CASE REPORT

Multiple brown tumours from parathyroid carcinoma

Daryl Jade Tardo Dagang, Jerico Baliton Gutierrez, Mark Anthony Santiago Sandoval, Frances Lina Lantion-Ang

Section of Endocrinology, Diabetes and Metabolism, Department of Medicine, Philippine General Hospital, University of the Philippines Manila, Manila, Philippines

Correspondence to

Dr Daryl Jade Tardo Dagang, daryldagang@gmail.com

Accepted 14 June 2016

SUMMARY

We report a case of a 29-year-old woman who suffered from severe bilateral inguinal pain and left mandibular mass. CT scan showed innumerable expansile osteolytic bone masses on the iliac wings, femur, ribs and vertebral bodies, diffuse skeletal osteopaenia, calyceal lithiasis on the right kidney and a left thyroid mass. Ionised calcium and intact parathyroid hormone (PTH) were elevated. Parathyroid sestamibi scan showed a hyperfunctioning left inferior parathyroid gland. Biopsy of the left mandibular mass was consistent with brown tumour. The patient underwent parathyroidectomy of the enlarged parathyroid gland. Final histopathology, however, revealed parathyroid carcinoma, 4.7 cm in widest dimension, with capsular and vascular space invasion. The patient underwent repeat surgery, specifically, left thyroid lobectomy, isthmectomy and central node dissection. Intact PTH decreased from 681.3 to 74 pg/mL (normal range: 10–65) 24 hours postoperatively. Follow-up at 6 months showed normal serum calcium levels, size reduction of bone lesions and improvement of quality of life.

BACKGROUND

Brown tumours are focal, benign bony lesions caused by rapid osteoclastic turnover of bone, resulting from direct effects of parathyroid hormone (PTH). The development of large multiple brown tumours is a rare complication of primary hyperparathyroidism; and even rarer is parathyroid carcinoma as the cause. Occurring in 15% of patients with primary hyperparathyroidism, brown tumours from excessive skeletal resorption can affect any bone in the body, particularly the ribs, clavicle and pelvis. Since the associated hypercalcaemia is often discovered incidentally during routine laboratory testing, the incidence of brown tumours has reportedly declined to 0.1% recently.¹ Moreover, brown tumours are often reported as solitary tumours, and there are few reports of multiple cases. A solitary adenoma is the most common cause of primary hyperparathyroidism, followed by hyperplasia and carcinoma. Parathyroid carcinoma is a rare endocrine malignancy with a reported incidence of <1% of all primary hyperparathyroidism.²

CASE PRESENTATION

Our patient was a 29-year-old woman who presented with bilateral inguinal pain. Two years prior to admission, she had experienced vague hip and back pain while pregnant at 32 weeks of gestation. She had been admitted for preterm labour and discharged with the pain still persisting. She eventually

delivered a live baby girl via caesarean section; at this point, she was already experiencing intermittent left inguinal pain with visual analogue score (VAS) 5/10, stabbing in quality, and radiating to the left thigh. One year prior to admission, she had fallen from standing height, hitting her left hip to the ground, which caused severe left hip pain with VAS 8/10. She was still ambulatory but already needed assistance to walk. This prompted a consult, where hip radiographs were taken showing ill-defined lytic lesions in the ilium and ischium, interpreted as metabolic disease versus new growth. There was no intervention carried out except for the prescription of pain relievers. Six months prior to admission, palpable, tender, egg-shaped masses had been noted on the bilateral inguinal area, associated with extreme pain on passive and active movement of the hips, hence the patient became bedridden. She eventually decided to seek a consult at our institution, for further assessment and management.

Pertinent in the review of systems was that she only had weight loss but with no anorexia. Neurological, cardiovascular, pulmonary, gastrointestinal and genitourinary systems were unremarkable. She had no known comorbidities, no prior history of tuberculosis, no known allergies and no prior surgical interventions except for her recent caesarean section. She had a strong family history of diabetes from parents; one of her sisters had goitre, and she had an aunt with breast cancer and an uncle with colon cancer. She was G2P1 with one history of spontaneous abortion. She had one child delivered via caesarean section, who was breast fed for 2 months. She denied illicit drug use, alcoholism and smoking. She was a college graduate but was unable to work and was partially dependent for her activities of daily living due to her illness.

On physical examination, she was bedridden, with normal vital signs. There were deep-seated palpable 8.0×5.0 cm masses on bilateral hips and 5.0×3.0 cm masses on bilateral knees. There was tenderness and pain on, active and passive motion of hips, knees and shoulders. A 3.0×3.0×2.0 cm gingival mass was noted on the left mandible, with soft tissue necrosis (figure 1). The rest of the systemic physical examination was unremarkable.

