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Case Report

# Uremic Leontiasis Ossea due to Resistant Secondary Hyperparathyroidism

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ABSTRACT

*Background/Objective:* Severe progressive overgrowth of the facial bones known as uremic leontiasis ossea (ULO) is a rare complication of resistant hyperparathyroidism in end-stage renal disease (ESRD). The objective of this report is to describe the presentation and treatment of ULO.
*Case Report:* A 48-year-old woman with a history of hypertension, coronary artery disease, and ESRD on hemodialysis presented with severe secondary hyperparathyroidism and calciphylaxis. She had significant changes to her face in the last 3 months leading to oropharyngeal dysphagia and difficulty articulating. Physical examination revealed bony overgrowth in her upper jaw and hard palate, widely spaced teeth, and calcinosis cutis. Her parathyroid hormone (PTH), calcium, and phosphorus levels were 5066 pg/mL (normal range, 12-88 pg/mL); 10.0 mg/dL (8.4-10.2 mg/dL); and 5.4 mg/dL (2.7-4.5 mg/dL); respectively. Using a multidisciplinary approach, she successfully underwent a 3.5-gland parathyroidectomy (immediate postoperative PTH level, 600 pg/mL). She was discharged without complication. Pathology showed hypercellular parathyroid glands with reactive changes.
*Discussion:* ULO, the most severe form of renal osteodystrophy, results in hypertrophy of the craniofacial skeleton. It carries the risk of significant comorbidities due to cranial nerve compression, respiratory compromise, dysarthria, and dysphagia.
*Conclusion:* With prolonged, uncontrolled PTH stimulation in ESRD, significant facial disfiguration with disabilities can occur. It is of utmost importance to adhere to guideline-specified PTH targets in persons with ESRD to prevent patient harm from permanent physical deformities.


## Introduction

The term “leontiasis” was previously used to refer to the lion face–like appearance of patients with leprosy. In 1869, Virchow used the term “leontiasis ossea” to describe craniofacial overgrowth that resembles a lion face, which can be observed in various diseases such as Paget's disease, fibrous dysplasia, gigantism, and renal osteodystrophy (ROD). The term “uremic leontiasis ossea” (ULO) was first used in 1953 to describe the facial manifestations in secondary hyperparathyroidism (SHPT) in persons with chronic kidney disease (CKD).[1,2]

ROD is defined as altered bone mineral metabolism in the setting of CKD. In 2005, KDIGO changed the term ROD to CKD–mineral and bone disorder, which includes 1 or more of the following: (1) abnormalities in calcium, phosphorus, PTH, or vitamin D metabolism; (2) abnormalities in bone turnover, mineralization, volume, linear growth, or strength; and/or (3) vascular or other soft tissue calcification.[3]

The maxilla and mandible are primarily involved in ULO with progressive hypertrophy of the bones resulting in encroachment of the sinuses, nasal cavities, and orbital cavity, which may result in optic nerve compression, exophthalmos, and possible airway obstruction.[4-6] Unique imaging characteristics include bones that

*Abbreviations:* CT, computed tomography; ESRD, end-stage renal disease; FGF-23, fibroblast growth factor 23; HD, hemodialysis; PTH, parathyroid hormone; ROD, renal osteodystrophy; SHPT, secondary hyperparathyroidism; ULO, uremic leontiasis ossea.

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often appear marbled with alternating bands of hyperdensity and hypodensity throughout the bony matrix.[7] Here, we discuss a case of rapidly progressing ULO in a middle aged woman.

## Case Report

A 48-year-old woman with a medical history of end-stage renal disease (ESRD) due to focal segmental glomerulosclerosis on hemodialysis (HD) for the past 11 years, hypertension, coronary artery disease, and cerebrovascular disease presented to our outpatient clinic seeking evaluation for SHPT. Her largest concern was changes to her face and mouth over the past year, which have substantially impacted her ability to eat, drink, and speak over the last 3 months due to her inability to close her mouth. She also described a 50-lb weight loss and had an L3 fracture leading her to become wheelchair-bound over the past year. All these changes impacted her quality of life leaving her dependent on her family members. She was saddened by her inability to function as a mother and wife, and her greatest despair was no longer being able to kiss her loved ones.

