
Localized jaw enlargement in renal osteodystrophy: Report of a case and review of the literature

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Renal osteodystrophy is a common long-term complication of end-stage renal disease. Involvement of the jaws is common and radiographic alterations are often one of the earliest signs of chronic renal disease. However, marked enlargement of the jaws is a rare complication of renal osteodystrophy.

A case of localized asymptomatic enlargement of the mandible in a 38-year-old woman with chronic renal failure is presented. The clinical, radiographic, and histological findings were consistent with renal osteodystrophy. To our knowledge, this is the third case of localized mandibular enlargement of renal osteodystrophy reported in the English-language literature. (*Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2004;97:68-74)

INTRODUCTION

Chronic renal disease (CRD) is a multifactorial syndrome characterized by progressive and irreversible loss of renal mass and function, representing a major health concern in the industrialized world.^{1,2} Diabetes mellitus, hypertension, chronic glomerulonephritis, and systemic lupus erythematosus are the most common causes of the disorder.^{1,2} The gradual increase in the annual incidence rate of chronic renal failure over the last decade has been attributed primarily to the increasing incidence of diabetes mellitus.² Patients with chronic renal failure usually develop end-stage renal disease, a potentially fatal condition necessitating hemodialysis or renal transplantation.²

Chronic renal disease is associated with a multitude of complications that are influenced by etiology, residual renal function, response to treatment, and individual variation.² The most common complications of CRD are cardiovascular diseases including secondary hypertension, secondary hyperparathyroidism, immunosuppression, infection, anemia, bleeding disorders, and metastatic calcification.¹⁻³ Common oral manifestations of CRD include xerostomia, candidiasis, metallic dysgeusia, uremic odor, petechiae and ecchymoses, gingival bleeding, and uremic stomatitis.²

A frequent long-term complication of end-stage renal disease is renal osteodystrophy, a spectrum of bone metabolism disorders associated with different pathogenetic pathways.⁴⁻⁷ Histopathologic evidence of renal osteodystrophy can be found in over 50% of patients with chronic renal insufficiency, and its recognition is of major prognostic significance as it is associated with high morbidity.⁸ Diffuse involvement of the jaws occurs with significant frequency and radiographic alterations of the facial skeleton may represent one of the earliest signs of the disease.⁶ In some patients marked jaw enlargement and malocclusion may occur.^{3,9}

A case is presented of a patient with chronic renal failure and localized enlargement of the mandible. To our knowledge this is the third case of localized mandibular enlargement in renal osteodystrophy reported in the English-language literature.

CASE REPORT

A 38-year-old woman was referred to the Clinic of Oral and Maxillofacial Surgery, University of Athens, by her dentist for an asymptomatic swelling of the right mandible. According to the patient, the swelling had been present for approximately 10 years and was enlarging at a slow, steady pace. Her medical history was significant for CRD due to glomerulonephritis. She had been receiving hemodialysis for 7 years and was receiving a calcium-free, aluminium-free phosphate binder (sevelamer hydrochloride), an anti-hypertensive drug (captopril plus hydrochlorothiazide), and salicylic acid.

On clinical examination, neither extraoral jaw enlargement nor facial disfigurement were evident. Intraorally, a well-circumscribed swelling covered by normal mucosa was seen in the edentulous alveolar ridge and buccal sulcus of the right mental nerve region (Fig. 1). The lesion was hard and painless on palpation. The patient recalled that the mandibular right second premolar and first molar teeth had been extracted approximately 10 years ago. The remainder of the oral mu-

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Fig 1. Well circumscribed swelling in the edentulous alveolar ridge and buccal sulcus of the right mental nerve region.

cosa was unremarkable, and cervical lymph nodes showed no enlargement.

