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Case Report

Three Rare Concurrent Complications of Tertiary Hyperparathyroidism: Maxillary Brown Tumor, Uremic Leontiasis Ossea, and Hungry Bone Syndrome

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A 48-year-old woman in her 40's with end-stage renal disease and tertiary hyperparathyroidism (HPT) presented for a rapidly progressive maxillary tumor. Initial workup was notable for elevated intact parathyroid hormone (PTH) and diffuse thickening of skull and facial bones on computed tomography, and maxillary tumor biopsy with multinucleated giant cells. She underwent subtotal parathyroidectomy (with removal of a parathyroid adenoma and 2 hyperplastic glands) and partial resection of maxillary brown tumor. The patient's post-operative course was complicated by hungry bone syndrome, with hypocalcemia refractory to aggressive calcium repletion. Teriparatide (recombinant PTH) was utilized with rapid resolution of hypocalcemia. To our knowledge, this is the first case of maxillary brown tumor in tertiary HPT to be reported in the USA. This case also supports teriparatide as a novel therapeutic for hungry bone syndrome refractory to aggressive calcium repletion.

Key Words: Brown tumor · Hungry bone syndrome · Maxilla · Teriparatide · Tertiary hyperparathyroidism · Uremic leontiasis ossea

CASE REPORT

A woman in her 40's with history of lupus nephritis, end-stage renal disease (ESRD) of renal transplant on intermittent hemodialysis, type 2 diabetes mellitus, and tertiary hyperparathyroidism (HPT) presented to the emergency department for a rapidly progressive palate mass. The patient had a long-standing history of ESRD due to lupus nephritis and was dialysis-dependent for 10 years prior to renal transplant 18 years ago. Her ESRD had been complicated by renal osteodystrophy and severe osteopenia based on forearm radiographs, however, she did not complete dual energy X-ray absorptiometry screening. Her renal transplant failed 3 years ago, necessitating re-initiation of hemodialysis. Her ESRD had been complicated by HPT, which progressed with failure of her transplant. Two months previously, the patient noted an oral palate mass and was referred to the Head and Neck Surgery clinic for biopsy. She was to return to the clinic for pathology results

and surgical planning, however, she presented to the Emergency Department for progressive difficulty eating, speaking, and mouth pain due to the oral mass.

On initial hospital evaluation, the patient was noted to have a firm, non-tender, exophytic mass approximately 5 cm in size on the right anterior aspect of the hard palate and malocclusion of related teeth. She had maxillofacial abnormalities including an expansion of the maxilla and malocclusion of related teeth (Fig. 1). Laboratory studies on presentation were notable for normal corrected calcium, elevated phosphorus, elevated alkaline phosphatase and intact parathyroid hormone (PTH), and stable normocytic anemia (Table 1). Given the rapid progression and location of the mass, the patient was admitted for debulking of her maxillary tumor and parathyroidectomy. Computed tomography (CT) demonstrated extensive diffuse sclerosis and thickening of the calvarium, facial bones, and skull base (Fig. 2). Nuclear bone scan was also performed, showing diffuse increased uptake in the skull and mandible (Fig. 3). Pathology from the outpatient biopsy showed a fibrous background with scattered and clustered multinucleated giant cells, consistent with a diagnosis of maxillary brown tumor (Fig. 4).

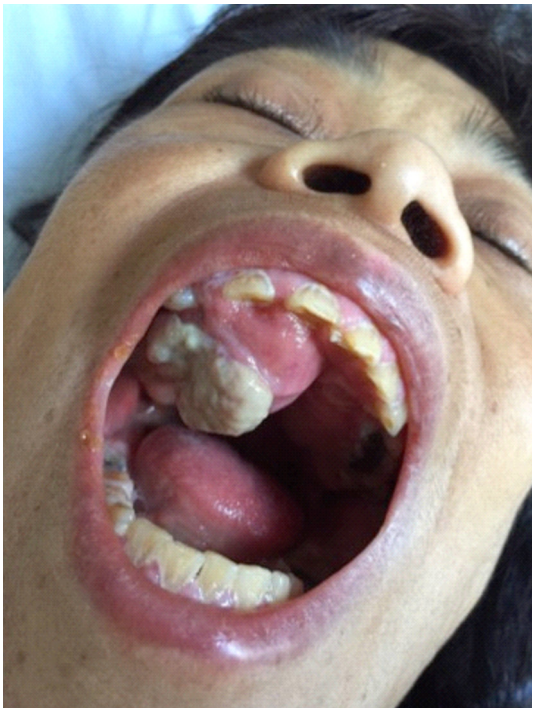

Fig. 1. Gross appearance of maxillary brown tumor. Color photograph of the maxillary tumor. The mass was sub-mucosal with visible ulceration of the mucosa due to trauma from the mandibular dentition.

