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Painful Facial Disfiguring Swelling in A 33 Year-Old Male with End-Stage Kidney Disease: A Case Report of Sagliker Syndrome With 2-Year Follow-Up Outcomes

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Abstract

Dialysis-dependent stage 5 chronic kidney disease with renal osteodystrophy can develop a rare and extreme form of cranial deformities called Sagliker syndrome, a condition driven by extreme parathyroid hormone production and characterized by disordered skeletal remodeling resulting in severe facial abnormalities, dental deformities, and possible psychological changes. This paper reports a 33-year-old African American male with end stage kidney disease on maintenance hemodialysis secondary to systemic lupus erythematosus, who presented with severe Sagliker syndrome features in 2019. Herewith, we are describing his course after surgical parathyroidectomy and subsequent course with excessive propensity for hypocalcemia and interval need for medical therapy, biochemical control and the evolution of facial symptoms and disfiguring abnormalities over the next 2 years' duration.

Introduction

Severe facial distortion is a rare but severe complication of severe secondary hyperparathyroidism in End-Stage Kidney Disease (ESKD) patients, almost exclusively observed in those receiving kidney replacement therapy [1]. This uglifying and physically disabling scenario represent an immediate indication for surgical parathyroidectomy [2,3]. However, long-term outcomes after surgical parathyroidectomy, including the persistence or resolution of facial disfiguration remains insufficiently understood.

Case report

A 33-year-old African American male with ESKD on hemodialysis (thrice weekly for 7 years prior to presentation), tertiary hyperparathyroidism, and history systemic lupus erythematosus presented in 2019 with severe facial pain, swelling, and deformity with associated tooth loss. Symptom onset was relatively sudden, with development over a 1-month period prior to evaluation. He denied odynophagia, dysphagia, shortness of breath or neck symptoms, but evaluation was positive for speech difficulties and severe headaches. He reported inconsis-

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tent cinacalcet (30 mg daily) dosing over the year prior to presentation; the cost being the limiting factor.

On physical exam, significant facial deformity consisting of maxillary and mandibular enlargement with associated hypertrophic gums, widening of the dental spaces and tooth loss was noted. A CT scan showed extensive osseous expansile hyperostosis with marked extension into the buccal spaces **(Figure 1 a-c)**. Laboratory studies revealed markedly increased intact parathyroid hormone level between 1,483-4,000 pg/mL (normal: 18.4 - 88.0 pg/mL) over a 40-week period prior to intervention **(Table 1)**. Other lab results included a corrected serum calcium of 9.16 mg/dL, serum 25-hydroxy-vitamin D of 9.8 ng/mL (25.00 - 80.00 ng/ml), serum phosphorus of 7.1 mg/dL, and alkaline phosphatase of 581 U/L (35-150) with normal liver enzymes within 2 weeks of intervention **(Table 1)**. Per radiologic evaluation via parathyroid scan, there was retained radiotracer uptake within the superior aspect of the left thyroid lobe and inferior aspect of the right thyroid lobe consistent with parathyroid adenomas. Diffuse musculoskeletal sequela of hyperparathyroidism was also noted.

Urgent subtotal parathyroidectomy with autotransplantation of the right superior parathyroid into the left sternocleidomastoid muscle was completed. Intraoperative parathyroid hormone corrected from 2,500 pg/mL to 170 pg/mL. High-calcium bath (3.5 mEq/L) on hemodialysis preceded parathyroidectomy in preparation for hypocalcemia after surgery, but severe hungry bone syndrome ensued post-operatively. Corrected calcium decreased from 9.7 mg/dL the day prior to parathyroidectomy to 7.8 mg/dL immediately post-operatively with a nadir of 7.1 mg/dL approximately 10 hours post-operatively. Magnesium and phosphorus dropped to 1.7 mg/dL and 5.3 mg/dL, respectively. To account for hypocalcemia, the patient was treated with calcium acetate 2,001 mg with meals, calcium carbonate 1,500 mg four times daily, and calcium gluconate 2 mg IV on post-operative day one as well as hemodialysis with calcium bath of 3 mEq/L, with increase in corrected calcium to 8.2 mg/dL by then end of post-operative day one.

Due to further downward corrected calcium (7.9 mg/dL) trends on post-operative day two, the patient was started on p.o. calcitriol 2 mcg twice daily and, with a further drop in corrected calcium (7.5 mg/dL), intravenous calcium gluconate infusion for the next 2 days. Calcium acetate 2,001 mg with meals and calcium carbonate 1,500 mcg four times daily were continued in the interim, as well.

