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Letter to the Editor

Challenging diagnoses in oral ulcers with large atypical CD30+ cells: EBV-positive mucocutaneous ulcer differentials

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TO THE EDITOR

Ikeda T *et al* (2019)[1] recently published an article about EBV-positive mucocutaneous ulcers (EBVMCU) in the *Journal of Clinical and Experimental Hematopathology*. The authors explained many clinical and pathological aspects of this disease which pathologists must be attentive to during their diagnostic routine. At the end of the article,[1] the authors pointed out that clinicians and pathologists need to be able to distinguish EBVMCU from lymphomas, especially classic Hodgkin lymphoma, because of the Reed-Sternberg cells with positivity for CD30. Although malignancies are important, we must not forget benign lymphoproliferations that may be a differential diagnosis for EBVMCU. The oral cavity is a good example to discuss benign and malignant differentials for EBVMCU. To that end, we wrote this letter and used two real examples of our diagnostic routine.

The diagnosis of ulcerative lesions affecting the oral mucosa is usually difficult because different processes may share a similar clinical appearance, such as infectious disorders, autoimmune diseases and tumors, especially oral squamous cell carcinoma.[2] In this context, a biopsy may be necessary to rule out a neoplasm. Microscopically, the occasional observation of large atypical lymphoid cells could represent a lymphoproliferative disorder. Although rare, accounting for 5% of all head and neck malignancies,[3] oral lymphomas should be included in the differential diagnosis of ulcerative lesions of the oral cavity.

The images shown in Figure 1 (A-F) are from a 50-year-old woman with a gingival ulcer on the edge of an implanted tooth. The patient's medical history was remarkable, as she had systemic lupus erythematosus. There was no lymphadenomegaly and PET-CT was negative at the onset of the ulcer. A biopsy was performed and showed a granulation tissue under the ulcerated mucosa associated with an inflammatory infiltrate consisting of small lymphocytes, eosinophils and plasma cells. A dense and diffuse lymphoid proliferation with atypical large cells often with Hodgkin/Reed-Sternberg (HRS) cell-like morphology was also observed below the epithelium. These cells were strongly positive for CD30, LMP-1 and CD20 and negative for CD15. The ulcer regressed spontaneously in three months. On the basis of the history, clinical examination, immunohistochemistry with LMP-1 positivity and good outcome, a final diagnosis of EBV-positive mucocutaneos ulcer (EBVMCU) was made.

Figure 1 (G-L) represents ulcers on the tongue sides of a 30-year-old man, with periods of improvement and worsening, and a history of traumatic tongue bite. Histologically, there was a polymorphous inflammatory infiltrate with a considerable number of eosinophils, with few lymphocytes and neutrophils, in addition to a population of atypical large mononuclear cells with large nucleoli extending to the deeper muscle fibers and nerves. Immunohistochemistry showed a T cell population greater than the B cell population, and CD3+ cells were also CD4+. Occasional large CD30+ cells were also observed. These cells were LMP-1 and EBER-ISH negative. The lesion improved after treatment with dental guard to avoid persistent mucosal trauma. The diagnosis was an eosinophilic ulcer of the oral mucosa (EUOM).

EBVMCU is recognized as a clinicopathological entity in the last WHO classification of hematological malignancies,[1,4] with Hodgkin-like features and a self-limited indolent course, generally responding well to conservative management, and associated with iatrogenic immunosuppression or age-related immunosenescence.[1,4] EUOM is a rare self-limited oral condition, best regarded as a reactive pattern of unclear etiology, although a local traumatic event has been often incriminated.[2]

Both entities manifest themselves as an oral ulcer and the observation of large CD30+ cells could simulate an oral lymphoma, such as CD30+ primary cutaneous lymphoproliferative disorders,[2] and Hodgkin lymphoma[5] (Table 1). As there are similar histologic and clinical features, EUOM and EBVMCU have to be possible diagnosis in this context, and the combination of clinical, morphologic and immunophenotypic parameters is imperative to reach the correct diagnosis, thus avoiding aggressive and iatrogenic treatments.

When comparing the two cases, we observe that the morphological aspects are very similar to each other, and the differential diagnosis of malignancy is quite important. Immunohistochemistry is a useful tool, but its interpretation needs to be combined with a careful clinical history. Increasingly, pathologists and clinicians need to act together for a more accurate diagnosis of patients. In the case of oral lesions, dentists are important allies as well. With these cases, we show that, in addition to malignancies, EBVMCU also has a differential with benign lesions, for example, non-infectious conditions as we discussed in the second case. Thus, we believe that our letter adds information to the article