1. Treatment

Head and Neck Surgery was consulted for sub-total parathyroidectomy and curettage of the maxillary tumor. Endocrinology and nephrology were also consulted for coordination of peri-operative care. The patient's pre-operative parathyroid hormone was over 4,400, and normalized to 25 after subtotal parathyroidectomy. She was able to fully close her mouth after the palatal bone mass curettage with less mouth pain and improved oral intake. Surgical pathology demonstrated hypercellular parathyroid tissue, hard palate brown tumor, and 6 benign cervical lymph nodes.

After parathyroidectomy, the patient became symptomatically hypocalcemic with calcium as low as 6.2 mg/dL, albumin 3.1 g/dL, ionized calcium 0.65 mMol/L (ref. 1.13-1.32 mMol/L), phosphorus 1.8 mg/dL, and magnesium 2.1 mg/

Table 1. Pertinent laboratory results on presentation

	Range	Admission	1 month before admission	2 months before admission
Corrected calcium (mg/dL)	8.5-10.6	8.6	8.2	8.7
Phosphorus (mg/dL)	2.7-4.5	5.1	5.1	4.7
Magnesium (mg/dL)	1.6-2.6	2.1	2.3	2.1
Intact PTH (pg/mL)	15-65	3,089	4,477	3,073
Alkaline phosphatase (U/L)	35-140	1,098	1,349	1,396
25(OH)D (ng/mL)	30-80	13	-	-
Creatinine (mg/dL)	0.51-0.95	2.92	3.73	4.31
Albumin (g/dL)	3.5-5.2	3.4	3.9	4.0
WBC (K/μL)	4.0-10.0	7.3	6.6	7.6
Hemoglobin (g/dL)	11.2-15.7	11.2	11.7	11.3
Platelets (K/μL)	140-370	204	173	150

PTH, parathyroid hormone; 25(OH)D, 25-hydroxy-vitamin D; WBC, white blood cell.

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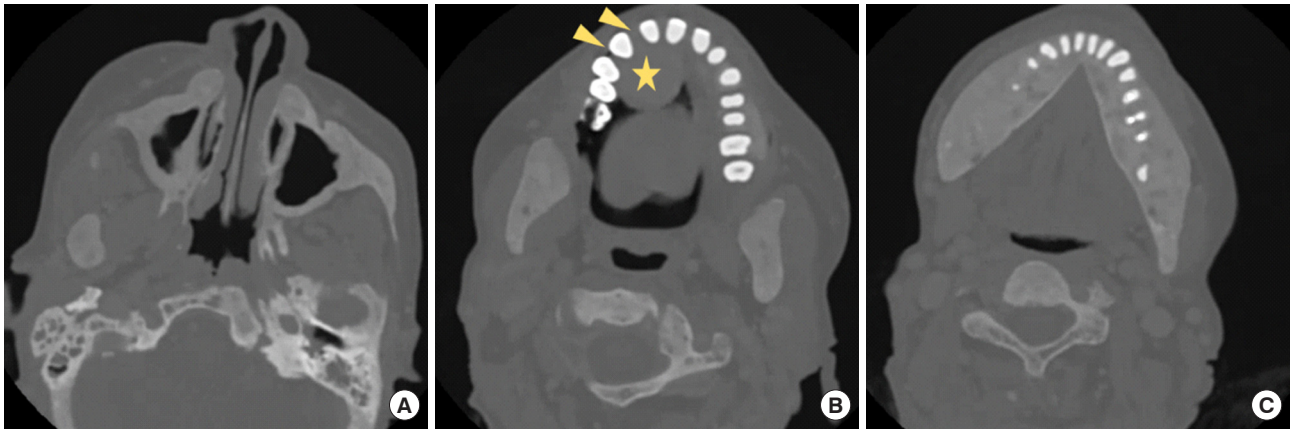

Fig. 2. Computed tomography (CT) appearance of oral tumor. Three panels of axial CT images, without contrast, demonstrating skull bone changes resulting from renal osteodystrophy. Thickening of the maxilla and zygoma (A), mandibular rami (B), and mandibular bodies (C). The maxillary tumor is visible in the center image as a round mass on the right anterior palate (star). The maxillary teeth are splayed (arrows).

