A sessile nodule in the dorsum of the tongue

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CLINICAL PRESENTATION

In June 2017, a 52-year-old male patient was referred by his nephrologist to the Dental Service of the Clinics Hospital of the Federal University of Minas Gerais (HC-UFMG) for evaluation of an asymptomatic swelling in the tongue. The patient reported rapid enlargement of a swelling on the posterior region of his tongue; the swelling had started a few days ago. The patient denied any pain or discomfort. He had a medical history significant for end-stage renal disease (ESRD) caused by focal segmental glomerulosclerosis diagnosed 20 years ago. He had been undergoing regular hemodialysis for 8 years. In 2015, the patient had received a renal transplantation and undergone parathyroidectomy to control hyperparathyroidism secondary to chronic renal failure (CRF). The patient also had hypertension and a history of multiple calcifications of the mitral valve and of the aortic and renal arteries. The patient's medications included tacrolimus (1.5 mg), mycophenolate sodium (360 mg), and prednisone (5 mg) for the prevention of transplant rejection; hydralazine (50 mg), atenolol (50 mg), amlodipine (5 mg), acetylsalicylic acid (100 mg), clopidogrel (75 mg), and clonidine (0.100 mg) for the control of hypertension and cardiovascular diseases; allopurinol (100 mg), calcitriol (0.25 mg), sodium bicarbonate (1 g), magnesium oxide (250 mg) and calcium carbonate (150 mg) for the management of CRF; and sulfamethoxazole-trimethoprim (800 mg) to treat a respiratory tract infection. The family history was positive for kidney disease, and his older brother was undergoing hemodialysis. Socioeconomic data and extraoral examination were noncontributory.

On intraoral examination, a firm, sessile, irregular, and yellowish nodule, measuring 10 × 8 × 4 mm, was observed on the dorsal surface of the posterior third of the tongue (Figure 1). Oral hygiene was unsatisfactory, and the presence of a white-coated tongue was noted. There was no history of local trauma.

Panoramic radiography was performed, and it was possible to observe linear radiopaque areas on the left and right sides, superior to the hyoid bone and lateral to the vertebrae, as well as paired linear areas next to the right mandibular angle. These radiopaque areas were suggestive of calcification of vessel walls and calcified atherosclerotic plaques in the carotid artery, respectively. Decreased radiolucency of pulp chambers/root canals, poor differentiation of dentin/enamel radiodensity, and reduction in mandibular trabecular bone were also noted (Figure 2).

At the time of the dental appointment, laboratory examination results showed serum ionic calcium and parathyroid hormone levels within the normal range, 1.08 mg/dL and 17.1 mg/dL, respectively. The serum phosphorus concentration (5.5 mg/dL), creatinine (3.76 mg/dL), and blood urea nitrogen (96 mg/dL) were all elevated, based on reference values: 2.5 to 4.5 mg/dL, 0.70 to 1.30 mg/dL, and 19 to 43 mg/dL, respectively.

DIFFERENTIAL DIAGNOSIS

On the basis of the clinical features and the systemic condition, the diagnostic hypotheses were benign mesenchymal tumors, such as granular cell tumor (GCT), schwannoma, or neurofibroma, and non-neoplastic reactive lesions, such as oral focal fibrous hyperplasia. CRF-induced calcification abnormalities and choristoma were also considered.

GCT is an uncommon benign neoplasm that affects various locations of the body.[1] GCTs can occur in the esophagus, skin or subcutaneous tissue, and lungs[2] but do have a preference for the tongue,[3] the most common site of the lesion in the head and neck region.[1,4] Currently, the most accepted hypothesis for its etiology is a neural origin, in particular from the Schwann cells. The clinical presentation is very similar to that of the

