Localized mandibular enlargement in end-stage renal disease: two case reports and a review of the literature

Mark A. Lerman, DMD,[a] Catherine Do, DMD,[a] Lakshman Gunaratnam, MD,[b] Cyelee Kulkarni, DMD,[a] Kevin Tucker, MD,[b] and Sook-Bin Woo, DMD,[a] Boston, Massachusetts
BRIGHAM AND WOMEN'S HOSPITAL

Enlargement of the jaws is an infrequently reported complication of chronic kidney disease mineral and bone disorder (CKD-MBD). Two cases of localized mandibular swellings in young patients with histories of end-stage renal disease are discussed with a review of the literature. Although 17 of the first 19 cases that were reported exhibited diffuse enlargement, these reports increase the number of localized swellings to 8 and support the contention that localized expansion of the jaws as a manifestation of CKD-MBD is more common than originally recognized. (Oral Surg Oral Med Oral Pathol Oral Radiol 2012;113:384-390)

End-stage renal disease (ESRD) frequently leads to development of the broad clinical syndrome chronic kidney disease mineral and bone disorder (CKD-MBD). The term renal osteodystrophy has recently been redefined to refer to bone pathology that results from this syndrome.[1] Although asymptomatic radiographic changes, including loss of lamina dura and/or altered trabecular pattern may be noted in the jawbones of up to 45% of patients with ESRD,[2] clinical expansion of the jawbones is less common.

Nathan et al. first reported enlargement of the maxilla and mandible in a patient with secondary hyperparathyroidism in 1966.[3] A review of the English-language literature revealed 23 additional cases of expansion of the jaws in the setting of CKD-MBD, the majority of which presented as generalized enlargement.[4-15]

Two cases are presented, each involving a young patient with ESRD and a localized enlargement of the mandible. A review of the literature demonstrates that this pattern of expansion is more common than originally recognized.

CASE 1

A 33-year-old Hispanic man with ESRD presented to the Emergency Department with pulsatile bleeding from an arteriovenous graft in his left upper arm after hemodialysis earlier the same day. One week before presentation, he had been evaluated by his vascular surgeon for a presumed skin infection over the graft and had been started on intravenous vancomycin. Incidentally, the patient was noted to have significant swelling of the left mandible. The patient first noted this painless swelling 6 months earlier and reported that it had been growing steadily since then. He had a history of ESRD secondary to interstitial nephritis, intravenous drug use, hepatitis C, hypertension, and poor compliance with medical and dialysis therapies. His medications included acetaminophen, albuterol, aspirin, bisacodyl, clonazepam, clonidine, docusate, hydromorphone, ibuprofen, labetalol, levofloxacin, magnesium hydroxide, methadone, mirtazapine, multivitamin, promethazine, and vancomycin.

Clinical examination revealed a blood pressure of 185/110 mm Hg, a heart rate of 104 beats/min, and a temperature of 100.0°F. Cardiovascular, pulmonary, and abdominal examinations were unremarkable. No active bleeding or cellulitis was noted over the graft at the time of examination. Extraoral examination showed a left mandibular swelling; intraoral examination showed a firm 3.5 × 2.5 cm jaw mass of the left mandible associated with buccal and lingual expansion of the alveolar bone (Fig. 1). There was a focal tender ulceration ~0.5 × 0.3 cm on the occlusal surface of the swelling likely caused by trauma from the opposing maxillary tooth. His dentition included multiple carious and/or fractured teeth and generalized moderate-severe horizontal bone loss. Panoramic and periapical radiographs of his jaw demonstrated a subtle ground-glass appearance of the bone throughout the mandible. There was a more prominent area of opacification extending from the fractured root of the left mandibular third molar to the left mandibular second premolar involving the full height of the mandible. In addition, absence of lamina dura was noted throughout the mandible (Fig. 2).

