Endocrinology, Diabetes & Metabolism CASE REPORTS

A Casteràs and others | Brown tumor in MEN1

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Brown tumor of the jaw after pregnancy and lactation in a MEN1 patient

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Summary

Skeletal manifestations of primary hyperparathyroidism (pHPT) include brown tumors (BT), which are osteoclastic focal lesions often localized in the jaws. Brown tumors are a rare manifestation of pHTP in Europe and USA; however, they are frequent in developing countries, probably related to vitamin D deficiency and longer duration and severity of disease. In the majority of cases, the removal of the parathyroid adenoma is enough for the bone to remineralize, but other cases require surgery. Hyperparathyroidism in MEN1 develops early, and is multiglandular and the timing of surgery remains questionable. To our knowledge, there are no reports of BT in MEN 1 patients. We present a 29-year-old woman with MEN 1 who developed a brown tumor of the jaw 24 months after getting pregnant, while breastfeeding. Serum corrected calcium remained under 2.7 during gestation, and at that point reached a maximum of 2.82 mmol/L. Concomitant PTH was 196 pg/mL, vitamin D 13.7 ng/mL and alkaline phosphatase 150 IU/L. Bone mineral density showed osteopenia on spine and femoral neck (both *T*-scores = −1.6). Total parathyroidectomy was performed within two weeks, with a failed glandular graft autotransplantation, leading to permanent hypoparathyroidism. Two months after removal of parathyroid glands, the jaw tumor did not shrink; thus, finally it was successfully excised. We hypothesize that higher vitamin D and mineral requirements during maternity may have triggered an accelerated bone resorption followed by appearance of the jaw BT. We suggest to treat pHPT before planning a pregnancy in MEN1 women or otherwise supplement with vitamin D, although this approach may precipitate severe hypercalcemia.

Learning points:

- Brown tumors of the jaw can develop in MEN 1 patients with primary hyperparathyroidism at a young age (less than 30 years).
- Pregnancy and lactation might trigger brown tumors by increasing mineral and vitamin D requirements.
- Early parathyroidectomy is advisable in MEN 1 patients with primary hyperparathyroidism, at least before planning a pregnancy.
- Standard bone mineral density does not correlate with the risk of appearance of a brown tumor.
- Removal of parathyroid glands does not always lead to the shrinkage of the brown tumor, and surgical excision may be necessary.

Background

In recent years, the majority of patients with primary hyperparathyroidism (pHPT) in developed countries are asymptomatic, detected on routine testing and less than 5% display classic skeletal lesions named osteitis fibrosa cystica (OFC) (1). Brown tumors (BT), a localized form of OFC, are central giant cell lesions that are believed to occur in patients with severe or longstanding hyperparathyroidism. Very high PTH levels are frequently

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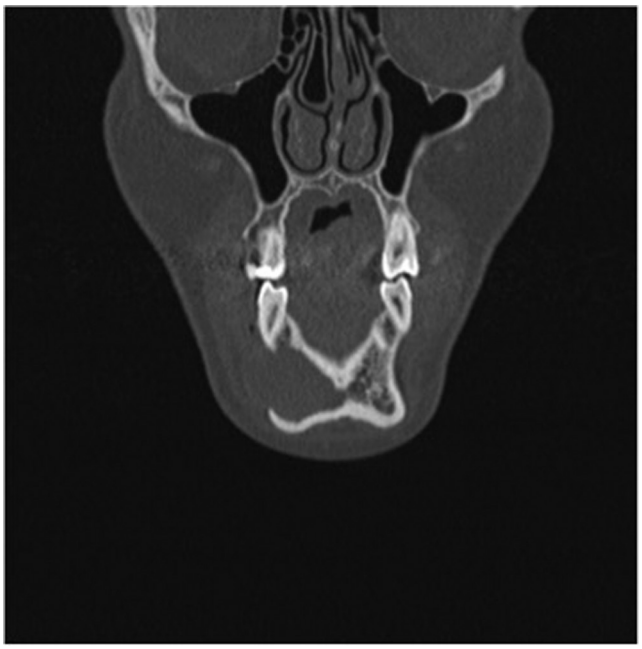

Figure 1
Computed tomography: well-demarcated monolocular osteolytic lesion on the right side of the mandibular body. Cortical bone is expanded and thinned.

found/associated in/with brown tumors, which have also been reported in secondary HPT, parathyroid carcinoma as well as paraneoplastic syndrome (PTHrP) (2). Although they are a rare finding in Europe and USA, brown tumors are common in developing countries affecting more than half of the patients (3). These figures are attributed to malnourishment and vitamin D deficiency, added to a delayed diagnosis. In that sense, pregnancy and breastfeeding have not been linked to BT development and only a couple of cases are found in literature. A hallmark of multiple endocrine neoplasia type 1 (MEN 1) is the early development of pHPT, but no cases of BT have been reported in adolescents and young adults, compatible with regular screening and early parathyroidectomy. BT generally shrinks or resolves after parathyroidectomy, but some cases may require surgery due to rapid progression or location affecting vital structures.

