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Uremic leontiasis ossea: A pictorial review of a rare complication of renal osteodystrophy

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Abstract

Uremic leontiasis ossea is a very rare manifestation of renal osteodystrophy with associated secondary or tertiary hyperparathyroidism, resulting in a diffuse and symmetrical enlargement of the craniofacial bones.

Although its pathophysiology remains uncertain, it seems that hyperphosphatemia and hypocalcemia secondary to chronic renal failure are the most likely precipitating factors.

Information regarding this disease consists mainly of case reports in the literature and some small series.

We describe four patients with ESRD on hemodialysis who had chronic progressive facial deformities and underwent imaging of the head and neck for further evaluation.

The aim of this work is to describe the characteristic imaging appearance of ULO and provide a broad review regarding its physiopathology, clinical presentation, biological assessment and treatment.

Knowledge of this disease is essential for every clinician involved in treating ESRD patients since treatment options aim to control hyperparathyroidism, resulting in stabilization of the facial deformities in most cases.

Keywords: uremic leontiasis ossea; Hyperparathyroidism; Hyperphosphatemia; CT scan; Renal osteodystrophy

1. Introduction

ULO is a severe and progressive benign overgrowth of facial bones complicating end-stage renal disease with secondary HPT. Its name is suggestive of the facial deformation resembling that of a lion, which can also be seen in other diseases such as craniofacial fibrous dysplasia, Paget disease and gigantism [1].

It is considered a rare manifestation of renal osteodystrophy, and its preferential localization in the craniofacial bones is still poorly understood.

Imaging, based primarily on CT, is usually performed to exclude other potential causes of facial deformity and is characteristic of the condition.

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Besides the aesthetic consequences, ULO can jeopardize the functional and sometimes vital prognosis by slow compression of the upper airways [2].

2. Materials and methods

Between 2017 and 2022, four patients with ESRD on hemodialysis and secondary or tertiary hyperparathyroidism had progressive facial deformities and were selected for the study. The mean age was 40 years, and there was a female predominance, displaying a 3F:1M ratio.

2 patients had a prior history of parathyroid adenoma resection and recurrent hyperparathyroidism. One patient has a pathologic femoral fracture and subsequent discovery of tertiary hyperparathyroidism, and one patient sought medical attention for a progressive mandibular swelling.

CT and Sestamibi scintigraphy were done in all cases and MRI in one case, showing diffuse and symmetric enlargement of the cranium and/or the facial bones, with a distinctive spongy bone pattern made of alternate hypodense and hyperdense rings in 3 cases and diffuse osteosclerosis in one case.

3. Discussion

ULO is a metabolic bony change that belongs to the large spectrum of renal osteodystrophy, occurring as a response to a chronic secondary HPT induced by ESRD. An accurate diagnosis can be achieved with the help of medical history, laboratory data and imaging characteristics.

Although parathyroidectomy may halt the progression of the disease, the cosmetic disfigurement and functional impairments make this condition hard to treat, stressing the importance of biochemical screening in ESRD patients on hemodialysis before the development of skeletal changes due to HPT.

3.1. Case 1

A 27-year-old woman, G3P2, has a history of recurrent tonsillitis and joint pain during childhood treated with steroids, pre-eclampsia complicated by renal failure for which she underwent an urgent caesarian section resulting in a stillbirth, and a recent post-traumatic rupture of the patellar tendon.

She has been followed for 4 years for arterial hypertension and ESRD of unknown etiology, and was on hemodialysis.

The biological tests showed a secondary HPT with a serum PTH value > 4000 pg/ml [12 – 88], normal corrected calcium of 90 mg/l [88 – 108], elevated serum phosphorus of 60 mg/ml [25 – 45] and alkaline phosphatase of 774 UI/l [30 – 120]. Imaging detected a parathyroid nodule, for which she underwent a resection. The histologic study found benign and nodular parathyroid hyperplasia.

8 months later, there was a biological recurrence of HPT with a PTH value of 2569 pg/ml without evidence of a parathyroid adenoma on parathyroid scintigraphy or cervico-thoracic MRI.

The patient was also complaining of bilateral galactorrhea and spaniomenorrhea, which started 8 months earlier, with 3 consecutive tests showing increased levels of prolactin measuring a maximal value of 103 ng/ml (< 25 ng/ml) and normal values of FSH, LH, and estradiol. The patient did not undergo a pituitary MRI because of financial constraints.

She was also noted to have a painless facial deformity that was clinically suspicious to be brown tumors, and she underwent a NECT scan showing a symmetric and diffuse expansion of the maxillary, the mandible and the palate, with an almost inexistent cortex and a heterogeneous appearance of the medulla consisting of alternating wavy hypodense and hyperdense lines (***figures 1 and 2***). No changes in the soft tissues were noted.

There was also a pepper pot skull appearance, subchondral erosions of the proximal clavicle and thinning of the distal clavicle, and focal cortical destruction as seen in the ribs (***figure 3***).

The patient was prescribed calcimimetics and continued her follow-up at another facility.

