CASE REPORT

Dramatic Alteration of the Skull in a Uremic Patient with Leontiasis Ossea

Su-Yan Duan, Chang-Ying Xing, Guang Yang, Ning-ning Wang and Bo Zhang

Abstract

The craniofacial skeleton represents a peculiar target of hyperparathyroidism in patients with end-stage renal disease who exhibit a dramatic pattern of uremic leontiasis ossea. Scant information regarding this condition is available in the renal literature, as the extreme and typical manifestations of leontiasis ossea have been described in only a small series of patients. We herein report a case of significant amelioration of massive modification of the facial appearance of a 30-year-old uremic Chinese woman with severe skeletal deformities who underwent total parathyroidectomy with a forearm autograft concurrently with effective drug treatment. This report may shed light on how to better understand and treat this metabolic derangement.

Key words: uremic leontiasis ossea, total parathyroidectomy with forearm autograft, hyperparathyroidism

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Introduction

Secondary hyperparathyroidism (SHPT) is a major complication of end-stage renal disease (ESRD) characterized by complex alterations in bone and mineral metabolism (1). With a high prevalence in China, this pathological modification of bone and mineral metabolism increases the risk of cardiovascular morbidity and mortality (2). The state of excessive secretion of parathyroid hormone (PTH) after longstanding secondary hyperparathyroidism resulting in hypercalcemia is termed tertiary hyperparathyroidism (3, 4). The effects of these altered metabolic levels on a range of musculoskeletal manifestations are referred to as renal osteodystrophy. At the extreme of this range is a complication of chronic renal failure (CRF) known as uremic leontiasis ossea (ULO) that clinically presents with macrognathia and severe facial deformities (5, 6).

ULO is a descriptive term applied to hyperostotic changes in the facial bones that can result in bilateral expansion of the malar processes, thus reducing the nasomaxillary angle. The term leontiasis was initially used to describe changes in the facial skin observed in patients with leprosy. Such chronic indurative cutaneous changes, as opposed to bony overgrowth, induce a lion-like facial expression (7-9). Although it is important to be aware of the diagnosis and management of this debilitating condition, there remain many unaddressed difficulties. First, the mechanisms underlying the craniofacial bone remodeling observed in patients with ULO are mostly unknown. SHPT is a complex and challenging condition. Metabolic parameters, such as the levels of calcium, phosphate, Ca×P, intact parathyroid hormone (iPTH), fibroblast growth factor 23 (FGF23) and vitamin D, must be maintained within target ranges in order to prevent bone disease and extraskeletal calcification and maintain homeostasis of other body systems (10).

Second, renal osteodystrophy is a complex metabolic disorder. The prevalence of this condition is increasing due to advances in the medical management of renal failure and the more frequent occurrence of renal transplantation. Massive thickening of the cranial vault and facial bones, called ULO, requires intensive management by a multidisciplinary team, since macroscopic features may involve skeletal, dental, nasal and facial and/or other organic abnormalities. Furthermore, this condition manifests a lack of sufficient predictive factors and well-accepted treatment strategies in the limited literature (11, 12). Sex, race and length of dialysis treatment or renal insufficiency do not appear to be predictive factors for the development of leontiasis ossea (13, 14). Moreover, the paucity of information with respect to dramatic amelio-
ration of the skull achieved using radiological measurements exacerbates the lack of knowledge regarding ULO.

We herein report a case of significant radiological amelioration of craniofacial deformations in a uremic patient with ULO achieved using vivid skull computed tomography (CT) with 3D reconstruction following successful treatment with total parathyroidectomy (PTX) and a forearm autograft performed concurrently with eight months of effective drug therapy.

**Case Report**

A 30-year-old woman with ESRD due to chronic glomerulonephritis (the type of renal pathology was unknown because no percutaneous renal biopsy was performed) had received two years of drug treatment before accepting regular hemodialysis therapy for four years at another center. She was admitted to our clinic due to severe disfigurement of her face. She was noncompliant with diet and did not take any phosphate binders or vitamin D systematically until marked enlargement of the facial bones developed, most prominently in the maxilla and mandible. She subsequently underwent maxillary polypectomy and began to take 0.25 μg of calcitriol soft capsules per day. Unfortunately, her symptoms deteriorated. For the month preceding admission, she experienced severe pain on the right side of the maxilla and in the legs, with functional eating problems and the inability to walk. She took 2 μg of calcitriol soft capsules twice a week; however, her parathyroid hormone level remained elevated at 3,000 pg/mL after two weeks of therapy.