A panoramic radiograph revealed an ill-defined triangular bone defect in the affected area with a focal density at its proximal side. Diffuse radiolucencies along the lower margin of the left side of the mandible and loss of normal trabeculation were also observed. On a lateral skull radiograph, the calvarium demonstrated a ground-glass appearance (Fig. 2). An axial computed tomography (CT) scan with a hard tissue algorithm disclosed localized expansion of the buccal plate and loss of the mandibular cortex in the right mental nerve region (Fig. 3). Panoramic reformatted images showed multiple diffuse radiolucent areas of the mandible (Fig. 4), and cross-section reformatted images confirmed right mandibular buccal expansion and loss of trabeculation.

Blood tests (Table I) revealed anemia with low red blood cells count, hematocrit, and hemoglobin and elevated serum creatinine, urea nitrogen, parathyroid hormone (PTH), alkaline phosphatase, and phosphorus. These findings were deemed consistent with chronic renal failure.

The tentative radiographic diagnosis included renal osteodystrophy, fibrous dysplasia, and Paget's disease. Accordingly, a bone biopsy was performed. A mucoperiosteal flap was raised and bone fragments from the lesion were obtained with an osteotome. After irrigating the area with saline, the flap was repositioned and sutured. Postoperative healing was uneventful.

Tissue specimens were fixed in 10% formalin, decalcified in 50% formic acid-sodium citrate solution and embedded in paraffin. Five- μ m-thick sections were stained with hematoxylin and eosin. Microscopic examination showed the specimens to be composed of interlacing bands of spindle-shaped fibroblastic cells on a collagenous stroma and numerous osteoid trabeculae. The trabeculae were cellular, with a contin-

uous osteoblastic rimming and many osteoclastic lacunae (Fig. 5). Multinucleated giant cells and interstitial hemorrhage were also seen (Fig 6). The histopathologic features were consistent with a benign, high-turnover bone lesion, in particular, osteitis fibrosa.

The clinical, radiographic, biochemical, and histologic features were consistent with renal osteodystrophy, and the patient was referred to her attending physician for further investigation and management. Shortly after, she underwent renal transplantation.

DISCUSSION

Renal osteodystrophy represents a spectrum of microscopically and pathogenetically discrete forms of bone disease that may be divided into two broad categories: high-turnover and low-turnover diseases.^{8,10} The most important form of high-turnover disease is osteitis fibrosa. Low-turnover disease includes osteomalacia and adynamic (aplastic) bone disease.¹¹

Osteitis fibrosa is the most common type of renal osteodystrophy, affecting approximately 30% of patients with end-stage renal disease.^{2,12} It is mainly the result of secondary hyperparathyroidism. Locally derived cytokines and a deficiency of 1(alpha),25-dihydroxycholecalciferol may represent contributory factors.^{5,6} The hallmark of the osteitis fibrosa is prominent peritrabecular fibrosis associated with an elevated rate of bone remodeling.⁶ The latter is characterized by increased bone resorption with increased number and activity of osteoclasts and numerous resorption lacunae producing a scalloped trabecular border, and increased bone formation showing increased numbers of osteo-



Fig 2. Lateral skull radiograph showing a ground-glass appearance of the calvarium.

blasts and osteoid, and nonlamellar bone.^{6,12} Osteopenia and bone fractures are the most frequent complications of osteitis fibrosa.⁶

Osteomalacia is a common complication of end-stage renal disease, whose frequency among CRD patients is decreasing.^{8,11} It is caused by accumulation of aluminum or other metals used in the treatment of end-stage renal disease, while the role of 1(alpha),25-dihydroxycholecalciferol deficiency is unclear.⁷ Clinical signs of osteomalacia include skeletal deformities, bone pain, fractures, and musculoskeletal disability.⁶ Osteomalacia is characterized by low bone turnover and defective mineralization; there is an accumulation of unmineralized bone matrix (osteoid) and a decrease in the activity and number of osteoclasts and osteoblasts.^{6,11}

Approximately 10% of patients with end-stage renal disease present signs of both osteitis fibrosa and osteomalacia, a condition known as mixed uremic osteodystrophy.^{2,6,12}

