Atypical Parathyroid Adenoma with Multiple Brown Tumors as Initial Presentation: A Rare Entity

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Abstract

Brown tumors seen in hyperparathyroidism are rare, non-neoplastic lesions because of abnormal bone metabolism, and they can mimic benign bone tumors or malignancy. Although biopsy is considered as the gold standard for diagnosis, it can be inconclusive. As the diagnosis of brown tumors is often challenging, a high index of suspicion is essential for diagnosis. We present a case of 21-year-old woman who presented with multiple painful bony lesions, which were initially misdiagnosed as fibrous dysplasia. Due to persistent bone pain and deterioration in her physical mobility, she was referred to tertiary care centre. After thorough clinical workup, she underwent Tc-99m methylene diphosphonate bone scintigraphy that raised strong clinical suspicion of hyperparathyroidism and brown tumors. Subsequently, Tc-99m-methoxy isobutyl isonitrile (MIBI) parathyroid scintigraphy revealed a solitary MIBI avid focal lesion, suggestive of left inferior parathyroid adenoma. Later parathyroidectomy was performed and histopathological examination confirmed it as atypical parathyroid adenoma.

Key words: *Atypical parathyroid adenoma, brown tumors, Tc-99mmethylene diphosphonate bone scintigraphy, Tc-99msestamibi scintigraphy*

Introduction

Primary hyperparathyroidism (PHPT) is a disorder caused by overproduction of parathyroid hormone (PTH). The clinical signs and symptoms are mainly due to abnormality in calcium, phosphate, and bone metabolism. Increased level of PTH results in hypercalcemia and hypophosphatemia. Initial presentation in many cases includes recurrent nephrolithiasis (10%-25%), neuropsychiatric disturbances, peptic ulcers, and less frequently extensive bone resorption resulting in multiple expansile fibrotic lesions, that is, brown tumors.[1] Here, we report a case of multiple brown tumors as initial presentation in hyperparathyroidism.

Case Report

A 21-year-old women presented to the orthopedic clinic with severe pain and swelling in right arm, which was aggravated following trivial trauma. On clinical examination, apart from the right arm pain and swelling, she also had painful swelling involving lateral aspect of left clavicle and proximal left humerus. There was no significant family history. In her initial workup, radiographic images showed expansile lobulated radiolucent lesions with thinned out cortex involving lateral aspect of left clavicle and proximal third of left humerus [Figure 1]. She also developed pathological fracture involving mid shaft of right humerus. Considering the clinical picture of multifocal bone disease, bone biopsy was done to confirm the diagnosis. Histopathology suggested possibility of fibrous dysplasia. Accordingly, patient was treated conservatively with immobilization of the right humeral fracture site with sling and Injection zoledronic acid 4 mg, i.v. infusion to improve the bone strength. As patient had persistent body pain with new sites of bone pain, she was referred to our institute, a tertiary care centre for a comprehensive workup.

On routine laboratory workup, her serum phosphorus was within normal limits, 3.8 mg/dl (normal range, 2.5-4.8 mg/dl), serum calcium was within upper limit of normal, 10.2 mg/dl (normal range, 8.0-10.5 mg/dl) and serum alkaline phosphatase was mildly

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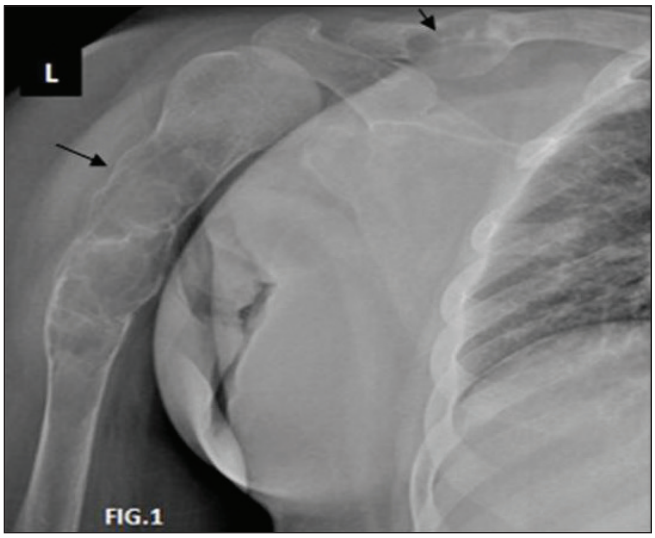