On admission, a physical examination revealed shortening of the patient’s height of 6 cm, unbearable skin itching, kyphoscoliosis, pectus carinatum and joint deformities. Her mandible and maxilla were symmetrically enlarged and pro-

*Figure 1. Skull CT scan with 3D reconstruction and cross-sectional images obtained before surgical and symptomatic drug treatment. A: Skull CT scan with 3D reconstruction vividly displayed prominent maxillary and mandibular skeletal hypertrophy and disappearance of the lamina dura of the alveolar bone concomitant with malocclusion, frontal bossing and exophthalmos prior to total parathyroidectomy with a forearm autograft and the administration of regular drugs. A typical cross-sectional image is shown in panel B. The arrow indicates the prominent maxilla before surgery.*
and stabilization of body height. The most striking result with easing of the maxillary and leg pain and skin itching was the amelioration of skeletal changes, particularly facial modification with corresponding improvements on skull CT scans (Fig. 2). Significant amelioration of the patient’s skull changes, including a reduced skull base, maxillary and mandibular modifications, occlusal correction and a recovery of the lamina dura of the alveolar bone, were achieved following surgical and symptomatic drug treatment. The maxillary volume before and after treatment was 31,258.96 and 25,550.16 mm³, respectively. Notable retraction of the front of the maxilla in the anteroposterior diameter, from 83.6 to 85.8 mm, and the transverse diameter of the content of the maxilla in the anteroposterior diameter, from 101.7 to 103.7 mm, was observed on cross-sectional images. Correspondingly, the mandible shrank in size, as demonstrated by a change in the anteroposterior diameter from 69.4 to 67.9 mm on skull CT.

Table 1. Laboratory Values and Various Characteristics before Surgery with Total Parathyroidectomy and Autotransplantation

<table>
<thead>
<tr>
<th>Time</th>
<th>4 years ago</th>
<th>1 year ago</th>
<th>1 month ago</th>
<th>2 weeks ago</th>
<th>On admission</th>
<th>Before surgery (after 20-days hospital treatment)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>No obvious metabolic osseous changes</td>
<td>marked enlargement of the facial bones</td>
<td>severe pain in maxillary right side and leg, with functional eating problems and an inability to walk</td>
<td>symptoms deteriorated</td>
<td>a 6-cm shortening of her height than 4 years ago, unbearable skin itching, kyphoscoliosis, pectus carinatum and joint deformities, face disfigurement</td>
<td>no surgical contraindication, with blood pressure of 125/85 mmHg and hemoglobin of 9 gm/dL</td>
</tr>
<tr>
<td>treatments</td>
<td>3 times/week hemodialysis</td>
<td>maxillary polypectomy+0.25μg calcitriol soft capsules twice a week</td>
<td>2 μg calcitriol soft capsules twice a week</td>
<td>2 μg calcitriol soft capsules twice a week</td>
<td>blood pressure control+ iron supplementation</td>
<td>total parathyroidectomy with forearm autograft</td>
</tr>
<tr>
<td>dietary restrictions</td>
<td>noncompliant dietary phosphate restriction</td>
<td>dietary phosphate restriction</td>
<td>dietary phosphate restriction</td>
<td>dietary phosphate restriction</td>
<td>dietary phosphate restriction</td>
<td></td>
</tr>
<tr>
<td>PTH(pg/mL)</td>
<td>/</td>
<td>2000</td>
<td>/</td>
<td>3000</td>
<td>3073.5</td>
<td>2063.50</td>
</tr>
<tr>
<td>Ca(mmol/L)</td>
<td>2.55</td>
<td>2.13</td>
<td>/</td>
<td>2.67</td>
<td>2.83</td>
<td>2.72</td>
</tr>
<tr>
<td>P(mmol/L)</td>
<td>1.63</td>
<td>2.25</td>
<td>/</td>
<td>1.58</td>
<td>1.77</td>
<td>1.33</td>
</tr>
<tr>
<td>Vitamin D(ng/mL)</td>
<td>/</td>
<td>36.9</td>
<td>/</td>
<td>28.2</td>
<td>31.3</td>
<td>32</td>
</tr>
<tr>
<td>ALP(U/L)</td>
<td>/</td>
<td>1058</td>
<td>/</td>
<td>2013.5</td>
<td>2397.8</td>
<td>2128.1</td>
</tr>
<tr>
<td>Osteocalcin (μg/L)</td>
<td>/</td>
<td>177.3</td>
<td>/</td>
<td>/</td>
<td>191.7</td>
<td>121.7</td>
</tr>
</tbody>
</table>

Table 1 displayed the time line of the patient’s symptoms and each clinical intervention, along with the evolution of metabolic parameters before total parathyroidectomy with forearm autograft.