Regarding her ESRD, she received HD 3 times weekly at another facility. She was prescribed cinacalcet to treat SHPT; however, she was intolerant with nausea and vomiting even at the lowest dose. She was never treated with etelcalcetide. She reported very high parathyroid hormone (PTH) levels over the last 3 years. Her medications were sevelamer 800 mg 3 times daily, calcitriol 0.5 mcg 3 times weekly, erythropoietin 60 mcg every 2 weeks, nifedipine ER 60 mg daily, carvedilol 25 mg twice daily, and atorvastatin 40 mg once daily.

On physical examination, her blood pressure, pulse rate, and body mass index were 176/95 mm Hg, 94 beats/min, and 20.7 kg/m$^2$, respectively. She had upper jaw widening, a prominent hard palate, and widely spaced teeth (Fig. 1 *A* through *C*). Additionally, calcified skin nodules were palpated on her forehead, and skin calcifications were observed on her lower extremities (Fig. 1 *D*).

Laboratory analysis revealed the following values: (1) PTH level, 4429 pg/mL (normal range, 12-88 pg/mL); (2) calcium level, 8.6 mg/dL (normal range, 8.4-10.2 mg/dL); (3) albumin level, 3.6 g/dL (normal range, 3.5-5.2 g/dL); (4) phosphorus level, 4.8 mg/dL (normal range, 2.7-4.5 mg/dL); (5) vitamin D level, 11 ng/mL (normal range, 20-120 ng/dL); and (6) alkaline phosphatase, 458 IU/L (normal range, 33-133 IU/L). Her vitamin D was replaced. Imaging studies, including computed tomography (CT) of the neck/face and thyroid ultrasound, identified a 0.9-cm right posterior medial nodule suspected of being a parathyroid adenoma and a separate 2.1-cm left inferior thyroid nodule with rim calcifications.

### Highlights

- Resistant secondary hyperparathyroidism can lead to uremic leontiasis ossea (ULO)
- ULO comprises craniofacial deformities leading to disabilities
- Prevention involves meeting parathyroid hormone targets in chronic kidney disease
- The goal of treatment is to reduce parathyroid hormone level to target range

### Clinical Relevance

Uremic leontiasis ossea is a rare, progressive form of renal osteodystrophy mostly affecting the craniofacial skeleton. This case highlights the importance of meeting parathyroid hormone targets in chronic kidney disease and the severe complications that can result from severe, resistant, untreated secondary hyperparathyroidism.

Cytopathology of the thyroid nodule showed atypia of undetermined significance. Genomic profiling of the left inferior nodule revealed that it was an ectopic parathyroid gland. CT of the face revealed renal osteodystrophic changes in the skull (Fig. 2). Three-dimensional CT noted mixed sclerotic and lytic changes predominantly on facial bones (Fig. 3). Numerous imaging studies demonstrated extensive arterial calcifications (Fig. 4).

Given the profound extent of her disease, she underwent a 3.5-gland parathyroidectomy with partial left thyroidectomy to remove the ectopic intrathyroidal parathyroid adenoma. Pathology confirmed “hypercellular enlarged parathyroid gland in all 4 glands and hypercellular parathyroid tissue along with normal thyroid tissue from the left thyroid.” Her PTH level decreased to 600 pg/mL immediately after parathyroidectomy and 10 pg/mL on the day of discharge. Her nadir corrected calcium and phosphorus levels were 8.4 mg/dL and 2.1 mg/dL, respectively. She was discharged on calcitriol 0.5 mcg daily, vitamin D 2000 IU daily, and calcium carbonate 1000 mg twice daily. She followed up with her outpatient nephrology center.

## Discussion

ULO is the craniofacial manifestation of severe hyperparathyroid bone disease (osteitis fibrosa cystica) in persons with ESRD.