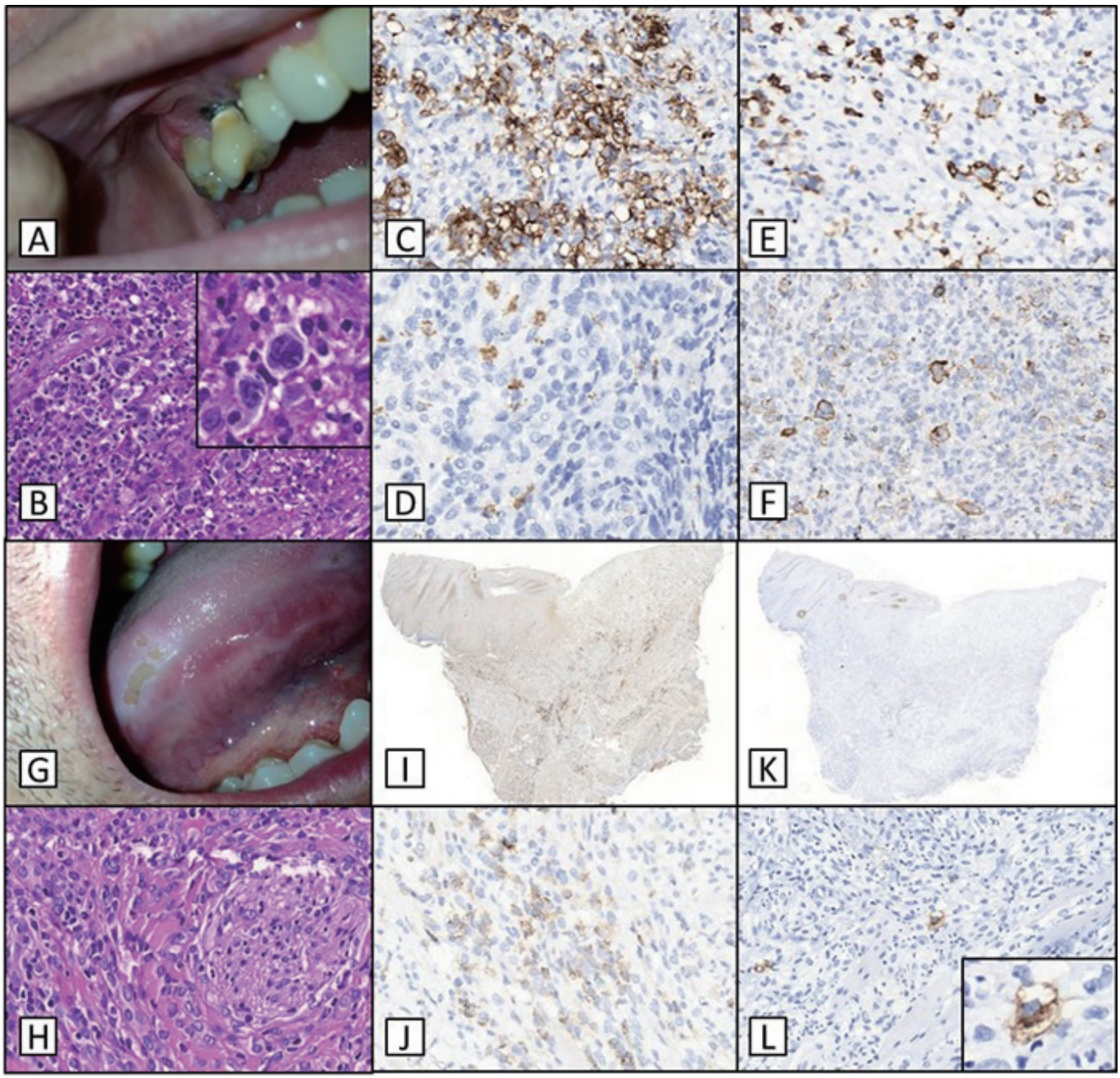

Fig. 1. ***A***, Gingival ulcer on the edge of an implanted tooth of a 50-year-old woman. ***B***, Dense and diffuse lymphoid proliferation with atypical large cells with Hodgkin/Reed-Sternberg (HRS) cell-like morphology (H&E,400x). ***C***, HRS-like cells showing CD30+ (IHC,400x). ***D***, HRS-like cells showing CD15- (IHC,400x). ***E***, HRS-like cells showing CD20+ (IHC,400x). ***F***, HRS-like cells showing LMP1+ (IHC,400x). ***G***, Ulcers on the tongue of a 30-year-old man. ***H***, Population of atypical large mononuclear cells extending to the deeper muscle fibers and nerves (H&E,400x). ***I***, T cell population CD3+ (IHC,20x). ***J***, B cell population CD20+ (IHC,400x). ***K***, T cell population CD4+ (IHC,20x). ***L***, Scattered population of large CD30+ cells (IHC,400x). H&E=hematoxylin and eosin. IHC=immunohistochemistry.

Table 1. Differential diagnosis of CD30+ atypical cells in oral mucosa

CD30+ lymphoproliferative disorders	Oral involvement of anaplastic large T-cell lymphoma (ALCL) Oral involvement of lymphomatoid papulosis (LyP) Classical Hodgkin lymphoma
Reactive inflammatoy disorders	Eosinophilic ulcer of the oral mucosa (EUOM) EBV-positive mucocutaneos ulcer (EBVMCU)

of Ikeda *et al* (2019),[1] improving clinical and pathological reasoning when faced with these challenging diseases.

CONFLICT OF INTEREST

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