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CLINICAL PATHOLOGIC CONFERENCE CASE 2: GINGIVAL ULCER IN A 34-YEAR-OLD MAN

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Clinical Presentation: The patient, a 34-year-old Caucasian male, was referred for diagnosis because of a slightly painful swelling in the right posterior maxillary gingiva that had started 2 months previously. The clinical history revealed that his dentist had performed periodontal and endodontic treatments in the right maxillary second molar, but no improvement was seen. Subsequently, extensive mobility of the right maxillary second molar was noted, and tooth extraction was performed. However, after 17 days, there was no healing of the socket. The medical history otherwise was unremarkable. No changes were observed during the extraoral examination. On intraoral examination, an ulcerated nodular and painful lesion, which showed hard and elevated edges, was noticed (Figure 1). No important bone abnormalities, other than the area corresponding to recent tooth extraction, were observed on panoramic radiographic examination. In addition to this, there was a band of mild erythema involving the free buccal gingival margin of the anterior mandibular teeth, which was associated with minimal gingival plaque (Figure 2).

Differential Diagnosis: The clinical differential diagnosis of a painful swelling associated with an extraction socket is extensive. The lack of response to the conventional treatments may indicate that the condition was longstanding and was recently exacerbated by the tooth extraction, leading to the present clinical presentation. It is also possible that this was a recently developed condition, unrelated to previous dental complaints. Because of presenting the nonspecific signs and symptoms described above, the differential diagnoses included reactive, neoplastic, and infectious conditions, which are listed below. In this case, the panoramic radiograph was unremarkable, which excluded lesions associated with the maxillary sinus.

Pyogenic granuloma is a hyperplastic growth of granulation tissue that sometimes arises postsurgically from a dental extraction socket, as a reaction to bony sequestra.[1] This postsurgical lesion can be misdiagnosed with lesions of similar appearance, such as herniation of either an antral polyp[2] or the maxillary sinus.[3] Although these lesions were considered in the differential diagnosis, the extension of the lesion up to the second premolar area was somewhat unusual.

Malignant neoplasms, including lymphoma or leukemia, metastatic disease, primary or secondary carcinoma, and soft and hard tissue sarcoma, were given serious consideration in the differential diagnosis. Non-Hodgkin lymphoma (NHL) develops more commonly in the lymph nodes but can also appear as extranodal disease that involves oral soft tissues or bone. Clinically, oral lesions of NHL can simulate inflammatory conditions, such as an endodontic lesion[4,5] or periodontal disease,[6] and can present as an exophytic mass associated with an extraction socket.[7] An uncommon subtype of NHL, plasmablastic lymphoma (PBL), shows marked tendency to present as extranodal lesions in the oral cavity. Although PBL is strongly

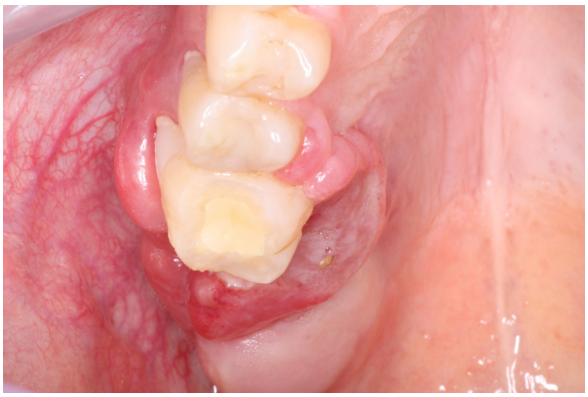

Fig. 1. Ulcerated gingival lesion, with hard and elevated edges.

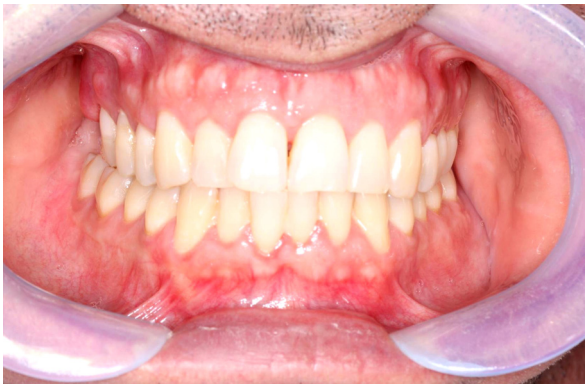

Fig. 2. Mild erythema involving the free buccal gingival margin of the anterior mandibular teeth.

associated with human immunodeficiency virus (HIV) infection, it has also been reported in HIV-negative patients.[8] Human herpes virus type 8 and Epstein-Barr virus (EBV) have been reported in association with PBL in patients with acquired immunodeficiency syndrome (AIDS).[9] In a similar way to NHL, leukemia may also present clinically as a painful, nonhealing tooth extraction socket.[10]