Adynamic bone disease is most prevalent in end-stage renal disease patients without secondary hyperparathyroidism.⁶ Possible risk factors are peritoneal dialysis, overuse of calcium-based phosphate binders and vitamin D, diabetes mellitus, age, and aluminum intoxication.^{5,6,13} Separation of aluminum-induced and nonaluminum-induced forms of the disease is recognized.¹¹ Incidence of the nonaluminum-induced form of the disease is increasing,^{11,12} accounting for up to 30% of predialysis CRD patients, and 15% to 60% of CRD patients receiving dialysis.¹³ Patients with aluminum-induced adynamic bone disease have an increased frequency of bone pain, proximal myopathy and pathologic fractures. The nonaluminum-induced form of the disease may be associated with musculoskeletal symptoms, increased frequency of metastatic calcification and a higher mortality rate as compared to patients with other forms of renal osteodystrophy.¹³ Adynamic bone disease is characterized by a defect in bone matrix formation and mineralization; the number of osteo-

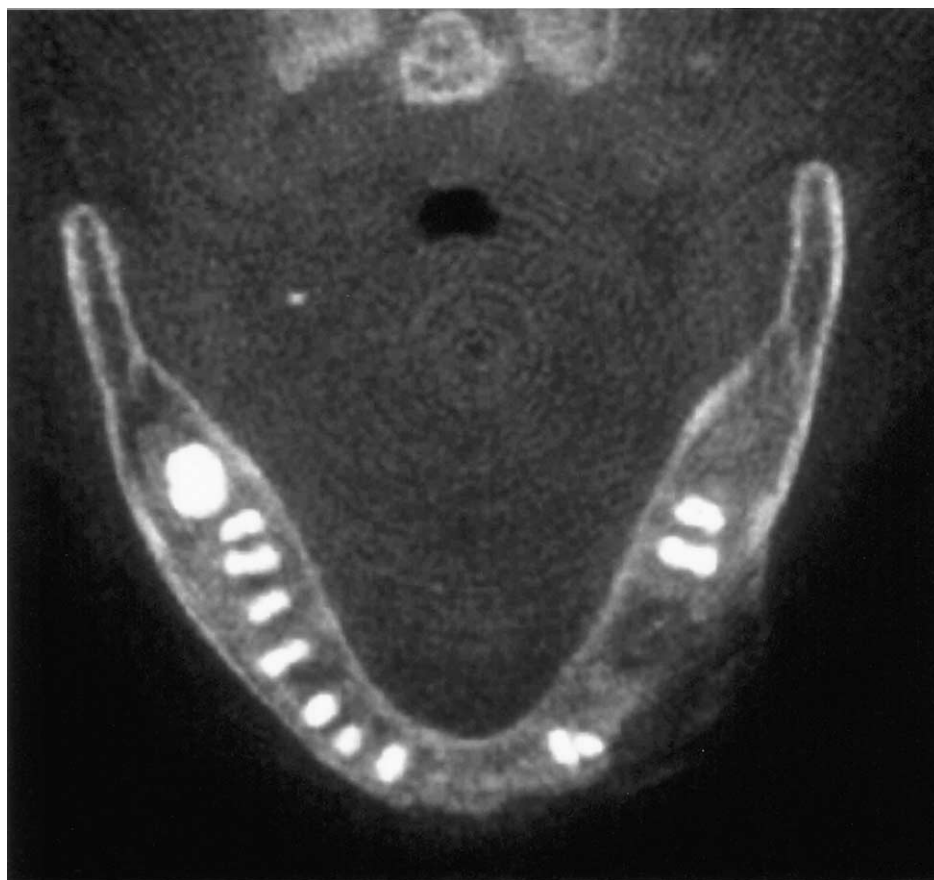


Fig 3. Axial CT slice showing localized expansion of the right buccal plate and loss of the mandibular cortex.

