Brown tumour: presenting symptom of primary hyperparathyroidism

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Abstract. Brown tumour: presenting symptom of primary hyperparathyroidism. The skeletal lesions of primary hyperparathyroidism, including brown tumour, are rare nowadays, with the practice of checking serum calcium levels leading to an earlier diagnosis of hyperparathyroidism. Clinical, laboratory, radiographic and histological investigations can lead to a correct diagnosis. Treatment of brown tumour focuses on the hyperparathyroidism, and is usually followed by a regression of the brown tumour. The diagnosis of hyperparathyroidism and brown tumour should be considered in patients with hypercalcaemia and an osteolytic expansive bone lesion. We present a patient where a brown tumour of the mandible was the presenting symptom of primary hyperparathyroidism.

Introduction

The practice of checking serum calcium in routine blood samples has led to the earlier diagnosis and successful management of primary hyperparathyroidism (HPT), which in turn have resulted in advanced disease becoming rare, and clinicians have lost familiarity with these end-stage manifestations. Classic skeletal lesions, which include bone resorption, bone cysts, brown tumour and generalised osteopenia, now belong to the past and occur in fewer than 5% of cases. Brown tumours (osteitis fibrosa cystica or von Recklinghausen disease) are focal lesions resulting from abnormal bone metabolism in HPT.1,2

We present a patient where a brown tumour of the condyle of the mandible was the presenting symptom of primary HPT in the absence of clinically manifest symptoms of elevated serum calcium.

Case report

A 57-year-old woman attended one of the University Hospitals of Leuven because of a lump anteromedially of the left temporomandibular joint (TMJ), causing some pain occasionally.

The history and the physical examination did not reveal abnormalities. A complete review of systems was unremarkable: there was no fatigue, malaise, joint pain, polyuria, or abdominal discomfort.

The patient had a history of meningioma (left frontoparietal region), managed surgically in 1994, and a relative thrombopenia of 108 10⁹/l diagnosed on the occasion of this surgery and of unknown origin, despite investigation. Clinical examination failed to identify any visible mass in the left temporal area. The mandibular movements were normal.

Computed tomography (CT) (Figure 1) and magnetic resonance imaging (MRI) (Figure 2) revealed a mass medially and anteriorly of the left condyle of the mandible, eroding the eminentia articularis and the root of the arcus zygomaticus. An enlarged lymph node, less than 1 cm in size, was also noted at the left mandibular angle.

Laboratory tests revealed elevated serum calcium of 11.34 mg/dl (nl 8.60–10.00 mg/dl) and...
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an albumin level of 46.6 g/l (nl 35.0–52.0 g/l).

A ⁹⁹mTc MDP bone scan showed an area of elevated osseous metabolism in the left TMJ (Figure 3).

A biopsy through a pre-auricular incision (pre-tragal) was performed and showed a giant cell granuloma with haemosiderin, suggesting the diagnosis of brown tumour (confirmation by histochemical analysis) (Figure 4).

Because of the coexistent presence of an osteitis fibrosa cystica and hypercalcaemia, screening for

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**Figure 1**
Mixed radio-lucent/radio-opaque (osteolytic lesion) mass medially and anteriorly of the left condyle of the mandible, eroding the eminentia articularis and the root of the arcus zygomaticus on computed tomography.

**Figure 2**
Mixed hypo-intense/hyper-intense and captating contrast mass medially and anteriorly of the left condyle of the mandible on magnetic resonance imaging.

