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Morphology, Clinical Aspects, and Treatment of Patients with Oral Manifestations of Erythema Multiforme: Case Series

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ABSTRACT

Introduction: Erythema multiforme (EM) is a bullous, ulcerative mucocutaneous condition with acute onset, characterized by symmetrically distributed lesions on the extremities and trunk, and it is self-limited. Approximately 70% of patients with erythema multiforme present oral lesions. The lesions may assume a wide range of clinical aspects, which may represent a diagnostic challenge. This study aimed to survey the cases of EM seen in the Stomatology Clinic and the Oral Diagnosis Center of the Dentistry Course of the Federal University of Espírito Santo, and to report the disease features and its treatment options.
Material and Methods: a search for patients clinically diagnosed with EM in the last 10 years in the registry files of the Oral Diagnosis Center was performed.
Results: six patients were initially selected; three were excluded from the study because the clinical presentations were incompatible with EM. The three studied patients were male, two adults and one child, who presented oral ulcerations and encrusted lesions, mainly located on the lips, oral mucosa, hard and soft palate, with 2 to 5 recurrences episodes.
Conclusion: three patients with oral manifestations of EM were selected. Oral lesions, composed of shallow erosions and ulcerations with irregular borders, edematous and cracked lips, bleeding, and encrusted lesions were the most common manifestations. No specific EM treatment is available and corticosteroids are still the most efficient drugs used.
Keywords: Erythema Multiforme; Pathology; Mouth Diseases; Mucocutaneous Diseases.

Introduction

Erythema multiforme (EM) is an acute onset, self-limited, bullous, ulcerative condition affecting the skin and/or mucous membranes, including the oral cavity[1-3]. The term "multiforme" refers to the variety of clinical features that lesions present and may change from patient to patient, as well as within a single patient, during disease progression[4-6].

The classic cutaneous lesion of EM is a target- or iris-shaped lesion characterized by concentric erythematous rings separated by rings of nearly normal color, ranging from 2 to 20 mm in size Oral lesions present as diffuse, widespread macules that progress to blisters and ulcerations[5,7].

When lesions involve only one mucosa site and are associated with skin lesions symmetrically distributed on the extremities, the EM is classified as minor. When it involves two or more mucosal sites, with variable cutaneous involvement, it is classified as major EM[5,8,9].

Erythema multiforme is a consequence of immunocomplex-related mechanisms involving antigen-antibody reactions that target small blood vessels in the skin or mucosa. In most cases, the precipitating event is infection-related[5,8].

Infection with herpes simplex virus (HSV) is identified as the most common cause of EM, but other infectious agents such as Mycoplasma pneumoniae, hepatitis C virus, Coxsackie virus, and Epstein Barr virus can also trigger EM, particularly in children. Regarding herpes simplex, EM is more often caused by HSV-1 than HSV-2 and can determine recurrent episodes of EM after periodic herpetic reactivation[6,10-15]. Recently EM triggered by COVID-19 has also been described[16].

The EM diagnosis is usually clinical. Some conditions are considered in the differential diagnosis, particularly autoimmune vesiculobullous diseases such as pemphigus vulgaris, bullous pemphigoid or paraneoplastic pemphigus, urticaria and Stevens-Johnson Syndrome (SJS). In some cases, biopsies and laboratory tests may help reach the final diagnosis[4,5,8,12,17].

The therapeutic approach should be based on the EM severity. Usually, EM shows a self-limited course, with complete healing of the lesions between 3 to 6 weeks. Treatment involves determining and controlling the etiology, and subsequently treating the possible infection or discontinuing a causative drug. Corticosteroids are the most commonly used

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medications, however, antivirals may be an option when a viral agent is detected as the triggering event[4,5,8,10,14,17,18].

This study aimed to survey the cases of EM diagnosed at the Oral Diagnosis Center (NDB) and related academic disciplines of the Dentistry Course of the Federal University of Espírito Santo (UFES), to report disease features and possible treatments.

Material and Methods

This is a descriptive, case series study. For the literature review, a search was conducted from the digital databases PubMed, Bireme, and Google Academic, in Portuguese and English languages, using the terms: "Erythema Multiforme" and "Oral Erythema Multiforme". Case reports, narrative literature review articles, clinical studies, and systematic literature reviews were selected.

First, a search was conducted, looking for the records of patients with a clinical diagnosis of EM in the last 10 years (2011 to 2021). Patients who attended the extension project of care to the population with oral lesions (Oral Diagnosis Center – NDB), as well as those diagnosed in the related disciplines of Stomatology and Interdisciplinary Clinical Internship I of the Dentistry Course - UFES. Then, a similar search was carried out in the archives of the Oral Pathological Anatomy Service, looking for patients with histopathological diagnoses of EM. The patients' files and dental records were then retrieved, when available, to collect data about the patients and their lesions, such as gender, age, lesion location, duration of symptoms, initial complaints, medications in use, previous infections, number of recurrences, treatment, and current condition. In addition, photographic documentation available in the NDB archives was used. Patients were contacted by telephone to report their health conditions at the current time.