Metastatic tumors to the oral cavity are uncommon and may mimic reactive lesions clinically. The initial presenting symptoms include pain, swelling, and loosening of teeth that lead to tooth extraction.[11,12] Although there was no history of malignant melanoma in this patient, metastatic malignant melanoma was considered in the differential diagnosis due to the patient's age and clinical presentation of a nonhealing extraction site and associated soft tissue mass. Squamous cell carcinoma was also considered because it may mimic localized periodontal disease or an endodontic−periodontal lesion,[13,14] with fast growth after tooth extraction. Sarcomas arising within the oral cavity are rare and often present with swelling, variable pain, and loosening of teeth mimicking inflammatory or infectious processes.[15]

Other potential, but less likely, lesions, including benign soft tissue tumors, were also considered in the differential diagnosis. Central leiomyoma is very rare and can arise in association with a maxillary tooth socket,[16] similar to the situation that occurred in the current case. Odontogenic tumors were also considered, not only because of their location but also because they may simulate periapical or periodontal lesions leading to tooth extraction and subsequently a nonhealing socket associated with the development of swelling.[17]

With regard to infectious diseases, paracoccidioidomycosis, which is endemic in Brazil and is caused by *Paracoccidioides brasiliensis,* was included in the differential diagnosis. This deep mycosis occurs more commonly in middle-aged male patients. Oral manifestations are frequent, and the gingiva and palate are the most commonly affected sites. The lesions are usually multiple and painful. The oral lesions may appear after extraction of periodontally involved teeth.[18,19] Tuberculosis (TB) is a chronic infectious granulomatous disease caused by *Mycobacterium tuberculosis.* It is also endemic in Brazil. Oral lesions of TB, although uncommon, may appear as chronic ulcers and nodular or granular lesions and can involve extraction sites.[20]

Furthermore, the presence of the previously mentioned gingival band of erythema required consideration. Although this may represent plaque-related marginal gingivitis, linear gingival erythema was also considered, thus calling into question the patient's immune status.

Diagnosis and Management: An incisional biopsy was performed with the patient under local anesthesia, and the specimen was sent for histopathologic analysis. At low-power microscopic view, a mass of monotonous cells were observed adjacent to epithelial tissue that covered the oral mucosa. High-power microscopic view showed neoplastic cells with round to oval vesicular nuclei, amphophilic and prominent nucleoli, and slight basophilic cytoplasm. Atypical mitoses were frequently found. Tingible-body macrophages were commonly found, imparting a starry-sky appearance (Figure 3, A). Immunohistochemical reactions were performed, and the tumor cells showed strong positivity for CD45, CD138, MUM-1, and vimentin, in addition to focal positivity for CD79a. Over 90% of the tumor cells were positive for Ki-67 (Figure 3, B−E). In addition, EBV was strongly positive as shown by in situ hybridization using an EBV-encoded small nuclear RNA (EBER)-1/2 probe (Figure 3, F). According to these histopathologic and immunohistochemical features, the diagnosis of oral plasmablastic lymphoma was established (Table I).

The patient was referred to a hematologist-oncologist, and several examinations, including HIV serologic test, computed tomography (CT), and positron emission tomography with 2-deoxy-2-(fluorine-18) fluoro-D-glucose integrated with computed tomography (PET/CT), were requested. CT revealed a large hypodense lesion infiltrating the adjacent soft tissue, maxillary sinus, and nasal cavity. Extensive maxillary destruction was also observed. PET/CT demonstrated a high metabolic activity only in the right maxillary region. No tumor activity was noted in other sites on the PET/CT (Figure 4). At the time of diagnosis, the patient's disease was in stage I. The serologic test revealed HIV infection, and the patient was referred to an infectologist. A CD4 positive count showed 142 cells/mm^3 and a viral load of 3597 copies/mL. Highly active antiretroviral therapy (HAART) was initiated 1 month after the initial evaluation, and during this period, there was extensive tumor growth, which caused displacement of the first molar (Figure 5).

With HAART treatment, the tumor stopped growing, and chemotherapy was started with infusion of rituximab in association with etoposide, vincristine, doxorubicin, cyclophosphamide, and prednisone (EPOCH). After the first cycle of chemotherapy, there was significant tumor involution, with slight fibrosis and residual ulcerated area. The oncologic treatment was concluded after six cycles of chemotherapy, which resulted in complete clinical tumor resolution (Figure 6). PET/CT confirmed complete tumor remission (Figure 7). The patient has remained under