ABSTRACT

Brown tumors are a rare non-neoplastic, osteolytic lesion caused by an increase in osteoclastic bone resorption. The increase in bone breakdown often leads to patients developing hypercalcemia and osteopenia as a result. Hypercalcemia associated with brown tumors arise due to primary, secondary, or tertiary hyperparathyroidism and in rare cases, occur from the development of a parathyroid gland carcinoma. Most cases of brown tumors are asymptomatic, however, on occasion it can present with pain or compressive symptoms. Common sites for these tumors include clavicle, ribs, pelvis, long bones, maxilla, and mandible. Additionally, it should be noted that brown tumors affect trabecular bone more frequently than cancellous bone.

We will be looking at a 35-year-old male patient who presented with chest pain. He was investigated thoroughly with blood tests, echocardiogram, coronary angiogram, bone marrow trephine biopsy, whole body CT scan, CT-PET scan and finally with excision rib biopsy. Only upon the excision, rib biopsy was the diagnosis of brown tumor confirmed. The development of this tumor was determined to be secondary to primary hyperparathyroidism. Following surgical treatment for hyperparathyroidism, the brown tumor resolved spontaneously.

Keywords
Chest pain, Chronic hypocalcemia, Hypertension.

Case Report

A 35-year-old athletic male presented to the GP with increasing chest pain over the last two weeks, which was exacerbated by moderate exercise. Notable past medical history included hypertension, which was well controlled on thiazide diuretics, and monoclonal gammopathy of indeterminate significance. He had regular follow-ups with his hematologists for this condition and had been reassured during his last assessment a month ago that his disease was not progressing. The patient does not smoke or use illicit substances and only drinks alcohol socially. His family history was noted to be unremarkable, with no significant cardiovascular disease.

On physical examination, no salient findings were elicited. Due to patient concerns, his GP referred him to a cardiologist for further investigations. An echocardiogram, coronary angiogram, and CT calcium score were arranged, all of which returned negative results. The patient was subsequently reassured and sent for an exercise ECG. During the stress ECG, the patient was not able to continue after the 10-minute due to worsening chest pain. It was noted that there were no significant changes in his ECG and blood pressure during those 10-minutes, and his heart rate rose appropriately as well.

He was admitted to the hospital for observation, where additional investigations were performed. These investigations included FBC, ESR, CRP, serum urea, creatinine, liver function tests, iron study, B12, serum folate, troponin, and BNP. The results of these investigations came back normal ranges, with the exception of an elevated alkaline phosphatase (ALP) at 300 iu/l (20-140). Following this, the patient was referred to the rheumatologist to exclude any rheumatic disease as a cause of the chest pain. Examination by the rheumatologist was unremarkable, and immune screen was negative. However, a chest x-ray found new multiple lytic lesions in the 5th and 6th left ribs, which was confirmed with a CT chest.
Patient was referred to an endocrinologist, who proceeded to arrange more investigations. The investigations include intact parathyroid hormone, parathyroid related peptide, thyroid functions, Synacthen test, 9 am cortisol, pituitary functions, serum glucagon, gastrin, vasoactive intestinal peptide, fasting serum insulin, C-peptide and blood sugar, serum calcitonin, pheochromocytoma screen, ultrasound for parathyroid glands, color doppler study for thyroid and parathyroid, 99mTc sestamibi scan, subtraction scan, and calcium creatinine ratio in urine. The investigations came back either normal or negative apart from the following:

Intact serum parathyroid hormone 250 pg/ml (10-65 pg/ml).
Serum calcium 4 mmol/L (2-205 mmol/l), serum phosphate 0.6 mmol/l (0.97-1.45 mmol/l).
Urinary calcium-creatinine ratio 30 (<10).

