Destructive maxillary radiolucency in a 20-year-old female

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CLINICAL PRESENTATION

A 20-year-old female was referred to the Department of Oral and Maxillofacial Surgery, Columbia University, for evaluation of a recurrent radiolucent lesion in the anterior maxilla. The patient reported that 8 months ago, she had presented to an outside oral surgeon with mobile, but vital, right lateral (#7) and central (#8) maxillary incisors and associated discomfort. During the initial presentation, the patient did not recall any trauma to the region, and her dentition was otherwise in excellent condition without caries or periodontal disease. The patient denied any significant past medical history, and her social history was likewise unremarkable. On imaging, an ill-defined radiolucent lesion was identified at the root apices of the two mobile incisors (radiograph not available). At that time, the lucent lesion was curetted and sent for pathologic analysis. The submitted tissue was diagnosed as "granulation tissue." Unfortunately, removing the periapical tissue failed to relieve the patient's discomfort, and a localized swelling subsequently developed over the following weeks. A repeat biopsy was performed, and the histopathologic result was similarly interpreted as granulation tissue formation. With no sign of healing and continued local expansion, the area was aggressively debrided, and teeth #7 and #8 were extracted.

When the patient presented to our institution for consultation, there was appropriate mucosal healing of the extraction sites (Figure 1); however, new-onset mobility of the left maxillary central incisor (#9) was noted. The overlying gingiva was erythematous but otherwise nontender to palpation. No cervical, axillary, or inguinal lymphadenopathy was noted. A computed tomography (CT) scan revealed a destructive and ill-defined radiolucent lesion involving the right anterior maxilla (Figure 2) and extending superiorly toward the nasal fossa.

DIFFERENTIAL DIAGNOSIS

Differential diagnoses for destructive radiolucent lesions with ill-defined borders presenting in a young adult can broadly be divided into infectious, reactive, and neoplastic processes. Within the category of infectious entities, osteomyelitis was considered. Gorham-Stout disease (GSD, or vanishing bone disease) was the primary reactive process included in our differential diagnosis. Possible neoplasms included histiocytic disorders, lymphomas, primary bone sarcomas, and metastatic malignancies.

Osteomyelitis, an inflammatory reaction of the medullary cavity and Haversian systems, can gradually extend to involve the periosteum and the overlying structures. It is typically caused by persistent bacterial foci, although primary idiopathic cases have been reported.[1] Osteomyelitis may be clinically staged as either acute (≤4 weeks) or chronic (>4 weeks), depending on the duration of symptomatology. Chronic osteomyelitis is further classified as either suppurative or nonsuppurative/sclerosing on the basis of clinical and radiographic findings. Maxillary osteomyelitis is rare, given the widespread availability of antibiotics and the excellent vascularity of the area; however, when it does occur, it is most often caused by either dental infections or sinusitis.[2] The mandible is more frequently involved compared with the maxilla because the former is less vascular, has thicker cortical plates, and has less abundant medullary outflow. Osteomyelitis is generally seen among those with underlying immunosuppression or a tendency for poor wound healing. In healthy individuals, such as our patient, osteomyelitis is an extremely uncommon infectious complication because intact host immunity is able to localize and limit disease spread by forming protective pyogenic membranes and abscesses.[3] The lack of dental caries or another clear source of infection in our patient also made this diagnosis less likely.

GSD is a rare idiopathic process whereby bone is replaced with vascular connective tissue.[4] Mild trauma

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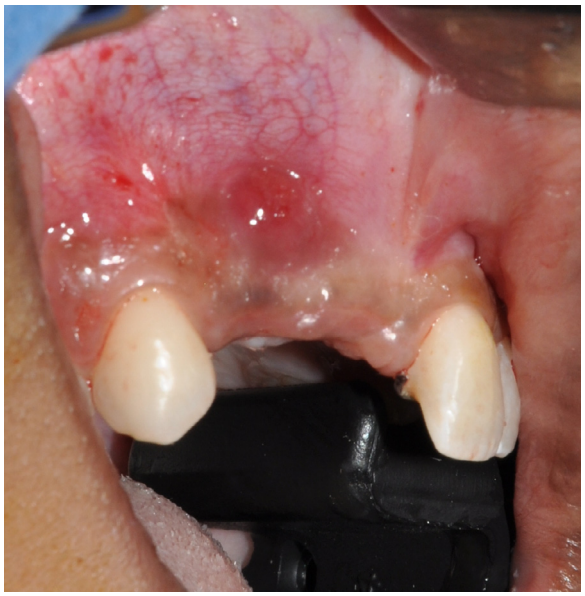