blasts and osteoclasts is decreased, and osteoid production is low.^{6,11,13}

Accurate diagnosis of the specific form of bone disease is of critical importance, as treatment modalities for each are different and frequently conflicting.¹² It should be noted, however, that renal osteodystrophy is not a static phenomenon and that transition from one form to another can occur and may be influenced by treatment regimens.^{8,13}

A variety of biochemical markers and radiographic findings have been employed in the diagnosis and monitoring of renal osteodystrophy, but there is no specific and sensitive noninvasive technique to identify the specific form of the disease in individual patients.^{8,12} Serum PTH and total alkaline phosphatase remain the most widely used biochemical tests for renal osteodystrophy.⁸ However, their value in the diagnosis of renal osteodystrophy is questionable,¹² but in the presence of disease they can aid in identification of osteitis fibrosa.⁶ Increased levels of PTH and total alkaline phosphatase were noted in the present case, in which histopathological findings were consistent with osteitis fibrosa.

Radiographic evaluation is considered less sensitive than PTH assay and is usually employed in symptomatic patients.⁸ The most common initial sign of disease is subperiosteal erosion of the phalanges due to hyperparathyroidism.⁸ Bone densitometry and quantitative ultrasound may be useful in the assessment of bone mass in uremic patients.⁸

Bone biopsy remains the most valuable means for determining the nature and severity of bone disease, although it may be associated with prolonged postsurgical pain and its value is influenced by many factors.^{7,8,12} In our case, no complication ensued after bone biopsy, and postsurgical healing was uneventful.

Renal osteodystrophy associated with jaw enlargement is unusual. A review of the English-language literature revealed 16 cases of jaw enlargement in dialysis patients. The major clinical features of all cases, including the present, are summarized in Table II. Ten patients were black, 4 were white, and 3 were Japanese. There were 9 males and 8 females. Patient age ranged from 19 to 59 years, with a mean age of 35 years. Phelps et al,¹⁴ Adornato and Mayne,¹⁵ Michiwaki et