**Figure 3**
⁹⁹mTc MDP bone scan with an area of elevated osseous metabolism in the left TMJ.

**Figure 4**
Giant cell granuloma or brown tumour with the multinucleated giant cells (broad arrow) and the accumulation of haemosiderin (fine arrow) which imparts the brown colour.
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Table 1

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
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<tbody>
<tr>
<td>Calcium (nl 8.60-10.00 mg/dl)</td>
<td>11.00 mg/dl</td>
</tr>
<tr>
<td>Phosphate (nl 2.30-4.70 mg/dl)</td>
<td>2.15 mg/dl</td>
</tr>
<tr>
<td>25-OH-vitamine D (nl 7.0-60.0 µg/l)</td>
<td>42.8 µg/l</td>
</tr>
<tr>
<td>1.25-OH-vitamine D (nl 20.0-80.0 ng/l)</td>
<td>57.3 ng/l</td>
</tr>
<tr>
<td>Parathormone (nl 3.0-40.0 ng/l)</td>
<td>13.6 ng/l</td>
</tr>
<tr>
<td>Osteocalcine (nl 11.0-43.0 µg/l)</td>
<td>32.4 µg/l</td>
</tr>
<tr>
<td>Thyroid stimulating hormone (nl 0.15-4.60 mL/l)</td>
<td>0.48 mL/l</td>
</tr>
<tr>
<td>Calculated calcium/creatinine clearance</td>
<td>0.024</td>
</tr>
<tr>
<td>Alkaline phosphatase (nl &lt;= 240 U/l)</td>
<td>208 U/l</td>
</tr>
<tr>
<td>Serum protein electrophoresis</td>
<td>normal</td>
</tr>
</tbody>
</table>

hyperparathyroidism was subsequently performed.

An extended blood analysis was performed to unravel the origin of the high serum calcium. The results are listed in Table 1. The high serum calcium with normal PTH was diagnostic for primary HPT, which was further investigated.

A bone densitometry revealed axial and femoral osteopenia (T-score femur: –1.33; T-score lumbar spine: –1.22).

Ultrasonography of the kidneys revealed no evidence of nephrolithiasis.

The parathyroid glands could not be visualised with ultrasonography and the size of the thyroid gland was normal.

A 99mTc Sestamibi – 123I subtraction scan of the parathyroid glands revealed an adenoma in, exceptionally, two parathyroid glands, one at the lower pole of the right thyroid and possibly one at the left upper pole (Figure 5). Both parathyroid glands were resected and microscopic examination confirmed the diagnosis of parathyroid adenoma in both glands (Figure 6).

The patient is currently free of symptoms and MRI shows a slight reduction of the lesion. PTH is normal (3.8 ng/l) with normocalcaemia (9.07 mg/dl).

Discussion

Definition and incidence

Brown tumour, first described by von Recklinghausen in 1891, is a focal osteoclastic defect of the bone resulting from HPT and leading to the formation of cystic-like lesions, which are sites of focal bone resorption. It usually affects the pelvis, ribs, clavicles, extremities and mandible.

The association between osteitis fibrosa cystica and parathyroid adenoma was first recorded in 1904 by Askanazy, whereas the link between PTH and calcium metabolism was not described until 1915.

Although primary HPT has a multitude of possible clinical presentations (the classic “bones, stones, abdominal groans and psychic moans”), it is becoming increasingly rare for the disease to present with only skeletal manifestations, as in this case. In recent years, primary HPT has been most often diagnosed by elevated serum calcium during routine or unrelated blood screening.

The incidence of primary HPT is approximately 50 cases per 100,000 population. The incidence of brown tumour is 3% per year in primary HPT, and it is caused by parathyroid adenoma (one or, exceptionally, two, as in this patient) or hyperplasia of the parathyroid gland.

Clinical features and diagnosis

The diagnosis of a brown tumour resulting from primary HPT is suggested by clinical history and confirmed by laboratory investigations, together with radiographic studies and pathological examination.

The differential diagnosis of concurrent hypercalcaemia and osteolytic lesions is limited to HPT and osteolytic metastases (malignancies).

Clinically, brown tumours most commonly present as slowly growing masses, which can be painful. Patients often have additional manifestations associated with HPT. In this case we had an occult osteitis fibrosa cystica: this patient complained of diffuse pain in the left TMJ area (due to the
brown tumour) but there was no clinically manifest symptom of primary hyperparathyroidism, except for the axial and femoral osteopenia on 99mTc MDP bone scan. In this case the differential diagnosis included a mass in the parotid gland at this stage.