Fig. 1. Preoperative intraoral examination after extractions of teeth #7 and #8 by another provider.

has been proposed as an inciting event, although this hypothesis remains unproven. The natural course of GSD is unpredictable, and resorption may either be spontaneously arrested or continue until the affected bone completely disappears. To date, only a few hundred cases of GSD have been reported in the literature.[5] Young adults and adolescents are preferentially afflicted, although it is important to note that cases have been seen in all age groups. Even though the disease is almost always unicentric and confined to a single location, contiguous polyostotic involvement of adjacent bones is not uncommon. In roughly 30% of GSD cases, lesions are found in the maxillofacial skeleton, with the vast majority occurring in the mandible.[5] Isolated maxillary involvement has never been reported. Swelling may or may not be present, and although the osteolytic process itself is often painless, localized pain is a common presenting complaint. Similar to other osteolytic processes, progressive resorption can produce tooth mobility, new-onset malocclusion, soft tissue atrophy, and pathologic fracture.[6] The initial radiographic appearance of hypodense medullary foci resembles patchy osteoporosis.[7] With time, the mandibular bone loss deepens toward the inferior border to evenly flatten the alveolar ridge along the length of the involved segment. On the basis of our patient's age and clinical and radiographic presentations, a diagnosis of GSD was strongly considered. Prior pathology reports presented further evidence supporting this diagnosis because histologically lesions of GSD frequently present as inflamed vascular connective tissue.

Given the rapid, focal, and otherwise painless loss of periodontal attachment, a neoplastic process was given serious consideration. Histiocytoses were briefly considered in the differential diagnosis. Histiocytic diseases are characterized by accumulation of cells derived from the monocyte and macrophage lineages and are divided into three categories: dendritic cell disorders, macrophage-related disorders, and malignant histiocytic disorders. Currently, there is debate as to whether this family of conditions represents a reactive process or a true neoplastic process. The most common histiocytic disorder is Langerhans cell histiocytosis (LCH), which arises from clonal proliferation of Langerhans-type cells. Over half of LCH cases occur in children who are usually younger than 15 years of age. The extent of dissemination determines the clinical appearance. Most cases present with isolated bony involvement, with the jaws being involved 10% to 20% of the time.[8] Rosai-Dorfman disease (RDD) is a macrophage-related disorder, in which histiocytes accumulate both inside and, less commonly, outside of lymph nodes. Because the most commonly affected extranodal site is the head and neck region, this diagnosis was given some consideration in our case. It is estimated that 10% of RDD cases have intraosseous involvement, preferentially in the cranium and the long bones.[9,10] Primary involvement of the facial bones is uncommon and usually results from direct extension from the paranasal sinuses.[11] For both LCH and RDD, radiographic findings demonstrate nonspecific osteolytic changes that appear as well-defined or poorly defined punched-out lucencies.[10] The previous diagnosis of inflamed granulation tissue suggested that a histiocytic disease may have been overlooked microscopically; however, continued progression despite curettage argued against the diagnosis of a localized histiocytic disease.

Non-Hodgkin lymphoma (NHL) represents a group of lymphocytic malignancies that may originate in either lymph nodes or extranodal tissues. The most frequently affected oral sites are the buccal vestibule, palate, and gingiva. NHLs in these locations present as nontender masses, often with a boggy consistency.[12] When the jaws themselves are involved, lesions often present as ill-defined radiolucencies. Diffuse large B-cell lymphoma is the most common subtype to involve the oral cavity and represents approximately 60% of oral lymphoma cases. Primary osseous lymphomas are uncommon and account for 5% of all extranodal NHLs. NHLs of the jaws account for 13% of these primary osseous lesions, and the maxilla is more frequently involved compared with the mandible.[13] The appearance and symptoms of NHL almost always mimic those of an odontogenic infection or an inflammatory periodontal condition. Persistent inflammation despite adequate infectious source control usually prompts additional workup, which can provide significant information. Because of the challenges encountered, the formal diagnosis of periapical NHL is often