Case presentation

A female patient carrier of a MEN 1 mutation (p.Val184Glu in exon 3 of MEN1 gene) was first screened for associated neoplasms at the age of 28 years. Primary hyperparathyroidism was the only comorbidity found

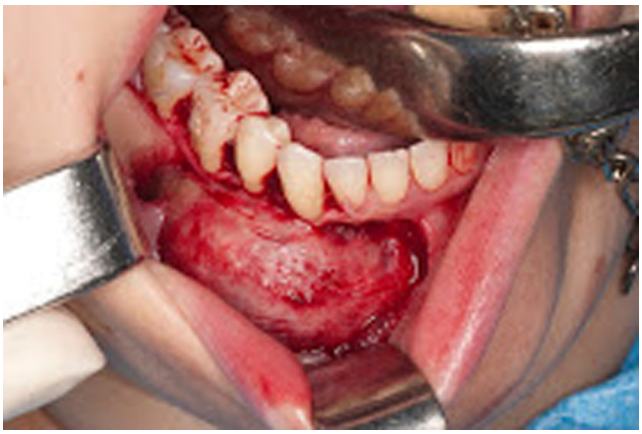

Figure 2
Surgical view during the removal of the mandibular tumor.

at that time. MRI images and hormonal studies failed to demonstrate gastroenteropancreatic neuroendocrine tumors, as well as pituitary adenoma.

Serum total calcium was 2.74 mmol/L initially (normal values 2.2–2.54), with normal serum phosphate (0.87 mmol/L, n.v. 0.8–1.45) and mildly elevated PTH (146 pg/mL; n.v. 14.5–87.1). Vitamin D status was suboptimal (15 ng/mL; n.v. 31–80), but no specific supplementation was recommended apart from diet and sun exposure. Bone mineral density (BMD) scan showed osteopenia in spine (T –1.05), but normal density in femoral neck. She did not suffer from complications such as nephrolithiasis, bone pain or deformities.

Localization studies found a cervical nodule compatible with parathyroid adenoma on the left side on ultrasound, which correlated with a high MIBI uptake on scintigraphy. At that time, surgery was advised, but she moved abroad and was postponed.

A year thereafter (29 years) she got pregnant and gave birth to a female healthy baby without obstetric problems. During pregnancy, calcium was maintained below 2.7 mmol/L. Abundant hydration was recommended, but no vitamin D or calcium supplementation was provided apart from a healthy diet.

Suddenly, 15 months after delivery, the patient noticed a palpable and visible swelling in the right-sided mandible, which doubled volume in 2 months. She was still breastfeeding but was advised against at that moment. At that point, serum calcium level had reached a maximum of 2.82 mmol/L, phosphate remained normal, concomitant PTH was 196 pg/mL, vitamin D 13.7 ng/mL and alkaline phosphatase

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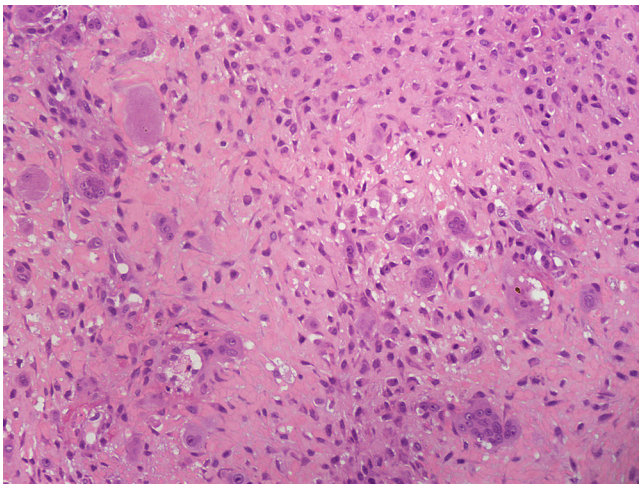

Figure 3
Hematoxylin-eosin staining (400× magnification) of the jaw mass. Proliferation of mesenchymal cells with oval nuclei and eosinophilic cytoplasm. Scattered throughout the stroma are numerous osteoclast-like multinucleated giant cells containing varying numbers of vesicular nuclei.