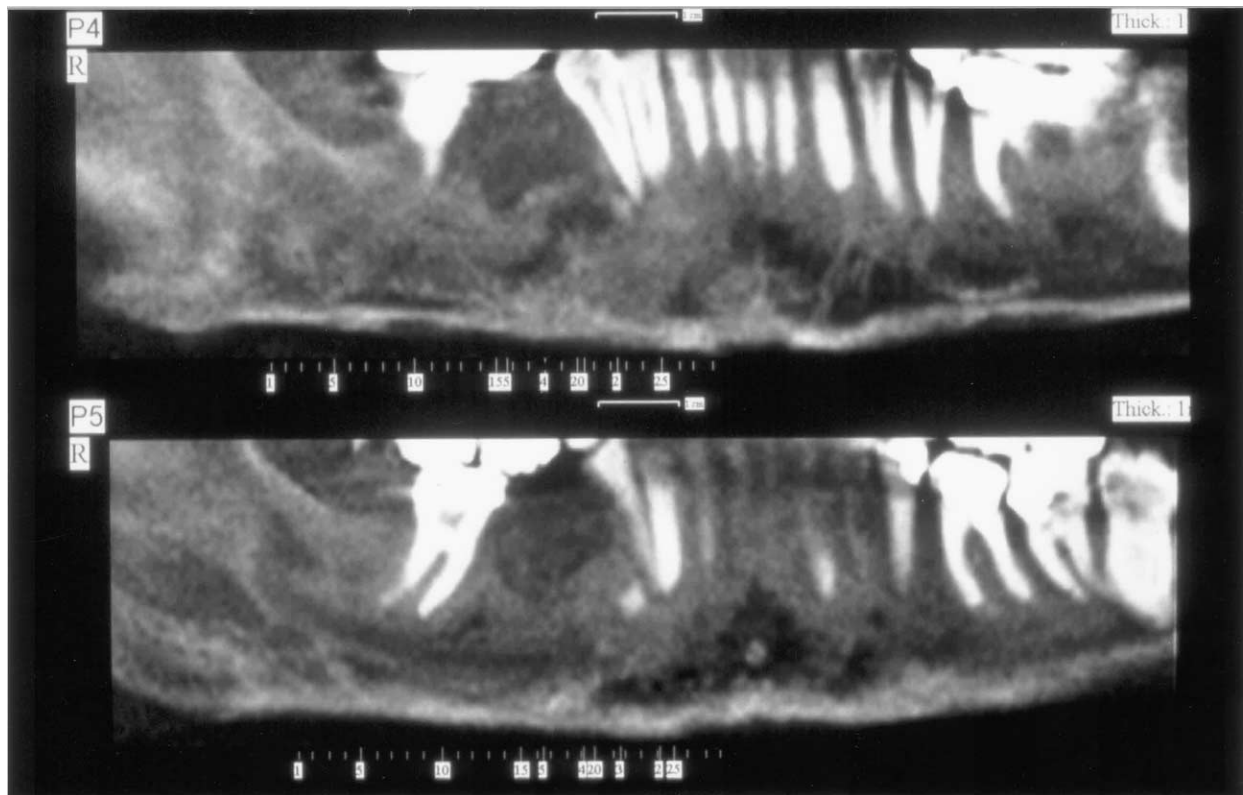


Fig 4. Panoramic reformed images showing multiple diffuse radiolucent areas of the mandible.

Table 1. Laboratory findings

Test	Value	Normal range
Red blood cells (RBC)	3.3 M/ μ L	4.2–5.4 M/ μ L
White blood cells (WBC)	6.1 K/ μ L	4.5–10.2 K/ μ L
Hematocrit (HCT)	28.5%	36.0–47.0%
Hemoglobin (HGB)	9.5 g/dL	12.0–16.0 g/dL
Platelets (PLT)	246 K/ μ L	150–450 K/ μ L
Creatinine	11.7 mg/dL	0.5–1.3 mg/dL
Urea (BUN)	260 mg/dL	10–50 mg/dL
Parathyroid hormone (PTH)	260 pg/ml	10–65 pg/ml
Alkaline phosphatase (ALP)	1306 U/L	98–279 U/L
Phosphorus (P)	6.9 mg/dL	2.7–4.5 mg/dL
Calcium (Ca)	10.3 mg/dL	8.5–10.4 mg/dL
Total protein	7.5 g/dL	6.2–8.5 g/dL

al,⁹ and Asami et al¹⁶ reported cases of diffuse swelling of both jaws in hemodialysis patients with long-standing CRD. In their multi-institutional study, Damm et al³ described 7 cases of diffuse swelling of both jaws secondary to renal osteodystrophy; all cases were associated with malocclusion and facial deformity. Two patients (cases 1 and 6) had localized enlargement of the mandible without occlusal disharmony or facial disfigurement, similar to the present one.

Jaw radiographic findings in renal osteodystrophy

include bone resorption with loss of cortical bone, lamina dura, and other anatomical landmarks and condensation of trabecular architecture producing a ground-glass appearance closely resembling fibrous dysplasia. Generalized involvement is in accordance with the diffuse swelling of the jaws reported in most cases.

Conventional radiographs are usually informative, but computed tomography and magnetic resonance imaging allow better recognition and delineation of bone lesions.¹⁶ Loss of lamina dura and ground-glass pattern may also be found in other diseases of the jaws, including craniofacial fibrous dysplasia and Paget's disease of bone. Histopathological features of those diseases share many similarities with those of renal osteodystrophy. Craniofacial fibrous dysplasia appears in childhood, stabilizes in early adulthood and is typically accompanied by a normal biochemical profile.^{3,15} Paget's disease affects older adults and, like CRD, demonstrates elevated serum alkaline phosphatase.³ A history of chronic renal disease and dialysis is very useful in distinguishing renal osteodystrophy from the other diseases. Furthermore, the radiographic changes of renal osteodystrophy are diffuse rather than monostotic or multifocal as seen in the aforementioned conditions.¹⁵ Any fibro-osseous lesion of the jawbones in a patient