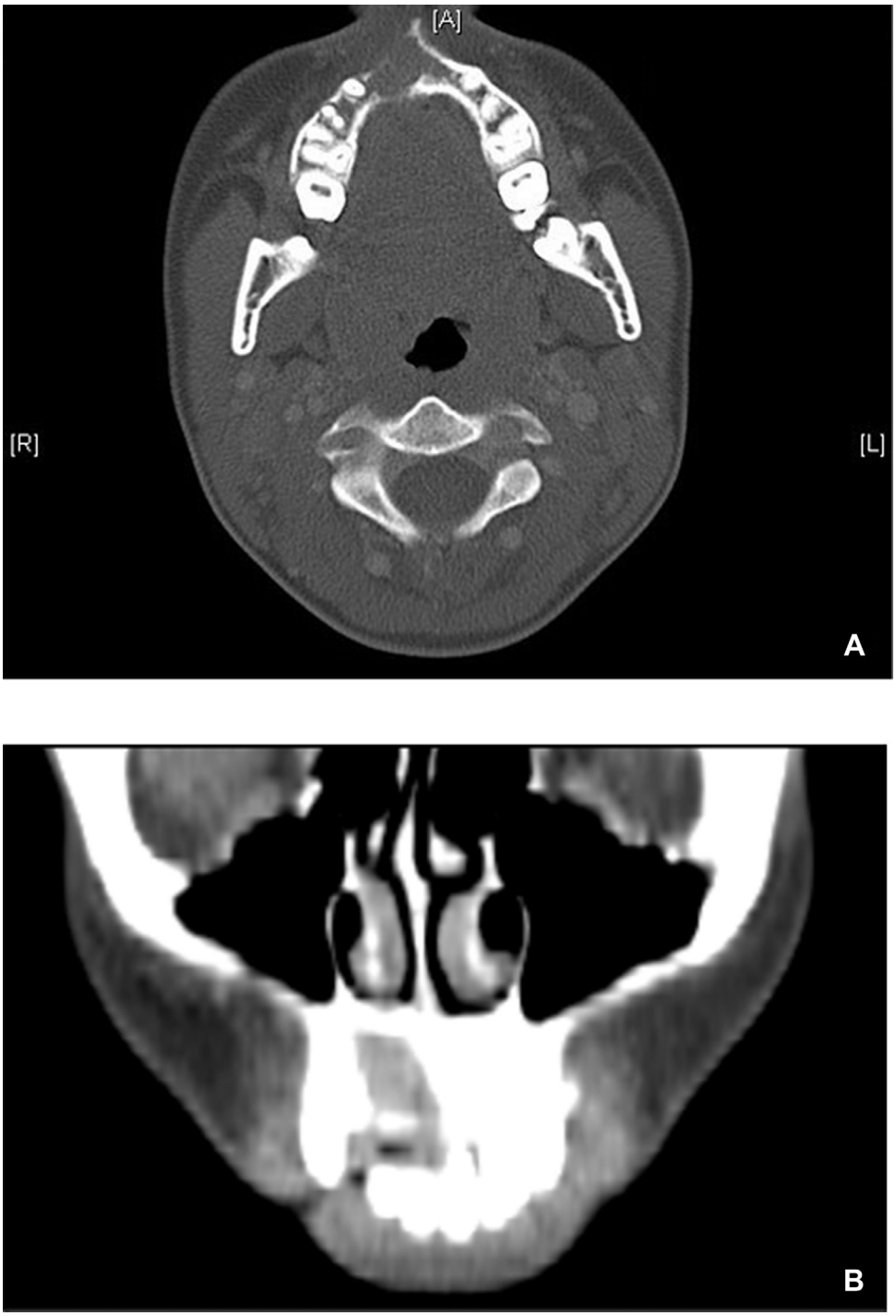

Fig. 2. Preoperative computed tomography (CT) scan without contrast, demonstrating an ill-defined radiolucency involving the right anterior maxilla **(A)** and its superior extent abutting the nasal floor **(B)**.

delayed by months.[14] In the setting of persistent osteolytic changes occurring after an atraumatic extraction in this case, lymphoma was considered in the differential diagnosis because it is known to mimic other infectious and inflammatory processes.