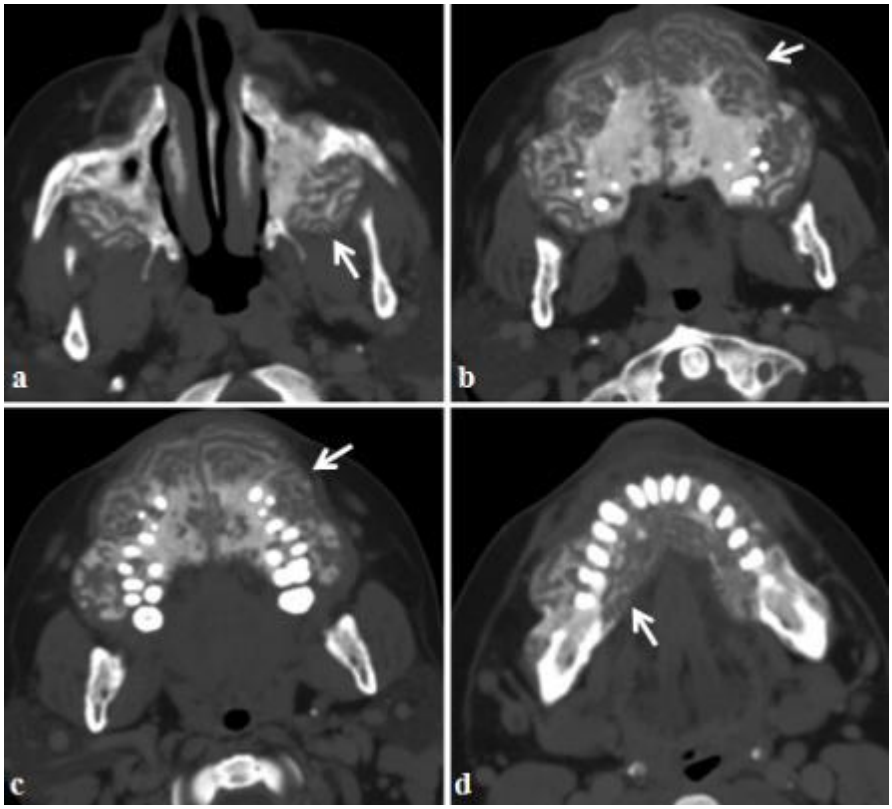

Figure 1 NECT axial images showing expansive lesions of the maxilla and mandible (white arrows). These abnormalities are bilateral and symmetrical, with alternating ostesclerosis and osteolysis

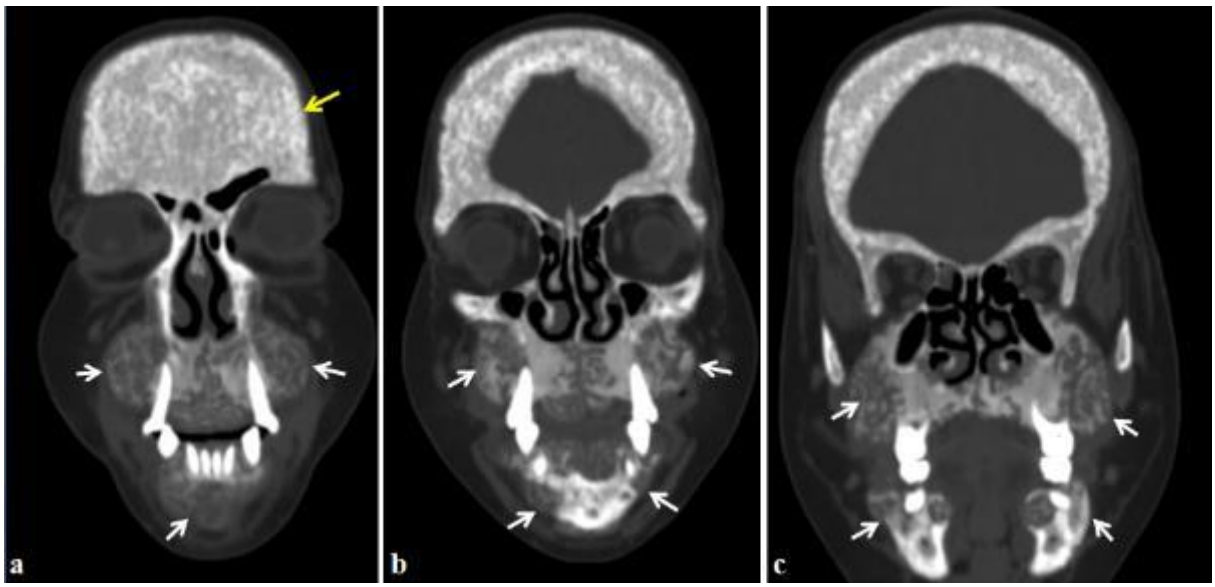

Figure 2 Coronal NECT sections show the expansive nature of the lesions (white arrows) as well as the speckled appearance of the diploe (yellow arrow) secondary to hyperparathyroidism, resulting in a “salt and pepper sign”

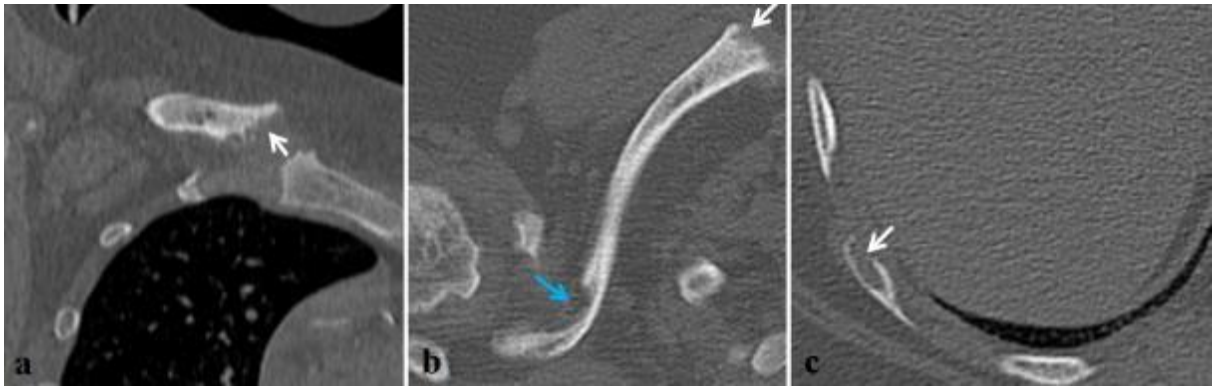

Figure 3 Coronal (a) and axial (b and c) images of a NECT scan show subchondral erosions of the right clavicle and cortical erosions of the inner cortex of a rib (white arrows). Note also a large erosion of the right distal clavicle (blue arrow)

3.2. Case 2

A 31-year-old man was on hemodialysis for chronic renal failure of unknown etiology for the past 7 years and was admitted to the emergency department for a pathological fracture of the right femur. He was receiving oral calcium supplementation and sevelamer for secondary HPT (his PTH value was 470 pg/ml when his ESRD was first diagnosed and > 2500 pg/ml for the two last years).

