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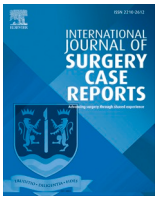

Case report

Lytic brown tumour of the mandible as the initial presentation of hyperparathyroidism in a 7-year old girl: A case report

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ABSTRACT

Introduction and importance: Maxillomandibular involvement with brown tumours is rare, especially in the paediatric population. We present a rare case of a young girl with brown tumour (BT) occurring in the mandible as the first manifestation of hyperparathyroidism.

Case presentation: A 7-year-old black female, presented with a 6-month history of a swelling on the left mandible. Patient had a history of intractable gastrointestinal symptoms such as nausea, vomiting and abdominal cramps. Biopsy confirmed the lesion as a giant cell lesion. Elevated parathyroid hormone (PTH) levels confirmed the diagnosis of a BT of hyperparathyroidism. The patient underwent surgical intervention involving parathyroidectomy. This was followed by segmental resection of the mandibular tumour two years later.

Clinical discussion: Brown Tumour is a rare, non-neoplastic lesion resulting from abnormal bone metabolism secondary to hyperparathyroidism. BT predominantly arise in long bones and the axial skeleton. Maxillomandibular involvement is very rare. In the present case, after parathyroidectomy, normal PTH and calcium levels were restored, and there was relief of gastrointestinal tract hypercalcaemic symptoms. However, there was no spontaneous regression of the mandibular tumour over a 2-year observation period. Hemimandibulectomy followed by reconstruction with a plate and costochondral graft was then performed.

Conclusion: It is difficult to differentiate BT from other giant cell lesions without blood chemistry revealing hyperparathyroidism. The distinction is imperative to avoid mutilating and aggressive treatment for BTs. Although BTs are amenable for conservative treatment, the present case illustrates that for bigger tumours, in the absence of spontaneous regression, aggressive surgical treatment may be required.

1. Introduction

Brown Tumour (BT) is a rare, non-neoplastic, reactive osteolytic lesion resulting from abnormal bone metabolism secondary to hyperparathyroidism (HPT) [1,2]. Parathyroid hormone (PTH) in HPT incites osteoclastic bone resorption with consequential hypercalcemia, hypophosphatemia and cyst-like resorptive lesions of bone, known as osteitis fibrosa cystica [2].

Brown tumours predominantly arise in long bones and the axial skeleton. Maxillomandibular involvement is very rare and occurs in approximately 4.5–11.8 % of cases, with the mandible more commonly affected than the maxilla [3].

Histologically, BT is similar to other giant cell lesions such as giant cell granuloma, aneurysmal bone cyst, and cherubism [4]. For this reason, diagnosis of BT is not exclusively based on histology but requires correlation between relevant clinical context, histopathological findings in favour of a giant cell tumour and a biological work-up showing HPT [3]. Without blood chemistry revealing hyperparathyroidism, it is difficult to differentiate BT from other giant cell lesions. Hypersecretion of PTH generally produces an increase of serum total calcium and alkaline phosphatase and a decrease of serum phosphate levels.

We report a case of a 7-year-old girl who presented with an osteolytic radiolucent lesion of the mandible with associated gastrointestinal symptoms, as the initial signs of HPT. We include a brief discussion on the differential diagnosis and current diagnostic approaches of BT.

The work has been reported in line with the SCARE criteria [5].

2. Case report

A 7-year-old black female, weighing 18 kg, presented to the

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Department of Oral and Maxillo-Facial Surgery with a 6-month history of an asymptomatic swelling on the left mandible. In the anamnesis taken from the mother, we learned that she had a history of intermittent food intolerance with associated intractable gastrointestinal tract (GIT) symptoms such as nausea, vomiting and abdominal cramps. Extraoral examination revealed a diffuse, painless bony hard swelling extending from the left body of the mandible to the pre-auricular area (Fig. 1. A) with no neural fallout. Skin over the swelling was normal in colour and texture. Intraorally, there was a non-tender bony-hard swelling (with buccolingual expansion) from tooth number 36 extending to the ascending ramus with obliteration of the buccal vestibule. Overlying mucosa was normal in colour (Fig. 1. B). Dental examination revealed that the patient was in the mixed dentition phase, with carious 65, erupting 42 and pit and fissure caries in tooth number 85.