Figure 1: X-ray left shoulder joint showing, expansile, radiolucent lesion involving meta-diaphyseal region of left humeral shaft and another similar lesion involving lateral third of left clavicle.

elevated, 258 IU/l (normal range, 90-120 IU/l). Bone scintigraphy was requested for whole body screening.

Tc-99m methylene diphosphonate (MDP) bone scintigraphy findings revealed multiple sites of focal expansile lesions with increased MDP uptake [Figure 2] that raised strong clinical suspicion of hyperparathyroidism with possibility of multiple brown tumors. Therefore, she was further evaluated with Tc-99m MIBI dual phase parathyroid scintigraphy that showed MIBI avid enlarged left inferior parathyroid adenoma [Figure 3]. Ultrasound examination of the neck revealed 1.8 × 0.6 cm in size hypoechoic lesion,

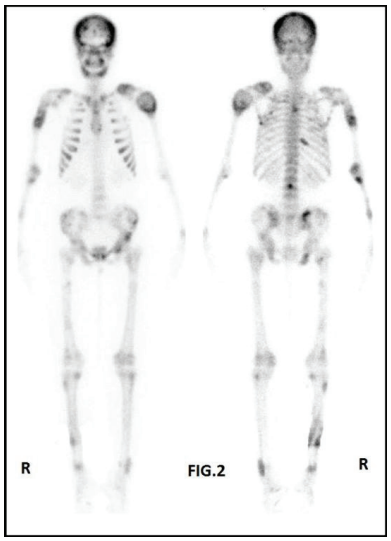

Figure 2: 99m Tc-MDP whole body bone scintigraphy showing multiple expansile lesions with increased MDP uptake, involving lateral third of left clavicle, proximal third of left humerus, proximal shaft of right humerus, subtle focal lesions involving pelvic bones, both proximal femurs and distal third of both tibiae. In addition, mild diffusely increased radiotracer uptake is seen in calvarium, axial and appendicular skeleton with prominence of bilateral costochondral junctions, evidence of tie sternum and pseudo fractures involving right third and ninth ribs.

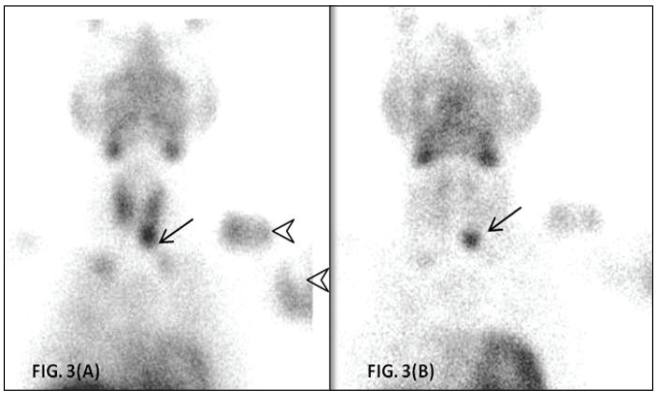

Figure 3: 99m Tc-MIBI dual phase parathyroid scintigraphy (a) early and (b) delayed images, showing, small rounded focus of moderately increased MIBI uptake adjacent to inferior pole of left lobe of thyroid gland (arrow) (a), with persistent tracer retention in this lesion in delayed images but normal washout from thyroid gland (b), suggestive of left inferior parathyroid adenoma. Additionally, MIBI avid brown tumors seen involving left clavicle and left proximal humerus (arrow heads).

inferior to left thyroid lobe, suggestive of parathyroid adenoma. Subsequently patient underwent left inferior parathyroidectomy with curative intent.