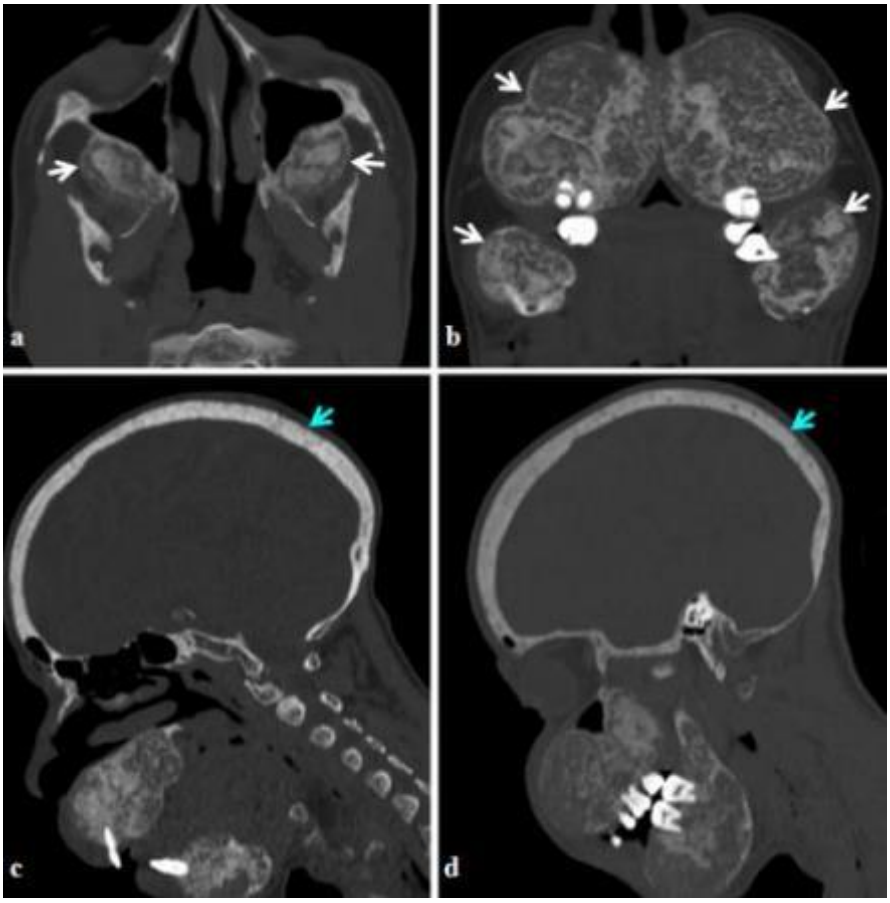

Figure 4 Axial (a and b) and sagittal (c and d) CT scan images show the characteristic maxillary and mandibular enlargements. There were also signs of renal osteodystrophy (blue arrow)

The laboratory workup at his admission showed a PTH value > 2500 pg/ml, with normal corrected serum calcium of 89 mg/l, increased serum phosphorous of 70 mg/l and alkaline phosphatase of 853 UI/l.

A cervical ultrasound showed a homogeneous goiter and two bilateral parathyroid nodules, which were hypoechoic and measured 11 and 15 mm in diameter. These findings were also confirmed by a ^{99m}Tc MIBI scintigraphy (***figure 6***).

He underwent closed intramedullary nailing for his femoral fracture and was then referred to the ENT department for the treatment of his secondary HPT.

The clinical examination showed a bilateral and painless jaw mass. The patient said he noticed the change a year ago.

A subtotal parathyroidectomy (7/8) and a thyroidectomy were performed, with consequent postoperative hungry bone syndrome. The pathological study of the specimens found adenomas, and postoperative PTH was continuously below 50 pg/ml.

A postoperative NECT scan demonstrated a symmetric and diffuse enlargement of the maxillary, the mandible and the hard palate, with cortical thinning and alternative rings of osteolysis and osteosclerosis (***figures 4 and 5***). In addition, a diffuse sclerosis of the diploe was observed, consistent with renal osteodystrophy.