The baseline bloods revealed Hyponatremic Hypochloremic acidosis (Sodium 134 mmol/L; Chloride 92 mmol/L, Bicarbonate 14 mmol/L, Anion gap 33 mmol/L) which was a consistent finding for a patient with a history of multiple vomiting episodes. Patient underwent fluid resuscitation and was treated with Maxolon to arrest the vomiting episodes. Panoramic radiograph showed a poorly defined, multilocular radiolucency in the left body mandible extending to condyle and coronoid processes. There was significant bowing of the inferior border of the mandible, with inferior displacement of unerupted 37 (Fig. 2).

CT scans showed an expansile lytic multilocular lesion of the left body and ramus of the mandible measuring 42 mm × 34 mm × 45 mm (Figs. 3.A, 3.B). 3-D CT reconstruction revealed an expansile lytic lesion in the left angle-ramus of the mandible up to the coronoid/condylar regions, with areas of cortical perforations (Fig. 4 A, B).

A provisional diagnosis of central giant cell granuloma, unicystic ameloblastoma or aneurysmal bone cyst was made. An incisional biopsy displayed microscopic proliferation of mononuclear spindled to ovoid cells with numerous multinucleated giant cells dispersed throughout the lesion, with trabeculae of reactive woven bone. The stroma was loose,

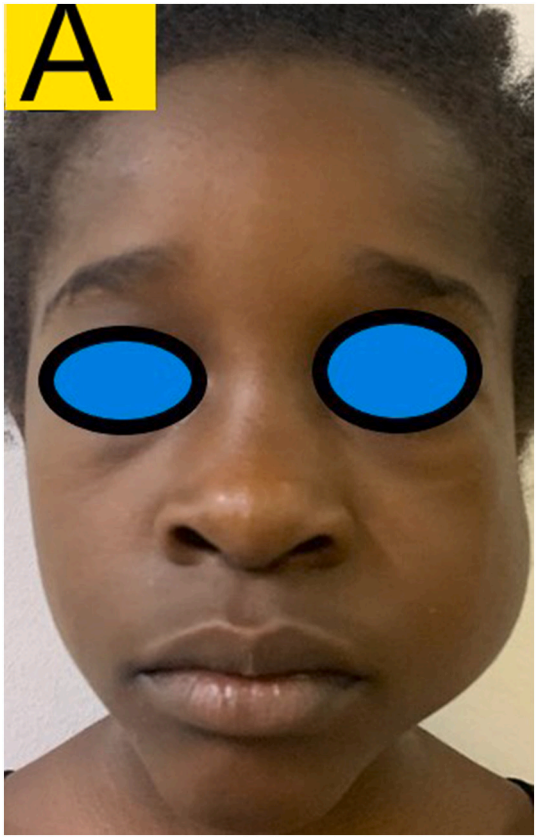

Fig. 1. A. Extraoral frontal view depicting left body-ramal swelling.

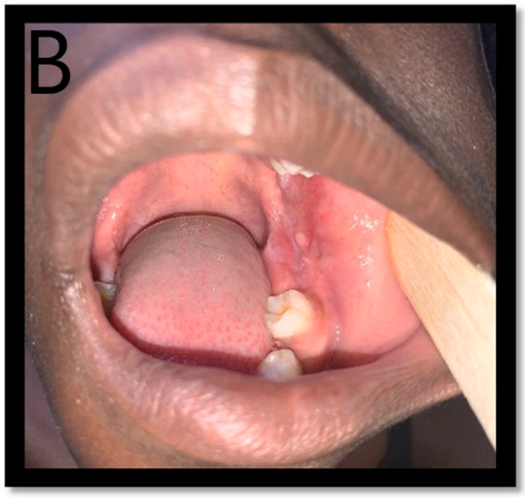

Fig. 1. B. Intraoral image showing buccolingual expansion from 36 to the left ascending ramus.

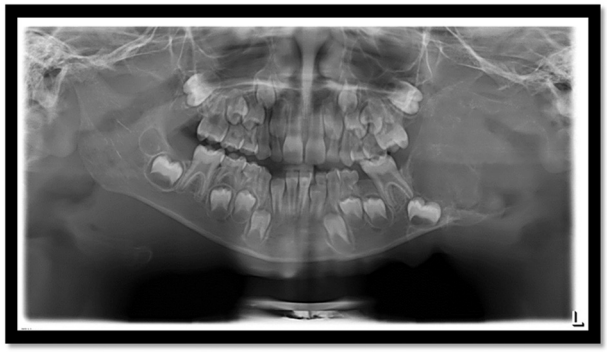

Fig. 2. A Panoramic radiograph showing a poorly defined, multilocular radiolucency in the body of the left mandible extending to condyle and coronoid processes.