Laboratory examination showed a leukocyte count of 4,210/μL (normal 4,000-10,000/μL), platelet count 146 × 10^9/L (normal 150-450 × 10^9/L), serum creatinine 6.75 mg/dL (normal 0.7-1.3 mg/dL), serum calcium 9.0 mg/dL (normal 8.8-10.5 mg/dL), serum phosphate 3.3 mg/dL (nor-

[a]Harvard School of Dental Medicine.
[b]Harvard Medical School.
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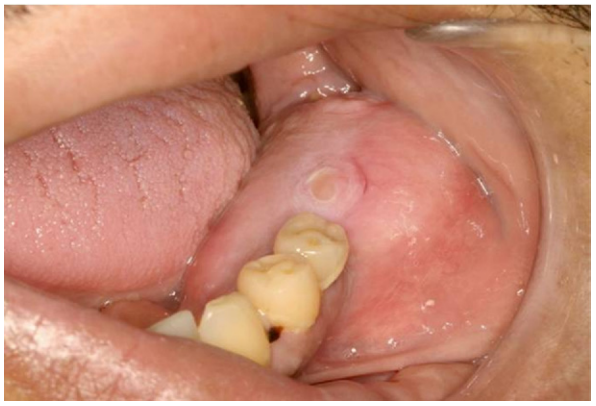

Fig. 1. A hard swelling of the alveolar bone of the left mandible demonstrates a focal ulceration distal to the left mandibular second premolar.

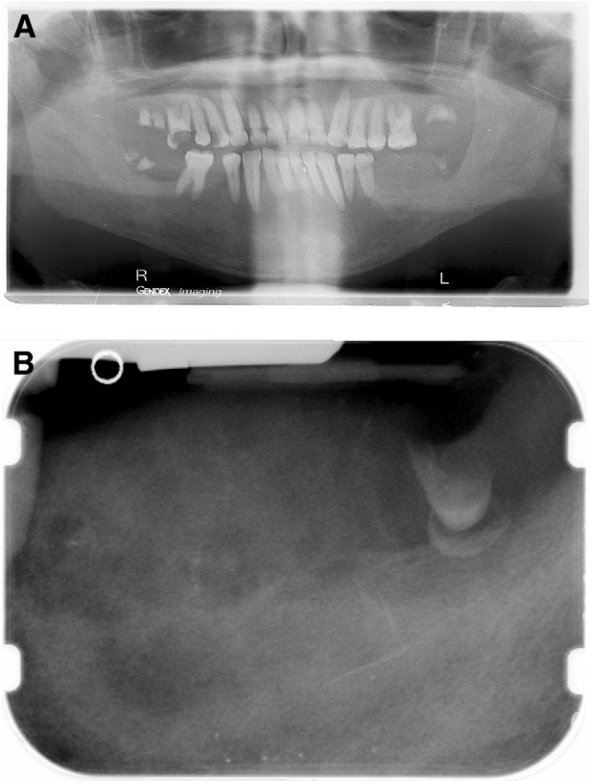

Fig. 2. **A,** Absence of lamina dura and a generalized ground-glass radiopaque appearance is noted throughout the mandible. **B,** A prominent mixed radiolucency-radiopacity is seen in the left posterior mandible.

mal 2.4-5.0 mg/dL), serum albumin 3.3 mg/dL (normal 3.7-5.4 mg/dL), and serum parathyroid hormone (PTH) 2,190 pg/mL (normal 11-80 pg/mL). A lateral chest radiograph demonstrated the typical "rugger jersey" sign (Fig. 3).

Case 2

A 23-year-old woman with a history of ESRD presented to the hospital in 2008 for the evaluation of a painless gingival

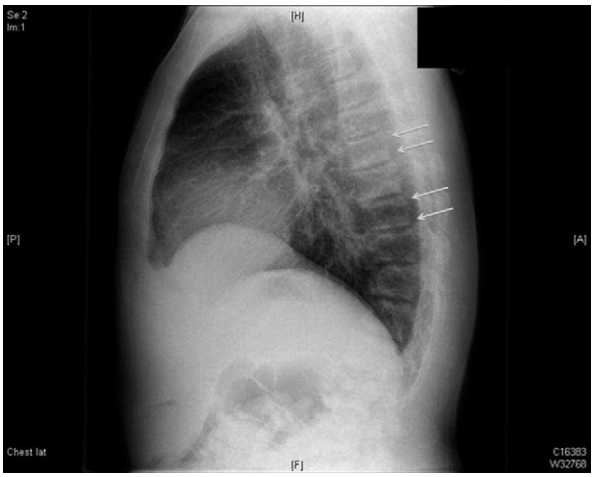

Fig. 3. A lateral radiograph of the thoracic spine shows increased opacity (*arrows*) along the superior and inferior aspects of the vertebral bodies due to osteosclerosis associated with secondary hyperparathyroidism, typical of the "rugger jersey spine."