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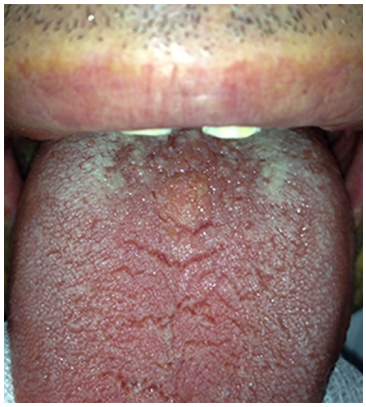

Fig. 1. The posterior third of the dorsal surface of the tongue presenting with a firm, sessile, irregular, and yellowish nodule measuring 10 × 8 × 4, with an associated white- coated tongue.

present case, characterized by an asymptomatic solitary nodule in the dorsum of the tongue with a yellowish or normal-colored surface.[4] There is a female predilection, with occurrence twice more common than in males[5]; this was inconsistent with our case because of our patient's gender. The lesion most frequently occurs in the fourth to sixth decades,[4,5] and this corresponds to the age of our patient.

Schwannomas are neural tumors found in the oral cavity, predominantly affecting the tongue. The lesion may occur at any age and in both genders, and it is an asymptomatic, solitary, slowly enlarging, nontender, encapsulated mass.[6] Another benign tumor with equal peripheral nerve origin and similar clinical findings, the neurofibroma, should also be considered in the differential diagnosis. It is composed of spindle-shaped cells with elongated nuclei in a myxoid stroma containing both S-100-positive Schwann cells and other CD34-positive mesenchymal cells, and this distinguishes neurofibromas from Schwannomas.[7] Both tumors are nodular, painless, and potentially cause tongue impairment, mostly when it is associated with neurofibromatosis type 1 syndrome.[8] The presence of neurofibromatosis was not applicable to our case, but solitary lesions are seen in nonsyndromic patients.

Oral focal fibrous hyperplasia is a reactive, inflammatory hyperplastic lesion of connective tissue. It usually presents as a yellowish-white or mucosal-colored, sessile or sometimes pedunculated, smooth-surfaced nodule. The consistency varies from soft or rubbery to firm, depending on the density of the collagen fibers.[9] Commonly affected areas are those subject to masticatory trauma, such as the buccal mucosa, lower lip, and dorsal tongue. Most cases occur in the second to fifth decades of life, with a female/male ratio of 2:1. The lesions are predominantly asymptomatic, and a history of local trauma is often related.[10] Although the clinical findings are consistent with the present case, there is no report of local trauma, an important aspect observed in fibrous hyperplasia.

Kidney disease is associated with several oral and maxillofacial alterations, mostly as a result of bone metabolism disorders. The group of chronic kidney disease−mineral and bone disorders (CKD-MBDs) includes calcinosis, hyperparathyroidism−jaw tumor syndrome, brown tumor of hyperparathyroidism, and renal osteodystrophy.[11] Soft tissue calcifications

