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 pHPT 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 MEN1 patients. We present a 29-year-old woman with MEN1 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 MEN1 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 MEN1 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
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 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 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

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

Figure 2
Surgical view during the removal of the mandibular tumor.
Brown tumor in MEN1

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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.

Table 1 Phosphor-calcium metabolism parameters.

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

AKP, alkaline phosphatase; *Brown tumor appearance

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

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.
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Brown tumors are rare benign bone tumors that result from increased bone remodeling, typically associated with hyperparathyroidism (HPT) or other hypercalcemic states. Although they are relatively uncommon, they can present a diagnostic challenge due to their variable clinical manifestations. Brown tumors are usually large lesions that may affect the craniofacial and long bones. 

**Reproductive aspects of brown tumors:**

Brown tumors can appear in women of childbearing age, and they are more common in women than in men. They may be encountered during pregnancy or lactation, which can be challenging, especially if there is associated hyperparathyroidism. The bone density in affected breasts may be lower than in non-affected breasts, and it is important to monitor bone density during pregnancy and lactation.

During pregnancy, the increased estrogen levels can contribute to bone loss, while lactation can lead to a decrease in maternal bone mass. These physiological changes can lead to an increased likelihood of osteoporotic fractures and may also be exacerbated by any underlying hyperparathyroidism.

**Prognostic factors for bone loss:**

Brown tumors can lead to bone loss in the affected bones. It is important to monitor bone density in affected areas and adjust medication as necessary. The presence of brown tumors in MEN1 syndrome can increase the risk of bone loss, and close monitoring of bone density is essential to prevent complications.

**Management of brown tumors:**

The primary goal in managing brown tumors is to control the underlying cause, such as hyperparathyroidism. Treatment options include surgical excision, medical management, and other interventions to improve bone density and prevent complications. Close follow-up and monitoring of bone density are essential to ensure effective management.

**Conclusion:**

Brown tumors can be a significant concern in women of childbearing age, particularly those with MEN1 syndrome or other hyperparathyroid states. Early recognition and effective management can help prevent complications and maintain bone health. Further research is needed to better understand the pathophysiology of brown tumors and improve treatment strategies.

http://www.edmcasereports.com

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

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**Patient's perspective**
The patient suggests that an earlier mandibular tumor resection would have been more practical.

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**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.

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**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 (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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**References**


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