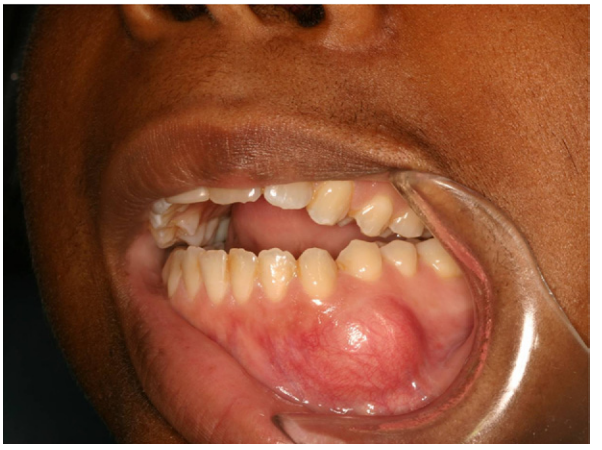

Fig. 4. A solitary hard swelling is noted inferior to the crowns of teeth #20 and #21.

mass that she had first noted 5 days earlier. She had been diagnosed with idiopathic collapsing glomerulopathy in 2004 and had undergone dialysis regularly since 2005; she had undergone renal transplantation 10 days earlier. Her medications included aspirin, calcitriol, calcium carbonate, levofloxacin, mycophenolate, omeprazole, prednisone, tacrolimus, trimethoprim/sulfamethoxazole, valganciclovir, and zolpidem.

Extraoral examination was unremarkable. Intraorally, there was a 2 × 1 × 1 cm, expansile hard mass on the gingiva facial to the left mandibular first and second premolars (Fig. 4). The panoramic and periapical radiographs showed more subtle but similar pattern to that seen in case 1. There was a faint ground-glass ill-defined lesion that blurred the border of the crestal alveolar bone and involved half the height of the mandible. There was no lamina dura noted surrounding the teeth in this region (Fig. 5).

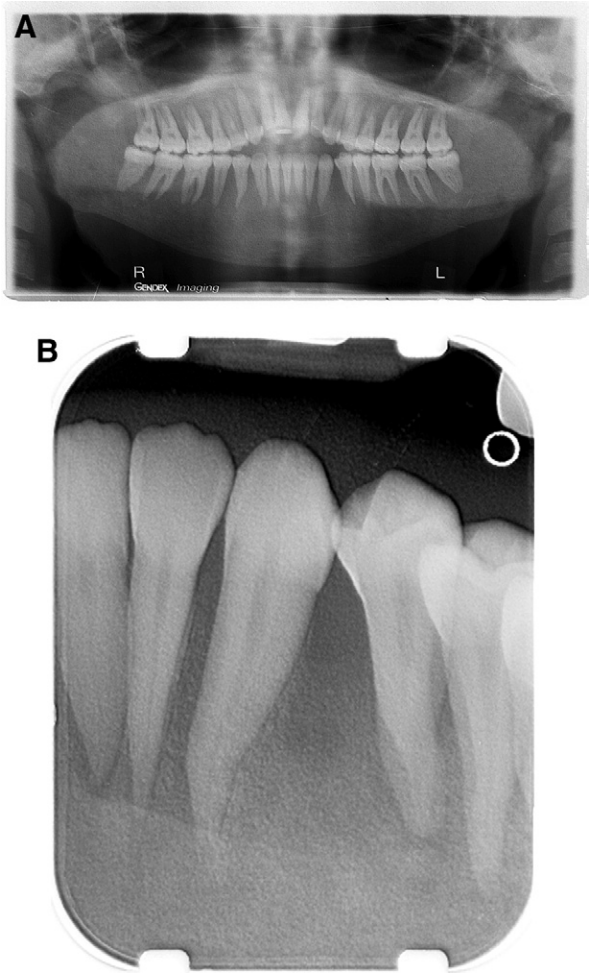

Fig. 5. **A,** A generalized ground-glass radiopacity is noted throughout the mandible. **B,** The mandibular left dentition lacks the presence of lamina dura.