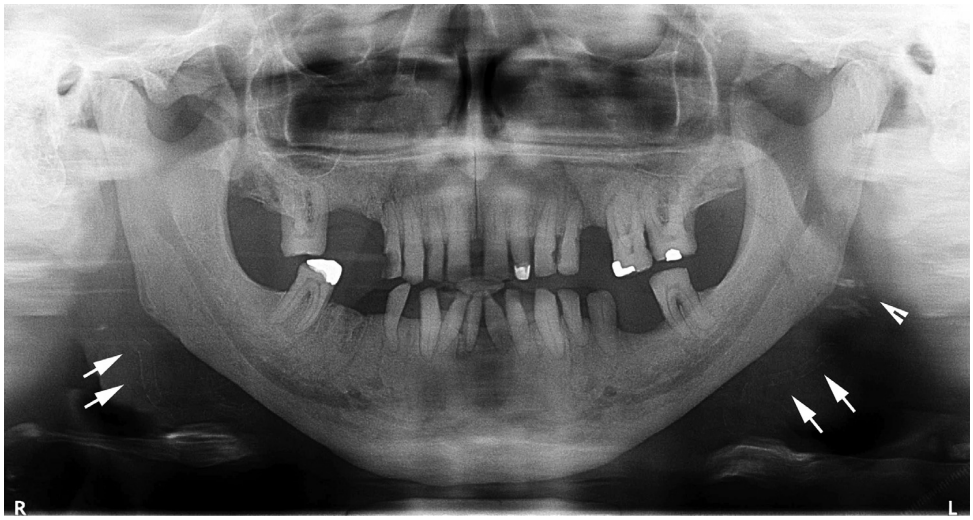

Fig. 2. Panoramic radiograph illustrating radiopaque areas in the left side, adjacent to the hyoid bone, displayed lateral to the vertebrae, which are suggestive of calcified atherosclerotic plaques *(arrowhead)*. Bilateral "pipe stem" linear radiopaque areas, which are suggestive of calcifications in the facial arteries *(arrows)*. Reduction of radiolucency of the pulp chambers and root canals and reduction in mandibular trabecular bone can be observed.

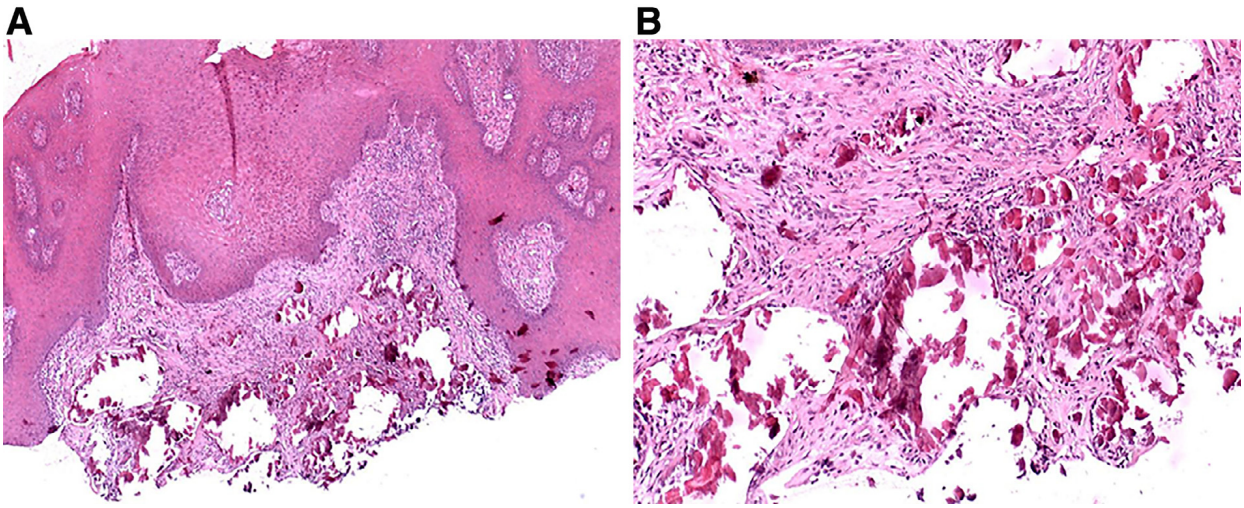

Fig. 3. **A,** Fragment of oral mucosa with hyperplastic stratified squamous epithelium and amorphous, basophilic, irregularly shaped acellular deposits within the fibrous connective tissue with moderate chronic inflammatory infiltrate (hematoxylin and eosin [H&E] stain, magnification × 40). **B,** Detail of calcified deposits (H&E stain, magnification × 100). *A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM05171.*

are also associated with ESRD and hyperparathyroidism. Metastatic calcinosis (MC) is a pathologic condition in which there is a deposition of calcified product in otherwise vital soft tissues associated with hyperphosphatemia with or without concurrent hypercalcemia.[12] The medical history of CRF and the presence of multiple calcifications in the mitral valve in addition to the carotid, aortic, and renal arteries prompted us to consider MC of the tongue as a potential diagnosis.