Analyzing clinicopathological information as well as the literature articles, cases that did not meet the criteria for EM were excluded. Exclusion criteria were: non-characteristic or absent cutaneous lesions in the presence of oral lesions with a clinical presentation or histopathological features suggestive of other diseases.

All procedures were carried out following ethical requirements and the present study was approved by the local Ethics Committee (HUCAM-UFES) under the number 5.136.596.

Results

Six patients with a diagnostic hypothesis of EM were initially included. Of these, three were excluded from the study because of the clinical presentation or histopathological results, which were not characteristic of EM. Considering selected cases, three were included in the study, diagnosed as EM based on clinical features and cytopathological or histopathological results.

Case 1

A 30 years-old male patient with a complaint of sore lesions in the palate and lips reported that the lesions appeared one month ago and the episode lasted for two weeks. After that, the lesions regressed but returned with pain. His medical history revealed controlled hypertension and hypothyroidism, controlled with drugs. The patient reported no occurrence of similar lesions in other members of his family.

Physical examination showed erythematous patches of approximately 2 cm observed on the dorsum of the hand and the skin of his back (Figure 1). On the oral

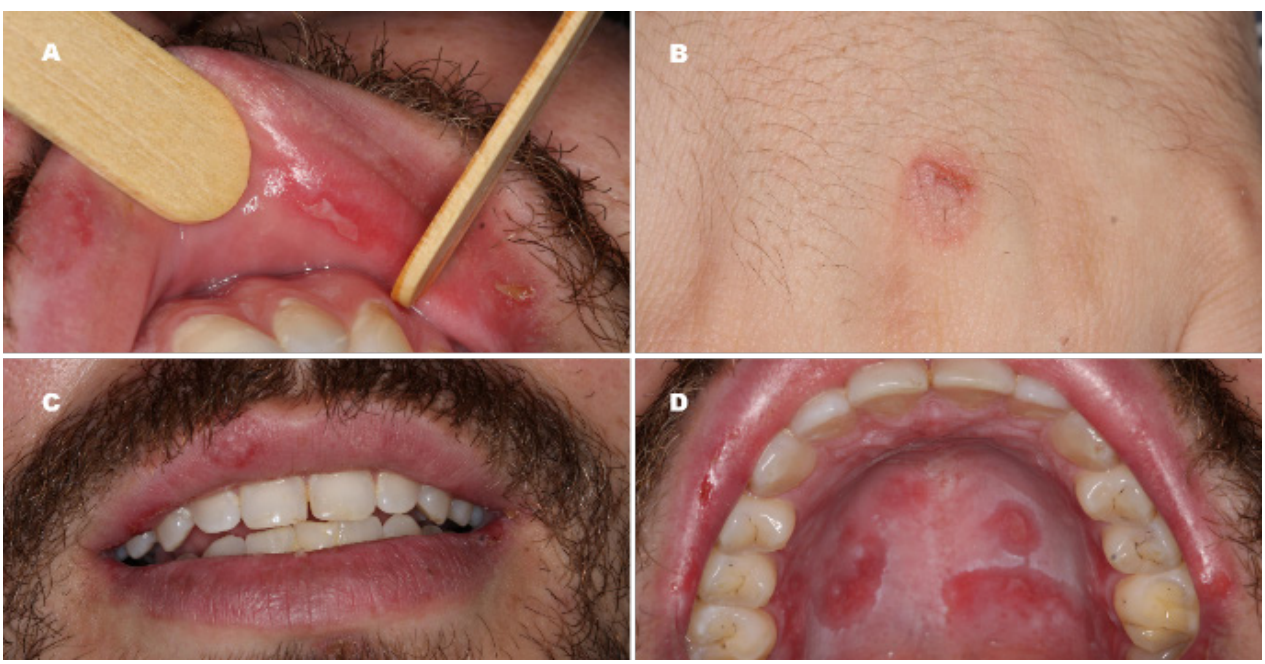

Figure 1. Patient presenting with several ulcer-like lesions, crusts and erosions on the oral mucosa and lips (A, C and D) and an erythematous patch on the back of the hand (B).

mucosa, ulcer-like lesions, encrusted lesions, and erosions of approximately 0.2 to 1.5 cm were observed, located on the lip vermilion, on the lower and upper lip mucosa, on the entire length of the hard palate, and on the left side mouth vestibule (Figure 1). He reported an altered sensation in his lip two days before the lesions appeared. The skin patch on the back of the hand appeared before the mouth lesions became evident. Exfoliative cytology of the oral lesions was performed, and the slides stained in hematoxylin and eosin, revealed signs of inflammation, with desquamative epithelial cells of different strata, and inflammatory infiltrate.