Sestamibi scan and subtraction scan using 123 iodide confirmed nodular parathyroid hyperparathyroidism. A surgical biopsy of the 5th and 6th ribs showed highly vascular stromal connective tissue with diffusely multinucleated giant cells. Additionally, there was evidence of hemorrhage, marked hemosiderin deposition, and intense skeletal demineralization. Differential diagnosis provided by the pathology report were bone metastasis, multiple myeloma, giant cell granuloma, giant bone cysts, Langerhans cell histiocytosis, non-ossifying fibroma, aneurysmal bone cysts, noncaseating granuloma, and leukemic infiltration.

Given the biochemical findings of elevated intact parathyroid hormone, elevated calcium, reduced phosphate, elevated urine calcium-creatinine ratio, subperiosteal absorption, bone cyst in imaging, and the nodular adenoma from subtraction scan, the most probable diagnosis is brown tumor secondary to uncontrolled primary hyperparathyroidism. The bone mineral density showed a T Score of -3 at the lower spine and -2.5 at the femur, both of which confirm a diagnosis of osteoporosis.

The patient was started on fluids, diuretics, calcitonin, zoledronic acid and dexamethasone to decrease serum calcium before surgery to prevent hypocalcemia from hungry bone syndrome post-surgery. The patient underwent a total parathyroidectomy with autologous parathyroid transplant. Intraoperatively, his intact parathyroid hormone reduced to 30 pg/ml. Post-operatively, the patient developed severe hypocalcemia because of hungry bone disease, which was treated with calcium gluconate and calcitriol.

Serum calcium normalized after 6 weeks, with complete resolution of his chest pain. A chest X ray revealed complete resolution of his lytic lesions on the 5th and 6th left ribs, with confirmation of remission by CT scan. An additional CT-PET scan showed complete resolution compared with the first CT-PET, the patient was discharged from all specialist clinics to have follow up with his GP. One year post-surgery, the patient continues to remain asymptomatic with normal metabolic panel. His repeat bone mineral density showed resolution of all osteoporosis with normal Z and T score on both the vertebrae and femur.

Discussion
Hyperparathyroidism is the third most common endocrine disease after diabetes mellitus and thyroid related diseases, and the most common cause of hypercalcemia worldwide [1]. In developed countries, hyperparathyroidism is usually diagnosed in asymptomatic patients due to widely available resources, which allows for the frequent utilization of a metabolic panel as an investigative tool, which includes serum calcium, serum phosphate and urine calcium-creatinine ratio. Although the disease is discovered early, hyperparathyroidism will often manifest with complications such as acute pancreatitis, gastric ulceration, nephrocalcinosis, nephrolithiasis, psychosis, polyurea, constipation, intestinal pseudo-obstruction, and brown tumors [2].

In cases of primary hyperparathyroidism, the most common cause is an adenoma, which accounts for 80-90% cases. This is followed by glandular hyperplasia at 5-10% of cases, and rarely, parathyroid carcinoma (1%) [3]. Primary hyperparathyroidism is characterized by increased secretion of parathyroid hormone due to hyperfunctioning of one or more glands. This leads to an increase in catabolism of cortical bone and enhanced anabolism in cancellous bone. As such, significant reductions of the Z score at the distal long bones (cortical bone) and minimal reduction at the lumbar spine (trabecular bone) are often witnessed in patients with primary hyperparathyroidism [4]. Additionally, excessive parathyroid hormone can cause cortical demineralization, and pathological fractures.

The function of the parathyroid gland is to maintain homeostasis of calcium and phosphate. Calcium plays a major role in metabolism, nerve impulse conduction, cardiac contractility, and clotting cascade. Parathyroid hormone increases calcium absorption from the small intestine by facilitating the formation of active vitamin D (1,25 -dihydroxycholecalciferol). The early diagnosis and treatment of hyperparathyroidism can prevent irreversible bone damage from occurring [5].