Choristomas are tumor-like lesions composed of normal tissue at regular or nonregular/heterotopic sites, respectively. Some types of intraoral choristomas are described in the dorsum of the tongue and classified on the basis of tissue components, such as cartilaginous, osseous, lingual thyroid, sebaceous, glial, and gastric mucosal choristomas.[13,14] The locations of these lesions are variable, but they are more prevalent in the posterior third of the tongue near the foramen cecum and most commonly around the circumvallate papilla. The lesions usually present as firm and solitary nodules, either sessile or pedunculated, with normal-colored overlying mucosa.[14] Patient age varies, depending on the origin of the tissue, but there are reports of cases from childhood up to the eighth decade of life, more commonly affecting females. The duration of the lesions range from several months to several years.[13] All these clinical findings are consistent with those in the present case.

DIAGNOSIS

An excisional biopsy was performed under cover of local anesthesia, with antibiotic prophylaxis consisting of 2 g amoxicillin administered 1 hour before the surgical procedure. Microscopically, the presence of amorphous, basophilic, irregularly shaped, and acellular deposits within the fibrous connective tissue was observed, also demonstrating a moderate chronic inflammatory infiltrate (Figure 3).

Scanning electron microscopy showed the presence of amorphous material with a lamellar-like aspect mixed with deposits of inorganic precipitates (Figure 4). Energy-dispersive X-ray spectroscopy showed a higher concentration of calcium and phosphorus at an acceleration voltage of 20 kV. Map analysis of calcium, phosphorus, and silica was performed to recognize the distribution at an acceleration voltage of 20 kV (Figure 5). Microscopy findings showing the distribution of calcium, phosphorus, and calcium−phosphorus complex deposits in addition to the medical condition of the patient led to the final diagnosis of MC.

MANAGEMENT

The patient was referred back to his nephrologist for evaluation of renal function and further investigations related to the assessment of other metastatic areas. Laboratory tests showed a slight increase of phosphate without simultaneous hyperkalemia. The creatinine and blood urea nitrogen levels were indicative of a kidney disorder, even after renal transplantation. The patient's current therapy is based on the control of kidney function with the medications in use, as reported above, and dietary restriction. Hemodialysis was not indicated at this time.

With regard to oral management, the nodule was totally removed (Figure 6). After 9 months, the affected area is completely healed with no signs of