On the day of the surgery, intraoperative PTH levels were assessed. There was a significant fall in PHT levels, immediately after the excision of adenoma (pre-incision PTH: 320 pg/ml and post-excision first sample PTH: 35 pg/ml, post-excision second sample PTH: 12 pg/ml) [Figure 4]. Excised adenoma was grey brown, congested, well capsulated & measuring 1 cm in size. Histopathological examination was suggestive of atypical parathyroid adenoma [Figure 5].

Postoperatively, she was followed up for a period of 1 year. There was significant improvement in her symptoms, quality of life, she was able to walk and perform her routine activities. Her follow-up biochemical parameters including serum phosphorus 3.3 mg/dl (normal range, 2.5-4.8 mg/dl), serum calcium 9.1 mg/dl (normal range, 8.0-10.5 mg/dl), and serum alkaline phosphatase 97 IU/L (normal range, 90-120 IU/l) were within normal limits.

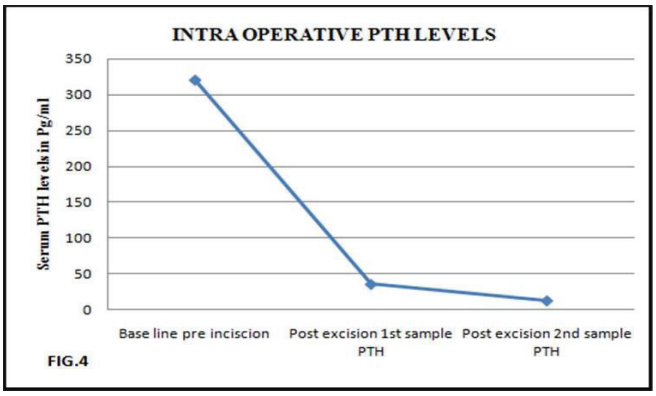

Figure 4: Intraoperative PTH monitoring chart showing, significant fall in PTH levels following excision of left inferior parathyroid adenoma.

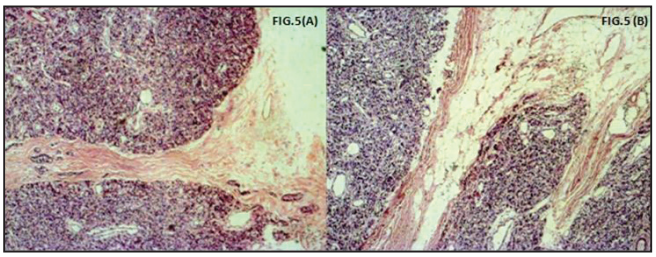

Figure 5: Photomicrograph (H and E × 100): (a) Showing large tumor cells arranged in sheets and islands with mildly pleomorphic nucleus and moderately eosinophilic to vacuolated cytoplasm, (b) partial invasion of capsule by islands of tumor cells without any vascular invasion with minimal mitotic figures.

Discussion

Diagnosis of hyperparathyroidism (HPT) is much easier nowadays with the advancements in routine biochemical and radiological tests, even in the asymptomatic stage.[2]

HPT is classified into primary, secondary, and tertiary types. PHPT is characterized by increased parathyroid hormone secretion, as a result of abnormality in one or more of the parathyroid glands. Usually it is due to parathyroid adenoma (80%-90%), parathyroid hyperplasia (10%-15%), or rarely parathyroid carcinoma (<2%). PHPT can also be associated with other rare familial disorders, including multiple endocrine neoplasia (MEN) type 1 and type 2A syndromes, familial hypocalciuric hypercalcemia, familial hyperparathyroidism-jaw tumor syndrome (HPT-JT), neonatal severe hyperparathyroidism, and familial isolated hyperparathyroidism. Secondary HPT is most commonly due to chronic renal failure, other causes include calcium deprivation and vitamin D deficiency. Hypocalcaemia act as a stimulus for parathyroid glands, which overfunction to compensate for this low serum calcium level. Tertiary hyperparathyroidism is due to development of autonomous, that is, unregulated parathyroid function after a long period of secondary hyperparathyroidism, resulting in a hypercalcemia.[2,3]

Patients with HPT usually present with symptoms of hypercalcemia, manifestations include nephrolithiasis, nephrocalcinosis, polyuria, and renal insufficiency. They may also have gastrointestinal symptoms of nausea, vomiting, peptic ulcer disease, constipation, and pancreatitis. Neuropsychiatric disturbances may vary and include lethargy, decreased cognitive and social function, depressed mood, psychosis. Many cases of PHPT are identified by the presence of hypercalcemia and hypophosphatemia on routine biochemical testing. Overt bone disease is seen as late manifestation of HPT.