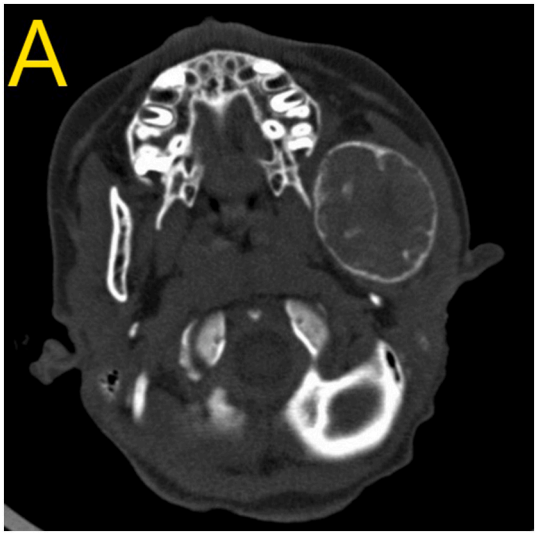

Fig. 3.A. Contrast-enhanced axial view showing lucent lesion with buccal and lingual expansion in the left ramus/angle region.

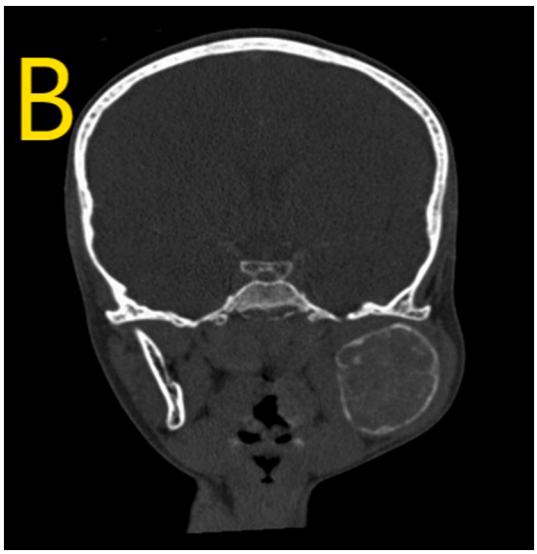

Fig. 3.B. Coronal CT scans showing lucent lesion with buccal and lingual expansion in the left ramus/angle region.

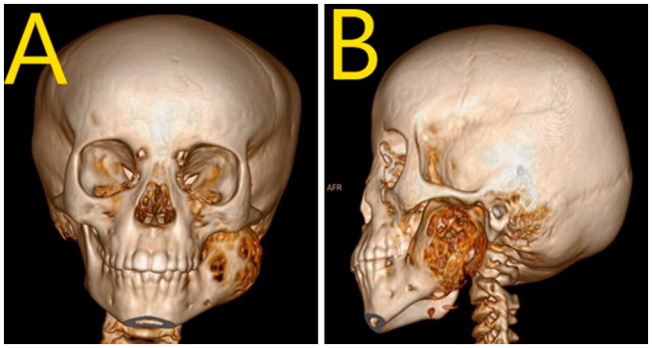

Fig. 4. A and B 3-D reconstruction CT scans showing expansion of the left body-ramus of the mandible up to the coronoid/condylar regions with extensive cortical perforations.

comprised of fibrovascular connective tissue with areas of hemorrhage (Fig. 5 A, B). The histological diagnosis was that of a giant cell lesion.

Definitive diagnosis of a Brown Tumour of hyperparathyroidism was made when PTH levels were markedly elevated at 19.6 pmol/L (normal range of 1.6–6.0 pmol/L) and Serum Calcium changed from normal 2,53 pmol/L at initial presentation to a high of 4.33 pmol/L.

Contrast enhanced CT scan was done and did not reveal any abnormal parathyroid glands. A thyroid ultrasound revealed no hyperplastic parathyroid tissue. A Parathyroid Scintigraphy (^{99m} Tc-sestamibi scintigraphy) scan revealed no hyperplastic or ectopic parathyroid tissue. An MRI revealed no abnormalities or ectopic parathyroid tissue. A series of radiographs including hand wrist (Fig. 6), chest and pelvic x-rays were carried out, all of which did not show signs of osteitis fibrosa cystica.