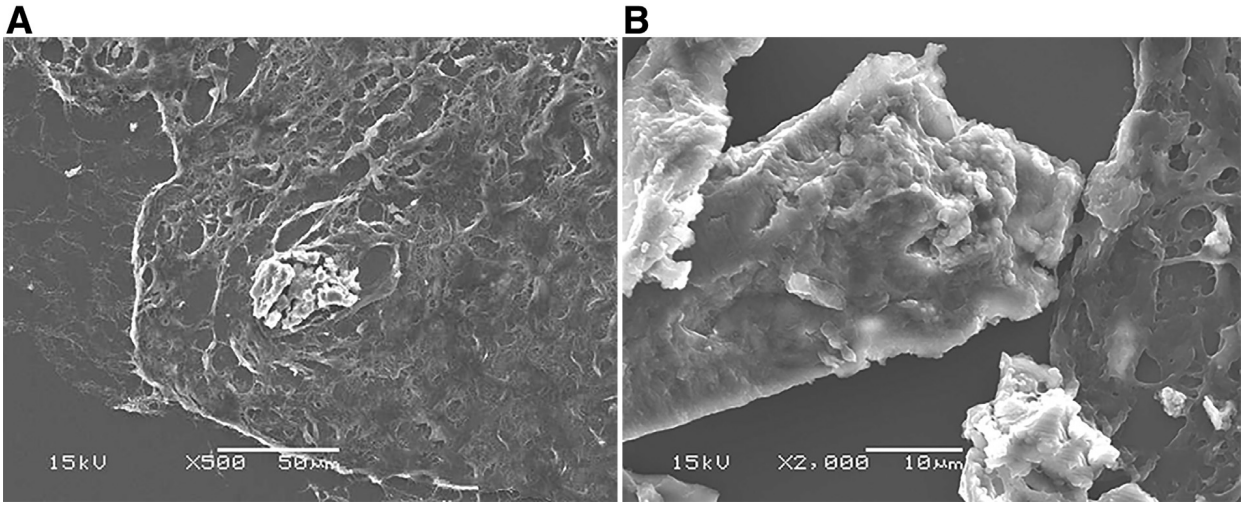

Fig. 4. **A,** Scanning electron microscopy demonstrating the presence of amorphous material with a lamellar-like aspect within the fibrous connective tissue (15 kV; magnification × 500). **B,** Deposits of calcified material with irregular surface (EM; magnification × 2000).

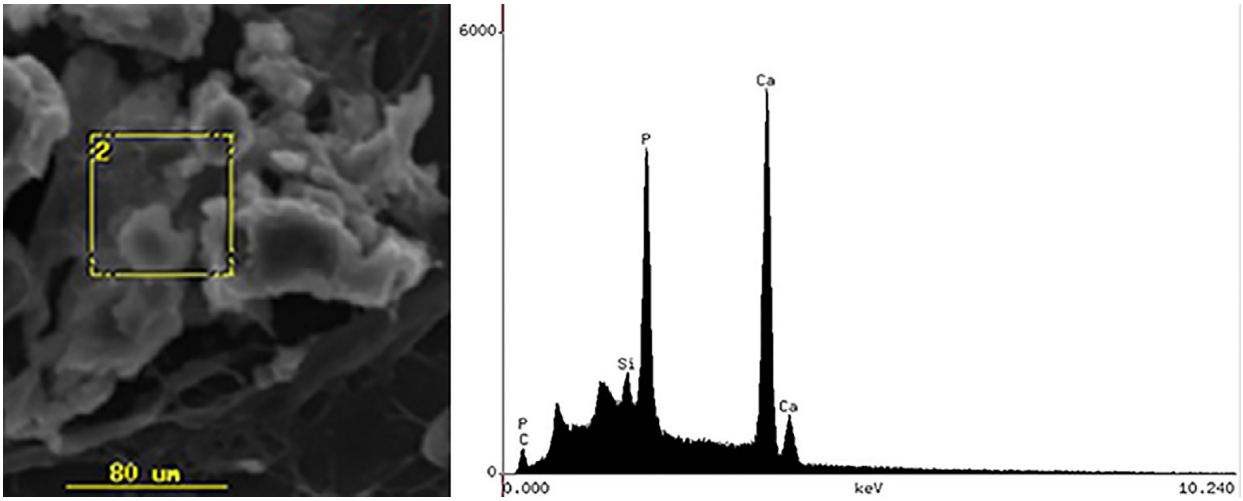

Fig. 5. Energy-dispersive X-ray spectroscopy analysis shows peaks of calcium (Ca) and phosphorus (P).

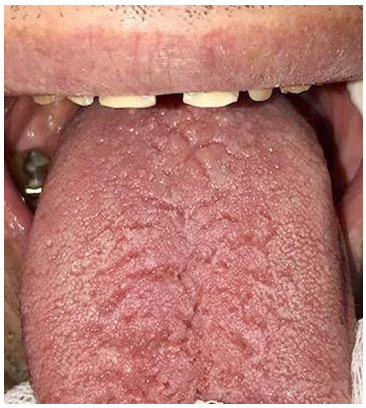

Fig. 6. Patient image 15 days postoperatively; the affected area is completely healed, with no signs of recurrence.

recurrence or any newly affected area. The patient underwentdentaltreatmentsforcompleterehabilitation.