On post-operative day three corrected calcium levels were measured at 7.7 mg/dL in the morning. Calcium carbonate was increased to 2,000 mg four times daily and calcium gluconate 2 g IV twice daily was added to his regimen. He also underwent high calcium bath (3 mEq/L) hemodialysis and continuation of the 8,000 mg/L calcium gluconate infusion. He remained on calcium acetate 2,001 mg with meals. Corrected calcium levels were measured at 10 mg/dL at the end of post-operative day three.

On the morning of post-operative day four, corrected calcium levels were measured at 7.8 mg/dL. The patient received calcium acetate 2,001 mg with meals, calcium carbonate 2,000 mg four times daily, calcitriol 2 mcg twice daily, and completed the last day calcium gluconate infusion. The patient also received two different doses of IV calcium gluconate for symptomatic hypocalcemia, one 1 g dose and a second 2 g dose. The patient also underwent high calcium bath (x3) hemodialysis with corrected calcium levels of 10.5 mg/dL and 9.6 mg/dL by the end of post-operative day 4.

He was discharged on post-operative day 5 on calcium acetate 1,334 mg with meals, calcium carbonate 2,000 mg four time daily, ergocalciferol 50,000 units (1 capsule every 7 days) and calcitriol 2 mcg twice daily as an outpatient. He was also scheduled outpatient dialytic sessions with high calcium hemodialysis baths.

The subsequent two years were characterized by tremendous need for both intra-dialytic and home supplementation of activated vitamin-D with calcitriol. Over the first-year post-parathyroidectomy, daily needs of calcitriol oscillated between 2 and 8 mcg per OS three times per week with dialysis and 1 mcg on non-dialysis days. The need for calcitriol supplementation peaked at 8 mcg with dialysis 22 weeks post-parathyroidectomy, with gradual decline back to 1.5 mcg over the next year. Alkaline phosphatase over the 2-year post-operative period averaged 146 U/L after gradually declining from 500s U/L pre-operatively and 397 U/L within a 1-month post-operative period. PTH remained suppressed in keeping of post-parathyroidectomy state **(Table 1)**.

At 2-year follow-up laboratory studies revealed corrected serum calcium of 7.5 mg/dL, serum phosphorus of 6.2 mg/dL, and intact parathyroid hormone of 36 pg/mL. Data beginning prior to his hospital admission in 2019 through 2021 is displayed in **Figure 2**. On interview with the patient at 2-year follow-up, his facial pain persisted, but with improvement. Pain is especially present with eating and talking; restricting food intake and preventing consumption of hard foods. He has lost 3 additional teeth since his parathyroidectomy. Facial swelling persists with only minimal improvement per his assessment. There does appear to be improvement in swelling based on initial versus follow-up imaging **(Figure 1-a; Figure 3)**. He has reduced vision in the left eye; per ophthalmology, this attributed to orbital compression of Sagliker syndrome. He also has difficulty with mobility and standing.

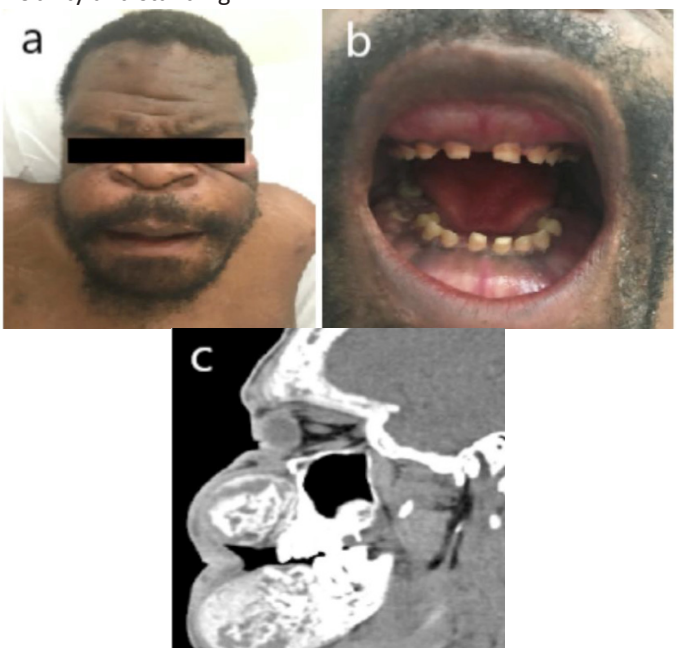

Figure 1: Gross appearance and radiology before surgical parathyroidectomy.
a. Anterior view of facial enlargement with mandibular and maxillary
b. Anterior view of hypertrophic gums and enlarged dental spaces
c. Sagittal computed tomography image revealing extensive osseous expansile hyperostosis with extension into the buccal spaces

Table 1: Summary of key bone-mineral metabolism parameters.