Chronic hypocalcemia is known to be a contributing factor to the development of normo-calcemic secondary hyperparathyroidism.
Causes of secondary hyperparathyroidism consist of chronic renal failure, malabsorption, and reduced intake of vitamin D, familial hypocalciuric hypercalcemia, and medication-induced hypercalcemia such as thiazide and lithium. Hence, a detailed drug history is essential when investigating hypercalcemia [6]. Chronic untreated secondary hyperparathyroidism can lead to autonomous hypersecretion of parathyroid hormone causing tertiary hyperparathyroidism.

In developed countries, patients with hyperparathyroidism will classically be postmenopausal women presenting with asymptomatic fracture and osteoporosis. This is in contrast to developing countries, where patients more often present with later stage complications, such as acute pancreatitis, nephrolithiasis, intestinal pseudo-obstruction, and brown tumors. Of note, hyperparathyroidism can also cause renal hypertension, prolonged P-R interval, decreased Q-T and ventricular arrhythmia, such as VT and VF, diastolic dysfunction, insulin resistance, type 1 Diabetes mellites, hyperuricemia, chondrocalcinosis and gout [7]. In most of the cases reported in literature, diagnosis was made possible with parathyroid ultrasound, 99m Tc-sestamibi scintigraphy, and SPECT/CT complemented by surgical biopsy [8]. Recently, 4D-CT has also played a major role in localizing parathyroid adenomas [8].

The formation of brown tumors is through an accumulative process of recurrent microfractures, ongoing bone remodeling with blood, hemosiderin, stromal fibrous and connective tissue. The multiple lytic lesions are a consequence of bone remodeling from hyperparathyroidism or paraneoplastic syndrome [9]. Malignant tumors of the parathyroid glands can contribute to the formation of brown tumors through the secretion of parathyroid hormone – related peptide, which mimics the effect of parathyroid hormone. Bone metastasis of these malignant tumors need to be ruled out before a diagnosis of brown tumor can be made [10]. The diagnosis of brown tumors is often difficult to make, owing to the many differential diagnoses that can present similarly and appear alike on imaging. They include giant cell tumors of the bone, aneurysmal bone tumor, and bone metastasis.

Concerning management of brown tumors, surgical treatment of hyperparathyroidism can result in a rapid decrease in parathyroid hormone and regression of lytic lesions, with remineralization of bone. The same applies to medical treatment in cases where surgery is declined or contraindicated [11]. A strong indication for surgical intervention would be the presence of compressive symptoms in the mandible or in the spine brought about by the growth of brown tumor.

<table>
<thead>
<tr>
<th></th>
<th>Primary Hyperparathyroidism</th>
<th>Secondary Hyperparathyroidism</th>
<th>Tertiary Hyperparathyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTH</td>
<td>↑</td>
<td>↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>Calcium</td>
<td>↑</td>
<td>↓/N</td>
<td>↑</td>
</tr>
<tr>
<td>Phosphate</td>
<td>↓</td>
<td>↑/N</td>
<td>↑</td>
</tr>
<tr>
<td>Vit D</td>
<td>↓</td>
<td>↓/N</td>
<td>↓</td>
</tr>
</tbody>
</table>

Brown tumor secondary to hyperparathyroidism

https://www.hindawi.com/journals/crira/2011/415476/

Bone metastasis

https://radiopaedia.org/articles/lytic-bone-metastases

Bone giant cell tumor


Aneurysmal bone cyst

https://radiopaedia.org/articles/aneurysmal-bone-cyst
Conclusion
Brown tumors are an uncommon complication of primary, secondary, and tertiary hyperparathyroidism. They form due to rapid osteoclastic activity, peri-trabecular fibrosis, microinfarct, and destruction due to uncontrolled hyperparathyroidism. Early diagnosis and treatment of hyperparathyroidism is curative of brown tumors that are secondary to hyperparathyroidism. Indication for surgical intervention of brown tumors include obstructive lesions of the mandible and compressive lesions of the spinal cord.

Acknowledgement
Professor Ekladious thanks Mike Zhang, medical student from Monash University for editing the manuscript.

References