Table 2. Follow-up Laboratory Values Obtained after Surgery with Total Parathyroidectomy and Autotransplantation

<table>
<thead>
<tr>
<th>Time</th>
<th>after surgery 10min</th>
<th>after surgery 20min</th>
<th>after surgery 3d</th>
<th>after surgery 4m</th>
<th>after surgery 8m</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTH(pg/mL)(transplantation side)</td>
<td>251.4</td>
<td>164.3</td>
<td>81.0</td>
<td>545.2</td>
<td>335.3</td>
</tr>
<tr>
<td>PTH(pg/mL)(non- transplantation side)</td>
<td>197.8</td>
<td>145.1</td>
<td>68.2</td>
<td>/</td>
<td>/</td>
</tr>
<tr>
<td>Ca(mmol/L)(non- transplantation side)</td>
<td>1.48</td>
<td>1.90</td>
<td>2.05</td>
<td>2.16</td>
<td>2.35</td>
</tr>
<tr>
<td>P(mmol/L) (non- transplantation side)</td>
<td>1.34</td>
<td>1.25</td>
<td>1.08</td>
<td>1.39</td>
<td>1.17</td>
</tr>
<tr>
<td>ALP(U/L)(non- transplantation side)</td>
<td>/</td>
<td>/</td>
<td>2.250.3</td>
<td>262</td>
<td>125</td>
</tr>
</tbody>
</table>

The normal range of the laboratory indicators: PTH: 12.0-88.0 pg/mL, Ca (serum calcium): 2.20-2.65 mmol/L, P(serum phosphate): 0.81-1.45 mmol/L, ALP(alkaline phosphatase): 30-120 U/L, Vitamin D: 52.5-117.5 ng/mL, Osteocalcin:11-43 μg/L

Table 2 showed the follow-up of serum PTH, serum calcium and serum phosphate levels after the surgery.

40 ml/hour of 5% calcium gluconate was administered intravenously if the serum calcium level fell below 1.8 mmol/L, with the aim of maintaining the level between 1.8 and 2.4 mmol/L. Three days after the procedure, calcium carbonate tablets were given in order to gradually reduce the intravenous dose of calcium gluconate. The patient was discharged on the seventh day after the surgery, with a regimen including the aforementioned blood pressure medications and iron supplements in addition to calcium supplementation, including 31.5 g of calcium carbonate (with the dose adjusted according to the serum calcium level) and 0.25 μg of calcitriol soft capsules daily. To our expectations, after eight months of therapy, the patient’s general condition greatly improved, with easing of the maxillary and leg pain and skin itching and stabilization of body height. The most striking result was the amelioration of skeletal changes, particularly facial modification with corresponding improvements on skull CT scans (Fig. 2).
Discussion

Leontiasis ossea is a term used to describe the progressive hypertrophy of the facial and cranial bones associated with a group of diseases, including Paget’s disease, fibrous dysplasia, CRF and secondary hyperparathyroidism (12-16). Inspired by the features of the present case, we hope to provide unique insight into this rare condition.

First, most previous studies have described fewer clinical improvements in bone deformities after treatment. Fourteen years ago, Lee et al. reported that five patients with renal osteodystrophy developed marked hyperostosis of the facial and cranial bones (12). Following parathyroidectomy, the facial changes in all patients either stabilized or mildly improved. Our report is comparable with the findings of a recent article from our department that showed PTX with autotransplantation to be an effective treatment for relieving insomnia and even increasing the cognitive function (21-25). The mechanisms responsible for the remarkable beneficial effects of PTX have not been identified; however, a dramatic reduction in the PTH level and improvement in the phosphate level with either parathyroidectomy or the administration of calcitriol in conjunction with phosphate binding agents and a phosphate-controlled diet. In the literature, there remains intense debate as to which is the better strategy for SHPT management, with some authors believing that treatment should start with the administration of vitamin D receptor activators (VDRAs) (18), whereas others prefer calcimimetics (19). A recently published study comparing the effects of calcimimetics with conventional therapy with VDRAs showed inconclusive results (20). Nevertheless, treatment with the aim of achieving pharmacological control of parathormone secretion should be seriously considered in such patients in the early phase of renal insufficiency.

PTX appears to improve high blood pressure, anemia, nutritional deficiencies, immunity, glucose and lipid metabolism, muscle strength and the quality of life, while also relieving insomnia and even increasing the cognitive function (21-25). The mechanisms responsible for the remarkable beneficial effects of PTX have not been identified; however, a dramatic reduction in the PTH level and improved control of the serum mineral levels are certainly involved. In patients with tertiary hyperparathyroidism-related mineral bone disorders, no matter the pattern or presence of organ damage, we believe that the primary treatment should be parathyroidectomy, which can be used to reduce the parathyroid mass and cell number and thus normalize the serum calcium concentration, in addition to medical interventions specially targeting hypercalcemia and the elevated PTH level. However, the pathogenesis of tertiary hyperparathyroidism is incompletely understood, and the strategy of intervention is determined on a case-by-case basis, as the further accumulation of long-term follow-up data is required.