Laboratory examination showed a leukocyte count of 2,960/μL (normal 4,000-10,000/μL), platelet count 252 × 10^9/L (normal 150-450 × 10^9/L), serum creatinine 4.65 mg/dL (normal 0.7-1.3 mg/dL), serum calcium 9.3 mg/dL (normal 8.8-10.5 mg/dL), serum phosphate 3.4 mg/dL (normal 2.4-5.0 mg/dL), serum albumin 3.5 mg/dL (normal 3.7-5.4 mg/dL), and serum PTH 6,672 pg/mL (normal 11-80 pg/mL).

Differential Diagnosis

In each of these cases, the patient's history, clinical presentation, and characteristic radiographic findings strongly suggested a diagnosis of osteitis fibrosa (renal osteodystrophy), commonly associated with secondary hyperparathyroidism. However, the differential diagnosis of a patient with localized expansion of the mandible presenting as a mixed radiolucency-radiopacity also includes benign fibro-osseous lesions (BFOLs) and other odontogenic and nonodontogenic lesions.

In particular, fibrous dysplasia was a possibility given the ground-glass radiographic appearance and lack of circumscription. However, working against this diagnosis was the adult onset in each patient because fibrous dysplasia typically arises in childhood. Although fibrous dysplasia and osteitis fibrosa share many clinical and radiographic characteristics, the latter must be considered as the diagnosis until proven otherwise in a patient with a history of dialysis.[7]

Another BFOL deserving of consideration is a cementoossifying fibroma. Although this lesion may demonstrate a mixed radiolucent-radiopaque appearance and is seen in adulthood, the ill-defined borders of the patients presented here ruled out this diagnosis.[16] Similarly, focal cemento-osseous dysplasia is a BFOL that may present as a mixed radioluency-radiopacity but tends to have well circumscribed borders and is rarely associated with the swelling noted in either of the present patients.[17,18]

Odontogenic cysts and tumors that may present as mixed radiolucent-radiopaque lesions include adenomatoid odontogenic tumors, calcifying epithelial odontogenic tumors (Pindborg tumors), calcifying odontogenic cysts (Gorlin cysts), and ameloblastic fibro-odontomas. However, each of these benign lesions typically presents as a well circumscribed radiolucency with focal radiopacities and not as the ill-defined homogenous ground-glass lesions in the present patients.[19-22]

In patients with ESRD in particular, brown tumors of secondary hyperparathyroidism must be considered. These also tend to present as sharply-circumscribed and primarily radiolucent lesions[23] unlike the lesions in these cases.

Although a generalized loss of lamina dura noted may also be associated in patients with Paget disease, this is typically a diagnosis of older individuals. In addition, this was ruled out because the characteristic "cotton-wool" radiopacities associated with this diagnosis were lacking in these patients.[24]

Management

Both patients underwent incisional biopsies under local anesthesia, and the histopathology of both lesions was similar. Variably sized trabeculae of woven bone containing numerous plump osteocytes were set in a fibrous background. There was minimal osteoblastic rimming of the trabeculae, many of which were surrounded by localized areas of fibrosis. The background stroma was moderately cellular and generally well collagenized (Fig. 6). The tissue biopsy in case 2 was not as well mineralized but still demonstrated seams of osteoid as well as numerous multinucleated osteoclast-type giant cells (Fig. 7). Given these findings and the patients' histories, the diagnosis rendered in each case was osteitis fibrosa, a specific pattern of renal osteodystrophy. Although the histopathology of osteitis fibrosa is not specific to this entity and may be difficult to distinguish from BFOLs, the patients' histories, clinical findings, and radiographs together rendered this the diagnosis in each case.

Although each patient's swelling was benign, the patient in case 1 was advised to undergo surgical recontouring to debulk the mass because of its extensive size and to reduce/eliminate the repeated trauma; the patient, however did not return for the procedure. He ultimately underwent parathyroidectomy and was then lost to follow-up. The patient in case 2 declined surgical recontouring, because