In 1891, von Recklinghausen described the classic bone disease termed osteitis fibrosa cystica. Osteitis fibrosa cystica is usually seen in severe cases of PHPT, manifested as generalized bone loss with increased bone resorption, including both subperiosteal and endosteal surfaces. Persistently high circulating levels of PTH results in increased osteoclastic bone resorption, that leads to local destruction, primarily in the cortical bone and occurrence of osteoclastomas, also named as "brown tumors." Incidence of brown tumor is around 2% in PHPT. The most common sites of involvement are ribs, long bones, and pelvis.[4,5]

The classical radiographic features of HPT are subperiosteal cortical bone erosions, generalized deossification, salt and pepper appearance of skull, bone softening, and local destructive bone lesions, that is, brown tumors. Brown tumors are non-neoplastic lesions because of abnormal bone metabolism in HPT but they can mimic a benign bone tumor or malignancy.[6,7]

Although, biopsy is considered as the gold standard for diagnosis, but it can be inconclusive and challenging; therefore, a high index of suspicion is essential for diagnosis. Imageological findings and biochemical tests including serum PTH, markers of bone metabolism can help in diagnosis.

Atypical parathyroid adenoma has an unpredictable clinical behavior. It shares some common features of carcinoma histopathologically. In this case, histopathologically features were suggestive of atypical parathyroid adenoma. This patient did not show any classical features of hypercalcemia but presented with multiple brown tumors causing bone pain and pathological fractures. Her serum calcium and ALP levels at the time of presentation to our institute were near normal to borderline high. The cause of borderline serum calcium levels in our case is possibly due to recent administration of Zoledronic acid that slows down bone resorption.[8]

The most significant point about this case is that patient presented with expansile bone lesions at a peripheral clinic with no other significant clinical hint to suggest hyperparathyroidism. That had delayed the diagnosis and caused significant morbidity to patient with limitation of her physical activity.

This case highlights the importance of early diagnosis of hyperparathyroidism with a thorough diagnostic workup, including imaging and biochemical markers of bone metabolism. Also, it is important to identify brown tumors from other forms of metabolic bone diseases and benign bone lesions, at an earlier stage in order to reduce the morbidity due to skeletal-related events.[9,10]

MDP bone scintigraphy is highly sensitive technique for detection of alteration in bone metabolism. It can help in differentiating causes of hypercalcemia, in particular, hyperparathyroidism versus malignancy.[11] As complete surgical resection in hyperfunctioning parathyroid tissue is crucial for curative treatment of PHPT. Preoperative imaging techniques play an important role in the surgical management of patients with PHPT, in order to localize and identify abnormal glands.

Tc-99m MIBI parathyroid scintigraphy is a well-established technique for the early diagnosis and preoperative localization of parathyroid adenoma. MIBI is lipophilic radiopharmaceutical, its uptake and retention depends on the regional blood flow, cell viability, cell membrane potential, and mitochondrial density. This agent accumulates preferentially in mitochondria-rich tissues, as typically is a hyperfunctioning parathyroid gland. A hyperfunctioning parathyroid adenoma appears as an area of early radiopharmaceutical uptake that persists on late imaging. MIBI scan has very high positive predictive value for detection of parathyroid adenoma with sensitivity, specificity, and overall accuracy of 89%, 98%, and 85% to 95%, respectively.[12]

This case also draws attention of general physicians, radiologists and endocrinologists, whose opinion can be vital for early diagnosis of HPT. As with timely diagnosis treatment can be started early in disease course that can prevent the significant morbidity, which may result if left untreated.

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Conflict of interest

There are no conflicts of interest

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