Severe GIT symptoms persisted on an intermittent basis for 5 months and blood calcium levels remained elevated. Medical treatment instituted included calciferol (5000 IU/5 mL), metaclopromide (2.5 mg), Prednisone (18 mg) and calcitonin (56 IU Subcutaneously), periodically normalising the blood calcium levels for intermittent periods.

A right and left upper parathyroidectomy was performed of which the histology revealed parathyroid gland hyperplasia. Blood calcium levels normalised postoperatively at 2.25 pmol/L and the parathyroid hormone level however remained markedly elevated at 24.4 pmol/L.

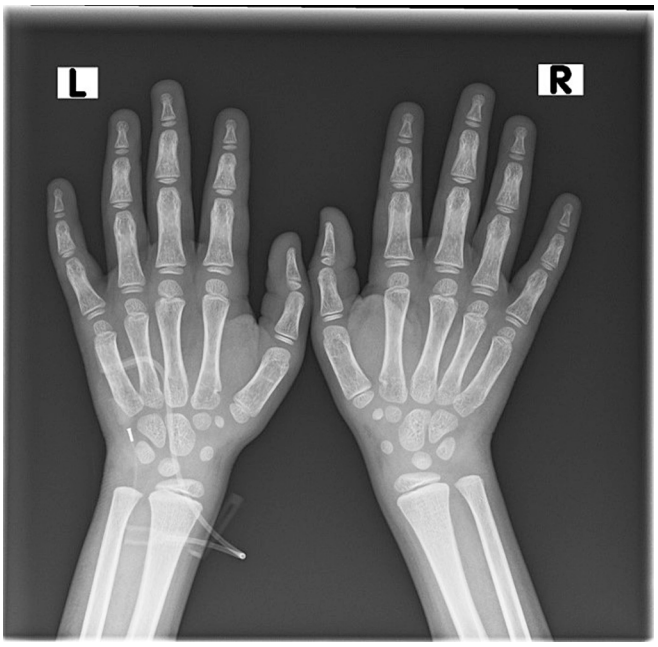

Fig. 6. A Hand wrist radiograph to rule out subperiosteal resorption.

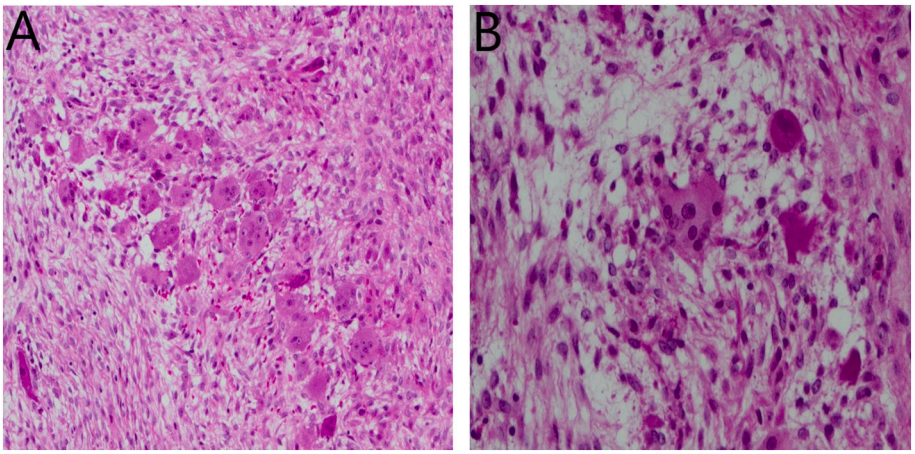

Fig. 5. A & B. Hematoxylin and Oesin (H&E, x 10 & 20 respectively) histological images showing a cellular proliferation of mononuclear spindle shaped cells in a loose fibrovascular stroma (A). Aggregations of multinucleated giant cells of osteoclastic type are present within the lesion (B).

At the 6- and 12-months follow-up after parathyroidectomy, normal calcium and PTH levels were restored but there were no changes observed in the size of the mandibular lesion. Instead, serial panelipse x-rays (Fig. 7 A, B, C, D) revealed marked calcification of the lesion. 24 months later, with no changes in the dimensions of the tumour and following resolution of the GIT symptoms, a left hemimandibulectomy (subperiosteal dissection) with disarticulation of the left condyle was performed, followed by placement of a reconstruction plate (Fig. 8 A, B) attached to the costochondral graft.

Histopathologic examination showed cellular proliferation of spindle-shaped cells in a loose fibrovascular stroma with aggregates of multinucleated giant cells of osteoclastic type. As the lesion occurred in the context of HPT, a diagnosis of Brown Tumour of HPT was confirmed after hyperparathyroidism jaw tumour syndrome was excluded.