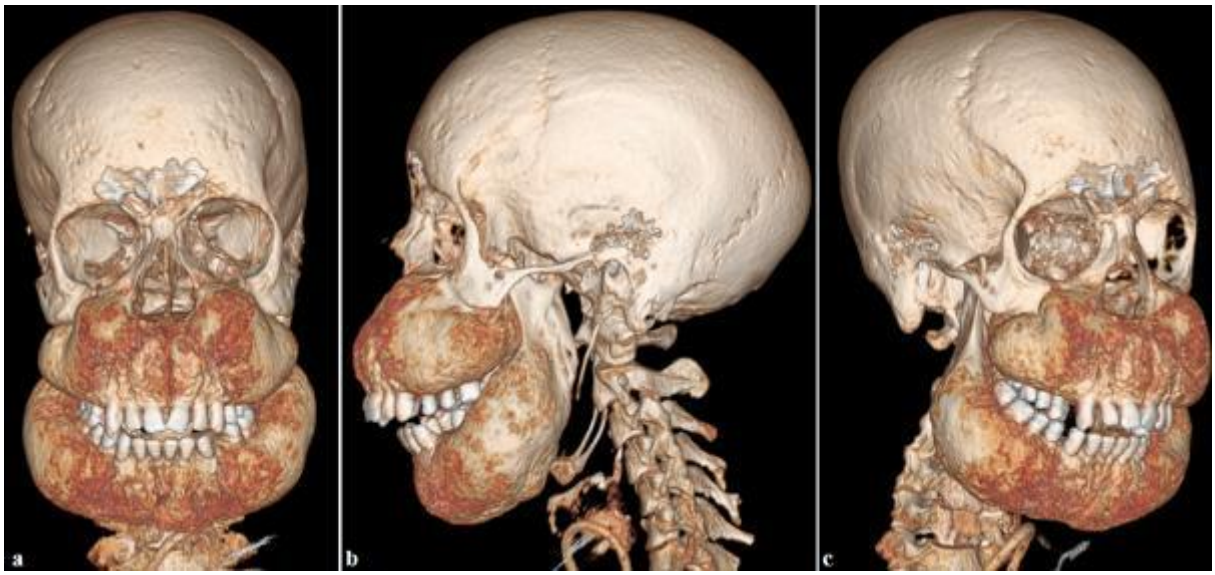

Figure 5 3D VR reconstructions showing the important enlargement of the middle and lower facial bones. An interdental diastema is also noted.

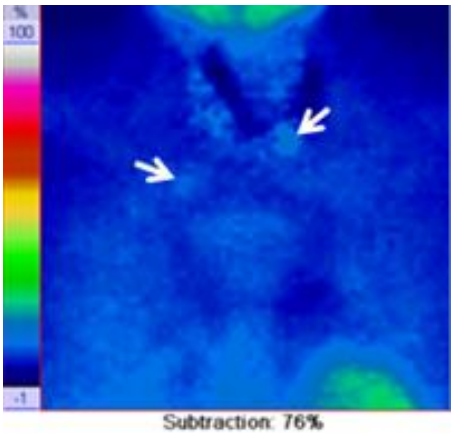

Figure 6 Parathyroid scintigraphy show the bilateral adenomas (white arrows)

3.3. Case 3

A 32-year-old woman was referred to the endocrinology department for the evaluation of hyperparathyroidism. She had been receiving medication for arterial hypertension and was on hemodialysis for chronic renal failure of unknown etiology for the past 10 years.

She also had three prior surgeries for parathyroid nodules at another facility and was receiving calcimetics for HPT, which failed to control the PTH levels.

Clinical examination noted a hard mandibular mass.

Laboratory tests included PTH > 2500 pg/ml, serum calcium of 78 mg/dl, serum phosphorus of 61 mg/l and alkaline phosphatase of 3081 UI/l.

A parathyroid sestamibi scan detected a left inferior parathyroid nodule (***figure 10***).

Analysis of the two parathyroid scintigraphies combined with CT showed diffuse osteosclerosis of the mandible and maxillary bones, followed by the expansion of these bones and disarrangement of the teeth 4 years later. The changes also included the hypertrophy of the zygoma, the conchae, the skull base and vault (***figures 7 and 8).***

The scout films showed other skeletal manifestations of HPT (***figure 9***): height loss, vertebral compression fractures, kyphosis, rib abnormalities leading to the reduction of pulmonary volume and osteolysis of the subchondral surfaces of the clavicles.

A pituitary MRI was indicated for secondary amenorrhea during her hospitalization, with laboratory data showing hypogonadotropic hypogonadism. The pituitary gland volume was decreased with a diffuse enlargement of the craniofacial bones; the cancellous bone was hypointense in T1 and T2 weighted sequences, and enhanced homogeneously. Some well-marginated T2 hypointense nodules were also observed in the diploe, with variable enhancing patterns (***figure 11***).

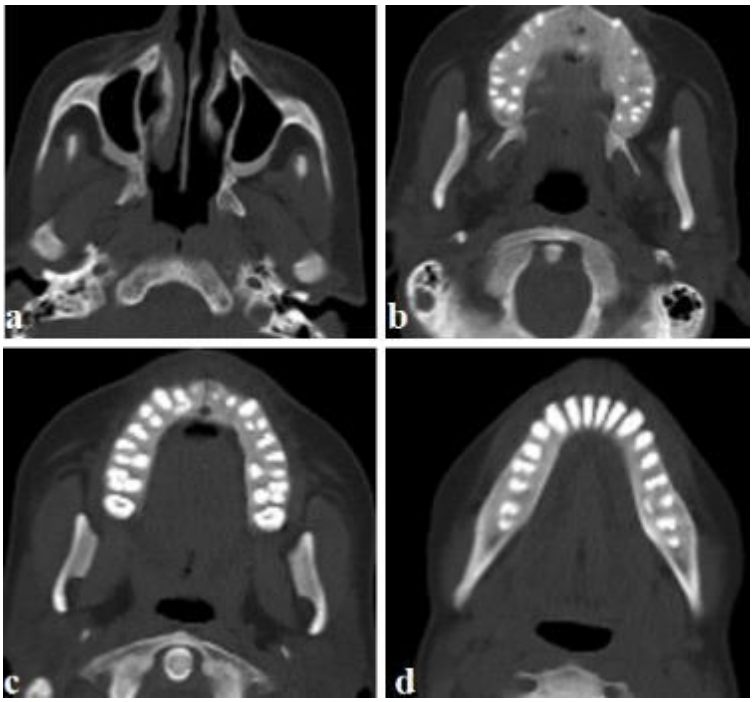

Figure 7 Axial CT images done during her first Sestamibi scintigraphy show diffuse sclerosis of the facial bones, vertebrae and skull base, consistent with renal osteodystrophy. Note the normal teeth arrangement.

The patient was prescribed calcium supplementation and a calcimimetic, with a decrease of her PTH value (833 pg/ml) a month later. She was eventually lost to follow-up.