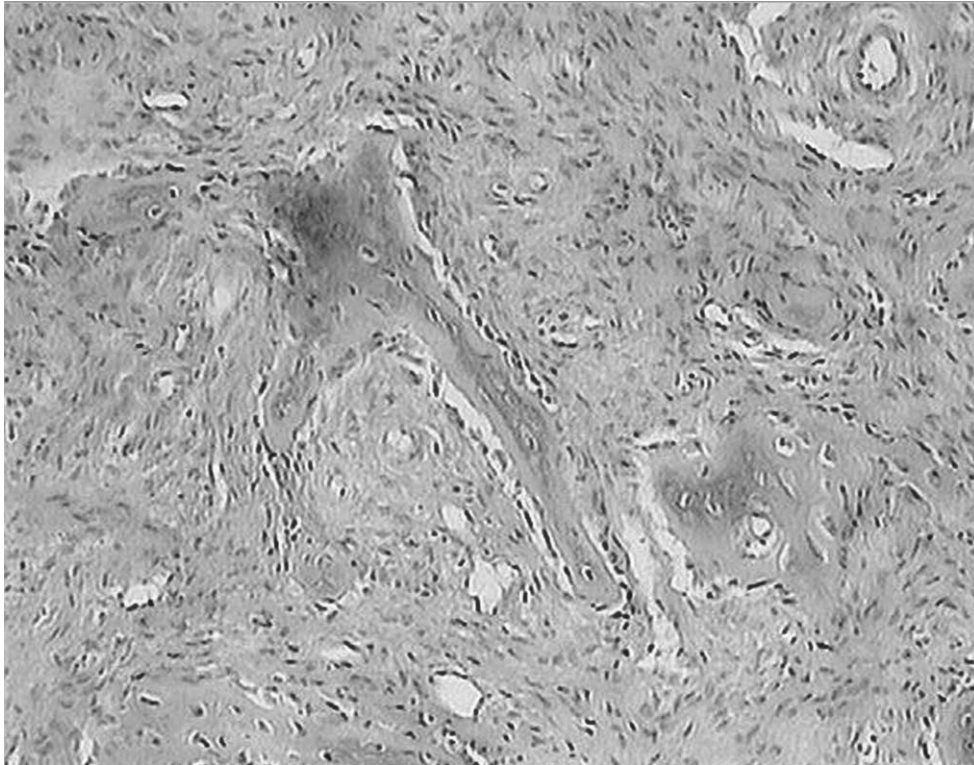


Fig 5. Cellular osteoid trabecula with osteoblastic rimming in a vascular fibroblastic stroma (hematoxylin & eosin stain, original magnification $\times 100$).