Week	Date	Phosphorus	Ca Adjusted	PTH	Alkaline Phosphatase
1	10/3/18			>4000	
14	1/2/19			2647	
21	2/20/19	4.4	8.2		393
25	3/20/19	6.4	8.9		590
27	4/3/19			1483	
29	4/17/19	7	9.2		674
34	5/20/19	7.1	9.16		581
39	6/28/19		8.3		1052
Parathyroidectomy					
41	7/10/19			29	
43	7/22/19	4.2	5.64		397
47	8/21/19	2.5	7.4		176
52	9/23/19	3.1	7.16		184
53	10/2/19			40	
56	10/23/19	3.8	6.3		163
60	11/20/19	3.5	6.9		156
63	12/11/19	4.5			
66	12/30/19		5.26		111
68	1/15/20	3.6	8.02	35	158
72	2/10/20	5.6	6.8		143
76	3/11/20	6	6.88		136
79	4/1/20	6.8	8.1	14	132
85	5/11/20	10.1	8.3		100
85	5/13/20	10.3	8.3		94
88	6/3/20	3.5	9.46		92
95	7/22/20	6.4	10.2	8	122
99	8/19/20	6.4	8.78		131
103	9/16/20	6.7	7.9		151
108	11/18/20	6.3	8.06		156
109	12/16/20	6.7	7.96		179
111	1/20/21	7.1	7.84	34	160
116	1/29/21	5.7	8.36		170
121	2/22/21	6.7	7.86		175
124	3/29/21	5.7	8.4		108
126	4/21/21	6.2	7.5	36	158
128	5/19/21	7	8.2		203

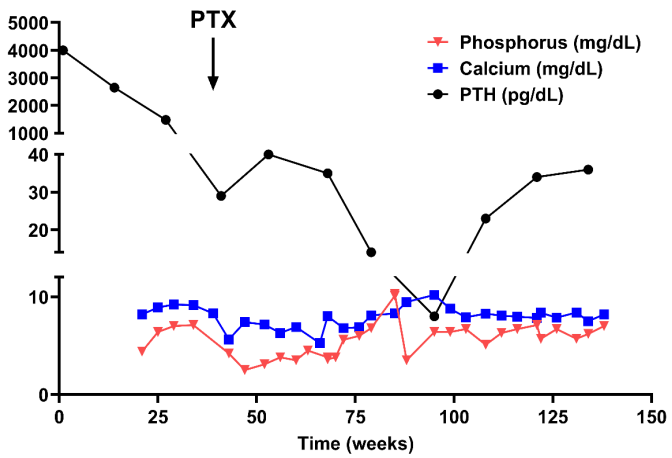

Figure 2: Parathyroid hormone, calcium, and phosphorus levels over time: 39 weeks prior to and 98 weeks post parathyroidectomy.

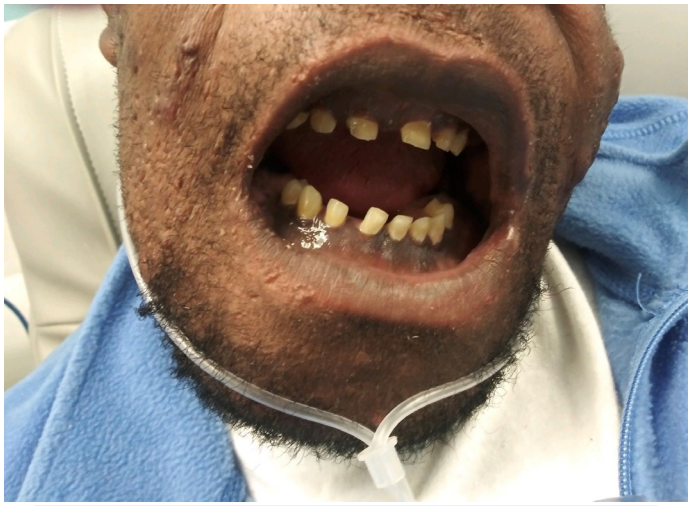

Figure 3: Facial swelling and dental abnormalities 2-year post-parathyroidectomy.

Discussion

Sagliker syndrome was first described in publication in 2004 by Sagliker et al. defining the characteristic findings of diagnosis cumulatively seen together in patients with chronic kidney disease and severe secondary hyperparathyroidism[1]. Classic symptoms include maxillary and mandibular deformities and enlargement associated with class II malocclusion of the jaws, dental abnormalities including widely and irregularly spaced teeth with possible tooth loss, benign soft tissue hyperplasia and tumors of the oral cavity, hearing loss, short stature with ambulation difficulties, bone density loss, scapular deformities, fingertip curvature, as well as psychiatric and neurologic disorders [1,4-6].