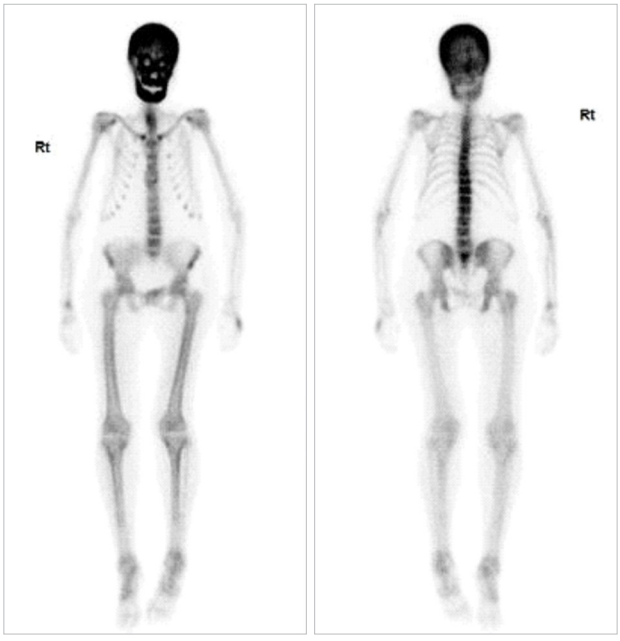

Fig. 3. Tc-99m MDP whole body bone scintigraphy. Nuclear bone scan images showing diffusely increased uptake in the skull, mandible, and spine consistent with renal osteodystrophy and uremic leontiasis ossea. Areas of mild focal uptake also seen in the manubrium and right 6th rib corresponding to lytic lesion on computed tomography.

dL, consistent with hungry bone syndrome. Despite the degree of hypocalcemia, her corrected QT interval did not prolong (410 ms compared to 445 pre-operatively). She was started on calcitriol, calcium carbonate, and IV calcium gluconate, and her hemodialysis sessions were increased to 3 times per week with a 3 mmol/L calcium dialysate. Despite doses as high as calcium carbonate 2,500 mg every 3 hr, calcitriol 2 mcg twice a day, and increased hemodialysis, the patient still required up to 12 g of IV calcium gluconate daily to keep her calcium in the 7 to 8 mg/dL range. Calcium citrate was attempted but led to a drop in calcium level despite dosing with equivalent elemental calcium. Our patient was started on teriparatide 20 mcg twice daily on post-operative day 25. Her ionized calcium in the days prior to initiation ranged between 0.79 and 0.83 mmol/L. After several days of teriparatide, her ionized calcium normalized, and over time IV calcium requirement decreased. Phosphorus and magnesium were repleted as needed but were not as difficult to maintain within normal ranges.

She remained an inpatient for 1 month due to difficulty maintaining calcium levels. By time of discharge however, calcium became elevated to 11.0 mg/dL, and teriparatide was stopped. She was later readmitted to the hospital for hypercalcemia of 13.8 likely due to a combination of resolving hungry bone syndrome and excessive pharmacologic supplementation. The patient did not have evidence of recurrent oral mass on post-surgical follow up and reported significant improvements in maxillofacial discomfort and oral intake.