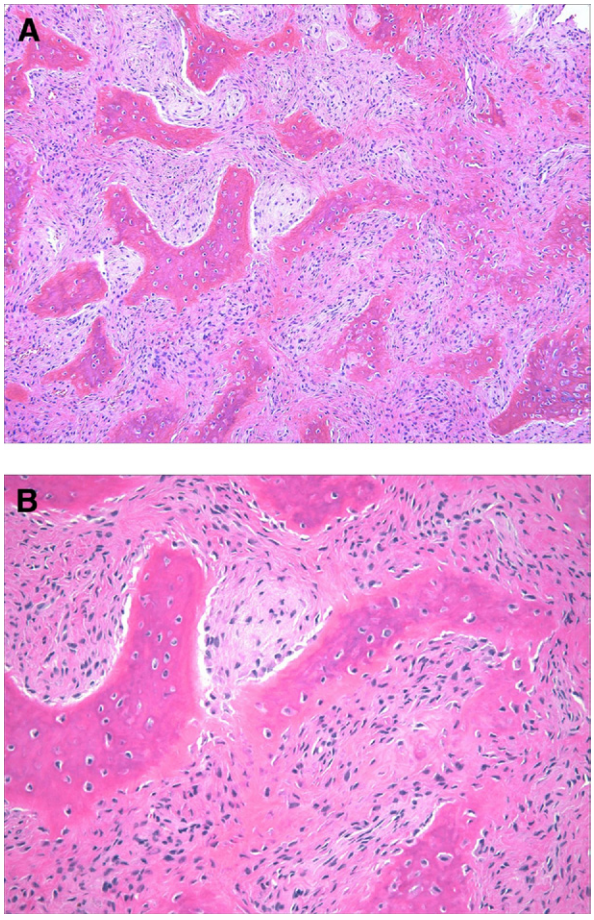

Fig. 6. **A,** Trabeculae of vital woven bone are set in a cellular fibrous stroma (×10). **B,** Seams of variably calcified material rimmed by scattered plump osteoblasts are noted (×20).

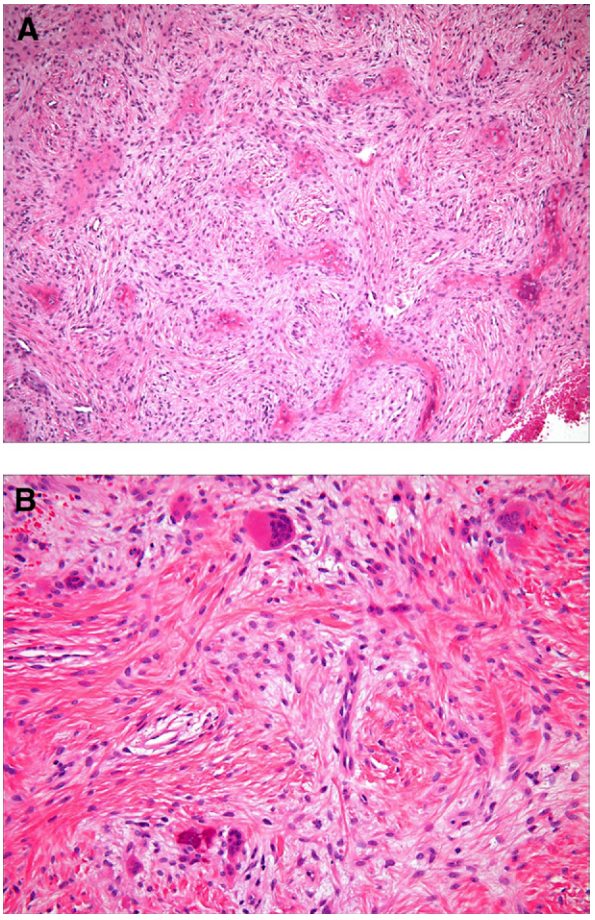

Fig. 7. **A,** Seams of immature mineralized material arise in a fibrous stroma (×10). **B,** Multinucleated giant cells are scattered throughout the cellular stroma (×20).

the swelling was not particularly bothersome to her. Her hyperparathyroidism was subsequently treated with a subtotal parathyroidectomy. Clinical follow-up 3 months after surgery revealed no significant change in the appearance of her jaw lesion.

DISCUSSION

ESRD often leads to the development of metabolic bone disease and the broad clinical syndrome CKD-MBD. Manifestations may include: abnormalities of calcium, phosphorus, PTH, and vitamin D metabolism; abnormalities of bone turnover, mineralization, volume, linear growth, or strength; and vascular or other soft tissue calcifications.[1] The term renal osteodystrophy (ROD) previously alluded to many of these changes but is now used exclusively for the biopsy-proven bone changes that result from this syndrome and are due to secondary hyperparathyroidism and a deficiency of calcitriol.[25] Although 24 cases involving the jaws have been reported, the majority have presented as diffuse enlargements of the maxilla and mandible rather than localized swellings as described in the present patients.