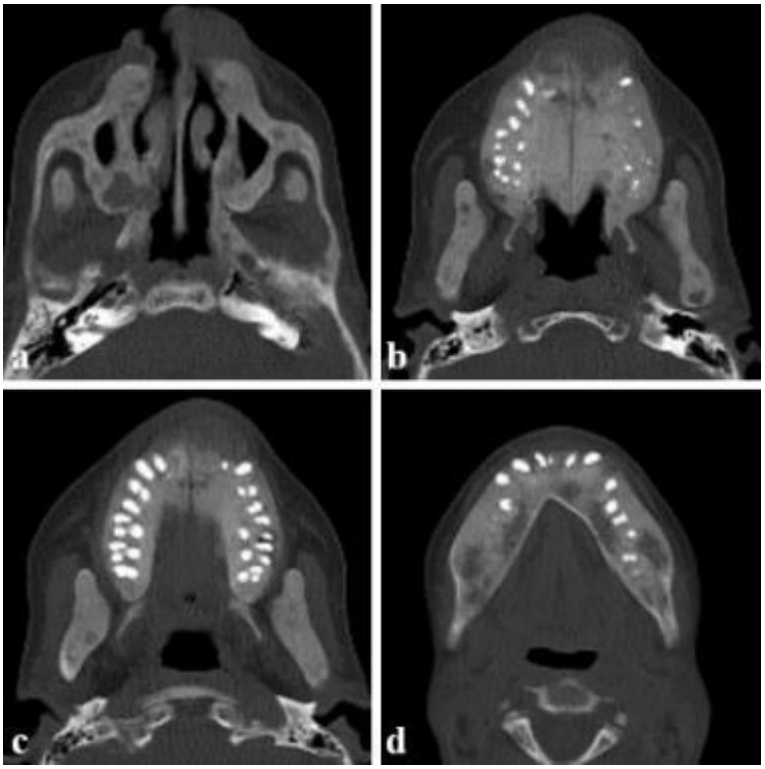

Figure 8 Axial CT images done during her second SestaMIBI scintigraphy (4 years later) show hypertrophy of the facial bones and a reduction of the maxillary sinus lumen, with a dominant sclerosis pattern. The diastema is also evident

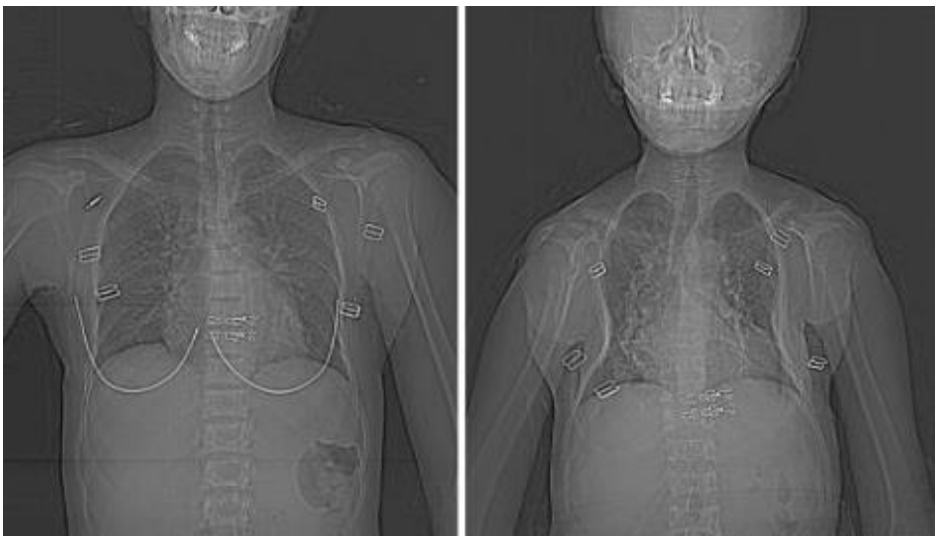

Figure 9 Comparative scout CT films done during the Sestamibi scans show the severe skeletal HPT involvement that occurred in 4 years, with a striking height loss, craniofacial enlargement and a bell-shaped chest

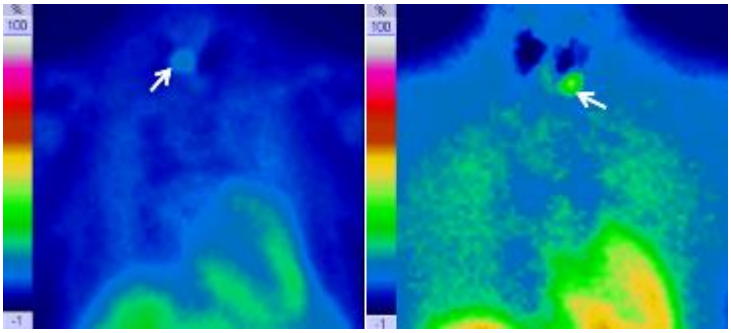

Figure 10 The first Sestamibi scan shows the right lower lobe resected adenoma (left). The right image shows a left lower lobe nodule in the most recent Sestamibi scan

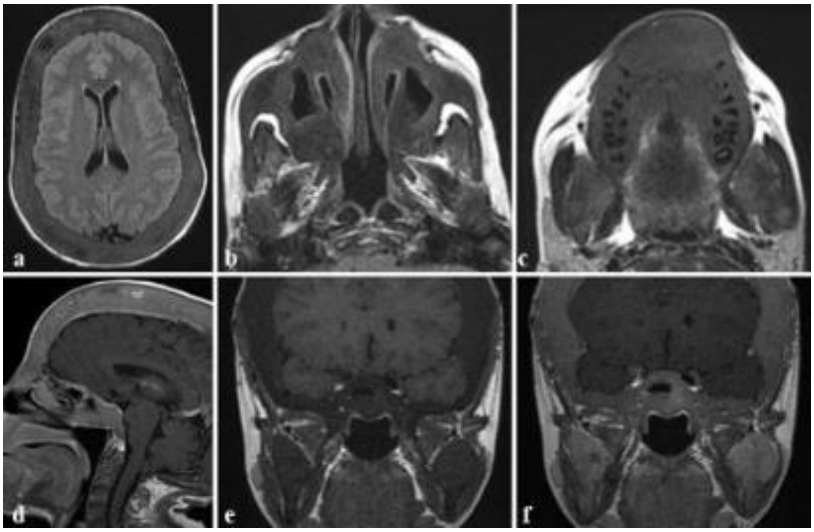

Figure 11 a, b and c. Axial FLAIR images show the diffuse hypertrophy of the skull and the facial bones, with the presence of some T2-hypointense foci in the diploe. **d.** Sagittal enhanced T1WI shows the enlargement of the palate and annular contrast enhancement of one of the focal T2-hypointense lesions previously described. **e.** and **f.** coronal T1WI before and after injection of gadolinium show the homogeneous enhancement of the spongy bone.