The frequency of occurrence is 0.5% in patients with chronic kidney disease and severe secondary untreated hyperparathyroidism [1,7]. Although the exact cause leading to the development of Sagliker syndrome in a subset of those with chronic kidney disease is unknown, several studies have been carried out on Sagliker populations in an attempt to identify genetic abnormalities or other factors that may place individuals with chronic kidney disease at risk. Within their studied population sample, Demirhan et al. found mutations in the stimulatory alpha subunit of the Guanine Nucleotide-Binding Protein Gene (GNAS1) a signal transduction modulator (73.9% of patients), fibroblast-derived growth factor-23, and fibroblast-derived growth factor-FGFR3(7). Yildiz et al. also found GNAS1 missense gene mutations in 40% of Sagliker patients within the population they studied [5]. No gene abnormalities within the calcium-sensing receptor exons 2 or 3, nor any significant hormonal or biochemical abnormalities were identified [5]. Multiple studies have found no notably difference in thyroid function (including thyroid stimulating hormone, free thyroxine and triiodothyronine levels), growth hormone levels, or sex hormone levels (luteinizing and follicle stimulating hormone levels) in those with Sagliker syndrome and those without[5,6,8].

Commonalities between case studies seem to indicate a young age of onset to be more typical and point towards longer duration of dialysis, female gender, and higher serum parathyroid hormone, phosphate, and alkaline phosphatase levels as potential risk factors [9-12]. Early lack of treatment for chronic kidney disease is also a significant factor, with financial difficulties many times being the underlying cause of delayed treatment[5]. Prior to starting chronic renal replacement therapy, Sagliker syndrome patients typically have serum calcium levels ranging between 6-7 mg/dL, while phosphate and alkaline phosphatase range between 7-8 mg/dL and 120-240 U/L respectively and with intact parathyroid hormone levels at least 3.5 times higher than normal [4,6]. Sagliker syndrome is more typical in anuric subjects, as even minimal renal function can provide phosphate balancing capabilities that prevent extreme parathyroid hormone levels [6,13]. Radiologic appearance may even imitate multiple myeloma and the expected "brown tumor" may not be uniformly present of treated severe secondary hyperparathyroidism, with medical therapy of high-dose cinacalcet and activated vitamin-D products in the current era [14,15].

Sagliker syndrome is treated via parathyroidectomy to reduce parathyroid gland mass; with partial, total, or total with auto-transplantation all being viable surgical options. While partial parathyroidectomy and total with auto-transplantation preserve calcium balance, they place patients at small risk of recurrence [6,10]. Total parathyroidectomy with prior nuclear scan to localize all parathyroid tissue may be the best option, especially for those with indeterminate follow-up potential due to financial concerns[6,10]. Post-operative hypocalcemia can be excessive, necessitating prolonged course of inpatient I.V.calcium, prolonging length of inpatient stay[16]. Previous reports have suggested cessation of further disfigurement or clinical symptoms post-parathyroidectomy[10]. However, as outlined in this case-report, our patient suffered the loss of multiple additional teeth as well as delayed onset orbital compression in the two-year period following parathyroidectomy. Many literature sources report disfigurement attained prior to parathyroidectomy to be permanent, and some patients report only minimal or mild improvement in facial deformity[10,11]. As seen with our patient, swelling persisted, but was overall reduced during the 2 years follow-up. The differential diagnosis, especially for those who fail to improve after surgical parathyroidectomy, should include co-morbid Paget's disease. Indeed, is possible that the presence of co-morbid severe tertiary hyperparathyroidism is modulating bot the course and severity of co-existing Paget's disease, which may be difficult to recognize if other peripheral manifestations are missing[17].

One peculiar feature of this case was the extend and severity of hypocalcemia and the amount of calcitriol needed to maintain low-normal range of calcium. While hypocalcemia is common, indeed the rule after surgical parathyroidectomy in end-stage kidney disease[18], the duration and severity with calcitriol requirements were unlike we have seen before. While excessive hypocalcemia may be a feature of pharmacologic acid suppression or achlorhydria, interfering with effective absorption of calcium carbonate he did not receive proton-pump inhibitor therapy[19,20]. Moreover, after approximately 1.5 years of high-dose therapy, his calcitriol requirements normalized to a customary and expected range[14].

Conclusion

We have documented persistence of facial abnormalities and excessive nature of post-parathyroidectomy hypocalcemia and calcitriol requirement in an ESKD patient with phenotypical features of Sagliker syndrome.

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Dr. Fülöp is current employee of the United States Veterans Health Administration. However, the views and opinions expressed herewith do not reflect the official views or opinion or endorsed by the United States Veteran Health Administrations.

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