Follow-up: Patient has been reviewed 6 monthly for the past two years with some evidence of bone formation in the body-ramus region on the x-ray (Fig. 9) and restoration of good facial contour (Fig. 10) and complete resolution of the GIT symptoms.

3. Discussion

Bone disease due to HPT, also known as osteitis fibrosa cystica, occurs following excessive, long-standing exposure to PTH which promotes both osteoclastic and osteoblastic activities [6,7]. Characteristic radiological features of osteitis fibrosa cystica include osteopenia, subperiosteal bone resorption, osteolysis of the ends of the clavicles, cysts and brown tumours. Well-defined lytic lesions ("salt and pepper demineralisation patterns") may be seen on plain film radiographs of the skull [7–9].

Brown tumours are part of giant cell tumours, which are classified into five types by WHO: cherubism, aneurysmal bone cysts, brown tumours, central giant cell granuloma and giant cell tumours [10]. BT is named after its brown appearance caused by increased osteoclastic activity which results in the replacement of bone matrix and marrow with haemorrhagic foci, haemosiderin deposit and highly fibrovascularised tissue.

The aetiology of the brown tumour is hyperparathyroidism, which can be primary, secondary or tertiary. Primary hyperparathyroidism (PHPT) is defined as hypercalcemia with increased or inappropriately normal plasma parathyroid hormone and is often due to parathyroid adenomas or glandular hyperplasia, whereas secondary HPT is one of the most important complications of chronic renal failure, manifested by compensatory hypersecretion of parathyroid hormone due to the disturbance of phosphocalcic balance that accompanies chronic renal failure. Calcium deficiency and phosphate excess are observed in the blood values of secondary HPT patients, unlike primary HPT [11]. Hypersecretion of PTH generally produces an increase of serum total calcium and alkaline phosphatase and a decrease of serum phosphate levels.

Brown tumour is most prevalent in females, and mainly affects individuals over 50 years of age [12]. Although it may occur at any age it rarely occurs in younger children as in the present case [13].

Clinically browns tumour presents as a slow growing, painless, brownish-red bony swelling, as it presented in this case or as a painful exophytic mass [12]. It may occur as a solitary or multifocal lesions, predominantly arising in long bones and the axial skeleton [14]. Maxillofacial brown tumour is very rare, accounting for about 2–4.5 % of cases [12,15]. It rarely manifests in young females in the mandible thus making this case unique. A pathognomonic radiographic feature in the mandible is that of "floating teeth" caused by the loss of the lamina dura around the apices of the teeth with an associated well-demarcated unilocular or multilocular radiolucency [1].

Some brown tumours are discovered from the classic constellation of symptoms described by the mnemonic "stones, bones, groans, and moans." These include symptomatic nephrolithiasis (stones), bone pain (bones), nausea and vomiting (gastrointestinal groans), and stupor (psychiatric moans). These characteristic symptoms associated with hypercalcemia are reported to be a rare occurrence in Western countries due to early detection primarily from the routine measurements of serum calcium [16]. In Africa however, the incidence of symptomatic presentation is higher with an increased prevalence in the Black population [17,18]. The present case presented with GIT symptoms secondary to hypercalcemia.

In Brown tumour associated with primary HPT, patients present with hypercalcemia and the associated GIT symptoms, most commonly attributed to a parathyroid adenoma, in 80 % of cases [19,20]. In the present case, parathyroid imaging in the form of Ultrasound and MRI failed to confirm the presence or location of parathyroid adenoma or hyperplasia. A full body Technetium Tc-99 m sestamibi scintigraphy test was then performed as (Technetium (99mTc) sestamibi is regarded as the most sensitive radioisotope for the detection of parathyroid hyperfunction and ectopic parathyroid tissue [21,22]. This however did not indicate any increase in the uptake of the dye. Lack of positive imaging however does not preclude parathyroidectomy in diagnosed patients as