3.4. Case 4

A 70-year old woman, who had a history of poorly controlled arterial hypertension, was receiving hemodialysis twice a week for the past 6 years for chronic renal failure secondary to nephroangiosclerosis.

She was complaining of a chronic hard mandibular mass and loss of weight, and was referred to our department for a cervical CT scan.

Laboratory investigations found PTH levels > 2500 pg/ml, a normal corrected serum calcium of 107 mg/l as well as increased phosphatemia 58 mg/l and alkaline phosphatase at 747 UI/L.

She had uncontrolled secondary HPT since her ESRD diagnosis, with PTH levels of 2183 pg/ml the first year then > 2500 pg/ml for the three consecutive years.

NECT showed a symmetric enlargement of the mandibular symphysis and body, and of the palatine and alveolar processes of the maxillary bones, with the succession of hyperdense and hypodense lines in the spongy bone.

CECT images demonstrated 3 bilateral well-defined parathyroid nodules, with the biggest one exhibiting some calcifications and measuring 16 x 7 mm in diameters (**figure 12**).

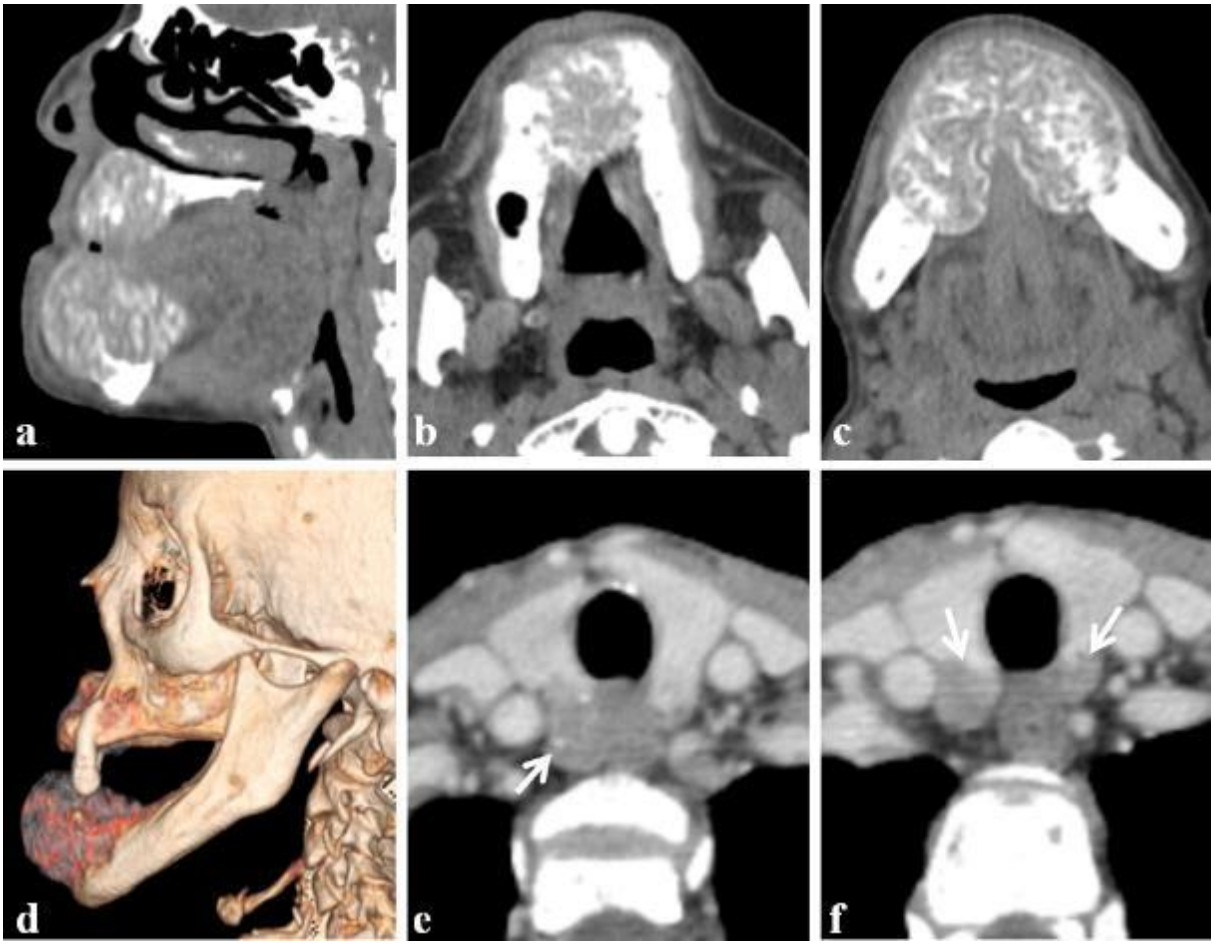

Figure 12 a, b, c and d. Axial, sagittal and a 3D rendering NECT images showing the diffuse medial hypertrophy of the maxilla and mandible. **e.** and **f.** Axial CECT images show parathyroid bilateral nodules, exhibiting some calcifications for the right lower one