Based on the clinical findings of oral crusts and ulcerations, painful symptomatology, skin lesions, and recurrence of the lesions, as well as the cytopathological result showing inflammatory infiltrate, the diagnosis of EM was made. Prednisone 20 mg, 2 tablets a day for 3 days and Dexpanthenol at nighttime, on the lips, were prescribed. The lesions regressed in one week and, by telephone contact, the patient declared he had had no more episodes.

Case 2

A 55 years-old male patient, sought health care with a complaint of constant pain in the mouth for 2 weeks. He reported the onset of fever 4 days before the appointment, however, he did not measure it. He also reported weight loss (approximately 5 Kg) for 2 months and tiredness upon great efforts. The patient's medical history was unremarkable. Intraoral examination revealed multiple shallow ulcers of varying sizes on the buccal mucosa bilaterally. The ventral tongue, the alveolar ridge on the right side, and the hard palate were also committed (Figure 2).

An incisional biopsy of the buccal mucosa on the left side was performed. Microscopy revealed absence of epithelium, compatible with a area of ulcer, and underlying it, fibrous connective tissue, exhibiting diffuse, mononuclear, perivascular inflammatory infiltrate, as well as the presence of muscle tissue and adipocytes (Figure 3). Based on the clinical findings of the ulcerated oral lesions, as well as the histopathological features that may be found in EM, the diagnosis was made. A topical corticosteroid was prescribed and after one month there was significant improvement of the lesions.

The patient returned to the clinic after three years and reported having three episodes similar to the first one, but in an initial form, which soon regressed after early use of topical corticosteroid. On oral examination, the patient had no mucosal lesions, but there was a need for dental treatment due to the presence of extensive caries, with coronal loss and abscess formation.

Case 3

A 7 years-old male patient presented a complaint of mouth sores. The child guardian reported the initial lesions were similar to herpes, and then spread throughout the mouth 15 days before the appointment, with pain when eating. He was taking amoxicillin and miconazole and using benzocaine, bicarbonate and hydrogen peroxide to treat the oral lesions. This was the fifth episode in two years. Clinically, diffuse oral lesions, most ulcerated and some encrusted, were observed on the upper and lower labial mucosa extending to the lip vermilion and buccal mucosa. Also lesions on the soft palate, palatine uvula and pharynx were observed (Figure 4). Blood tests showed no alterations: white blood cell count was 12,500/mm3; hemoglobin 13.8 g%; platelet count: 331,000/mm3; C-reactive protein: less than 6 mg/dL; VDRL: non-reactive.