Like ROD, brown tumors of hyperparathyroidism may be seen in patients with ESRD and cause expansion of the jawbones.[23] A recent report and review of the literature integrated both brown tumors and ROD as maxillary and/or mandibular enlargements.[26] However, it is important to recognize that these are unrelated entities that can be distinguished by histopathology if not by the typical sharply circumscribed and radiolucent appearance of brown tumors.[27] Brown tumors were in fact described in patients with primary hyperparathyroidism well before they were also noted in patients with secondary hyperparathyroidism due to renal disease.[23] Although ROD may demonstrate the presence of multinucleated giant cells, as was seen in the present case 2, these are typically scattered and rarely accompanied by the extensive hemorrhage and deposition of hemosiderin that is characteristic of brown tumors.

Table I. Enlargement of the jawbones in ESRD: Clinical data

Study	Case	Not reported	Gender	Age	Location	Involvement	Years on dialysis
Nathan, Traiger, and Berman (1966)[3]2	1	Black	F	40	Maxilla/mandible	Generalized	0
Nadimi, Bergamini, and Lilien (1993)[4]	2	Black	F	28	Maxilla	Generalized	20
Phelps, Bansal, and Twersky (1994)[5]	3	Black	F	45	Maxilla/mandible	Generalized	8
	4	Black	M	38	Maxilla/mandible	Generalized	13
	5	Black	F	28	Maxilla/mandible	Generalized	6
Michiwaki, Michi, and Yamaguchi (1996)[6]	6	Asian	M	42	Maxilla/mandible	Generalized	6
Damm et al. (1997)[7]	7	White	F	28	Mandible	Localized	5
	8	Black	F	23	Maxilla/mandible	Generalized	2.5
	9	Black	M	58	Maxilla/mandible	Generalized	9
	10	White	M	25	Maxilla/mandible	Generalized	8
	11	Black	F	22	Maxilla/mandible	Generalized	10
	12	White	F	21	Mandible	Localized	6
	13	Black	M	19	Maxilla/mandible	Generalized	7
	14	Black	M	40	Maxilla/mandible	Generalized	13
	15	Black	F	31	Maxilla/mandible	Generalized	12
Adornato and Mayne (2000)[8]	16	Black	M	59	Maxilla/mandible	Generalized	Not reported
Vigneswaran (2001)[9]	17	Black	F	28	Maxilla/mandible	Generalized	6
Asaumi et al. (2002)[10]	18	Asian	M	33	Maxilla/mandible	Generalized	7.5
	19	Asian	M	7	Maxilla/mandible	Generalized	10
Rothstein and Schneider (2003)[11]	20	Not reported	F	16	Maxilla	Localized	?
Kalyvas et al. (2004)[12]	21	White	F	38	Mandible	Localized	10
Hata et al. (2006)[13]	22	Asian	F	52	Maxilla/mandible	Generalized	6
Adachi et al. 2007)[14]	23	Not reported	F	39	Maxilla/mandible	Localized	4
Daneshbod (2008)[15]	24	Not reported	M	20	Maxilla	Localized	8
Lerman et al.	25	Hispanic	M	33	Mandible	Localized	4
	26	Black	F	23	Mandible	Localized	3

Parathyroid hormone regulation and hyperparathyroidism

PTH secretion from the 4 parathyroid glands is regulated by serum calcium concentrations through a feedback loop. Higher concentrations of serum calcium, and vitamin D and its metabolites reduce the secretion of PTH.[28] Excess levels of PTH may be produced in patients with a primary disorder of the parathyroid glands (primary hyperparathyroidism) or as a response to chronically low levels of serum calcium.

Primary hyperparathyroidism is the result of increased levels of PTH secreted due to an intrinsic increase in parathyroid gland function. Solitary parathyroid adenomas are the source of 85% of the cases of primary hyperparathyroidism; other causes include multiple parathyroid gland adenomas, glandular hyperplasia, polyclonal hyperfunction, and parathyroid carcinomas.[29]