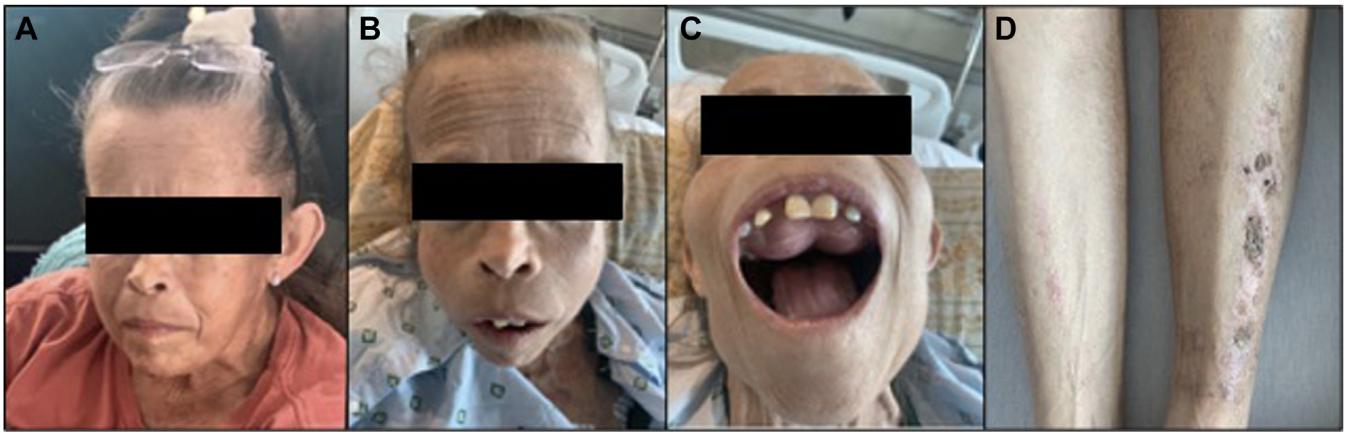


**Fig. 1.** Physical findings in uremic leontiasis ossea. *A*, Facial structure before visible changes were noticed. Bony enlargement of maxilla (*B*), hard palate with teeth spacing (*C*), and calcinosis cutis of the lower extremities (*D*) 3 months after visible changes were noted.