Sarcoma is the most common primary bone malignancy in the pediatric population. The peak age of incidence is 10 to 19 years, coinciding with puberty and the period of rapid bone growth. The most common primary pediatric bone sarcomas in the head and neck region are osteosarcoma, Ewing sarcoma, and chondrosarcoma.[15] Both osteosarcoma and chondrosarcoma demonstrate mixed density features on imaging, which were not found on our patient's CT scan. Ewing sarcoma

is an aggressive, small, round, blue cell tumor of unknown origin. The poorly differentiated cells have a lymphocytic appearance on microscopy, and Ewing sarcoma can be mistaken for lymphoma or osteomyelitis. Patients with Ewing sarcoma may also have signs and symptoms of an inflammatory systemic illness, further confounding the diagnosis. Roughly 85% of tumors carry the characteristic t(11;22) translocation. The mandible is preferentially affected as in other osseous head and neck sarcomas. Like lymphoma, Ewing sarcoma was considered in the differential diagnosis because of its ability to masquerade as other more common inflammatory conditions.

Breast, lung, thyroid, kidney, and prostate carcinomas are the most common tumors that metastasize to bone. Malignant cells travel via the hematogenous route to occupy hematopoietically active marrow spaces.[16] The maxilla and the mandible have comparatively less active marrow compared with other skeletal sites and, therefore, represent an uncommon destination for metastatic cancer. Still, the posterior mandible has been shown to contain hematopoietic marrow remnants. As a result, the mandible is 5 times more likely than the maxilla to present metastatic lesions. Given our patient's age, the unremarkable past medical and family histories, and the location of the lesion in the anterior maxilla, metastasis from an unknown primary malignancy was entertained but not deemed likely.

DIAGNOSIS AND MANAGEMENT

Previous histologic specimens were retrieved and reviewed at our institution. On low-power magnification, a diffuse acute and chronic mixed inflammatory infiltrate with numerous histiocytes, not unlike that of a typical periapical granuloma, was observed (Figure 3A). Upon higher magnification and careful inspection, it was noted that some histiocytes were unusually large and showed emperipolesis (Figure 3B). Immunohistochemical staining found that these histiocytes were S-100 positive and CD-1a negative (Figure 4). A diagnosis of RDD was rendered on the basis of these microscopic findings. Abdominal and neck CT ruled out the presence of additional lesions.

Because multiple prior attempts at curetting the maxillary lesion had failed to prevent localized progression, a partial maxillectomy was performed with 1.5- to 2-cm margins (Figure 5A). After resection, an immediate temporary prosthesis was secured with bone screws and interdental wires to obturate the maxillary defect (Figure 5B). Chemoradiation was deferred, given the localized findings and clear surgical margins. Follow-up examination demonstrated well-healed mucosa with an anterior communication into the right maxillary sinus and nasal passage (Figure 6). A definitive maxillary obturator was designed to replace the immediate prosthesis and span

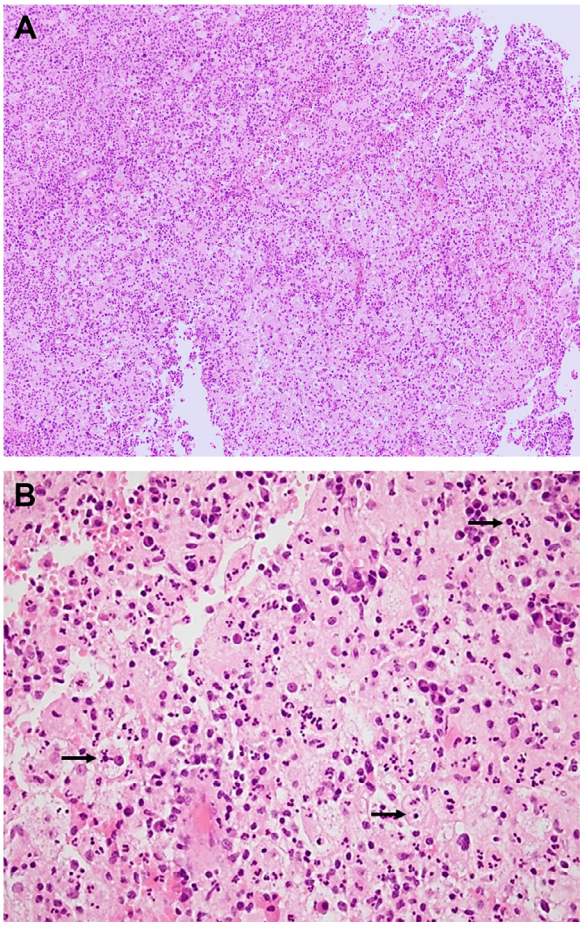

Fig. 3. **A,** Medium-power photomicrograph showing acute and chronic mixed inflammatory infiltrate (hematoxylin and eosin [H&E], original magnification × 100). **B,** High-power photomicrograph showing emperipolesis *(arrow)* (H&E, × 400). *A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM05688.*

the final Brown Class IIa maxillary defect. Three years after resection, our patient continues to remain disease free, with no clinical or radiographic recurrence. Although she functions well and maintains excellent oral hygiene with the maxillary obturator, she has expressed interest in future autologous reconstruction.

