Clinicopathological and immunohistochemical analysis of 19 cases of oral eosinophilic ulcers

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Objective. The aim of this study was to describe the clinicopathological and immunohistochemical features of 19 cases of oral eosinophilic ulcers and discuss the hypothesis that this entity could represent a spectrum of the $CD30^+$ lymphoproliferative disorder.

Material and Methods. Clinical data concerning gender, age, affected site, and clinical presentation of 19 patients were collected and a broad immunohistochemical panel was carried out. Eosinophil distribution in relation to muscular tissue was evaluated using an Aperio ScanScope CS scanner.

Results. The mean age of the patients was 58.6 years, with a male preponderance. A single painful ulcer in the tongue was the most common clinical presentation. There was no predilection of eosinophils for surrounding muscular fibers because this population was equally distributed in areas adjacent to and distant from these structures. The inflammatory infiltrate was mainly formed by cytotoxic T lymphocytes and CD30 expression was not limited to large atypical cells; it also stained small reactive lymphocytes.

Conclusions. Considering the clinical, histopathological, and immunohistochemical characteristics, oral eosinophilic ulcers must be considered a self-limiting reactive condition. (Oral Surg Oral Med Oral Pathol Oral Radiol 2013;115:532-540)

Eosinophilic ulcers of the oral mucosa are lesions with rapid onset that may persist for some weeks before spontaneous regression.[1,2] These ulcers were first described in adults by Popoff in 1956 and first recognized as an independent entity in 1970 by Shapiro and Juhlin, although a similar condition restricted to the infant population had already been clinically described years before by Riga (1881) and microscopically by Fede (1890) and was later accepted as a spectrum of the adult eosinophilic ulcer.[2,3]

Different terms including traumatic granuloma of the tongue, eosinophilic ulcer of the tongue, and traumatic granuloma with stromal eosinophilia have been used in the literature to describe this entity, most of them highlighting the involvement of the tongue, which is by far the most frequently affected site.[2,4] Trauma has been suggested to be the cause of this eosinophilic ulceration, but the exact pathogenic mechanisms remain obscure.[5]

Oral eosinophilic ulcers are characterized by an intense reactive inflammatory infiltrate with abundant eosinophils that deeply extends to involve muscular fibers.[1,5] Large atypical cells may also be scattered and have been shown to be positive for CD30 antigen, suggesting that eosinophilic ulcers would, in fact, represent a spectrum of the $CD30^+$ lymphoproliferative disorders affecting the oral cavity.[5-7] Although several studies have investigated this hypothesis, most have been limited to individual case reports, whereas only a few small series have been conducted with this purpose.[5,7-9] Therefore, we herein describe the clinicopathological and immunohistochemical features of 19 cases of eosinophilic ulcers affecting the oral mucosa to better understand the main characteristics of this entity.

MATERIAL AND METHODS

A 15-year retrospective review for the period from 1998 to 2012 was performed for the files of the Department of Oral Diagnosis (Oral Pathology) at the University of Campinas (Piracicaba Dental School, Brazil) and all cases diagnosed as eosinophilic ulcers or any of its synonyms were retrieved. Clinical informa-

Statement of Clinical Relevance

Oral eosinophilic ulcers have been suggested to represent a spectrum of $CD30^+$ lymphoproliferative disorders. Herein, the authors investigate their clinicopathological and immunohistochemical features and suggest that this entity should be considered a reactive local process.

This study was presented in part at the 16th Meeting of the International Association of Oral Pathologists, 20th Congress of the Brazilian Society of Oral Pathology and Medicine, São Pedro, Brazil, July 2012.

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Table I. Antibodies used in the immunohistochemical analysis

Antibody	*Clone*	*Source*	*Dilution*	*Antigen retrieval*
CD3	Polyclonal	Dako	1:300	Citrate buffer (pH 6.0); 3 minutes of pressure-cooking
CD8	C8/144B	Dako	1:100	Citrate buffer (pH 6.0); 3 minutes of pressure-cooking
Granzyme B	GrB7	Dako	1:50	EDTA/Tris (pH 9.0); 40 minutes of water bath
CD20	L26	Dako	1:1.000	Citrate buffer (pH 6.0); 3 minutes of pressure-cooking
CD68	PG-M1	Dako	1:400	Citrate buffer (pH 6.0); 3 minutes of pressure-cooking
Mast cell	AA1	Dako	1:10.000	Citrate buffer (pH 6.0); 3 minutes of pressure-cooking
Plasma cell	VS38c	Dako	1:200	Citrate buffer (pH 6.0); 3 minutes of pressure-cooking
Myeloperoxidase	Polyclonal	Dako	1:5.000	Citrate buffer (pH 6.0); 3 minutes of pressure-cooking
CD34	QBEnd10	Dako	1:50	Citrate buffer (pH 6.0); 3 minutes of pressure-cooking
Desmin	D33	Dako	1:800	Citrate buffer (pH 6.0); 3 minutes of pressure-cooking
CD30	Ber-H2	Dako	1:500	EDTA/Tris (pH 9.0); 40 minutes of water bath