INVESTIGATIONS

Pelvic X-rays showed ill-defined lytic lesions in bilateral iliac bones and right ischial bone. Pelvic MRI showed multiple cystic foci and focal bone expansion on iliac wings. Neck, chest and

CrossMark

To cite: Dagang DJT, Gutierrez JB, Sandoval MAS, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2016-215961

Figure 1 Left mandibular mass.

abdominal CT scan also showed innumerable expansile osteolytic bone masses on bilateral iliac wings, bilateral femurs, ribs and vertebral bodies (figure 2), diffuse skeletal osteopaenia, calyceal lithiasis on the right kidney and a 3.8×2.6×1.8 cm left thyroid mass (figure 3). Ionised calcium was at 1.66 mmol/L (normal range: 1.10–1.40) and intact PTH was at 681.3 pg/mL (normal range: 10.0–65.0). Parathyroid sestamibi scan showed a hyperfunctioning parathyroid gland inferior to the left thyroid lobe (figure 4). Serum protein electrophoresis showed normal findings. Bone marrow core biopsy showed fragments of mature trabecular bone with fibrosis. Core needle biopsy of the left mandibular mass was interpreted as peripheral giant cell granuloma (figure 5), which was histologically identical to a brown tumour, considering the patient's clinical picture. Bone densitometry was not performed due to technical difficulty on positioning, as the patient had severe pain on hip flexion.

DIFFERENTIAL DIAGNOSIS

Although the majority of cases occur among the elderly, multiple myeloma has been known to occur in younger patients; but the normal serum protein electrophoresis and non-diagnostic bone marrow examination practically rules out this diagnosis. The most common of all bone tumours, metastatic bone disease is also a likely pathology due to the multifocal skeletal involvement, along with constitutional symptoms such as weight loss and severe bone pain. When the CT scan was reviewed, no primary tumours were seen in the chest and abdomen, but the CT scan of the neck revealed a mass in the left cervical area and confirmed that the gingival tumour identified was indeed a lytic lesion in the mandible. One scenario considered was a possible thyroid malignancy with multiple bone metastases; however, the biopsy of the said gingival tumour was interpreted as a peripheral giant cell tumour. Brown tumours are easily confused with giant cell tumours by histology.³ The occurrence of brown tumours in hyperparathyroidism, once part of the classical form, is now considered rare in the first world, but is still found in developing countries. While an enlarged parathyroid adenoma may be difficult to distinguish radiologically from the thyroid gland, the parathyroid sestamibi scan showed a hyperfunctioning gland, thus brown tumours were highly considered. In the absence of clinical renal disease, and with significantly elevated serum calcium, primary hyperparathyroidism causing brown tumours appeared to be the most likely aetiology.

Osteoporosis in pregnancy was considered less likely in our case because the patient had worsening symptoms and bone lesions even after a year postpartum. It is during this period that we expect some resolution or even normalisation of bone status if we suspect this condition.

Figure 2 Radiology findings. Plain pelvic radiograph showing ill-defined lytic lesions in bilateral iliac bones and right ischial bone (white arrows) (A). Pelvic MRI showing multiple short-T1 inversion recovery hyperintense foci and focal bone expansion on iliac wings (white arrows) (B). CT scan of the pelvis, axial view, showing the lytic lesions on the femoral heads (white arrows) (C). CT scan of the abdomen, sagittal view, showing osteolytic masses on the vertebral bodies (white arrows) (D).

Figure 3 CT scan of the neck, coronal view, showing a left inferior thyroid mass (blue arrow).

TREATMENT

The patient underwent focused parathyroidectomy of the enlarged parathyroid gland. Final histopathology, however, revealed parathyroid carcinoma, 4.7 cm in widest tumour dimension, with capsular and vascular space invasion (*figure 6*). There was immediate decrease of intact PTH to 74 pg/mL 24 hours postoperatively. Owing to the malignant nature of the tumour, the patient underwent repeat surgery, specifically, left thyroid lobectomy, isthmectomy and central node dissection. Histopathology showed two reactive lymph nodes and unremarkable thyroid tissue.

OUTCOME AND FOLLOW-UP

The resection of the tumour resulted in severe hungry bone syndrome, for which calcium and calcitriol supplementation was required. Acute management of hypocalcaemia involved calcium gluconate intravenous infusion and calcitriol per orem. The patient was discharged on calcium carbonate 3000 mg/day and calcitriol 1.5 µg/day. Follow-up at 6 months showed normal

Figure 4 Parathyroid sestamibi scan, blue arrow pointing to the hyperfunctioning gland.