DISCUSSION

Pathologic calcifications of soft tissues in the lungs, skin, blood vessels, kidneys, and heart have been reported.[15-17] Some authors have classified the disease into 3 broad categories: (1) dystrophic calcification, when it occurs in injured or degenerating tissue with normal calcium and phosphate levels; (2) metastatic calcification, in which the calcium and phosphate metabolism are altered[12]; and (3) a less well defined calcification that has no known pathogenetic mechanism, commonly referred to as *idiopathic calcinosis*.[18]

Idiopathic calcinosis is calcification with an unclear etiology and pathogenesis. It is characterized by bulky,

tumor-like, periarticular calcium deposits, with neither local tissue injury nor systemic metabolic disorder. This is the rarest subtype of calcinosis, characterized by a solitary calcified nodule, and it is mostly reported in children, adolescents, and young adults. Excision of the mass is an option for treatment, but recurrence is not uncommon.[19] The dystrophic calcification of soft tissue is associated with inflammation and degeneration as local factors in the pathogenesis and progression of the lesion. This type of calcification is characterized by deposition of calcium salts in necrotic or injured tissues in patients with normal calcium and phosphorus serum levels.[16] Bernstein and Neal[20] reported a case of intraoral calcification associated with connective tissue disease. They suggested that the causes of dystrophic calcification can be associated with systemic inflammatory diseases (e.g., systemic lupus erythematous and rheumatoid arthritis), as well as traumatic, vascular, or degenerative processes and local degenerative changes in neoplasms.

In the present case, because the patient had kidney disease, the dystrophic and idiopathic types of calcinosis were excluded, and diagnostic efforts were focused on possible CKD-MBD calcification associated with CRF, such as MC.

Clinical features of the types of intraoral calcifications are not unique.[21] Microscopy findings, including energy-dispersive X-ray spectroscopy analysis, are also nonspecific in that they can be similar among the forms of soft tissue calcification.[15] Thus, the diagnosis is supported by the association of clinical and histologic findings and the possible etiology/pathogenesis. Briefly, clinical or microscopy findings of overt soft tissue calcification and systemic disturbance in calcium and phosphate metabolism should lead the clinician to suspect the possibility of MC. If normal calcium and phosphate levels are observed, local factors, such as inflammation and degeneration of the tissue, must be considered and may indicate the diagnosis of dystrophic calcification. In contrast, when the etiology is unclear and there are no signs of systemic disturbance or local injury, the diagnosis of idiopathic calcinosis can be made.

MC or metastatic calcification is a pathologic process that occurs in undamaged tissues as a result of hyperphosphatemia with or without concurrent hypercalcemia.[12] The imbalance of bone metabolism must be present.[15] Furthermore, several systemic diseases may induce hyperphosphatemia and hypercalcemia, including ESRD, hyperparathyroidism (primary or secondary), milk−alkali syndrome, hypervitaminosis D, sarcoidosis, disseminated malignancy, and destructive bone disease.[22] MC commonly affects the kidneys, lungs, and gastric mucosa, as well as joints and arteries,[15-17,23] whereas oral mucosa involvement is very rare. To date, 7 previous cases with diagnostic criteria of oral soft tissue calcifications associated with metabolic impairment and hyperphosphatemia have been reported in the English language literature (Table I).

The first report of a case of oral MC was made by Shear and Copelyn in 1966.[15] Of note, the patient was a female, who had renal disease with increased plasma phosphate but without an increase in serum calcium. Oral examination revealed a firm, well-circumscribed mass over the edentulous right mandibular ridge, whereas the overlying mucosa appeared normal. The review of reported cases revealed that the ages of affected individuals ranged from 41 to 80 years, and there was no gender predilection. The most common clinical manifestation was a firm, well-circumscribed submucosal mass that could be mobile or fixed with normal overlying mucosa.[15,16,21-23]