2. Methodology of Literature Review

PubMed, Google Scholar, ScienceDirect, and Wiley databases were searched for all published cases of craniofacial brown tumors. A broad search strategy was employed using any combination of keywords from the following 2 groups: (1) group 1 – "craniofacial," "intraoral," "maxillofacial," "facial," "maxillary," "mandibular," and "orbital"; and (2)

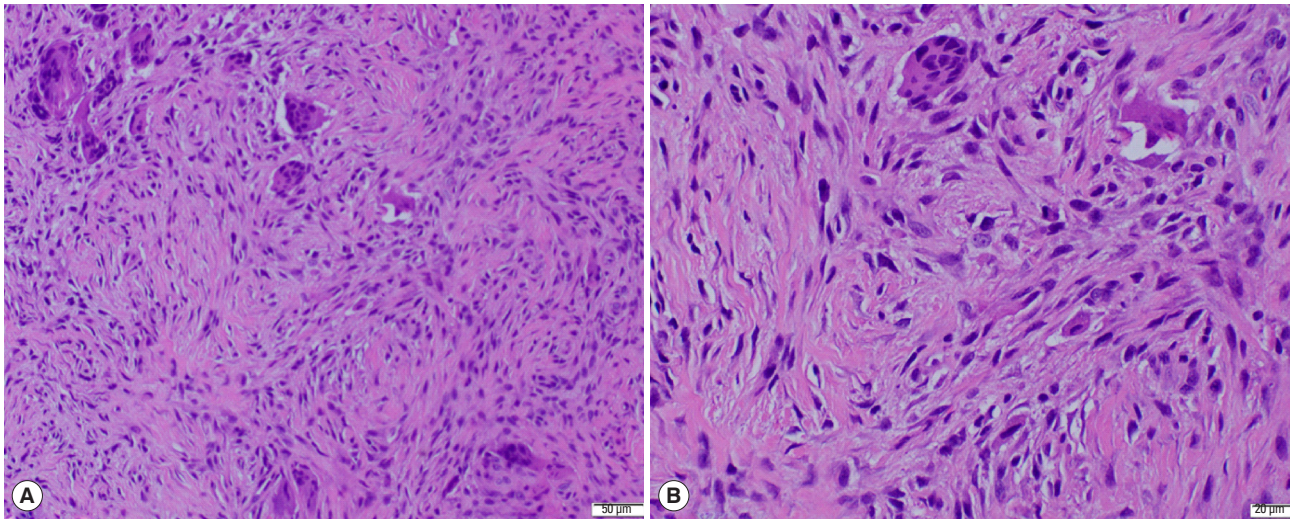

Fig. 4. Histopathology of tumor biopsy. Photomicrographs of tumor biopsy, showing scattered and clustered multinucleated giant cells in a fibrous background.

group 2 – "brown tumor" and "tumor of hyperparathyroidism." There were no constraints made on the date of publication. Search results were screened by title and abstract to select for case reports of craniofacial brown tumors. Many papers were drawn from references made in other relevant case reports found using our search strategy. Papers that met the following criteria were included in our data: (1) involvement of any brown tumor of the craniofacial region; (2) a well-described clinical course; and (3) a diagnosis of primary, secondary, or tertiary HPT. Author NPB performed the literature review.

DISCUSSION

We present a patient with 3 unique complications of tertiary HPT: maxillary brown tumor, uremic leontiasis ossea (ULO), and post-parathyroidectomy hungry bone syndrome. Tertiary HPT most commonly occurs in the setting of renal transplants. This condition results from prolonged hypocalcemia from vitamin D deficiency, leading to loss of feedback regulation to and autonomous function of parathyroid chief cells. Our patient's risk factors for developing this condition included failed renal transplant and ongoing hemodialysis. While tertiary HPT is classically caused by hyperplasia of all four glands, some reports indicate that over 20% may have single or double adenomas as the underlying pathology, as was the case for our patient who had one adenoma and 2 hypercellular glands on histopathology.[1]

1. Uremic Leontiasis Ossea

On presentation, our patient demonstrated thickened facial and skull bones, characteristic of ULO. ULO is a rare complication of secondary and tertiary HPT, resulting from mineralization defects and high bone turnover. On CT scan, ULO shows diffuse expansion of the maxillae and mandible with obliteration of the maxillary sinuses and protrusion of the mandible.[2-4] It is unclear why the cranial and facial bones are preferentially affected. As ULO progresses, the patient can experience dysphagia, speech impairment, vision loss due to compression of the optic nerve,[5] life-threatening airway obstruction, and exophthalmos. The only treatment to prevent further progression of ULO is parathyroidectomy, however, there is evidence that parathyroidectomy leads to improvement in the bone deformities. Fibrous dysplasia and Paget's disease of the bone can also resemble ULO but can be differentiated by history and biochemical evaluation.

