Jaw tumor in primary hyperparathyroidism is not always a brown tumor

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Summary

Primary hyperparathyroidism (PHPT) is a common endocrine disease. It results from an inappropriate parathyroid hormone (PTH) secretion relative to serum ionized calcium level. Clinical manifestation of severe PHPT include bone disease called osteitis fibrosa cystica which reflects an increase osteoclastic resorption and osteoblastic activity. This high bone turnover is responsible of the occurrence of osteoclastomas, also named “brown tumors” (1). Rarely, PHPT may occur in inherited forms with association to fibrous jaw tumor that are unrelated to hyperparathyroidism. In this uncommon disease: hyperparathyroidism-jaw tumor (HPT-JT) syndrome, parathyroid tumor is frequently malignant and usually associated with nonendocrine malignancies (2). We report a case of a HPT-JT syndrome to focus on the differential diagnosis with brown tumors.

KEY WORDS: hyperparathyroidism-jaw tumor syndrome; primary hyperparathyroidism; ossifying fibroma; brown tumor.

Introduction

PHPT is the most common cause of hypercalcemia. A solitary adenoma of the parathyroid gland is in cause in 80% of cases, a bilateral hyperplasia affecting all four glands is in cause in 15% of cases and only 1% of PHPT is due to parathyroid carcinoma. Less than 10% of PHPT occur secondary to genetic disorders and are then part of a familial disease. These are familial hypocalciuric hypercalcaemia, multiple endocrine neoplasia type 1 and type 2A, rarely type 2B, and finally hyperparathyroidism - jaw tumor (HPT-JT) syndrome (3). These rare inherited forms are clinically important and must lead to a familiar genetic counseling.

Case report

A 53-year-old woman was admitted in endocrinology for major hypercalcemia that appeared one week after a maxillectomy for a left jaw ossifying fibroma. The patient reported a one-week history of impaired general condition, extreme fatigue and weight loss, anorexia, diarrhea and vomiting. On examination, she was cachectic with a BMI of 18.8 kg/m², her blood pressure was 100/80 mmHg. Neck examination found a firm left nodule with a normal sized thyroid and no lymphadenopathy. Admission laboratory data showed a hypercalcemia: 180 mg/l. PTH was at a high level of 1534 pg/ml, 24-hour urinary calcium was at 452.2 mg/24h (N<300), she had a functional renal failure rating with a serum creatinine at 14 mg/l which passed to 8 mg/l after rehydration. The electrocardiogram showed electric signs of hypercalcemia. Her bone mineral density was at -3.5 (lumbar T-score) and -2.3 (Hip T-score). The vitamin D level was subnormal at 29 ng/ml. Neck ultrasonography revealed a 33mm postero-inferior extrathyroidal left node, which was hypoechogeneous, heterogeneous with positive doppler signal.

The initial management consisted on rehydration, parenteral diphosphonates, corticosteroids and diuretics. The normalization of mineral status allowed further investigations. Neck computer tomography showed an oval structure regarding the lower left parathyroid gland descending until the upper cervicothoracic hole (Figure 1). TechnetiumTc-99m sestamibi computed tomography showed an unique uptake in the left lower parathyroid (Figure 2). The overall features were consistent with HPT-JT syndrome. The investigation for CDC73 germline mutation was not conducted because it is not common practice in our context.

Surgical management was performed. Ablation of the left lower parathyroid and ipsilateral isthmolobectomy was performed. The pathological examination revealed a parathyroid adenoma without evidence of malignancy. The post-operative period has been characterized by no sign of hungry bone syndrome and by a normalization of serum calcium and PTH levels. The patient is currently on ambulatory care.

Discussion

HPT-JT syndrome is an autosomal dominant disorder that includes multiple or recurrent parathyroid adenomas. These tumors are most of the time (25%) associated with non endocrine neoplasms that are unrelated to hyperparathyroidism. Patients may present ossifying fibroma of the maxilla and mandible in 25% of cases, renal tumors in 15% of cases, and uterine tumors have been reported in 75% of cases (4). The pathogenesis of HPT-JT syndrome is associated with inactivation of CDC73 gene which encodes for an ubiquitously nuclear protein named parafibromin. Parafibromin is
a component of the highly conserved human nuclear transcriptional regulator: the PAF1 complex. The occurrence of parathyroid carcinoma is about 15% in HPT-JT. Importantly, somatic inactivation of CDC73 gene is recently found in number of patients with apparently sporadic parathyroid carcinomas (4, 5). This fact suggests a possible rapid malignant transformation of parathyroid cells in HPT-JT syndrome and makes mandatory a close observation of the patient.

Bone disease that is related to hyperparathyroidism is called osteitis fibrosa cystic. It has been the first manifestation of hyperparathyroidism described by Von Recklinghausen (6). Bone problems in hyperparathyroidism include generalized and focal bone pain with fragility fractures. Radiologic changes appear in severe forms and reflect a generalized increase in osteoclastic and osteoblastic activity. This high bone turn-over shows in radiography a general demineralization, a subperiosteal resorption that may progress to extensive cortical resorption, bone cysts of central medullary portions, salt-and-pepper radiographic appearance of skull bones and brown tumors that are frequent in trabecular portions of the jaw, ribs, and long bones. Histopathologically, osteoclastomas are composed of giant cells mixed with stromal cells (7). There is controversy about the necessity of surgical treatment for brown tumors because it may cause delayed bone regeneration and unnecessary bone defect. However, spontaneous resolution after parathyroidectomy may take years (8).

The ossifying fibroma which is distinct of brown tumors is a rare osteogenic benign tumor. It is composed of fibrous tissue with varying amounts of calcified and like-bone material. It is related to a disorder of congenital dental tissue maturation so that it occurs exclusively in maxillofacial skeleton. Ossifying fibroma is clinically revealed by slow growth and indolent bone tumefaction. It has the ability to represses adjacent organs without destroying them (9). Complete surgical removal is then recommended with a possible recurrence in HPT-JT syndrome.

The contemporary approach of PHPT allows the diagnosis of hyperparathyroidism at an early stage well before bone and renal events. The presence of a jaw bone tumor can lead to the diagnosis of a brown tumor; however, an ossifying fibroma should not be omitted. Indeed, the painless character, insidious evolution and the absence of giant cells at pathology are all arguments in favor of the ossifying fibroma. On the other hand, we believe that screening for PHPT in ossifying fibroma could be well-founded. In our patient, no associated tumor involvement has been found. The benign parathyroid lesion does not exempt us of a close medical monitoring.

Conclusion

HPT-JT is a rare condition in which PHPT may be recurrent with increased risk of parathyroid malignancy. The association with other non-endocrine malignancies should initiate a systematic investigation. Patients and selected relatives must undergo genetic analyses and a long time follow-up.

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