Radiologically, brown tumours appear as well-defined lytic lesions and are the result of extensive localised bone resorption. They should be differentiated from osteolytic metastasis.6,7 Radiology could exclude a lesion in the parotid gland.

99mTc MDP and 99mTc MIBI accumulates within skeletal lesions of primary and secondary HPT and pathological examination is very typical.

Macroscopically, brown tumours are smooth, brown masses that may have cystic spaces. Microscopically, they represent localised areas of marrow replacement by vascularised fibrous tissue and osteoclast-like giant cells; haemorrhage and haemosiderin pigmentation impart the characteristic brown color.10

It is impossible to distinguish a brown cell tumour from a reparative granuloma on histological grounds, as they both exhibit multinucleated macrophages with ingrowth of reactive fibrous tissue secondary to micro-fractures of the thinned bone.6,10

The pathological examination could exclude malignancy.

Due to the radiological and histological similarities between brown tumours, reparative granulomas and true giant cell tumours, diagnosis of brown tumour relies on finding evidence of HPT.11 In this patient, a distinct hypercalcaemia of 11.00 mg/dl (nl 8.60-10.00 mg/dl) was present. Parathormone (PTH) level was 13.6 ng/l (nl 3.0-40.0 ng/l). A PTH level of 13.6 ng/l with a calcaemia of 11.00 mg/dl is diagnostic of primary hyperparathyroidism.

The location of the secreting parathyroid can be determined by localisation techniques, such as ultrasonography, CT or MRI (in our patient these examinations failed to detect parathyroid adenoma with certainty) and nuclear medicine techniques. Numerous studies have shown that 99mTc Sestamibi is the most adequate technique for the detection of parathyroid adenomas and offers advantages over 201Tl - 99mTc subtraction scanning.12

The 99mTc Sestamibi - 123I subtraction technique is superior to the single-tracer, double-phase technique in the detection of parathyroid adenomas or hyperplasia; it is useful in planning parathyroid surgery and it is cost-effective.13

In this patient, a 99mTc Sestamibi - 123I subtraction scan revealed a parathyroid adenoma at the lower pole of the right thyroid and possibly one at the left upper pole. Both localisations were confirmed by histological examination after surgical resection.

Hyperparathyroidism-jaw tumour syndrome (HPT-JT syndrome) is an autosomal dominant disorder characterised by parathyroid adenoma or carcinoma, fibrous osteous lesions (ossifying fibroma) of the mandible and maxilla, and renal cysts and tumours. The recently identified gene associated with the HPT-JT syndrome, HRPT2, maps to 1q25-q32 and encodes a novel protein of unknown function called parafibromin. The presence of inactivating HRPT2 mutations in the HPT-JT syndrome suggests that HRPT2 may be a tumour-suppressor gene.14

This mutation was not present in our patient.

Treatment and outcome

Treatment of brown tumour depends on the treatment of hyperparathyroidism. In patients with primary hyperparathyroidism, parathyroidectomy results in the normalisation of biochemical values, increased bone mineral density and regression of brown tumour to a significant degree.15

The literature includes a description of the spontaneous healing of a brown tumour.16
Brown tumour

If there is no regression, and if the lesion is symptomatic, surgical resection or curettage of the brown tumour is feasible.

In this patient, a slight reduction in volume has now been observed, nine months after parathyroidectomy. There is no indication for surgical resection, as the patient is free of symptoms.

Conclusion

Primary hyperparathyroidism presenting with bone lesions and without any other symptom of hypercalcaemia is now uncommon. However, this patient with primary hyperparathyroidism (and, exceptionally, two parathyroid adenomas) presenting as an ostitis fibrosa cystica demonstrates that, even today, the spectrum of the clinical manifestations of this disease still includes bone lesions.

The diagnosis of hyperparathyroidism and brown tumour should be considered in any patient with hypercalcaemia and a destructive expansive bone lesion.

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References


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