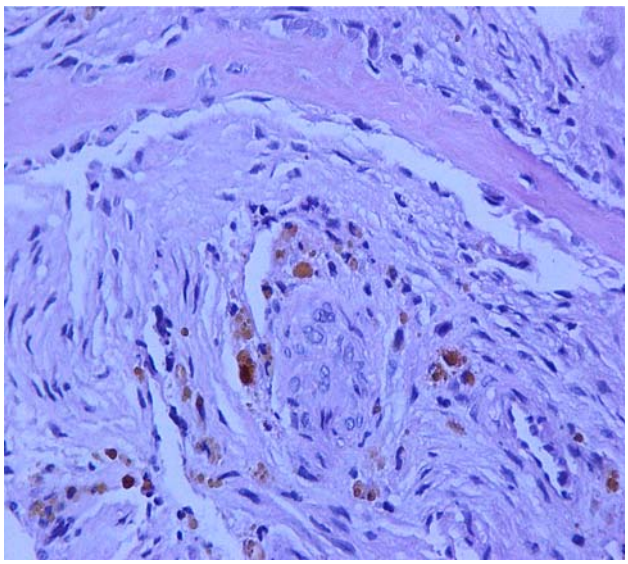

Fig. 5 Photomicrograph showing histologic section of the bone biopsy exhibiting fibroblastic-type stromal cells, giant cells, osteoblastic activity, and clusters of hemosiderin-laden macrophages. HE 125X

of primary hyperparathyroidism (calcium: 15.4 mg/dl, phosphorus: 2.5 mg/dl, PTH: 952 pg/ml, nv: 10–65, urine calcium: 750 mg/dl, nv: 100–300). The patient was admitted to the hospital for correction of hypercalcemia and further exploration. Parathyroid scintigraphy with Technetium-99 m-sestamibi was negative, but MRI of the neck revealed at the left paratrachea space the presence of pathologic tissue with precise edges, biggest diameter of 15 mm, and increased uptake of paramagnetic substance. Bone mineral density of lumbar spine exposed osteopenia (T-score: –2).

The patient underwent excision of the left lower parathyroid gland. The histopathological examination of the excised gland was compatible with parathyroid adenoma. Postoperatively serum calcium, phosphorus and PTH returned to normal (9.6 mg/dl, 3.8 mg/dl and 58 pg/ml, respectively). The patient's symptoms and diffuse bone pain improved significantly post surgery. In the postoperative period, PTH levels decreased toward normal values, and a new MRI of the affected region 3 months later showed almost complete regression of the lesion (Fig. 6).

Discussion

This case demonstrates, in a premenopausal woman, the characteristic bone lesion of primary hyperparathyroidism, advanced osteitis fibrocystica, as the presenting manifestation. In the past, bone lesions were recognized in 80–90% of patients with primary or secondary hyperparathyroidism,

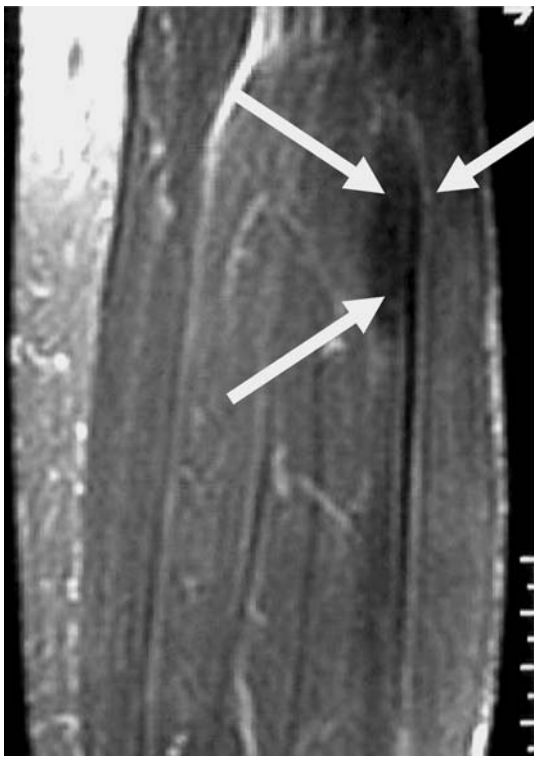

Fig. 6 Coronal T_2W MR image 3 months post surgery shows the diminished size of the lesion at the same level of the image of Fig. 3

but since 1970s mild hypercalcemia became easily detectable with the introduction of the auto analyzer. Additionally, new and more objective PTH radioimmunoassay techniques commercially available since 1990s allowed the early diagnosis and successful treatment of hyperparathyroidism. Consequently, since brown tumors (BTs) represent the terminal stage of the disease, the incidence of BTs has declined to 3% in patients with primary hyperparathyroidism and to 1.7% in patients with secondary hyperparathyroidism [5]. Brown tumors can occur as solitary or multiple lesions in any bone. The common sites of occurrence are the jaws, clavicles, pelvic girdle, ribs, and femur. Clinically, BTs most often manifest as slowly growing, painful masses. BTs can be locally aggressive and destructive without metastatic potential. They are rarely associated with complications but occasionally may compress neural structures as they enlarge. However, initial presentation with a pathological fracture is uncommon [6, 7].