150 IU/L (n.v. 30–120) (Table 1) . Bone mineral density showed increasing osteopenia on spine and femoral neck (both *T*-scores = –1.6).

Physical examination by maxillofacial surgeon detected cortical bulging and fluctuation in vestibular inner side. Computed tomography showed a mandibular cyst, compatible with a brown tumor according to the medical information.

Physical exam at this time gave a body weight of 80 kg, height 165 cm, blood pressure 107/67, with no signs of pituitary hyper/hypofunction.

Investigation

Computed tomography (Fig. 1): well-demarcated monolocular osteolytic lesion on the right side of the mandibular body. Cortical bone is expanded and thinned.

Bone scintigraphy: retention only on mandible.

Tumor biopsy: giant cell tumor.

Treatment

Parathyroidectomy was performed two weeks thereafter, four glands were removed and half of one was transplanted into the left sternocleidomastoid muscle. Pathological exam revealed a parathyroid adenoma sized 2 × 1 × 0.5 cm in the left superior gland, and hyperplasia on another gland. Prophylactic thymectomy was done in the same act. Postoperatively mild hypocalcemia developed, probably related to hungry bone syndrome. Besides, the parathyroid graft failed, and permanent hypoparathyroidism is under control with calcitriol 1 µg and calcium carbonate 2400 mg daily. The mandibular cyst did not shrink 2 months after parathyroidectomy, and even displayed some growth, putting teeth in danger. Enucleation was then carried out (Fig. 2) with good aesthetic results.

Outcome and follow-up

Pathology study showed a 4 cm giant cell granuloma (Fig. 3). The mandibular tumor has not reappeared after 20-month follow-up. As a collateral adverse event, she displays anesthesia on the mentonian area.

Discussion

Skeletal involvement in classic pHPT is characterized by a strikingly high rate of osteoclastic bone resorption. It is accompanied by a cellular repair process that results in the accumulation of fibrous stroma and connective tissue cells along with multinucleated giant cells. Brown tumors are osteolytic focal giant cell lesions localized in areas of intense bone resorption, preferentially facial skeleton (e.g. mandible, maxilla) but also clavicle, ribs and pelvic bones.

BTs are not true neoplasms, but they can be locally aggressive and mimic malignancies. Histological features alone cannot establish a certain diagnosis; thus, it should be confirmed by the endocrine status of the patient. Among differential diagnosis of giant cell lesions, we have to consider

Table 1 Phosphor-calcium metabolism parameters.

			Pregnancy		Postpartum; Lactation		
Parameters	**Reference values**	**At diagnosis** (28 y)	1st trimester (29 y)	3rd trimester	7 months	15 months*	**2 months after parathyroidectomy**
Calcium (mmol/L)	2.2–2.54	2.74	2.54	2.57	2.67	2.82	2.22
Phosphor (mmol/L)	0.8–1.45	0.87		1.06	0.87	0.8	1.19
PTH (pg/mL)	14.5–87.1	146		106	123	196	14
Vitamin D (ng/mL)	31–80	15.1		16.3	14	15.2	20
AKP (IU/L)	30–120	119				150	104

AKP, alkaline phosphatase; *Brown tumor appearance

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reparative giant cell granuloma, cherubism, aneurysmal bone cyst or true giant cell tumors. When localized in jaws, BT can also simulate ameloblastoma or odontogenic cysts. Ossifying fibromas of the mandible or maxilla, also known as cementifying fibromas occur in 30–40% of individuals with hyperparathyroidism-jaw tumor syndrome, included in CDC73-related disorders, but these tumors show different radiologic and histologic traits. On imaging, brown tumors appear as lytic lesions with regular borders and thinned cortical bone, not accompanied by periosteal reaction or inflammatory signs. Concomitant signs like salt-and-pepper bone changes, subperiosteal bone resorption and disappearance of the lamina dura around the roots of the teeth may help with the differential diagnosis.

The incidence of brown tumors varies considerably among regions. In developing countries (e.g. India), OFC/BTs are quite common, seen in 50–90% of patients. Primary HPT presents at younger ages than in Western countries, with higher levels of calcium and PTH, and larger adenomas, compatible with vitamin D depletion and skeletal PTH resistance. In Western countries, pHPT is uncommon in adolescents and young adults (3% of parathyroid surgeries) (5), BTs account for around 1.5% of all cases, and are rarely the first manifestations of pHPT.