Figure 5 H&E stain of the gingival mass showing giant cell granuloma (blue arrow) on light microscopy.

serum calcium levels, reduction in the size of the bone lesions in the pelvis, bilateral femur and vertebral bodies on plain radiographs, decrease in the size of the left mandibular mass and improvement of quality of life as the patient became ambulatory and pain-free. Guided by serum calcium levels, calcium carbonate and calcitriol are gradually being tapered down. The duration of treatment may last for more than a year after the surgery.⁴

DISCUSSION

Brown tumours are bone lesions that arise in the setting of excessive osteoclastic activity such as hyperparathyroidism. These tumours are not neoplastic as the name suggests; they occur in the long bones, jaw and skull and may be multiple. They are highly vascular lesions and may contain necrotic centres and hemosiderin deposition, thus the characteristic brown colour. The reported prevalence of brown tumours has decreased to <0.1%. Owing to the standard of medical care and screening in developed countries, it is increasingly rare to find accompanying bone disease in primary hyperparathyroidism.⁵ Reported cases of extensive multiple brown tumours, some of which were mimicking cancer metastasis, were due to hyperparathyroidism from parathyroid adenoma.^{6–9} There are only a few cases reported where brown tumours were caused by parathyroid carcinoma—two cases of mandibular brown tumour and two cases of multiple brown tumours in the lower extremities.^{10–13} A comprehensive online literature search yielded no other cases of parathyroid carcinoma presenting with multiple brown tumours as extensive as in this case.

Ninety per cent of parathyroid cancer is hormonally functional. These cases exhibit symptoms and complications of profound hypercalcaemia at presentation, due to elevated PTH. As the majority of parathyroid cancers are functioning tumours, many clinical symptoms are similar to those of benign primary hyperparathyroidism, such as fatigue, muscle weakness, depression, weight loss, abdominal pain, polyuria, bone disease, nephrolithiasis, peptic ulcer and pancreatitis. However, certain conditions are considered to be associated with a higher risk of parathyroid carcinoma. Young age, severe hypercalcaemia (albumin-corrected calcium levels >3.0 mmol/L) or hypercalcaemic crisis, concomitant renal and bone involvement, as well as the presence of a palpable neck mass (more than 3 cm) should raise the suspicion of parathyroid carcinoma. Patients with this combination of symptoms have a 4.5-fold increased risk of having parathyroid carcinoma. More than 10 times elevated intact PTH has 81% positive predictive value for parathyroid carcinoma.¹⁴ The 3+3 rule, which is a combination of tumour

Figure 6 Parathyroid histology. H&E stain of parathyroid carcinoma showing capsular invasion (blue arrow) and vascular space invasion (green arrow) on light microscopy.

size >3.0 cm and hypercalcaemia >3.0 mmol/L, can be used to identify patients at risk of parathyroid cancer when compared with less symptomatic patients.¹⁵ Up to 80% were observed to have a tumour size >3.0 cm and 85% had pre-surgical serum calcium >3.0 mmol/L. Parathyroid cancers tend to be larger and metabolically more active than benign adenomas. This rule of thumb cannot establish a diagnosis of cancer but can help to identify those patients with primary hyperparathyroidism who should undergo further preoperative investigation.¹⁶

The single most effective therapy for parathyroid carcinoma is complete resection of the primary lesion at the time of initial operation, when extensive local invasion and distant metastases are less likely. When the gross pathological findings suggest malignancy, en bloc removal of the lesion together with the ipsilateral thyroid lobe and isthmus should be carried out.¹⁷ The diagnosis of carcinoma is very difficult in the absence of massive local invasion or regional metastasis. There are specific findings on ultrasound that are suggestive of malignancy, such as heterogeneity, calcification, size more than 38 mm, tissue invasion and presence of lobulation as described in a study of 28 parathyroid carcinoma cases.^{18–19} Only internal calcifications were seen on the thyroid ultrasound of our patient. In a large retrospective study in 1999, for 86% of patients, the diagnosis of parathyroid carcinoma could not be established during surgery. Frozen section analysis is of little value.²⁰ Therefore the diagnosis is made through a combination of intraoperative findings and postoperative histological examination of the pathological tissue.²¹ Based on the histopathological examination of 70 parathyroid cancer cases, the primary histological features that distinguish a carcinoma from an adenoma are the presence of parenchymal mitosis, trabeculated parenchyma including thick fibrous bands and capsular or vascular invasion. Capsular or lymphovascular invasion is the most specific histopathological feature.²²