Radiographically, MC lesions appear radiopaque or mineralized and may be close, but not attached, to bone.[15,22,23] In the present case, panoramic radiography was performed, but no alterations were observed. Possibly, the localization of the lesion made it difficult to observe radiographic observation of calcified deposits inside the lesions. However, in the same examination, radiopaque areas lateral to the vertebrae, suggestive of calcified atherosclerotic plaques, were observed. Bilateral linear radiopaque areas with a “pipe stem” appearance were also seen, characterizing an entity termed *Mönckeberg medial calcinosis*. This type of calcification of the vessel walls is strongly associated with CRF and affects only the tunica media of small- and medium-sized muscular arteries.[24] Observed changes in mandibular trabecular bone were possibly related to ESRD and secondary hyperparathyroidism.[11] Also, the patient had a medical history of calcifications that occurred in the mitral valve as well as in the aortic and renal arteries. These findings are common in MC, and except for 2 cases,[22,25] all patients presented with other sites of MC, mostly localized in organs and/or blood vessels.[15-17,21,23]

Microscopically, MC is composed of extensive basophilic, amorphous, variably sized, irregularly shaped, submucosal, calcified deposits in the connective tissue. These deposits are frequently surrounded by large foreign-body giant cells, epithelioid histiocytes, and a variable chronic inflammatory infiltrate.[21] In our case, giant or epithelioid cells were not visualized. The distribution of calcified deposits is also demonstrated through a qualitative analysis of these deposits on the electron probe X-ray microanalyzer, which quantifies the presence of calcium and phosphorus.[23] In the present case, we also observed a high

Table I. Clinical aspects of previously reported cases of oral metastatic calcinosis

References	*Age/Gender*	*Clinical Presentation*	*Site*	*Medical history*	*Metabolic impairment*
Shear and Copelyn,- 1966[15]	44/F	Mass, firm, well circumscribed, nonmobile, and overlying normal oral mucosa	Edentulous mandibular ridge	CRF	Hyperphosphatemia
Wiggins et al., 1975[16]	68/M	Mass, firm to rubbery in consistency and overlying normal oral mucosa	Floor of the mouth	Milk-Alkali Syndrome	Hyperphosphatemia
Walker et al., 1993[17]	41/F	Mass, white and draining	Lateral tongue border	CRF	Hyperphosphatemia and hypercalcemia
Omovie et al., 1995[22]	80/M	Swelling, with diffuse margins, tender on palpation, slightly mobile, and overlying normal oral mucosa	Lower labial sulcus	CRF	Hyperphosphatemia
Yamada et al., 2000[23]	75/M	Mass, hard on palpation, mobile, and yellow	Edentulous maxillary ridge	CRF	Hyperphosphatemia
Alawi and Freedman, 2001[21]	61/M	Mass, firm, tender on palpation, focally ulcerated, bilobed, and pink	Maxillary vestibule/Nasal septum	CRF	Hyperphosphatemia
Verma et al.,2015[25]	65/F	Normal oral mucosa with nontender granular aspect on palpation	Floor of the mouth	CRF	Hyperphosphatemia
Rocha et al., 2018 (current case)	52/M	Mass, firm, sessile, irregular, and yellowish surface	Dorsum of the tongue	CRF	Hyperphosphatemia

CRF, chronic renal failure; *F*, female; *M*, male.

concentration of these components in the calcified areas of the specimen.

Treatment protocols for MC are generally based on the normalization of calcium and phosphate serum levels through improvement of renal function and control of parathyroid hormone levels.[17,25] Dietary control (e.g., restriction of phosphorus), use of medications (e.g., oral phosphate chelating agents and intravenous vitamin D), parathyroidectomy, and, in several cases, renal transplantation are indicated.[21] With regard to treatment of MC oral lesions, if the calcifications are asymptomatic, surgical intervention is not necessary.[25] In the present case, the nodule was excised because of the patient's complaint of rapid enlargement. Treatment was based on only dietary control and medications because the patient had already undergone renal transplantation and parathyroidectomy.

CONCLUSIONS

Oral MC is an extremely rare condition, and little is known about this entity compared with other dysfunctions resulting from CRF. There are no pathognomonic signs of the disease, which makes it difficult to diagnose it, possibly leading to misdiagnosis. However, the early recognition of the disease is important to detect unknown systemic disorders or to recognize pre-existing diseases and imbalances.

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