BTs are in general more probable in people aged more than 50 years, as a manifestation of longstanding hyperparathyroidism, but there are several reports in young adults, presumably depending on the existence of vitamin D deficiency or other pathogenetic factors (3).

Proposed predictors of OFC or brown tumors are high levels of PTH and large parathyroid adenoma. BTs usually go with high alkaline phosphatase (more than 1000 IU/L), reflecting high bone turnover (4). Bone densitometry seems not predictive for BT, but this is not well studied.

BTs are in general three times more common in women than in men. The female predominance could be related to different phosphocalcic metabolism, with less sun exposure, and more calcium and vitamin D requirements during maternity. Although this has not been addressed properly, there are 2 reports of BT occurring in pregnant women (5, 6), but vitamin D status is not reported. Indian series do not inform of a temporal relationship with eventual pregnancies or breastfeeding among affected women.

During lactation, maternal calcium and bone metabolism must adapt to an extra demand for calcium (300–400 mg/days). The major source calcium in this setting is bone, and to a lower extent, increased dietary calcium intake and renal retention (7). It is known that maternal bone mass declines during lactation, about 10% over the first 6 months (predominantly trabecular bone), whereas calcium levels rise slightly and PTH decreases. Lactating breast secretes PTHrP into the systemic circulation and into milk and is the only instance in which circulates, apart from malignancies. PTHrP mobilizes skeletal calcium stores to be delivered to the breast for milk. Concomitant estrogen deficiency secondary to hypogonadotrophic hypogonadism may increase bone turnover and bone loss. On the other hand, polymorphisms in vitamin D receptor (VDR) gene could contribute to differences in the skeletal response to lactation (8). These mechanisms, added to an underlying primary PTH in our patient, would have worsened bone lytic lesions, although these are speculative explanations.

In regard to MEN1, to our knowledge, there are no reports of brown tumors. In a wide French series (9), pHPT was present in 96% of patients, and already in 75% of those younger than 21 years (10). Mean age of diagnosis of pHPT was 16 ± 4 years and was very rare before 6 years. PHPT was the first manifestation of the disease in 56% of them, the majority by biological screening, being only 17% symptomatic (urolithiasis 86%, fatigue 33%, bone pain 1%). No gender-related differences in MEN1 hyperparathyroidism occurrence were detected.

Opinions are divided on the course and management of the bony lesions once parathyroidectomy has been carried out. Reséndiz-Colosia *et al.* (1) reported that of 22 patients with BT (68.2% in the mandible, 31.8% in maxilla) all presented a spontaneous progressive regression after parathyroidectomy; indeed, in 18 cases it was resolved after 10 months. However, the tumor can display different response patterns (3), and if it is very destructive, disfiguring or causes functional problems, surgical excision may be indicated as in our case.

On the other hand, OFC may regress at least in renal secondary hyperparathyroidism after oral therapy with vitamin D and subsequent reduction of PTH. Vitamin D receptor genotype may also regulate the response to the vitamin D supplementation.

Here arises the question whether pHTP should be replaced with vitamin D as it may not worsen hypercalcemia and can prevent skeletal disturbances, as well as ameliorate hungry bone syndrome after resection. Current guidelines recommend the measurement of serum 25-hydroxy-cholecalciferol and supplement if levels are less than 20 ng/mL. According to the present case, we fully agree, especially in childbearing age, aiming to avoid OFC. However, it seems safer to surgically solve pHPT before planning maternity.

In our case, PTH, calcemia or alkaline phosphatase was not too high, and standard bone density was not very

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low; therefore, we attribute the development of BT to an acute bone mineral and vitamin depletion in gestation and breastfeeding.

Patient's perspective

The patient suggests that an earlier mandibular tumor resection would have been more practical.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent

Written informed consent was obtained from the patient for publication of this case report.

Author contribution statement

Anna Casteràs (medical doctor) is responsible for the endocrine care of the patient and wrote the paper. Carles Zafon (medical doctor) and Jordi Mesa (head of endocrine department) participated in medical decisions and helped with the discussion. Juan Antonio Hueto and Lídia Darder (maxillofacial surgeons) performed the surgical removal of the BT and contributed with photographs. Enric Caubet is the endocrine surgeon for parathyroidectomy. Margarita Alberola provided the pathology report.

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