DISCUSSION

RDD is an extremely rare benign non−Langerhans cell histiocytic disorder of unknown etiology. It is characterized by significant but painless bilateral cervical lymphadenopathy that results from exuberant histiocytic proliferation and that may be accompanied by constitutional symptoms and elevated inflammatory markers. There appears to be a slightly higher prevalence rate in males, with symptoms typically appearing during the first 2 decades of life.[17] The lesions of RDD are histologically distinguished by the presence of enlarged

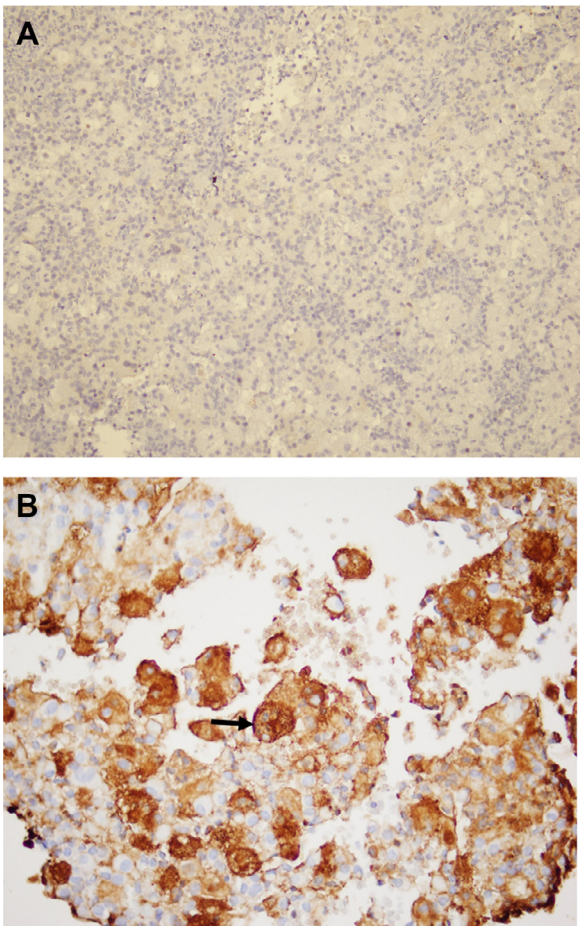

Fig. 4. Immunohistochemical staining demonstrating S-100 positive **(A)** CD-1 a negative **(B)** specimen (× 200). *A high-resolution version of this slide (part a) for use with the Virtual Microscope is available as eSlide: VM05689.*