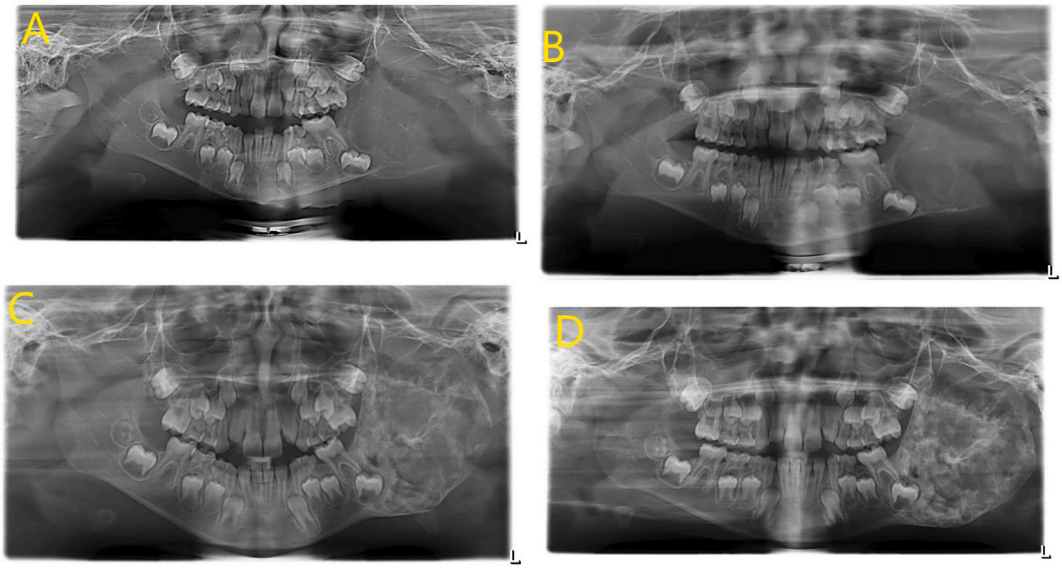

Fig. 7. Panelise radiographs depicting gradual calcifications: A- Initial, B- 3 months, C- 6 months, D- 9 months.

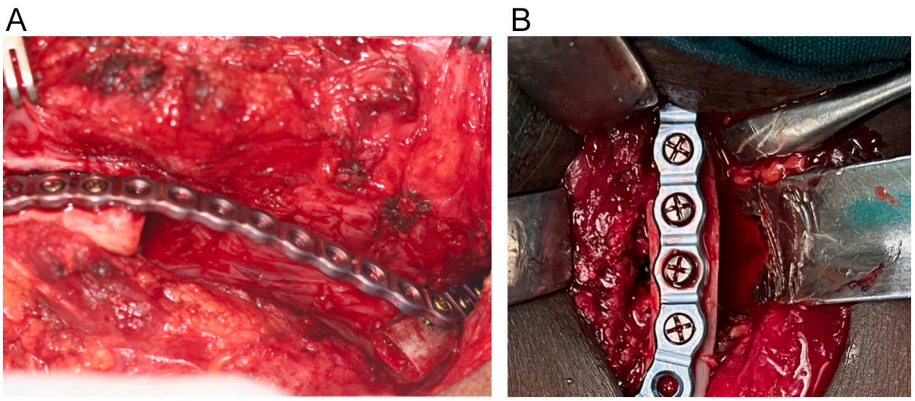

Fig. 8. A & B. Intraoperative clinical photographs showing a reconstruction plate in the left mandible region (A). Also shown is the costochondral graft attached with screws to the reconstruction plate (B).

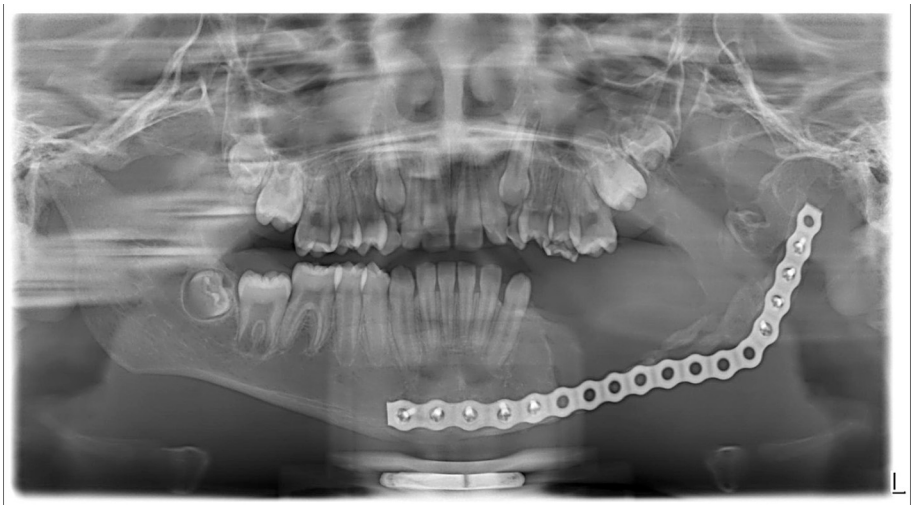

Fig. 9. 2-year post-operative panelipse depicting some bone formation in the left body-ramus region with reconstruction plate in-situ.

experienced surgeons will find abnormal parathyroid glands.