2. Craniofacial Brown Tumor

Our patient presented with a rapidly progressive maxillary mass, which was diagnosed as a brown tumor. Brown tumors area rare complication of HPT manifesting as focal, bony lesions with increased osteoclastic activity and trabecular fibrosis.[6] This metabolic bone lesion derives its name from the abundant hemorrhage, hemosiderin depo-

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sition, and hypervascularity, which gives the tissue a dark red to brown color.[7] Although brown tumors may occur at any age, they occur more frequently in patients over 50 years of age. The prevalence is approximately 3 times greater in female patients.[8] Radiographically, brown tumors appear as radiolucent, uni- or multilocular lesions. They are often solitary but can also be multiple, and they can generate significant expansion of cortical bone in the long term.[9,10] Histologically, brown tumors are characterized by highly vascular fibroblastic stroma with numerous multinucleated giant cells resembling osteoclasts.[7] This histopathology is not specific to brown tumors. Therefore, diagnosis is made using clinical, radiographic, histological, and laboratory data.

Brown tumors have become a rare entity in the developed world and are most commonly seen as an end-stage manifestation of primary HPT. The reported prevalence is 0.1%.[11] They are reported to occur in 4.5% of patients with primary HPT and 1.5% to 1.7% of patients with secondary disease.[8,11] Prevalence in patients with tertiary HPT is unknown and has rarely been reported.[10,12-16] Our systematic review of the medical literature yielded 95 cases (published from 1962 through 2020) of craniofacial brown tumors. Table 2 summarizes the results of the literature review.[6-82]

On review of the published cases of craniofacial brown tumors, we observed an equal distribution of tumors occurring in the maxilla and mandible (35.3% and 37.6%). There was a female predominance noted in both maxillary and mandibular tumors (70.0% and 75.8%, respectively). Like our patient, many cases involved patients on hemodialysis (37.9%), however, these patients primarily had secondary rather than tertiary HPT. To our knowledge, the present study represents the only case of maxillary brown tumor to be reported in a patient with tertiary HPT in the USA. We noted a paucity of data regarding the duration of HPT prior to development of brown tumors, with only 6 studies reporting this data (mean 108.6 months). The majority of cases were treated with either total or subtotal parathyroidectomy (48.6%) alone, with tumor debulking or excision (24.3%), or both (27.1%). Remission was achieved in 91.2%, 100%, and 94.7% of these cases, respectively.

First-line medical therapies for tertiary HPT focus on controlling hyperphosphatemia with dietary restriction, phosphate binders, vitamin D replacement, calcimimetic agents such as cinacalcet, and calcium supplementation.[83] National Kidney Foundation's Kidney Disease Quality Outcomes Initiative (KDOQI) recommends that patients with severe HPT (PTH >800 pg/mL) with hypercalcemia and/or hyperphosphatemia refractory to medical therapy be offered parathyroidectomy.[83,84] With maxillary bone brown tumor involvement, the bone lesion usually regresses after parathyroidectomy.[48] However, in some instances, the bone brown tumors can continue to grow after 2 years despite parathyroidectomy.[31] Thus, surgical excision of the brown tumor itself may be considered, especially if there are anatomic complications such as facial pain or compro-

Table 2. Literature review of published cases of craniofacial brown tumors

	Value
Age	38.7±15.7
Sex	
Male	24 (28.2%)
Female	61 (71.8%)
Brown tumor location	
Maxillary	30 (35.3%)
Mandibular	32 (37.6%)
Both	23 (27.1%)
Hyperparathyroidism type	
Primary	39 (45.9%)
Secondary	40 (47.1%)
Tertiary	6 (7.1%)
Patient on HD	
No	41 (62.1%)
Yes	25 (37.9%)
Months on HD before brown tumor diagnosis (n=25)	108.6±51.2
Reported lab values	
iPTH (n=61)	1,468.3±987.6
Ca (n=56)	11.2±2.8
Phos (n=47)	4.6±2.2
ALP (n=40)	1,122.7±1152.1
Treatment	
Parathyroidectomy	34 (48.6%)
Remission	31 (91.2%)
Local Excision	17 (24.3%)
Remission	17 (100.0%)
Both	19 (27.1%)
Remission	18 (94.7%)

The data is presented as mean±standard deviation or number (%).
HD, hemodialysis; iPTH, intact parathyroid hormone; Ca, calcium; Phos, phosphorus; ALP, alkaline phosphatase.

mised vision, hearing, chewing, speaking, and breathing.[76,79] In this patient, her maxillary brown tumor significantly increased in size (doubling over 1 month), causing impaired oral intake and facial pain. Thus, surgical curettage of the maxillary bone lesion and parathyroidectomy were performed to palliate her pain and allow early-resumption of oral diet as her calcium homeostasis stabilized.