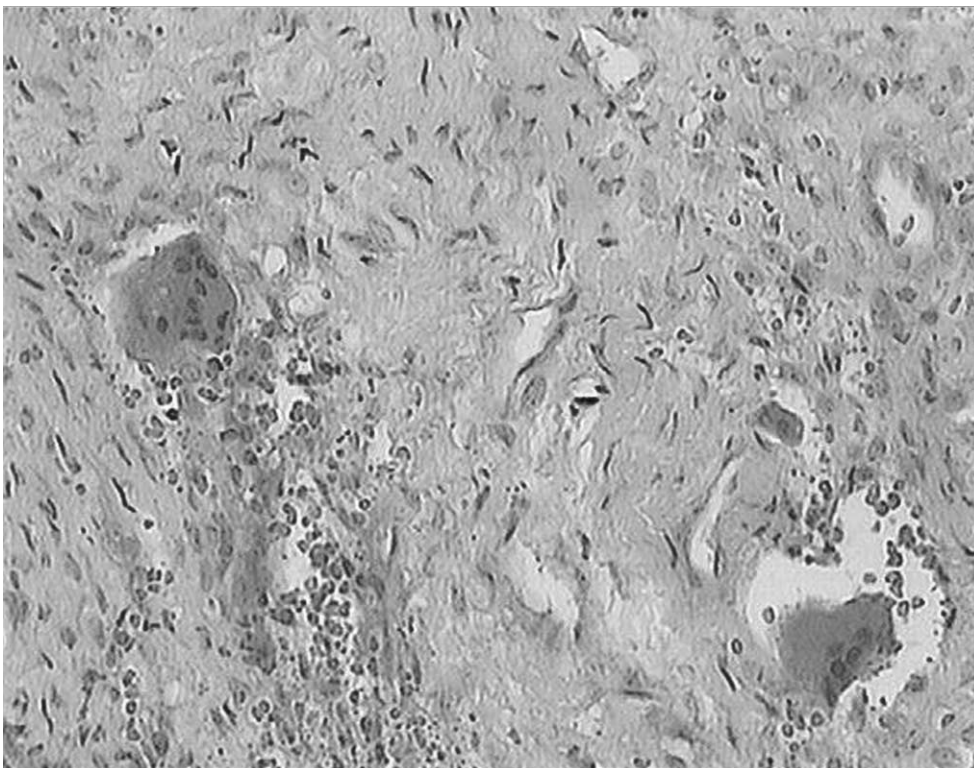


Fig 6. Multinucleated giant cells and interstitial hemorrhage (hematoxylin & eosin stain, original magnification $\times 100$).

Table II. Race, sex, age, jaw involvement and clinical presentation of jaw enlargement in 17 cases of jaw enlargement of renal osteodystrophy

Reference	Race	Sex	Age	Jaw	Presentation
Phelps et al (1994) ¹⁴	B	F	45	U/L	Diffuse
	B	M	38	U/L	Diffuse
	B	F	28	U/L	Diffuse
Michiwaki et al (1996) ⁹	J	M	42	U/L	Diffuse
Damm et al (1997) ³	W	F	28	L	Localized
	B	F	23	U/L	Diffuse
	B	M	58	U/L	Diffuse
	W	M	25	U/L	Diffuse
	B	F	22	U/L	Diffuse
	W	F	21	L	Localized
	B	M	19	U/L	Diffuse
	B	M	40	U/L	Diffuse
	B	F	31	U/L	Diffuse
	B	M	59	U/L	Diffuse
Adornato and Mayne (2000) ¹⁵	B	M	59	U/L	Diffuse
Asaumi et al (2002) ¹⁶	J	M	33	U/L	Diffuse
	J	M	47	U/L	Diffuse
Present case	W	F	38	L	Localized

B, Black; J, Japanese; W, White; M, Male; F, Female; U, maxilla; L, mandible.

with end-stage renal disease must be considered as renal osteodystrophy until proven otherwise.³

Issues in prevention and management of renal osteodystrophy recently have been reviewed by Kaplan et al.⁷ In general, the management of renal osteodystrophy seeks to control factors responsible for the development of bone lesions.^{7,10} Jaw enlargement in renal osteodystrophy may cease with treatment of the underlying cause, but in some cases it fails to return to normal contour,¹⁴ necessitating surgical intervention.³ The course of the disease after renal transplantation is not well known.¹³

Increased prevalence of renal osteodystrophy with gnathic involvement should be anticipated, as therapeutic developments have increased the longevity of patients with chronic renal failure.^{2,9,16} Every jaw enlargement in this group of patients should be carefully investigated, as renal osteodystrophy may mimic inflammatory, neoplastic, or reactive jaw lesions. Fur-

thermore, defective bone metabolism in CRD patients with uncontrolled renal osteodystrophy is considered as a contraindication for gnathic surgery, in particular, implant placement.²

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