Elevated levels of parathyroid hormone induce osteoclastic activity which leads to subperiosteal and subligamentous resorption of bone. For unknown reasons, certain focal areas of bone may undergo more extensive resorption, followed by a cellular repair process that results in the accumulation of intensely vascularized fibrillar stroma and connective tissue cells, along with multinucleated giant cells. In addition, hemorrhage and hemosiderin deposition occur. The surrounding bone is shaped to a great extent by the newly formed osteoid and partially by trabecules, some of which are immature, showing osteoblastic activity on their surface. This process; results in the formation of a brown tumor [8].

The occurrence of sclerotic and non-sclerotic lesions in patients with hyperparathyroidism may reflect different stages of bone disease process; in particular, non-sclerotic lesions represent an early short-lived reabsorptive phase with increased size of the osteoclast pool, increased bone reabsorption, and decreased size of the osteoblast pool. However, this phase is followed by a sclerotic lesion constructed from an increased number of osteoblasts due to the chronic PTH stimulus, representing the healing stage [9].

Brown tumor microscopically is characterized by intensely vascular fibroblastic stroma serving as a scaffold for numerous osteoclast-like multinucleated giant cells, diffused or arranged in clusters, in a background of proliferating fibroblasts, and mononuclear oval or spindle stromal cells. The term “Brown tumor” is derived from the characteristic macroscopic appearance of a brownish material, which is the result of rich vascularity, hemorrhage, and hemosiderin deposition within the cystic lesion.

Initial bone changes in hyperparathyroidism may be as slight as to be imperceptible on radiographic examination. However, usually BTs on plain radiographs present as round areas of osteolysis, ranging from purely lytic to sclerotic, sized up to 7 cm, expanding the cortex without invading the soft tissues. Their margins are regular, have a sclerotic rim, often single, and sometimes are septated. Intracortical bone resorption can produce radiographically detectable intracortical linear striations. Endosteal bone resorption can be detected as localized defects along the inner margins of cortex [10]. CT scans of a BT demonstrate a relatively well-defined, soft-tissue mass with local bone erosion and expansion. This mass usually shows contrast enhancement. Attenuation values observed on tomography scans usually fall within the range found in blood and fibrous tissues.

The broad pathologic nature of brown tumor may influence the morphologic heterogeneity and signal intensity of the tumor on MR imaging. It is therefore suggested that BTs have a wide spectrum of MR features; therefore, on MR imaging findings are nonspecific. Usually, BTs are detected as hypointense on T1W images and hyperintense on T2W images [11], but Kanaan et al. reported a case with hypointensity on both T1- and T2-weighted images. In addition, Davies et al. reported three cases of brown tumors, which were multiloculated cystic lesions and cyst content was blood-fluid; thus, a fluid-fluid level was demonstrated on MR imaging [12, 13]. BTs on bone scans

show increased uptake of the radio-labeled isotope, usually Technetium-99-MDP, although positive results have been obtained with the use of Technetium-99m-sestamibi [14, 15]. Increased activity observed in bone scans should be attributed to osteoid formation, rapid bone turnover, and the affinity of bone-seeking agents for non-osteoid organic matrix produced in BTs.

Differential diagnosis of a BT includes several pathologies, namely, chondroma, chondromyxoid fibroma, fibrous dysplasia, bone cyst (simple or aneurysmal), fibroxanthoma, telangiectatic osteosarcoma, Langerhans cell histiocytosis, and mainly giant cell tumor. The diagnosis is based on a combination of clinical, biochemical, and radiological findings. Histologically, brown tumors may be indistinguishable from giant cell tumors of the bone, and correlation with clinical and radiographic studies is essential in making the correct diagnosis.

Therapeutic management of brown tumors depends on the origin of hypeparathyroidism, and the localization and evolution of BT. If osteitis fibrosa cystica is a result of end-stage renal disease Mourad et al. showed partial regression of BTs with intravenous administration of alfacalcidol [16]. In the case of parathyroid adenoma successful removal eliminates excessive activation of PTH and usually leads to significant regression of small and medium-sized brown tumors, as in our case [17]. Recurrence of BTs, if the serum calcium is normalized, is extremely unlikely. If localized in certain anatomical sites, decompression of the brown tumor is urgently needed. This is particularly true for maxillary lesions, which may lead to serious deformities of the face and even a lethal outcome.

In conclusion, we present a case of Brown tumor of the left fibula in a woman, who underwent laborious and expensive testing, because she was misdiagnosed. This case illustrates the urge for awareness of serious long-term complications even in diseases which today can easily be diagnosed with routine screening.

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