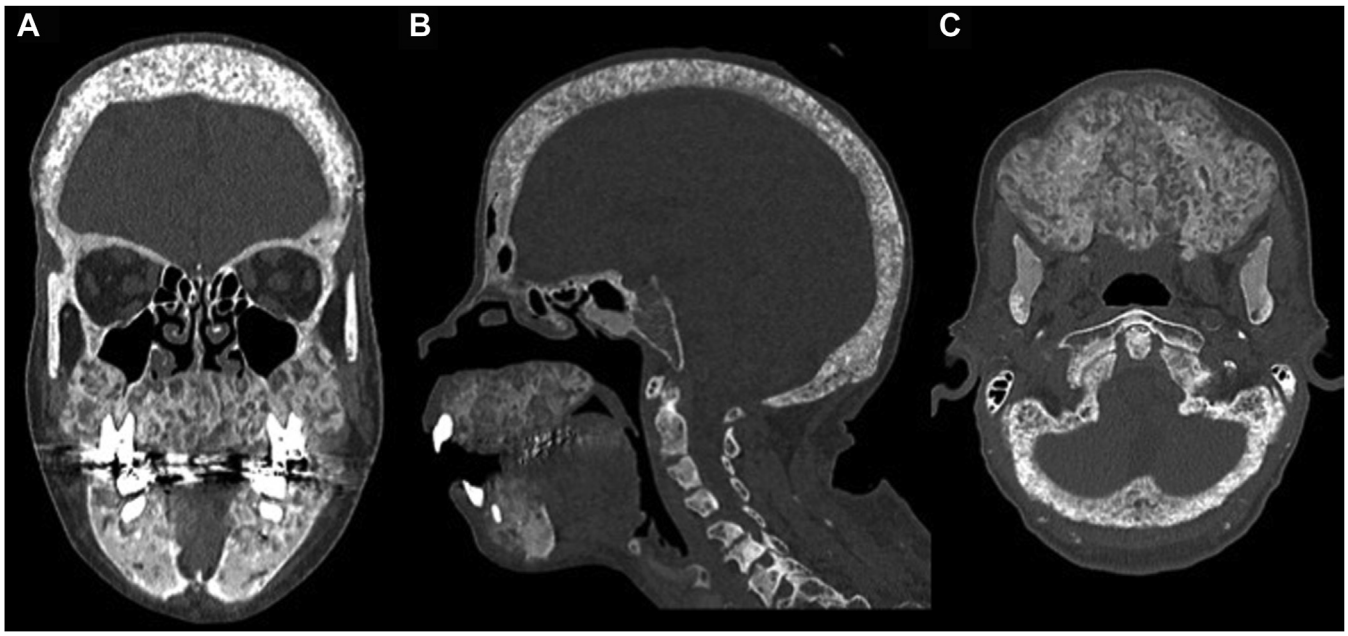


**Fig. 2.** Computed tomography coronal (*A*), sagittal (*B*), and transverse (*C*) view images of the head showing extensive renal osteodystrophic changes involving the entire imaged skeleton, although greatest within the skull and maxilla/mandible with arterial sclerosis and calcified skin areas also noted.

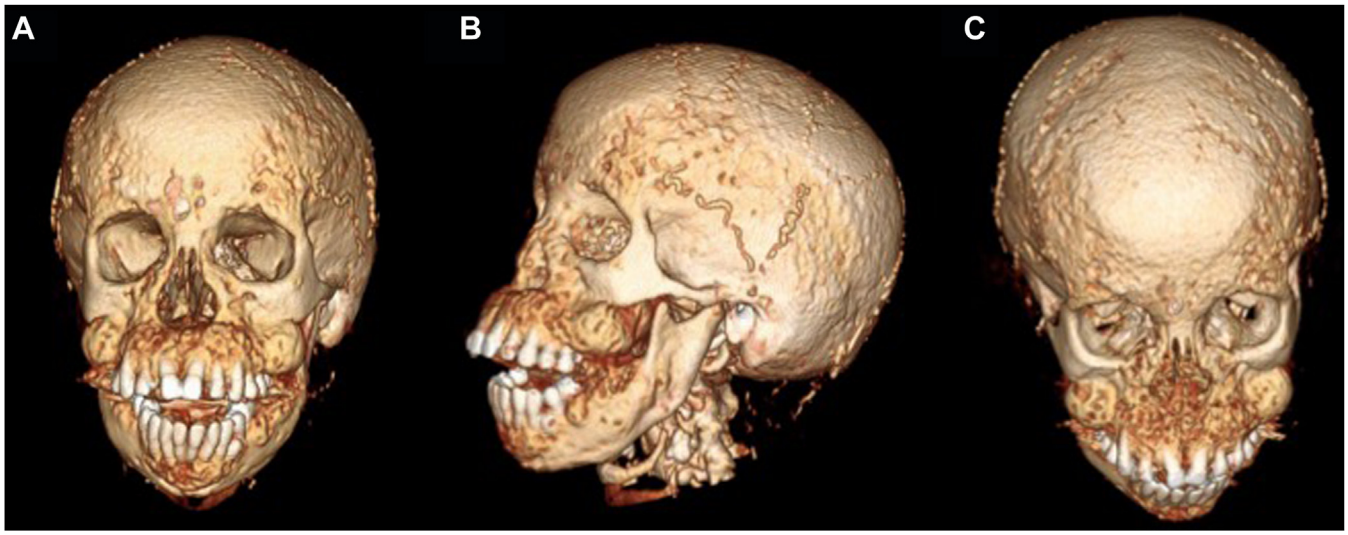


**Fig. 3.** Three-dimensional computed tomography coronal (*A*), sagittal (*B*), and superior (*C*) images of the head showing extensive bone deformities predominantly of the mandible, maxilla, and calvaria with overbite. Diffuse mixed sclerotic and lytic changes in all visualized bone noted.