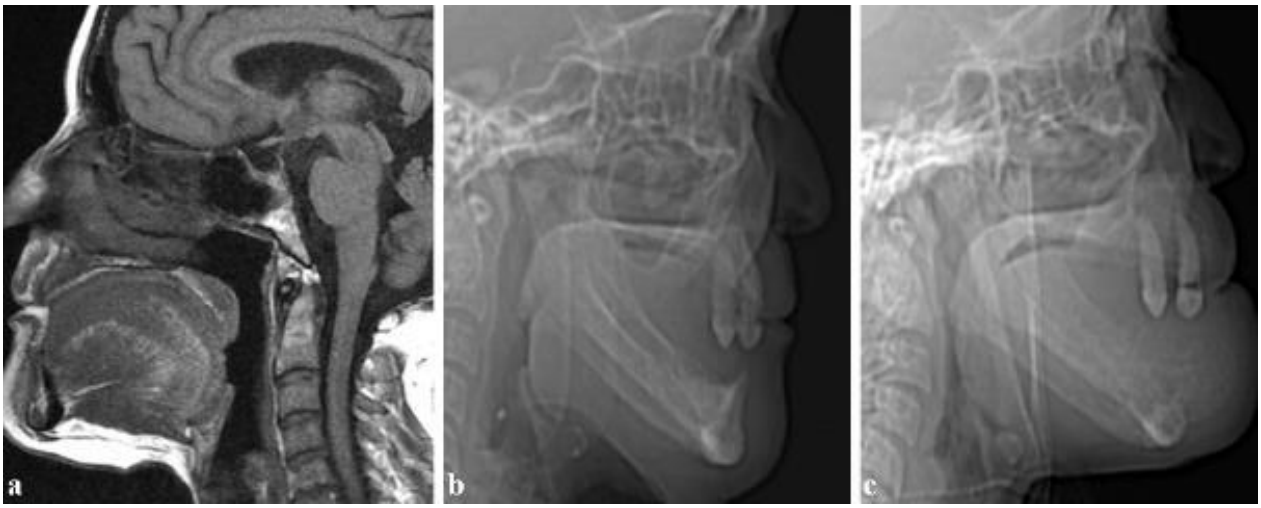

Figure 13 a. and b. Sagittal T1 and CT-scout film shows no abnormality of the palate, maxilla and mandible. c. CT-scout film done 4 years later shown the loss of corticomedullary differenciation and hypertrophy of the maxilla and mandible, with macrognathism

Further research lead to a former head CT scan and MRI done 4 years earlier, which were ordered to rule out cranial hypertension. No evidence of the facial abnormalities was found, although a salt and pepper skull appearance was noted (**figure 13**).

A parathyroidectomy was performed at another hospital, and the patient has recurrence of HPT with increasing values of PTH.

4. Discussion

ULO is a rare craniofacial condition that occurs in patients with end-stage renal disease associated with uncontrolled hyperparathyroidism, and manifests clinically as a massive enlargement of the craniofacial bones leading to cosmetic insult and compressive consequences.

Although its exact mechanisms are unknown, it is most probably due to the alterations of the phosphocalcic metabolism during ESRD, leading to an increase of serum PTH levels in response to hypocalcemia, hyperphosophatemia and hypovitaminosis D [3].

Lee and al [4] pointed out that bighead disease in animals and ULO in humans are nearly identical diseases. Veterinary studies found that dieterary hyperphosphatemia might be central in the development of osteitis fibrosis in uremia and nutritional secondary hyperparathyroidism in horses with bighead disease [5]. Another laboratory animal study induced an advanced renal failure in healthy dogs and showed that secondary hyperparathyroidism failed to develop in animals on low phosphate diet, contrary to animals subjected to a high phosphate diet [6]. In humans, advanced chronic renal disease is the main cause of hyperphosphatemia.

The natural history of ULO seems to happen in four years or less as seen in cases 3 and 4, who had evidence of uncontrolled hyperparathyroidism in the laboratory tests and skeletal involvement in CT scans consisting mainly of a pepper and salt skull appearance before the occurrence of the bone enlargement.

Our study shows that females are more affected than males, with most patients being in their late twenties and early thirties. These results are in concordance with reported literature with a sex ratio of 1,3 F:M and a mean age of 34 years (cf. references). It may be due to the fact that the different subtypes of hyperparathyroidism generally affect females more. Furthermore, female gender is associated with an increased risk of parathyroid nodular hyperplasia and parathyroidectomy rate in dialysis patients [7] and a higher severity of secondary hyperparathyroidism is also observed in uremic women [8 – 10].

In addition, there is a negative association between age and bone mineral density in women with ESRD but not in men with the disease [11], which may result in greater bone damage in females when there is an increase of PTH to maintain normal serum levels of calcium.

Another possible aggravating factor of osteopenia is hypogonadism, with two patients of reproductive age having secondary menstrual disturbances and one of them having hyperprolactinemia, the latter known to cause decrease of bone density [12].

Since the normal craniofacial development often continues into the third decade of life [13], an insult when active modeling and remodeling normally occur in these bones may conceivably predispose them to develop bony deformities [14]. It may explain partially the severity of the musculoskeletal involvement of hyperparathyroidism seen in our 3 youngest patients who exhibited the most extensive lesions, in contrast to the eldest patient who has moderate and limited expansion of the mandible and maxilla. This notion was also seen in Lee's study [4] where the eldest patient, aged 51, developed a milder form of the disease.

Most patients with ULO complain of a progressive and painless facial deformity. Sometimes, the chief complaint is upper airway obstruction, speech impairement, change in voice [15], dysphagia [16] and cranial nerve compression due to foraminal stenosis in the involved skull base such as compressive optic neuropathy [17], facial nerve palsy and sensorineural hearing loss [18]. In one case, it may have aggravated a respiratory failure caused by pulmonary edema [19]. Psychological problems and depression because of these deformities have also been reported [20].

Physical examination finds a non tender mandibular and maxillary hypertrophy, flattening of nasal bridge, widening of the nares and interdental space, as well as bulging and expansion of the hard palate inside the buccal cavity.

Laboratory findings are consistent with severe HPT, and imaging is usually indicated to eliminate other clinical etiologies of leontiasis ossea, such as Paget disease, fibrous dysplasia, craniometaphyseal dysplasia, metastatic disease, multiple osteomas and acromegaly [21].

Histologic evaluation may be unhelpful because ULO has similar features with fibrous dysplasia and Paget's disease.

The main characteristic of ULO is its symmetrical distribution, contrary to fibrous dysplasia, Paget's disease and brown tumors. The latter may be unifocal or multifocal, monostotic or polyostotic. Asymmetrical multifocal rather than diffuse involvement in is one of the most important differentiating factors for these pathologies [22].

Additionally, there are no abnormalities of the phosophocalcic markers in the patients with fibrous dysplasia, and the biochemical profile of patients with Paget disease shows elevated bone biomarkers with increased levels of alkaline phosphatase [23], with increased PTH levels present in 12–18% of Paget disease patients [24].

Brown tumors occur most frequently in the setting of primary HPT, with a normal glomerular filtration rate, although they can be seen in secondary HPT. Involvement of the craniofacial bones consists of unique or multiple expansive masses without loss of corticomedullar bone differenciation in the spared bones, unless a renal osteodystrophy is associated.

Non-enhanced CT is the imaging modality of choice [15], and 3D reconstruction may be helpful for preoperative planning for facial surgery [4].

3 imaging patterns of renal osteodystrophy have been described in the craniofacial bones: brown tumors, ULO and dystrophic calcification [17]. Others craniofacial manifestations of HPT include osteomalacia, osteosclerosis, erosion of the cortical bone, loss of the dental lamina and resorption of the lamina dura [25].

In ULO, the normal bony architecture is replaced by a thinned cortex and expanded spongy bone, with individualization of alternate patterns of hyperdense and hypodense wavy lines. A less frequent pattern is diffuse osteosclerosis of the spongy bone [17, 22, 26], as seen in patient 3.

The enlargement of the maxillary may result in an obliteration of the maxillary sinuses and widening of the spaces between the teeth.

MRI can be requested when CT findings are inconclusive [4]. On MRI, the expanded bone marrow appears as intermediate signal intensity onT1-weighted images and low-to-intermediate signal intensity on T2- weighted images [1].

Well-defined small lesions were detected in the spongy bone [4, 17], and Lee [4] speculated that the small bony nodules seen in MRI may represent brown tumors.

Reversibility of ULO after treatment of the HPT is still debated, with most studies showing stabilization of the facial deformity [4, 27, 28]. It is mostly irreversible even after correction of hyperparathyroidism [29]. Phelps and al [30] stated that the jaws do not return to their normal contours after parathyroidectomy.

To our best knowledge, we found 2 case reports describing partial regression of the facial deformity [2, 31], with clinical and radiological signs of improvement with subsequent mineralization of the spongy bone [2].

In Duan's study [31], this regression may be due to the moderate bony expansion instead of the classical prominent form that is usually reported, as seen in patient 4.

It's important to note that increased levels of PTH can be detected in blood test analysis prior to clinical features of calcium impaired metabolism, thus it is important to emphasize on patients preventive screening during haemodialysis [1]. Gabay et al stressed the need to preserve bone prior to commencement of dialysis [11].

The treatment of HPT primarily relies on correcting the calcium and vitamin D levels and reducing the phosphate level with either parathyroidectomy or the administration of calcitriol in conjunction with phosphate binding agents and a phosphate-controlled diet [31].

Because of the lack of cases published so far in the literature, a proper surgical management is not developed [32]. 3 types of surgeries, including subtotal parathyroidectomy, total parathyroidectomy with autotransplantation and total parathyroidectomy, have been proposed [33]. A high recurrence rate (60%) was observed in patients who underwent total parathyroidectomy with autotransplantation within 1 year [34], which was attributed to graft-dependent secondary HPT.

Albeit lesser (25%), recurrence rate of hyperparathyroidism was also described after total parathyroidectomy [35].

Hungry bone syndrome had been observed postoperatively after total parathyroidectomy [2, 26, 34].

Following parathyroidectomy, the facial changes either stabilized or mildly improved [4, 27, 33]. Surgical recontouring of the enlarged facial bones has been described in 3 cases [36 – 38], indicated in one case after respiratory distress requiring urgent tracheotomy [37].

A spontaneous compressive vision loss improved was reported following parathyroidectomy [39], and a progressive mild improvement was described after decompressive surgeries for cranial nerve compressions [18, 40], despite surgery being more difficult when the craniofacial bones are abnormally thick [40].

5. Conclusion

The diagnosis of ULO is based on a concordant history of chronic renal disease and dialysis, with laboratory test results showing HPT and imaging demonstrating a symmetrical enlargement of the craniofacial bones and a characteristic spongy bone pattern.

Its evolution is halted only by successful parathyroidectomy, and most studies report the stabilization or mild improvement of the severe disfigurement and occlusal disease after treatment.

A preventive measure of this disease would be an active monitoring of PTH serum levels in end-stage renal disease patients, because the increase level of PTH precedes macroscopic skeletal changes. In addition, a head and neck examination as well as a panoramic radiograph could be suggested for screening for this disease, especially when the medical therapy fails to control the HPT.

Abbreviations

- ALP: alkaline phosphatase
- CECT: contrast-enhanced computed tomography
- CT: computed tomography
- ESRD : end-stage renal disease
- HPT: hyperparathyroidism
- MRI: magnetic resonance imaging
- NECT: non-enhanced computed tomography
- PTH: parathyroid hormone
- Tc: technetium
- ULO: uremic leontiasis ossea

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare that they have no competing interest.

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