Differential diagnosis of PHPT in children and young adults must include hereditary/familial disorders such as Multiple endocrine neoplasia (MEN) types 1, 2 A and 4; hyperparathyroidism jaw tumour syndrome and familial isolated hyperparathyroidism [23]. MEN-1 involves multiple endocrine tumours involving the parathyroids, pancreatic islets and anterior pituitary and or duodenal endocrine cells. MEN-2 A is associated with medullary thyroid carcinoma. Hyperparathyroidism-jaw tumour syndrome (CDC73 gene mutation) is associated with tumours in the parathyroids, kidneys, uterus, mandible and or maxilla. Hereditary forms of PHPT are also suspected in patients with other endocrine disorders or tumours, which the present case did not have. Investigations for the source of HPT in the present case included genetic testing for MENS Type 1, MEN 2 A, MEN 4 and familial isolated primary hyperparathyroidism (FIHP) to exclude a hereditary cause for HPT [24]. These included serum prolactin, insulin-like growth factor-1, 24-h urine vanillylmandelic acid and free cortisol levels. Although these yielded negative results, it is imperative to contemplate them as a cause, especially when no increased uptake on bone scans is observed.

The diagnosis of browns tumour was reached with a combination of elevated serum calcium in the presence of an elevated or inappropriately normal PTH and the presence of multinucleated giant cells in the mandibular lesion.

Histologically brown tumour however cannot be distinguished from other giant cell lesions which consist of mononuclear spindle or stromal cells and multinucleated osteoclast like giant cells. Thus, without blood chemistry revealing hyperparathyroidism, it is difficult to differentiate this lesion from other giant cell lesions of mandible such as central giant cell granuloma, giant cell tumour, cherubism and aneurysmal bone cyst. The distinction is imperative as their management is immensely different [2,25].

Treatment of BTs relies on management of hyperparathyroidism. 75.3 %, of cases are treated by parathyroidectomy followed by observation of the brown tumour for regression [19]. Other surgical treatment options include osteoplasty, intralesional steroids for tumour shrinkage followed by enucleation or enucleation for small lesions [4]. Tumour resections with bone grafting are reserved for larger lesions. Medical management include intralesional steroid injections, interferon alpha, vitamin D and calcium supplements, calcium reduction (cinacalcet), low phosphate diets, bisphosphonates, and renal transplant [4,26–29].

The rationale for intralesional steroid injections was the histologic resemblance of giant cell lesions to sarcoid. It was thought that since steroids are effective in the treatment of sarcoid, the same treatment would work for these lesions [29]. Some success has been reported in unilocular lesions. In the present case, the size of the bony hard lesion, multilocularity and presence of cortical breakthrough precluded the use of intralesional steroid injections. There were also concerns about the risk of complications such as cushinoid features reported by El Hadidi et al. [28]

Interferon is a cytokine with antiviral and antiangiogenic properties, and its use is based on the assumption that giant cell lesions may be

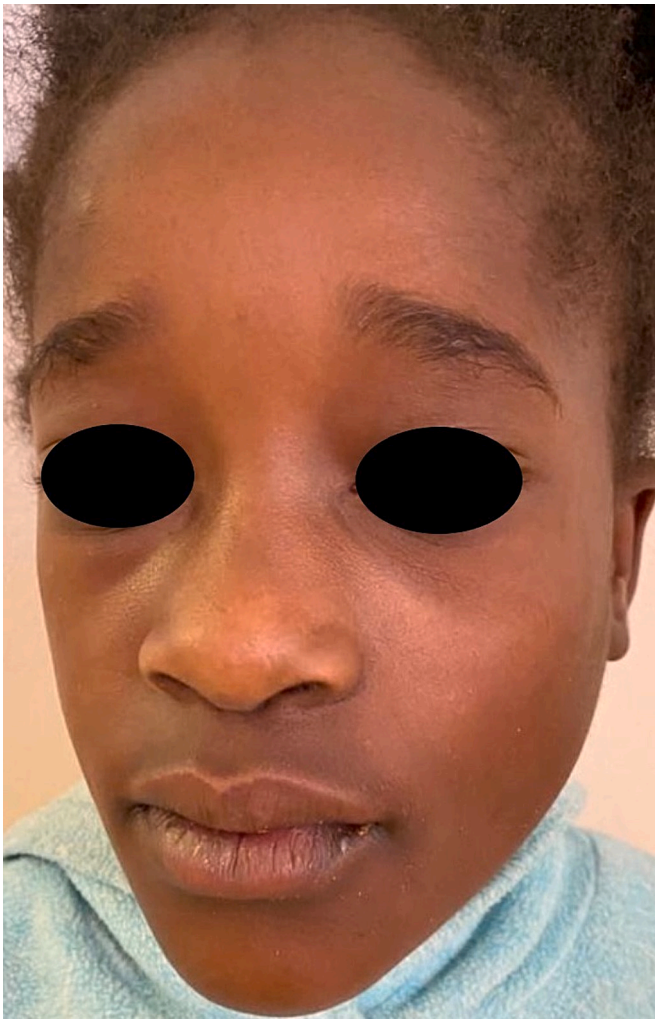

Fig. 10. Post-operative clinical photograph at 24 months showing restoration of facial form and contour.

vascular in origin [27,29]. The use of interferon alpha either as a monotherapy or in combination with surgery is however limited by its side effects, which include malaise, headache and flu-like symptoms, and was therefore not considered for this case.

In the present case the patient was treated medically with calcitonin for 7 months with no regression in the size of the tumour nor resolution of GIT symptoms. Harris was the first to report the use of calcitonin (administered subcutaneously or as a nasal spray) to treat central giant cell tumours of the jaws [30]. The use of calcitonin (the antagonist for PTH) was based on the hypothesis that giant cells of central giant lesions were osteoclasts and therefore would be immobilized by calcitonin. The lesion however, in the present case, showed ongoing growth and no resolution while calcitonin was administered.

Because of the persistent symptoms of hypercalcaemia plus elevated PTH, in consultation with paediatric surgeons, parathyroidectomy was performed. Histopathologic analysis showed the presence of parathyroid hyperplasia, thus confirming the diagnosis of primary hyperparathyroidism. After the parathyroidectomy, normal PTH and calcium levels were restored, and there was relief of GIT hypercalcaemic symptoms.

Following removal of parathyroid glands, progressive calcification of the lytic mandibular lesion was observed. Although there was remineralisation and calcification of the lesion, there was no spontaneous and progressive regression of the tumour over a 2-year observation period, which would have obviated the need for surgical intervention. As this tumour was extensive, cosmetically disfiguring and refractory to medical treatment, a decision on surgical treatment was made. A left segmental resection of the mandible from tooth number 35 with disarticulation of the left condyle was performed. A reconstruction plate and CCG were used to reconstruct the body and ramal/condylar component of the mandible respectively. With sub-periosteal dissection, the periosteum was left intact with only the pathological lesion removed, and thus increasing the body's ability to form new bone, especially in children. For this reason, definitive reconstructive surgery will be delayed to mid-to-late teen stage. The lesion resolved without evidence of relapse 24 months later, with complete resolution of the GIT symptoms also.

4. Conclusion

Better management of hyperparathyroidism has resulted in significant decrease in the incidences of BTs. Notwithstanding this, Brown tumour must be considered in any case of a giant cell tumour and calcium phosphate assessment must be undertaken. Differential diagnosis for giant cell tumours is possible only by complete evaluation of clinical, radiological and biochemical evidence. Without blood chemistry revealing hyperparathyroidism, it is difficult to differentiate BT from other giant cell lesions of the facial bones such as central giant cell granuloma, cherubism and aneurysmal bone cyst. The distinction is imperative to avoid mutilating and aggressive treatment for BTs, which are benign lesions mimicking neoplastic conditions.

We present a rare case of a 7-year-old girl who presented with brown tumour occurring within the facial bones as the first manifestation of HPT. Although BTs are amenable for conservative treatment, the present case illustrates that for bigger tumours, in the absence of spontaneous and progressive regression, aggressive surgical treatment may be required.

Informed consent

"Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request".

Author contribution

Rikhotso RE: 50 %: study concept, data analysis, writing the paper.

Khan F: 50 %: study design, data collection, data analysis, writing the paper.

Declaration of competing interest

No conflict of interest.

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