Features of ULO include severe craniofacial deformities, soft tissue changes, tumoral tissues in the mouth, fingertip changes, and psychological problems.[2]

As noted in our case, there was progressive thickening of the facial bones, transforming the architecture of the facial structures leading to disfiguration and disabilities. This can lead to impairment in speaking and chewing, oropharyngeal dysphagia, and decreased quality of life and mental health. In addition, compression of cranial nerves leading to decreased visual and hearing acuity and upper airway patency has been reported.[4-6] Laboratory findings are consistent with an extremely increased PTH level, hyperphosphatemia, and hypocalcemia, findings consistent with severe SHPT.[1,8] Interestingly, in most published cases, the person was young (mean age, 31.2 years), with 67% occurring in women; most were on HD, and the maxilla was affected in 73.2%.[9] Imaging modalities such as bone scintigraphy with increased bone reuptake in calvarium have been described.[10] Although ULO is a clinical diagnosis, imaging modalities help to differentiate it from other conditions and allow to compare progression or improvement after successful management and reconstructive surgeries.[2]

ROD represents a spectrum of metabolic bone abnormalities with histologic and skeletal abnormalities occurring in patients with CKD. Once kidney function declines, this leads to a cascade of mineral abnormalities disrupting normal bone homeostasis. Phosphate excretion is impaired, which results in hyperphosphatemia. An increased circulating phosphorus level stimulates PTH and

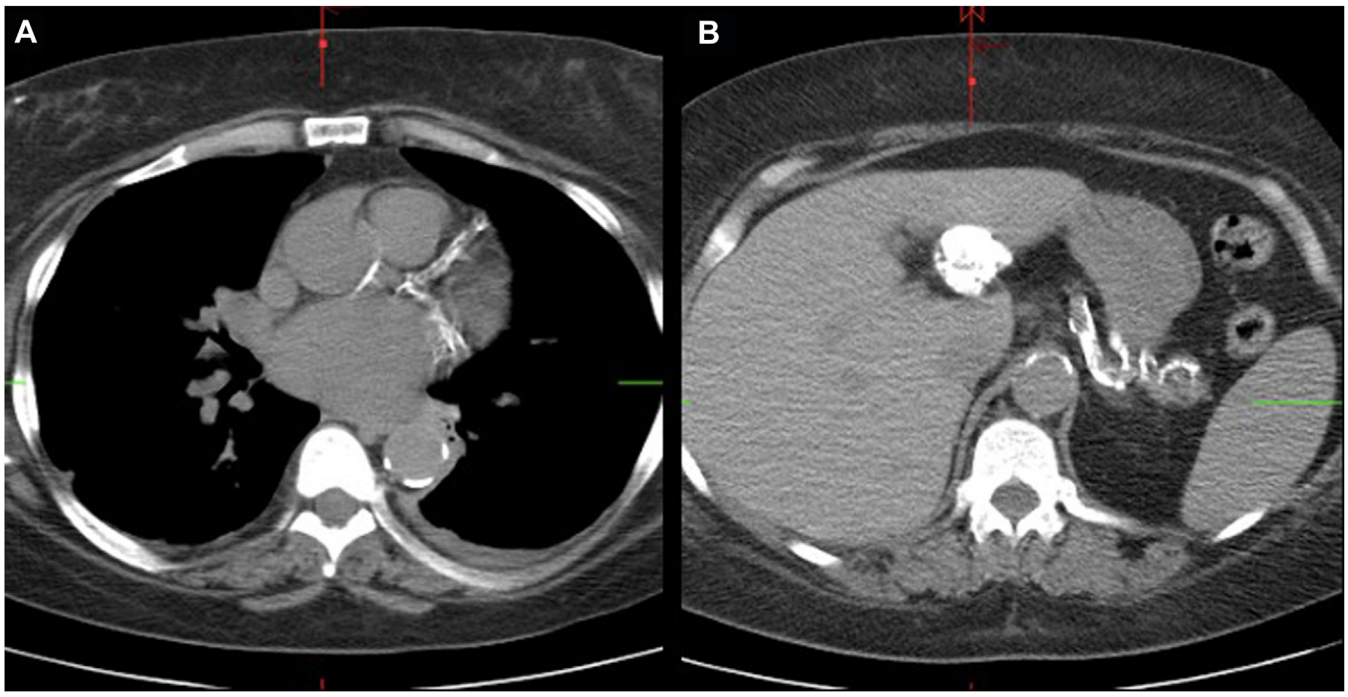


**Fig. 4.** Computed tomography transverse view of the abdomen showing atherosclerotic disease involving the aorta and multivessel coronary arterial disease (*A*) and calcified hepatic lobe and partial pancreas (*B*).