Currently, there is no widely accepted staging system for this disease, partly because of the rarity of the condition. Successful resection is dependent on preoperative suspicion and intraoperative recognition.^{16–21} Chemotherapy is generally ineffective in the treatment of parathyroid carcinoma. Dacarbazine as a single-agent and a combination regimen of fluorouracil, cyclophosphamide and dacarbazine did not show survival benefit among patients with metastatic disease.^{23–24}

Metastases occur via haematogenous spread and via the lymphatics. Lymph node metastasis occurs in ~15–30% of patients at their initial presentation. About 33% of patients have distant metastatic disease, usually in the lungs, liver and bone. The 5-year and 10-year overall survival rates were 82.3 and 66%, respectively. Median survival was 14.3 years with median follow-up of 65.1 months (range 1 month–26 years).²⁵ The

5-year local-regional progression-free survival was 56.6%.²⁶ Parathyroid cancer has a high recurrence rate of 50% after the initial operation, as cited in most studies.²⁷

Patient's perspective

(Translated from the Filipino language)

► My sickness started in 2012 while I was in the seventh month of pregnancy of my only child. I had difficulty walking because of the pain in my hips. I felt helpless because we do not have enough finances to go to the doctor to get treated. It was in June 2014 when I decided to seek consult. X-rays were taken and I was told I had tumours on hips. My doctor wanted me to undergo MRI, which confirmed bone tumours on hips. As a result of the findings, a bone marrow biopsy was performed.

July 2014, we went to the Philippine General Hospital for a second opinion. I was initially seen by the Orthopaedic service and was then referred to Haematology to undergo a second bone marrow biopsy. For the next 6 months, series of tests were carried out; bone marrow biopsy was performed two times; I got admitted to the hospital ward due to very high calcium levels, but still no definite diagnosis was given. I was even told that I had multiple myeloma and was quoted for chemotherapy. There was delay in the treatment because we could not afford the medications. I felt hopeless and depressed, until we were referred to general endocrinology in January 2015. I was confined for 2 weeks for all the tests to be carried out. During the admission, it was found out that I had a neck mass, through CT scan. I was told I had an enlarged parathyroid and was advised to undergo surgery. The biopsy showed that it was cancer, thus I would have to undergo another surgery to remove half of my thyroid to make sure my neck would be cancer-free.

► After the second operation, the thyroid removed was clean from cancer cells. I was eventually discharged and maintained on calcium carbonate and calcitriol. My bones are getting stronger. The bone pains eventually subsided; I no longer need to take pain medications. My body is getting stronger every day. I can already sit up instead of being bedridden. At present, after 1 year of physical therapy since my operation, I can already walk. I thought my world was going to end—it was a relief that my disease was actually treatable. I know it is cancer thus I make sure I have regular follow-up with my doctors. My experience was really life-changing and I thank the doctors for giving me hope, and for this second life.

Learning points

- ▶ Brown tumours from hyperparathyroidism should always be on the clinician's list of differential diagnoses when multiple osteolytic lesions are encountered.
- ▶ There should be a high index of suspicion for a carcinoma when presented with very high calcium of >3.0 mmol/L and over 10 times elevated intact parathyroid hormone levels, and overt skeletal and renal complications.
- ▶ Surgery is the only effective and curative treatment of parathyroid carcinoma and it should be performed as en bloc tumour resection with ipsilateral thyroidectomy and central neck dissection.

Twitter Follow Daryl Jade Dagang at @daryldagangmd

Acknowledgements The author would like to acknowledge his colleagues, namely Dr Patrick Labra, Dr Hderbert Arellano, Dr John Paul Quisumbing, Dr Majorie Palermo, Dr Ralph Jason Li and Dr Jerico Gutierrez, for being involved in the care of the patient and for contributing to the case report.