A high recurrence rate of 60% (3/5) within one year after the phosphate level with either parathyroidectomy or the administration of calcitriol in conjunction with phosphate binding agents and a phosphate-controlled diet. In the literature, there remains intense debate as to which is the better strategy for SHPT management, with some authors believing that treatment should start with the administration of vitamin D receptor activators (VDRAs) (18), whereas others prefer calcimimetics (19). A recently published study comparing the effects of calcimimetics with conventional therapy with VDRAs showed inconclusive results (20). Nevertheless, treatment with the aim of achieving pharmacological control of parathormone secretion should be seriously considered in such patients in the early phase of renal insufficiency.

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A high recurrence rate of 60% (3/5) within one year after
surgery of SHPT following PTX with autotransplantation in cases of leontiasis ossea has recently been reported in our department (17). Similarly, we observed a comparatively high concentration of serum iPTH in the present patient at postoperative month 4 on the transplantation side in this case. We consider that this finding was due to pathological changes in the parathyroid indicating nodular hyperplasia (data not shown), which was subsequently complicated with tertiary hyperparathyroidism after surgery, such that the grafts implanted in the forearms again secreted iPTH. The fact that radionuclide accumulation was observed in the forearms where the graft pieces were implanted with no radionuclide in the neck or chest after surgery (data not shown) supports our assumption. However, the lack of further examinations focusing on this problem and scant information gained from the previous literature make further large-sample clinical studies of the impact of PTX with or without autotransplantation on the rate of SHPT recurrence in ULO patients necessary.

Second, jaw enlargement and facial disfigurement are rare manifestations of renal osteodystrophy that are mostly associated with brown tumors or osteitis fibrosa, which constitute musculoskeletal manifestations of metabolic abnormalities in patients with CRF (26). The majority of cases are resistant to medications. Consistent with the previous opinion that, in patients with cosmetic and functional impairments, cross-sectional images with or without 3D reconstruction provide important information to the surgeon prior to reconstructive or corrective surgery (26), especially thin-section CT with 3D reconstruction, as recommended by Lee (12), this non-invasive and convenient technique was proven to be an indispensable diagnostic and prognostic tool for evaluating leontiasis ossea in this case.

Third, an increasing prevalence of this rare complication associated with SHPT has been observed in China. In our department, at least six patients with ULO underwent the above-mentioned therapy within the past 2.5 years (17). Why ULO frequently occurs in China primarily relies on two points. First, China assumedly has a high proportion of ESRD patients requiring renal replacement therapy, who are not yet on dialysis, due to the lack of financial and clinical resources and inequality in health care access compared to that observed in other countries. Therefore, the proportion of untreated SHPT patients may be large (27). Second, due to inadequate patient-level education regarding chronic kidney disease (CKD) in China, dialysis patients, particularly in rural areas, tend to accept formal therapy only when severe and unbearable complications occur. Therefore, extreme cases are not rare. Our patient, for example, refused to accept dialysis until two years of drug therapy proved to be ineffective.

It is noteworthy that obtaining the precise diagnosis of the causative disease of CKD is vital for discussing the prognosis of skeletal changes among ULO patients under PTX treatment with autotransplantation. In fact, the absence of active research of causative diseases of ESRD exacerbates the burden of management of patients with ULO in China. Early intervention for possible related glomerular diseases in patients with ULO may decrease the rate of SHPT in China; however, clinical data regarding the relationships between different pathologies of CKD and the incidence or prognosis of ULO are lacking. Furthermore, ULO is a special type of SHPT, that primarily presents with changes in the craniofacial skeleton, particularly in the skull, maxilla and mandible. Since the main factors of SHPT are hyperphosphatemia and FGF-23/klotho, it is necessary to observe the relationships between bone metabolism parameters, such as osteocalcin and alkaline phosphatase, and the level of FGF-23/klotho in patients with ULO. In the present case, the level of alkaline phosphatase declined dramatically four months after surgery; however, dynamic observation is required to explain why the once established skeletal deformity was ameliorated by correcting various circulating humoral factors (such as PTH, Ca and P) in our patient. In addition, this issue requires further study. We herein reported a case of vivid reversible skeletal changes achieved using cross-sectional imaging with 3D reconstruction that provided a distinctive description of uremic leontiasis ossea following the administration of comprehensive therapy, including surgical and symptomatic drug treatment of hyperparathyroidism. The details of this report may shed light on the efficacy of formal and proactive interventions in patients with rare and severe complications of CRF.

The authors state that they have no Conflict of Interest (COI).

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References

8. Reidy JM, Motamedi K, Berens D. Renal osteodystrophy with le-

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