fibroblast growth factor 23 (FGF-23) secretion. The kidneys also fail to convert 25-vitamin D to 1,25-vitamin D effectively. Low 1,25-vitamin D levels lead to decreased intestinal calcium absorption, further amplifying PTH secretion. There is also PTH and FGF-23 resistance at the kidney level, which worsens hyperphosphatemia and hypocalcemia due to impaired renal phosphate excretion and calcium reabsorption, respectively.[11] This imbalance leads to abnormal bone metabolism, including mineralization, turnover, volume, and strength, with associated systemic vascular and soft tissue calcification.[3] Despite the high worldwide prevalence of CKD–mineral and bone disorder in patients with stage 3 to 5 CKD, it is rare for facial deformities that impair eating and speaking to develop, such as in our patient. Of note, although our patient was known to have increased PTH levels over the years, major bone changes rapidly progressed over few months, which make her case more unique.

Genetic predisposition can explain why just a very few patients will develop severe and incapacitating jaw enlargement. In 23 persons with ULO, several sequence variation were found in the *GNAS1*, *FGF23*, and *FGFR3* genes. In 73.9% (17/23) of individuals, a variant in *GNAS1* was present. In addition, 10 variants in *FGF23* and 22 variants in *FGFR3* were reported.[12] Another multicenter study that investigated 60 persons with ULO also found *GNAS1* allelic variant in those individuals.[13] Interestingly, *GNAS1* has been implicated in other bone dysplasias, such as McCune-Albright hereditary osteodystrophy. Taken together, uncontrolled SHPT may unmask the underlying genetic predisposition for ULO; however, further research is needed.

There are unique radiological and histologic findings in leontiasis ossea. Imaging typically reveals hyperostosis of the craniofacial skeleton with serpiginous tunneling, poor visualization of cortical bone, and no distinct corticomedullary differentiation.[7] Although leontiasis ossea is characterized by the bony changes of the skull, in ULO, renal osteodystrophic changes involve the entire skeleton with sclerotic changes at the endplates, compression fractures on vertebrae, and radiolucency in the bone medulla.[8] Bone histology typically shows peritrabecular fibrosis, increased woven and irregular osteoid, moderate vascularization, and multinucleated osteoclast-type giant cells.[14,15]

The treatment for ULO is aggressive management of SHPT. Indications for subtotal or total parathyroidectomy with autotransplantation is recommended in resistant SHPT, persistent hypercalcemia, nephrolithiasis, calciphylaxis, and fragility fractures.[16] Parathyroidectomy has been reported to halt or even mildly reverse bone disease in ULO including improvement in skeletal changes, compressive optic neuropathy, and quality of life.[17,18] Hungry bone syndrome and hypoparathyroidism are known complications that require close monitoring and replacement of minerals as needed. However, biochemical recurrence has been reported in up to 60% 1 year following surgery. This is likely due to residual or ectopic parathyroid tissue that can be identified with a postoperative technetium-99 sestamibi scan. Because of the rarity of ULO, there is no specific maxillofacial surgery recommended in the literature.[2]

## Conclusion

ULO is a severe and rare form of ROD. Given the absence of a definitive therapeutic intervention, the critical imperative lies in early detection and aggressive management of SHPT with a low threshold for parathyroidectomy when medical management fails to mitigate the progression of deleterious sequelae.

## Statement of Patient Consent

Signed informed consent was obtained for the images in this manuscript

## Disclosure

The authors have no conflicts of interest to disclose.

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