3. Hungry Bone Syndrome

While there are no standard pre-operative medical treatments for parathyroidectomy, pre-operative correction of low vitamin D, and the use of bisphosphonates may assist in the prevention of complications such as hungry bone syndrome.[85] Hungry bone syndrome is defined as the rapid and prolonged hypocalcemia (longer than post-operative day 4) associated with both hypophosphatemia and hypomagnesemia that often follow parathyroidectomy.[85] The sudden decrease in PTH levels following removal of an adenoma and long-term suppression of the remaining glands lead to the arrest of bone resorption. In the face of continuing bone formation, this leads to increased skeletal use of calcium and subsequent hypocalcemia. Similar to the observed clinical course of our patient, hungry bone syndrome is usually associated with skeletal manifestations such as osteitis fibrosa cystica and brown tumors, as these indicate high pre-operative indices of bone turnover.[85] The prevalence of hungry bone syndrome after surgery is thought to be up to 13%, though data is somewhat scarce.[85] Risk factors for the development of hungry bone syndrome include older age at the time of surgery, high levels of PTH and alkaline phosphatase, lower levels of albumin and magnesium, and skeletal abnormalities including subperiosteal erosions, lytic lesions, and brown tumors.[85] Interestingly, our patient had several of these risk factors including a significantly elevated PTH and alkaline phosphatase and skeletal abnormalities.

Treatment of hungry bone syndrome is aimed at replenishing the depleted skeletal calcium stores. The amount of calcium supplementation required to treat this severe hypocalcemia typically varies between 6 and 12 g/day.[85] After several weeks of around the clock IV (intravenous) and PO (oral) calcium supplementation, the patient had persistent and symptomatic hypocalcemia. While hypocalcemic, her magnesium was within normal range, and she received aggressive vitamin D supplementation.

4. Teriparatide as a Novel Therapy for Hungry Bone Syndrome

An extensive review of literature on hungry bone syndrome was completed to determine if any additional therapies could more effectively treat her hungry bone syndrome. The authors came across several case reports and case series highlighting the use of teriparatide therapy in this setting. Teriparatide is a recombinant human PTH (PTH 1-34) currently used for treatment of osteoporosis. Studies indicate that teriparatide may be a safe and effective treatment for hungry bone syndrome.[86] In a case series highlighting 5 case reports, teriparatide therapy was initiated between 2 weeks and 2 months after parathyroidectomy, resulting in the increase of serum calcium levels and reduction of calcitriol doses in some patients. In addition, phosphatemia levels and calcium carbonate requirements exhibited declining trends with therapy.[86] Our patient was started on teriparatide during her hospitalization and was able to be discharged 8 days after initiation as her calcium levels normalized. Teriparatide was discontinued upon discharge. Of note, she was re-admitted approximately 1 week later with hypercalcemia. She received hemodialysis and subsequently had protracted hypocalcemia during her second admission. This case highlights the difficulty of maintaining appropriate calcium homeostasis after parathyroidectomy in patients with ESRD, and the effective use of teriparatide for prolonged and refractory hypocalcemia due to hungry bone syndrome.

CONCLUSIONS

In summary, we present a case of tertiary HPT presenting with several unique features: parathyroid adenoma and hyperplasia of 2 glands, maxillary brown tumor, ULO. This case was collaboratively managed with head and neck surgery, endocrinology, nephrology, and primary teams. Her hospital course was complicated by hungry bone syndrome, a condition of refractory hypocalcemia that persisted for approximately one month after parathyroidectomy. We employed a novel therapeutic, teriparatide, for treatment of hungry bone syndrome with rapid resolution of hypocalcemia.

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DECLARATIONS

Acknowledgments

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Ethics approval and consent to participate

Not applicable.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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