Secondary hyperparathyroidism is seen in patients with ESRD unable to produce adequate levels of vitamin D in the kidney. The resulting decreased absorption of calcium from the intestines leads to hypocalcemia, which, along with increased phosphate retention and decreased vitamin D levels are the primary factors that lead to the development of secondary hyperparathyroidism.[30-32] Tertiary hyperparathyroidism is a rare form of hyperparathyroidism defined by autonomous (unregulated) parathyroid function that does not respond to medical therapy after a period or persistent parathyroid stimulation; this is typically seen in patients with a history of secondary hyperparathyroidism treated by successful kidney transplantation.[33] This excessive secretion of PTH despite normalized serum calcium levels may result from autonomous expansion of the parathyroid cells due to an allelic loss in chromosome 11 after the chronic up-regulation of PTH from secondary hyperparathyroidism.[34,35]

Renal osteodystrophy

The radiographic features of ROD are varied and may include osteosclerosis, osteomalacia, or soft tissue calcifications and may resemble various infections, tumors, or arthritis.[36,37] The appearance of alternating sclerotic and lucent bands on the superior and inferior thoracic and lumbar vertebral body endplates (the "rugger jersey" spine sign) is considered to be nearly pathognomonic of ROD in the setting of secondary hyperparathyroidism.[38] Oral lesions of ROD may present with a ground-glass radiographic pattern that mimics fibrous dysplasia, as was noted in our 2 cases.[39] Computerized tomography and magnetic resonance imaging demonstrate these changes but may not offer additional information.[10]

Including the present 2 patients, there are now 26 cases of ROD involving the jaws reported in the English-language literature (Tables I and II). Of those

Table II. Renal osteodystrophy of the jaws: patient data

No. of cases	26
Race	14 Black
	4 White
	4 Asian
	1 Hispanic
	3 not reported
Gender	15 female
	11 male
Age range	16-59 years (mean 34; median 32)
Jaw	18 maxilla and mandible
	5 mandible only
	3 maxilla only
Involvement	18 generalized
	8 localized
Average time on dialysis	7 years

whose race was reported, 14 out of 23 (61%) were Black, reflecting a recent study demonstrating that this racial group is at an increased risk for developing secondary hyperparathyroidism.[40] Although 17 of the first 19 patients reported with the condition and the majority (69%) of all cases published to date presented with diffuse involvement, it should be noted that 8 out of 26 cases involved a patient with a localized lesion. In the largest series of cases reported, Damm et al. noted that radiographic involvement of the maxilla and mandible may be one of the earliest signs of ROD, appearing as subperiosteal bone resorption, partial or complete loss of the lamina dura, thinning of the cortical plates, and/or blurring of anatomic landmarks, such as the mental foramen, inferior alveolar canal, and maxillary sinus floor.[7]

The primary histologic subtypes of ROD are osteitis fibrosa, osteomalacia, and mild, mixed, or adynamic bone disease, although patients may demonstrate more than 1 pattern.[30] Adynamic bone disease has in recent decades replaced osteitis fibrosa as the most common form of renal osteodystrophy.[41,42] Osteitis fibrosa is a high-turnover bone disorder characterized by prominent peritrabecular fibrosis with osteoclastic bone resorption and concomitant osteoblastic bone formation.[25] These characteristic bone alterations result from secondary hyperparathyroidism and the activity of cytokines and other growth factors.[30] Osteomalacia is characterized by defective mineralization and increased osteoid production; mixed bone disease demonstrates features of both osteitis fibrosa and osteomalacia; mild disease exhibits a slight increase in remodeling; and adynamic bone disease features no remodeling and hypocellular bone surfaces.[25]

Management of jaw enlargement due to ROD often requires surgical recontouring.[7] There have been 2 reported cases that resolved after parathyroidectomy.[8,13] Although each of the patients presented here underwent this procedure, the first patient was lost to follow-up before his jaw lesion could be reevaluated and the second patient demonstrated no change 3 months after parathyroidectomy.

CONCLUSIONS

CKD-MBD affects young and frequently Black patients in the fourth decade of life. It may present with enlargement of 1 or both jaws, although diffuse enlargement (seen in 70% of cases) is more commonly reported than a localized swelling. Common odontogenic cysts and tumors must still be ruled out in a patient with CKD-MBD and a localized jaw swelling, but ROD must be strongly considered because jaw involvement may represent its initial occurrence.[14] Surgery is generally required for esthetic considerations; however, there have been reports of jaw swellings that have resolved after parathyroidectomy.[8,13]

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Reprint requests:

Mark A. Lerman, DMD
Division of Oral Medicine and Dentistry
Brigham and Women's Hospital
One Brigham Circle, Suite 3-028
Boston, MA 02120
mark_lerman@hms.harvard.edu