Contributors DJTD and JBG were involved in direct patient care and writing up this case. FLL-A and MASS were the consultant supervisors and editors.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Proimos E, Chimonas TS, Tamiolakis D, *et al.* Brown tumor of the maxillary sinus in a patient with primary hyperparathyroidism: a case report. *J Med Case Rep* 2009;3:7495.
- 2 Belizikian JP, Silverberg SJ. Clinical Presentation of Primary Hyperparathyroidism in the United States. *The Parathyroids. New York*, 2001:349–60.
- 3 Aoki J, Moriya K, Yamashita K, *et al.* Giant cell tumors of bone containing large amounts of hemosiderin: MR-pathologic correlation. *J Comput Assist Tomogr* 1991;15:1024–7.
- 4 Witteveen JE, van Thiel S, Romijn JA, *et al.* Hungry bone syndrome: still a challenge in the post-operative management of primary hyperparathyroidism: a systematic review of the literature. *Eur J Endocrinol* 2013;168:R45–53.
- 5 Khan A. Primary hyperparathyroidism: diagnosis and management. *Endocr Pract* 1997;3:22–6.
- 6 Miyakoshi M, Kamoi K, Takano T, *et al.* Multiple brown tumors in primary hyperparathyroidism caused by an adenoma mimicking metastatic bone disease with false positive results on computed tomography and Tc-99m sestamibi imaging: MR findings. *Endocr J* 2007;54:205–10.
- 7 Meydan N, Barutca S, Guney E, *et al.* Brown tumors mimicking bone metastases. *J Natl Med Assoc* 2006;98:950–3.
- 8 Atabek ME, Pirgon O, Sert A, *et al.* Extensive brown tumors caused by parathyroid adenoma in an adolescent patient. *Eur J Pediatr* 2008;167:117–19.
- 9 Hoshi M, Takami M, Kajikawa M, *et al.* A case of multiple skeletal lesions of brown tumors, mimicking carcinoma metastases. *Arch Orthop Trauma Surg* 2008;128:149–54.
- 10 Pahlavan PS, Severin MC. Parathyroid carcinoma: a rare case with mandibular brown tumor. *Wien Klin Wochenschr* 2006;118:175–9.
- 11 Masson EA, MacFarlane IA, Bodmer CW, *et al.* Parathyroid carcinoma presenting with a brown tumour of the mandible in a young man. *Br J Oral Maxillofac Surg* 1993;31:117–19.
- 12 Pai M, Park CH, Kim BS, *et al.* Multiple brown tumors in parathyroid carcinoma mimicking metastatic bone disease. *Clin Nucl Med* 1997;22:691–4.
- 13 Radulescu D, Chis B, Donca V, *et al.* Brown tumors of the femur and pelvis secondary to a parathyroid carcinoma: report of one case. *Rev Med Chil* 2014;142:919–23.
- 14 Schaapveld M, Jorna FH, Aben KK, *et al.* Incidence and prognosis of parathyroid gland carcinoma: a population-based study in The Netherlands estimating the preoperative diagnosis. *Am J Surg* 2011;202:590–7.
- 15 Schulte KM, Talat N. Diagnosis and management of parathyroid cancer. *Nat Rev Endocrinol* 2012;8:612–22.
- 16 Talat N, Schulte KM. Clinical presentation, staging and long-term evolution of parathyroid cancer. *Ann Surg Oncol* 2010;17:2156–74.
- 17 Shane E. Clinical review 122: parathyroid carcinoma. *J Clin Endocrinol Metab* 2001;86:485–93.
- 18 Hara H, Igarashi A, Yano Y, *et al.* Ultrasonographic features of parathyroid carcinoma. *Endocr J* 2001;48:213–17.
- 19 Sidhu PS, Talat N, Patel P, *et al.* Ultrasound features of malignancy in the preoperative diagnosis of parathyroid cancer: a retrospective analysis of parathyroid tumours larger than 15 mm. *Eur Radiol* 2011;21:1865–73.
- 20 Hundahl S, Fleming I, Fremgen A, *et al.* Two hundred eighty-six cases of parathyroid carcinoma treated in the U.S. between 1985–1995. *Cancer* 1999;86:538–44.
- 21 Wei CH, Harari A. Parathyroid carcinoma: update and guidelines for management. *Curr Treat Options Oncol* 2012;13:11–23.
- 22 Schantz A, Castleman B. Parathyroid carcinoma: a study of 70 cases. *Cancer* 1973;31:600–5.
- 23 Calandra DB, Cheffec G, Foy BK, *et al.* Parathyroid carcinoma: biochemical and pathologic response to DTIC. *Surgery* 1984;96:1132–7.
- 24 Bukowski RM, Sheeler L, Cunningham J, *et al.* Successful combination chemotherapy for metastatic parathyroid carcinoma. *Arch Intern Med* 1984;144:399–400.
- 25 Asare E, Sturgeon C, Winchester D, *et al.* Parathyroid carcinoma: an update on treatment outcomes and prognostic factors from the National Cancer Data Base (NCDB). *Ann Surg Oncol* 2015;22:3990–5.
- 26 Munson ND, Foote RL, Northcutt RC, *et al.* Parathyroid carcinoma: is there a role for adjuvant radiation therapy? *Cancer* 2003;98:2378–84.
- 27 Kebebew E. Parathyroid carcinoma. *Curr Treat Options Oncol* 2001;2:347–54.

Copyright 2016 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit

<http://group.bmj.com/group/rights-licensing/permissions>.

BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow