

Surgical management of Brown Tumor of the Mandible Associated with Ectopic Primary Hyperparathyroidism

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Abstract: Brown tumors are considered one of the most pathognomonic skeletal changes that accompany primary hyperparathyroidism (PHPT). It results from excessive secretion of parathyroid hormone (parathormone or PTH). The mandible is the most involved facial bone by brown tumor. Ectopic located parathyroid adenoma is uncommon, and thus, its diagnosis and management can sometimes be challenging. Difficulties in locating the mediastinum ectopic parathyroid adenoma may delay the diagnosis and subsequent surgery. A case of brown tumor of the mandible associated with ectopic mediastinum PHPT was reported. The tumor had caused facial asymmetry, open bite and bleeding. Laboratory tests revealed that the patient had hyperparathyroidism. Histopathological examination from the lesion revealed the presence of a giant cell tumor. Diagnostic imaging including the utility of 99mTc-sestamibi parathyroid scan denoted the presence of an ectopic mediastinum parathyroid adenoma. Parathyroidectomy and surgical removal of the brown tumor performed. Early diagnosis and successful treatment of PHPT have made clinical evidence of bone disease uncommon. Surgical removal of brown tumor of the mandible should be considered if the mass of serious facial deformity, lethal outcome and if the mass does not regress after parathyroidectomy. Finally the need to consider hyperparathyroidism (HPT) in the initial differential diagnosis of bony lesions of the jaw especially cases with histopathological features of giant cell tumor.

[Basma G Moussa, Ashraf Helal. **Surgical management of Brown Tumor of the Mandible Associated with Ectopic Primary Hyperparathyroidism.** *Biomedicine and Nursing* 2015;1(1):80-87]. <http://www.nbmedicine.org>, 15

Keywords: Mandibular brown tumor, ectopic mediastinum parathyroid adenoma, primary hyperparathyroidism, sestamibi scintigraphy, parathyroidectomy.

1. Introduction:

Brown tumors are erosive bony lesions caused by rapid osteoclastic activity and peritrabecular fibrosis due to hyperparathyroidism, Keyser and Postma (1996); Firman et al., (1999); Karunkaran et al., (2010).

The bony lesions associated with HPT was first described by Von Recklinghausen in 1891 and Jaffe (1972) was the first to coin the name "brown tumor" for bony lesions present in HPT, Desai and German (1990). Actually, mostly represent a reparative cellular process that can deform the bone and stimulate a neoplastic progress. In these areas, there are large numbers of capillaries, and endothelium lined space, multinucleated giant cells scattered within a delicate fibrocellular stroma. Accumulation of hemosiderin and extravasated red blood cells also is noted. As a result, the tissues may appear reddish brown, accounting for term brown tumor, Thronson and Sexton (2004); Daniels (2004); Selvi et al., (2009).

In mild hypercalcemia, the brown tumor may be asymptomatic and the condition is frequently discovered accidentally during routine laboratory screening. However, with the progress of the disease and increase of the level of parathormone which results in increase osteoclastic bone resorption and

hypercalcemia, it can provoke pathological fractures and even spinal cord compression when it involves the spinal column, Firman et al., (1999); Joshua et al., (2005) Moreover, when it affects the face, it can cause disfiguring deformities and difficulties to breath through the nose or to eat, Tarello et al., (1996); Morrone et al., (2001); Leal et al., (2006); Felix Jebasingh et al., (2008).

Greenspan et al., (1998); Hung et al., (2001). Reported that Between 80%-85% of patients with hyperparathyroidism have solitary or multiple hyperfunctioning adenomas of one or more of parathyroid gland. Familial hyperparathyroidism (FHPT) is a hereditary disease transmitted in autosomal dominant manner. It consists of a variety of diseases such as multiple endocrine neoplasia, with single adenoma, with multiple adenomas (or hyperplasia) and with jaw tumor, Watanaba. et al., (1998). Ectopic adenomas occur in 6%- 10% of all cases, and are usually located in areas such as the thymus, thyroid, pericardium, mediastinum or behind the esophagus. Less than 2% of parathyroid glands have been found in the region of the carotid sheath, Wang (1976).

Classic skeletal lesions, which are bone resorption, bone cyst, brown tumors and generalized osteopenia, now occur in fewer than 5% of cases,

Herowitz et al., (1994). The ribs, clavicles, pelvic, and the mandible are the most often involved bones, Rosenberg and Guralnick (1962); Keyser and Postma (1996).

Technetium-99m sestamibi parathyroid scan is a procedure in nuclear medicine which is performed to identify parathyroid adenoma. It is often used as the gold standard preoperative technique for localization of hyper functioning parathyroid tissue. It is used by surgeons to locate ectopic parathyroid adenomas which is most commonly found in the anterior mediastinum, Mariani et al., (2003).

In our study, we presented a case with brown tumor of the mandible provoked by PHPT associated with mediastinum hyperparathyroid adenoma with the involvement to its response to the decrease in PTH levels after parathyroidectomy (PTx) and surgical removal of brown tumor intraorally. In addition, described the management of that uncommon condition.

2. Material and Methods:

This is a case report study for a woman with 22 years old presented with a chief complaint from pain, bleeding and facial asymmetry from a lesion in the right side of the mandible. This condition has persisted for a year with gradual increase in size and pain till become fast growing after biopsy in a privat clinic four months before admission. Also the patient complained from generalized weakness and weight loss due to inability to eat and difficulty of breathing.

3. Results and the scheme of the work:

3.1. Extraoral examination:

It reveals facial asymmetry with right facial swelling and open bite. No trigeminal nerve paresthesia was noted. Intraoral examination shows a large soft tissue mass measuring about 7 cm × 5 cm × 3 cm³ extending from right mandibular canine to wisdom in the same side. There was buccal and lingual expansion of the mass that affect the tongue movement. The lower molars were free floating in the firm mass with upper molars indentation above the mass. Bleeding and pain were noted upon palpation of the soft mass. Then we noticed that the patient began to walk with waddling gait and soon complained of general fatigue and bone ache. (Fig. 1)

3.2. Radiographic dental changes:

Radiographic dental changes like loss of lamina dura, large multilocular radiolucent lesion in right mandible extending from canine to third molar with floating teeth without involving the lower border of the mandible and another small radiolucent lesion in left premolar area were seen in panoramic and plain films (Fig.2).

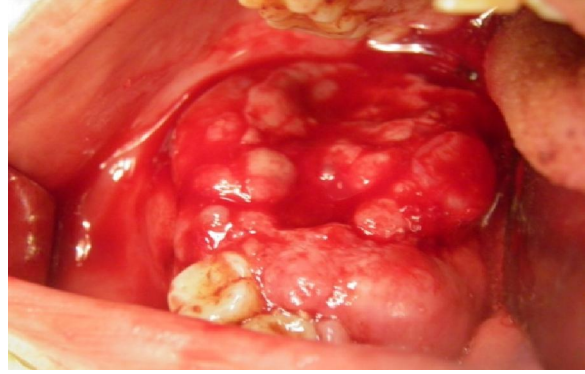


Figure 1: Soft tissue mass in the mandible with displacement of teeth



Figure 2: Panoramic view showing multilocular radiolucent lesion in the right mandible and floating of teeth related, and unilocular lesion seen in left periapical premolar area.

3.3. Post contrast 3 D CT scan of the mandible:

It revealed an osteolytic bony lesion that destructing inner and outer cortical plate of bone in the right side from first premolar to third molar. Another small radiolucent lesion was seen periapical to left premolars (Fig 3). Radiographic changes in the major bones and left hand were seen in plain films (Fig: 4). Biopsy of the mass revealed that it was a central giant cell tumor formed of numerous multinucleated giant cells dispersed in a fibrovascular stroma. Preoperative serum calcium level was 11.9 mg./100ml (normal 8.4-10.2), phosphorous was 2.3mg/dL (normal 2.3 – 4.7), serum alkaline phosphatase was 359 Kingarmstrong units (normal 35-104), parathyroid hormone was 440.7pg/ml (normal 150- 65.0), blood urea was 13 mg/100ml (normal 10-50), and creatinine was 0.49 mg/dL (normal 0.60 – 1.10). Increase the level of parathormone, calcium and alkaline phosphatase gave preliminary diagnosis of Primary hyperparathyroidism with brown tumor of the mandible. No evidence found about presence of parathyroid mass lesion in ultrasonography of the neck.

3.4. Screening with 99mTc Sestamibi parathyroid scan:

It showed a highly active solitary large ectopic parathyroid adenoma in mediastinum in early and late stage imaging. Normal intra-thyroid bio-distribution

of activity is noticed which washed out in delayed imaging. No other parathyroid adenoma could be detected (Fig:5).

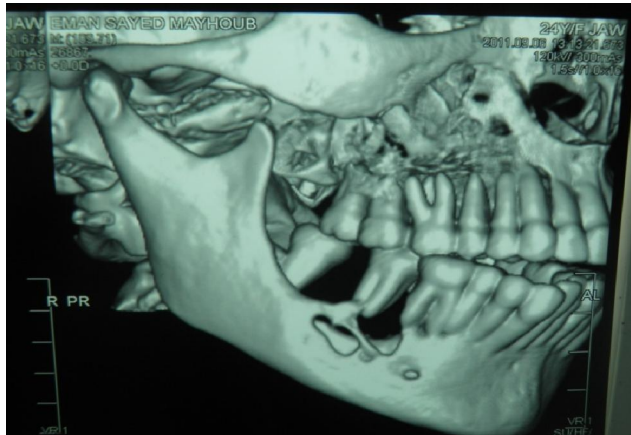


Figure 3: 3 D CT scan showing an osteolytic lesion of the mandible and floating of teeth related



Figure 4: Plain radiograph showing radiolucent cystic lesion in the hip bone.

3.5. CT scan of the neck and chest:

It revealed presence of hypo-dense soft tissue mass measuring 2 x 3 cm along its maximum dimension respectively in the superior retrosternal perivascular area while no abnormality in The neck. Ultrasonography of the neck gave negative involvement of parathyroid glands (Fig.6).

3.6. Results of the clinical, radiographic and histopathological and blood investigation findings:

Considering these findings we arrived to the final diagnosis of brown tumor of mandible and ectopic mediastinum parathyroid adenoma. Surgical removal of ectopic parathyroid adenoma (6X3 x 2 cm³) and intraoral local excision of mandibular mass (8X5 x 4 cm³) were done under general anesthesia in Cardiothoracic operating room, Cairo University hospital. In collaboration with Cardiothoracic surgeon, median sternotomy and a capsulated mass removed totally first, then followed by local excision and curettage of mandibular tumor mass with preservation

of inferior border of the mandible. The surgery was planned after routine clinical examination and laboratory investigation (Fig.7,8).

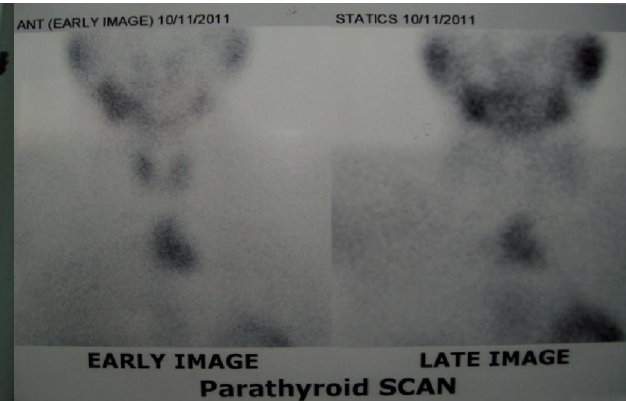


Figure 5: 99mTc Sestamibi parathyroid scan showing highly active solitary large ectopic parathyroid adenoma in mediastinum in early and late imaging.



Figure 6: The high resolution chest CT disclosing a 2 x 3 cm homogenous enhanced nodule in the retrosternal region of superior mediastinum.

Histopathological examination of the excised ectopic parathyroid gland revealed an adenoma. Histologically the mandibular lesion consisted of groups of osteoclasts type multinucleated giant cells in a well vascularized, cellular fibrous stroma. There was hemorrhage and cluster of hemosiderin. Reactive woven bone, which displayed osteoblastic activity, was seen in some areas (Fig.9, 10).

3.7. Results after surgery:

The patient underwent normalization of calcium level to avoid hypocalcaemia. Intravenous calcium replacement followed by oral calcium and Vitamin-D therapy. In the post operative period, PTH and Calcium levels decreased, the diffuse bone pain disappeared gradually and the patient could walk alone freely.



Figure 7: A resected encapsulated mediastinum ectopic parathyroid nodule 6X3 x 2 cm³.



Figure 8: Gross specimen of a resected brown tumor of the jaw 8x 5x4 cm³

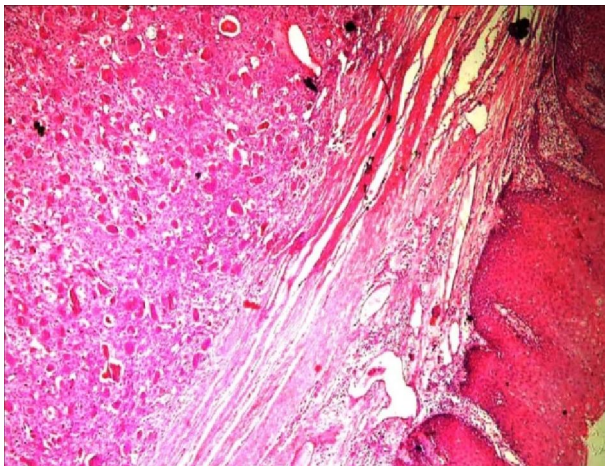


Figure 10: Photomicrograph showing parathyroid gland with sheet like arrangement of monotonous parathyroid cells (H and E x 200).

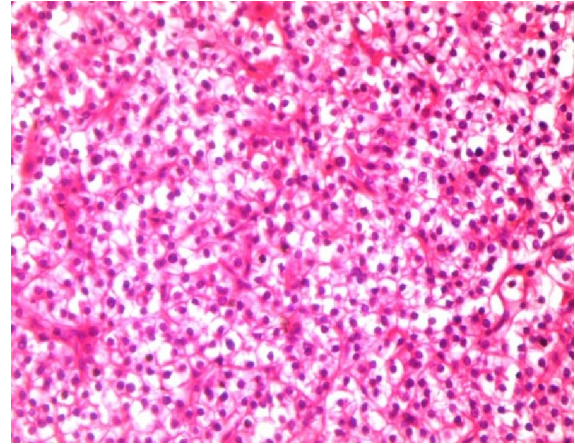


Figure 10: Photomicrograph showing parathyroid gland with sheet like arrangement of monotonous parathyroid cells (H and E x 200).

4. Discussion:

Parathyroid hormone is the chief regulator of calcium homeostasis in human body. Hyperparathyroidism is a condition caused by high circulatory levels of parathyroid hormone. It is classified into:

Primary: due to hyperplasia, benign or malignant neoplasia of one or more of the parathyroid glands.

Secondary: when the parathyroid gland are stimulated to produce increased amount of hormone to correct abnormally low serum calcium levels in different physiologic or pathologic conditions resulting in parathyroid hyperplasia.

Tertiary: when long standing secondary hyperplasia becomes autonomous in spite of correction of the underlying stimulant and develops into a type of primary, Smith and Bradley (1987).

Quartary and quintary: are rare conditions that may be observed after surgical removal of primary hyperparathyroidism, when it has led to renal damage that now again causes a form of secondary (quartary) hyperparathyroidism that may itself result in autonomy (quintary hyperparathyroidism), Kaiser et al., (1976).

Additionally, quarterly hyperparathyroidism may ensue from hungry bone syndrome after parathyroidectomy, Oltmann et al., (2011). The bony lesion of hyperparathyroidism is caused by increase circulating level of parathormon resulting in increase osteoclastic bone resorption, primarily in the cortical bone. This may explain why mandible is the most commonly affected facial bone, like our presented case, Lessa et al.,(2005); Leal et al.,(2006). Brown tumor arises secondary to primary and secondary HPT. They have been reported to occur in 4.5% of patients with PHPT and 1.5 to 1.7% of those with secondary disease, Bedard and Nichols (1974); Kanaan et al., (1998).

The tumors have a brown or yellow hue, Friedman et al.,(1974). In the case of this study, cross of the gross specimens of both mandibular lesion and mediastinum were faint brown in color.

At skeletal sites excess parathyroid hormone can lead to a condition called Osteitis fibrosa cystica. Osteitis fibrosa cystica is a diffuse resorptive process of the bone resulting from both primary and secondary hyperparathyroidism. Longstanding excessive levels of parathyroid hormone initiate both fibrous and osteoclastic reactions in the skeleton. An imbalance of osteoclastic and osteoblastic activity causes bone resorption with fibrous replacement of the marrow and thinning of the cortex, Habener et al., (1996). Clinical presentation of primary hyperparathyroidism has changed over the years. Prior to the mid-1970s, more than 50% of patients with primary hyperparathyroidism had evidence of skeletal and/or renal disease. Then after, the incidental finding of hypercalcemia determined by biochemical screening techniques in an asymptomatic patient is the most common method of diagnosis. Early detection and early treatment of primary hyperparathyroidism led to marked decrease in classical bony and renal manifestations of the disease, Bassler et al.,(1993).

Clinically, brown tumors most commonly present as slowly growing, painful masses. These tumors can behave aggressively and can be destructive. But they do not metastasize like a malignant tumor. Frequently associated multiple osteolytic lesions can be misdiagnosed as multiple myeloma or metastatic carcinoma, Habener et al., (1996). In the presented case, the patient complained from right side huge mass in the mandible but she had no idea about the other lesion seen in diagnostic imaging in the left side of the mandible and other skeletal bones, Habener et al., (1996). Ectopic placed parathyroid adenoma in anterior mediastinum is a rare cause of persistent or recurrent primary hyperparathyroidism (PHPT). For that once localized, should be surgically removed for cure, Lin et al., (2007). In this presented case, the location of parathyroid adenoma in the superior retrosternal perivascular area which is unusual. Of all the ectopic glands, 45% were intrathyroidal, 12.5% intrathyroidal, 7.5% retro-oesophageal, 7.5% in the carotid sheath, 5% interthyrotracheal, and 5% in the mediastinum (extrathyroidal), Arnalsteen et al.,(2004).

Mariette in his study looked at the reasons for reoperation for persistent or recurrent primary hyperparathyroidism reported that failed parathyroid operation was due to an ectopic parathyroid gland in 75% of cases. In another study involving patients reoperated for persistent or recurrent primary hyperparathyroidism, mediastinal approach was necessary in 15% of patients, Mariette. et al.,(1998). A

combination of imaging studies is often performed in patients with recurrent or persistent hyperparathyroidism. This involves the use of a functional study such as parathyroid scintigraphy and an anatomic imaging study such as USG, CT or MR imaging. Tc-99m sestamibi scintigraphy is often used for preoperative localisation. Its sensitivity is 71%–93%, depending on the imaging protocols utilized in early diagnosis of parathyroid adenoma specially an ectopic one, Lumachi et al., (2004).

Parathyroid scintigraphy with (99m)Tc-sestamibi is based on longer retention of the tracer in parathyroid than in thyroid tissue. Technetium (99mTc) sestamibi (trade name Cardiolite) is a pharmaceutical agent used in nuclear medicine imaging. The drug is a coordination complex of the radioisotope technetium-99m with the ligand methoxyisobutylisonitrile (MIBI). A scan of a patient using MIBI is commonly known as a "MIBI scan." Cardiolite is mainly used to image the myocardium (heart muscle). It is also used in the work-up of primary hyperparathyroidism to identify parathyroid adenomas, for radioguide surgery of the parathyroid and in the work-up of possible breast cancer, Vijayakumar and Anderson (2005); Lumachi et al., (2004); Phitayakorn and McHenry(2006).

The presented case imply beside clinical and laboratory examination, the utility of 99mTc Tc-sestamibi parathyroid scan which played a golden role in detection of ectopic parathyroid adenoma in mediastinum, while CT scan of the chest and head and neck defined the extension, size and anatomical places of brown tumors of the jaw right and left and mediastinum ectopic parathyroid adenoma areas. Plain radiography showed multiple skeletal cystic changes.

Although parathyroidectomy is considered to be curative, surgical removal of the bone tumoral mass may sometimes be required due to persistence of the lesion or the large destructive size. In certain anatomical sites, decompression of the brown tumor is urgently needed because these lesions expand and can cause local destruction, Balon and Kavalari (1998). This is particularly true for mandibular and maxillary lesions, which may lead to serious deformities of the face and even a lethal outcome, Morrone et al., (2001). A 3-D reconstruction of the computed tomography scan can be helpful in evaluating the facial deformities and in treatment planning, Michiwaki et al., (1996). In this case report, surgical removal of parathyroid adenoma via mediastinal approach was mandatory for curing the condition of hypercalcemia. Intraoral surgical enucleation of brown tumor of the mandible was done in the disfigured right mandibular lesion for relief of the patient symptoms, while the left side left for normal healing after parathyroidectomy.

Hypocalcaemia a common complication of parathyroid surgery. Up to 40% of the individuals who undergo parathyroidectomy for primary hyperparathyroidism develop hypocalcaemia postoperatively. Surgical cure was defined as a serum calcium level <10.5 mg/dL at 6 months after surgery. Recurrence was defined as a serum calcium level exceeding 10.5 mg/dL in consecutive samples at 6 months after surgery, Emin et al., (2004). In the presented case, calcium dropped to 6.1 mg/dL immediate after surgery. This may be due to hungry bone syndrome which is caused by massive calcium deposition in the bone after parathyroidectomy or suppressed normal parathyroid gland, for that intravenous calcium supplement continued a week after surgery followed by oral calcium and Vitamin D. Also there is marked decrease of parathormone level.

Giant cell lesions of hyperparathyroidism (brown tumors) are rare but histologically indistinguishable from central giant cell granulomas of the jaw. If therefore, a giant cell lesion is found, particularly in middle aged patient or in a patient with renal failure, parathyroid function should be investigated, Keyser et al., (1996).

The 10 Parathyroid Rules of Norman:

Norman is one of the most experienced parathyroid surgeon in the world and is considered the "father" of mini-parathyroid surgery, Norman (web site); Norman and Denham (1998); Murphy C, Norman (1999). He puts 10 rules for management of hyperparathyroidism. It is the world's leading authority on parathyroid glands and parathyroid disease:

1-There are no drugs that will make parathyroid disease better....None.

2-Nearly all parathyroid patients have symptoms; 95% know it--and feel bad. Most of the rest just don't know it until the disease is fixed.

3-Symptoms of parathyroid disease do NOT correlate with the level of calcium in the blood. Many patients with only slightly elevated calcium and parathyroid hormone will have BAD symptoms and develop severe osteoporosis.

4-All patients with parathyroid disease have calcium levels and PTH levels that go up and down. Fluctuating levels of calcium are typical of parathyroid disease.

5-All patients with hyperparathyroidism will develop osteoporosis.

6-Taking Fosamax, Actonel, Boniva, or Reclast (etc) will NOT help bones that are being attacked by a bad parathyroid. These osteoporosis drugs have no place in the treatment of parathyroid disease.

7-Parathyroid disease will get worse with time in all patients. It will not stay the same, nor will it get better on its own.

8-There is only one treatment for parathyroid disease (hyperparathyroidism): Surgery

9-Nearly all parathyroid patients can be cured with a minimal operation. The days of big dangerous parathyroid surgery are gone.

10-The success rate and complication rate for parathyroid surgery is very dependent upon the surgeon's experience.

Conclusions:

The first step treatment of brown tumor involves control of hyperparathyroidism regardless of its type. Treatment of PHPT requires parathyroidectomy. Once decreased parathormone level the tumor start to regress. In some cases like our case who have large, symptomatic tumor surgical removal is necessary. The accurate diagnosis and preoperative localization of an ectopic parathyroid adenoma by using combination of ^{99m}Tc sestamibi scintigraphy and CT scan of the neck and chest allows successful surgical treatment. Any giant cell tumor should be investigated for presence of hyperparathyroidism and hypercalcaemia.

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4/26/2015