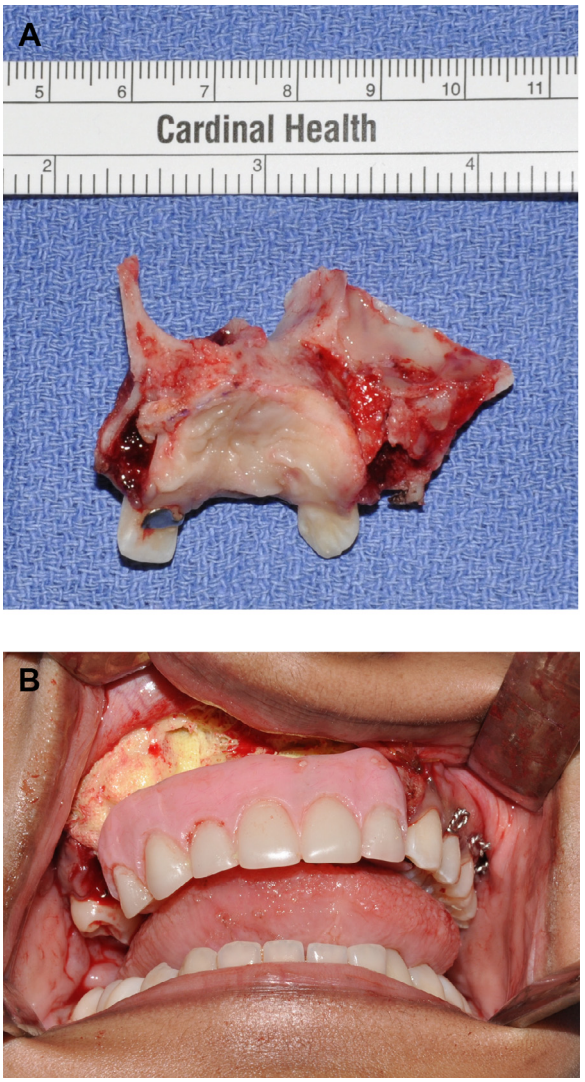

Fig. 5. Final surgical specimen **(A)**, with immediate obturator spanning a Brown Class IIa defect **(B)**.

histiocytes containing neutrophils and lymphocytes within their cytoplasm—a finding termed *emperipolesis*. As with LCH, immunohistochemical staining is positive for S-100 and CD68; however, the histiocytes in RDD are uniquely negative for CD-1a.[18]

RDD follows a variable and unpredictable course. Foucar et al. reported that approximately 70% of patients experienced permanent but stable disease, 20% experienced spontaneous and permanent remission, and 10% experienced progressive generalized disease.[19] Primary oral involvement in the absence of nodal or extraoral disease, as in the present case, makes for a challenging and often delayed diagnosis. Biopsy with histopathologic and immunoreactivity analyses remains the most appropriate approach to definitively diagnosing RDD. Because multifocal lesions are possible, it is important to assess for involvement of other sites when RDD is diagnosed. CT and magnetic resonance imaging are helpful in detecting disseminated lesions, and the addition of positron emission tomography may increase detection sensitivity.[20] However, the manifestations seen on imaging are largely nonspecific.[11]

The treatment of RDD lesions is case dependent, and conservative management is generally recommended, when possible.[21] Surgical resection, chemotherapy, radiation, and immunosuppression all have been shown to be effective. Localized RDD nodal lesions without vital organ involvement have shown propensity to spontaneously resolve with either observation only or treatment with corticosteroids.[22,23] However, intraosseous lesions have a chronic course and appear less likely to self-resolve, thus requiring more intensive treatment.[10] Surgical enucleation or resection should be considered in localized cases of significant nodal or extranodal disease extending to vital organs. Radiotherapy, either alone or as adjuvant therapy, has shown some benefit, whereas the optimal chemotherapy regimen is the subject of

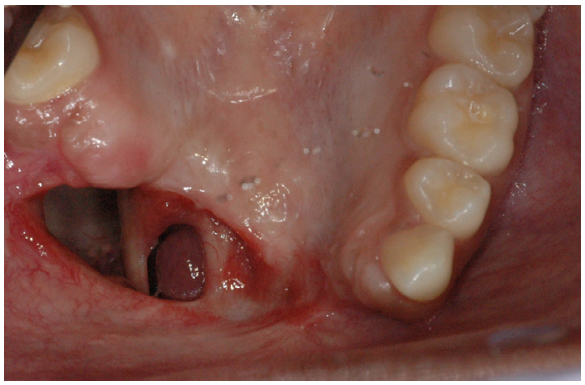

Fig. 6. Postoperative follow-up.

limited evidence and conflicting reports.[20,24] The prognosis for solitary bone lesions is typically excellent, and recurrences are generally limited. Foucar et al.[25] found that involvement of the oral cavity may be associated with a relatively unfavorable prognosis; however, all of their patients exhibited oral disease in association with disseminated nodal and extranodal involvement. Refractory or widely disseminated multifocal disease has a guarded prognosis and requires systemic therapy with corticosteroids, rituximab, interferon, retinoids, or chemotherapeutics, such as vinca alkaloids, anthracyclines, alkylating agents, methotrexate, cladribine, and clofarabine.[18]

CONCLUSIONS

RDD is a rare, but important, condition that clinicians should consider in their differential diagnoses, especially in younger patients presenting with ill-defined or poorly resolving radiolucent lesions of the jaws. Because of the infrequent occurrence of RDD, diagnosis is often delayed, and this may potentially lead to poorer long-term outcomes.

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