tion including gender, age, affected site, clinical presentation, symptomatology, and evolution was collected from the patients' charts. The diagnoses were then confirmed by 2 independent oral pathologists by reviewing the original 5-μm histologic sections stained with hematoxylin and eosin.

Immunohistochemistry was performed following the methods of Andrade et al.[10] Table I depicts the antibodies, dilutions, and antigen retrieval methods used. Briefly, the reactions were conducted in 3-μm sections of the original formalin-fixed, paraffin-embedded tissues that were dewaxed with xylene and then hydrated in an ethanol series. The antigen retrieval was performed and the endogenous peroxidase activity was blocked using 10% hydrogen peroxide in 5 baths, each of 5 minutes. After being washed in phosphate-buffered saline (pH 7.4), slides were incubated overnight with primary antibodies. All slides were subsequently exposed to avidin–biotin complex and horseradish peroxidase reagents (LSAB kit; DakoCytomation, Glostrup, Denmark) and diaminobenzidine tetrahydrochloride (Sigma, St. Louis, MO) and subsequently counterstained with Carazzi hematoxylin. Adequate positive control sections were used for each antibody, and the negative control was obtained by omitting the primary specific antibody. Semiquantitative analysis of the immunohistochemical reactions, adapted from the methods of Lo Muzio et al.,[11] was carried out by 2 independent observers. Considering the whole inflammatory infiltrate, cases with no reactivity were defined as negative; those showing reactivity <30% of the infiltrate as weak positive; those showing reactivity from 30% to 50% as moderate positive; and those showing reactivity in more than 50% of the infiltrate as strong positive. In cases of disagreement, the observers discussed the findings and performed the final evaluation. Because of the staining pattern of CD34 and desmin, a descriptive analysis was performed for these markers.

For quantitative analysis and distribution of the eosinophils, hematoxylin and eosin–stained slides were scanned using an Aperio ScanScope CS scanner (20× magnification; Aperio Technologies Inc., Vista, CA). Four areas of 70 mm^2 each were randomly selected, 2 containing at least 1 evident muscular fiber and 2 distant from muscles and from the lesion surface. Of the 19 cases, 9 offered adequate tissue to be analyzed in the four areas analyzed. Eosinophils present in 4 areas analyzed were counted and the results were submitted to statistical analysis using the *t* test at 5% significance (version 5.0, GraphPad Prism, La Jolla, CA, USA).

The current study was approved by the Ethical Committee of Piracicaba Dental School, State University of Campinas.

RESULTS

In the 15-year investigation period, 19 cases consistent with the diagnosis of oral eosinophilic ulcer were retrieved. Table II summarizes the main clinical features observed. A slight male preponderance was noted (1.3:1), with the age ranging from 35 to 84 years old with a mean of 58.6 years. The tongue was involved in 14 of 19 cases, especially the dorsum and lateral borders (Figure 1); other sites included the palate, floor of the mouth, gingiva, and lip (Figure 2). Pain was reported by most patients and a variable duration ranging from 2 to 48 months was reported. With the exception of 1 case who appeared with 2 intraoral ulcers, all other cases were characterized by a single ulceration commonly showing elevated borders and a yellowish central area that, depending on the affected location, raised different diagnostic hypotheses (Table II). Only in 7 of 19 cases (36.8%) was a possible traumatic factor identified, and no patient reported skin lesions (a clinical feature that can be observed in cases consistent with $CD30^+$ lymphoproliferative disorders) or recurrences during the follow-up period.

Microscopically, most cases appeared with a superficial fibrinopurulent membrane covering the ulcerated areas. An intense inflammatory infiltrate composed mainly of lymphocytes and scattered plasma cells, mast cells, and macrophages could be observed in all cases (Figure 3, A). Characteristically, the inflammatory in-

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