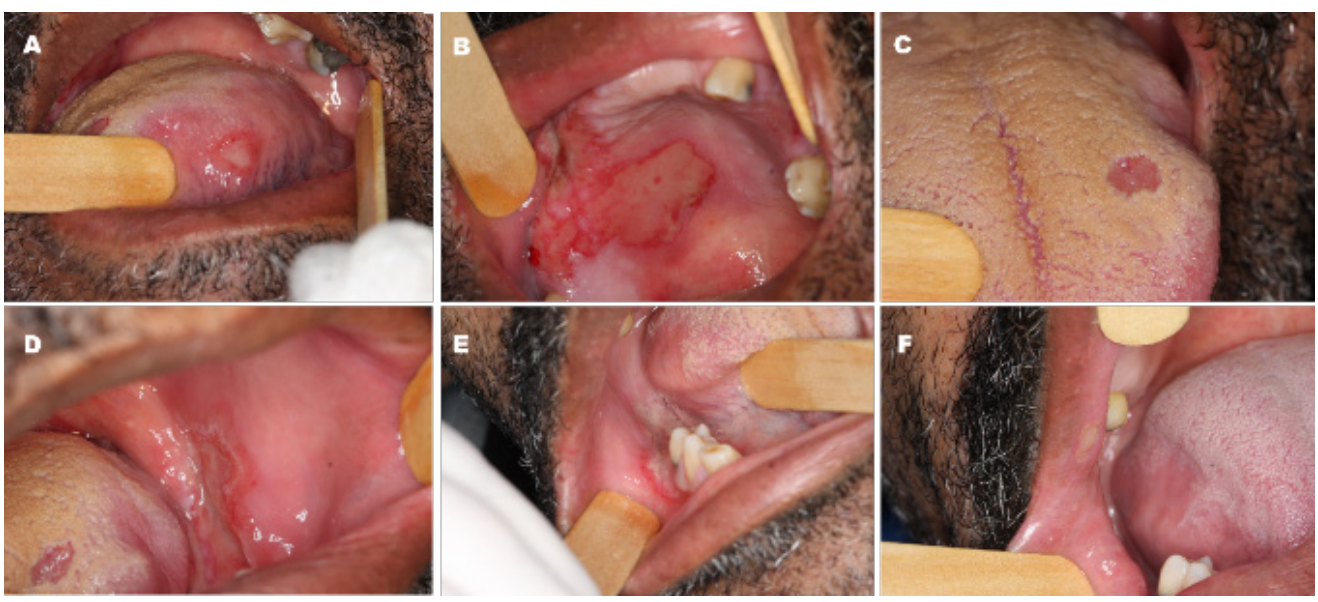

Figure 2. Patient presenting with several lesions on the oral mucosa with the appearance of multiple shallow ulcers of varying sizes (A, B, C, D and E) and lesion improvement after one month of treatment (F).

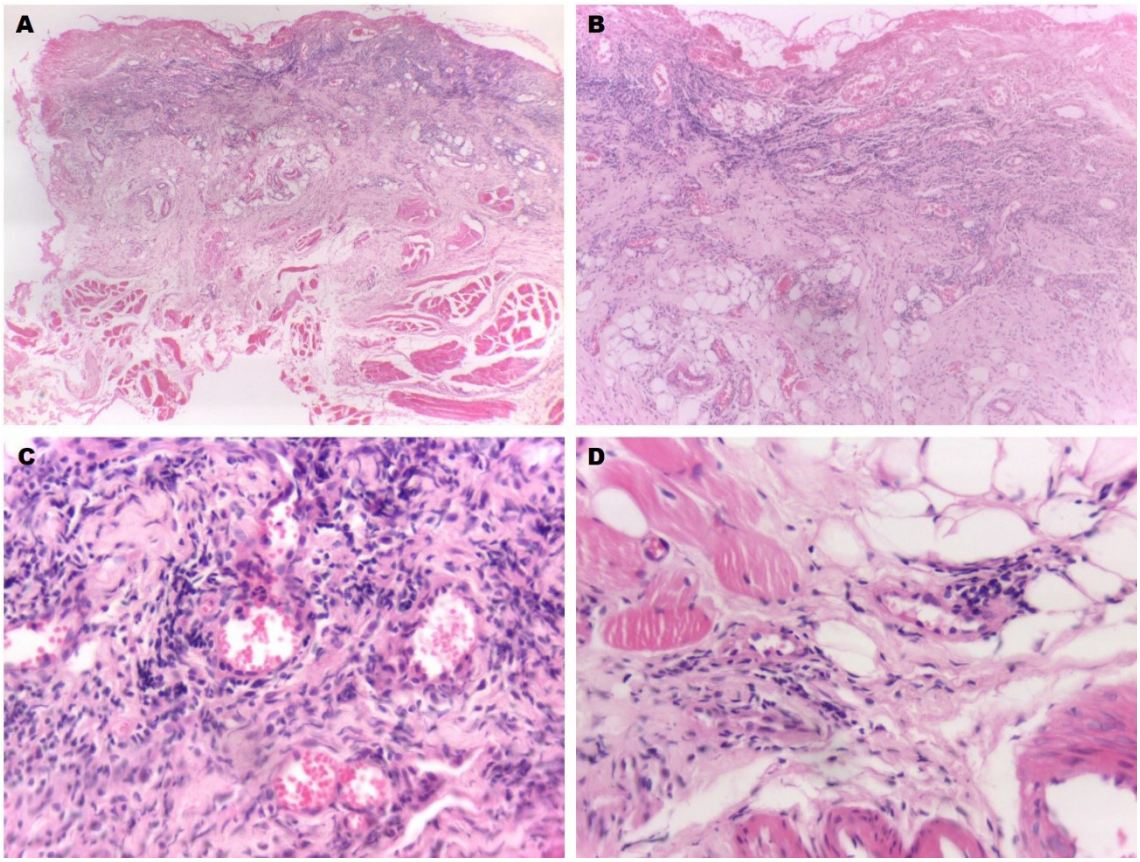

Figure 3. Histopathological analysis of the incisional biopsy performed on the second case. A and B – an ulcer was observed with a prominent superficial inflammatory infiltrate in vascularized fibrous connective tissue; (4x objective in A and 10x in B). Superficial (C) and deep (D) perivascular lymphocytic inflammatory infiltrate; fat cells were also observed deeply in the tissue (D). (40x objective).

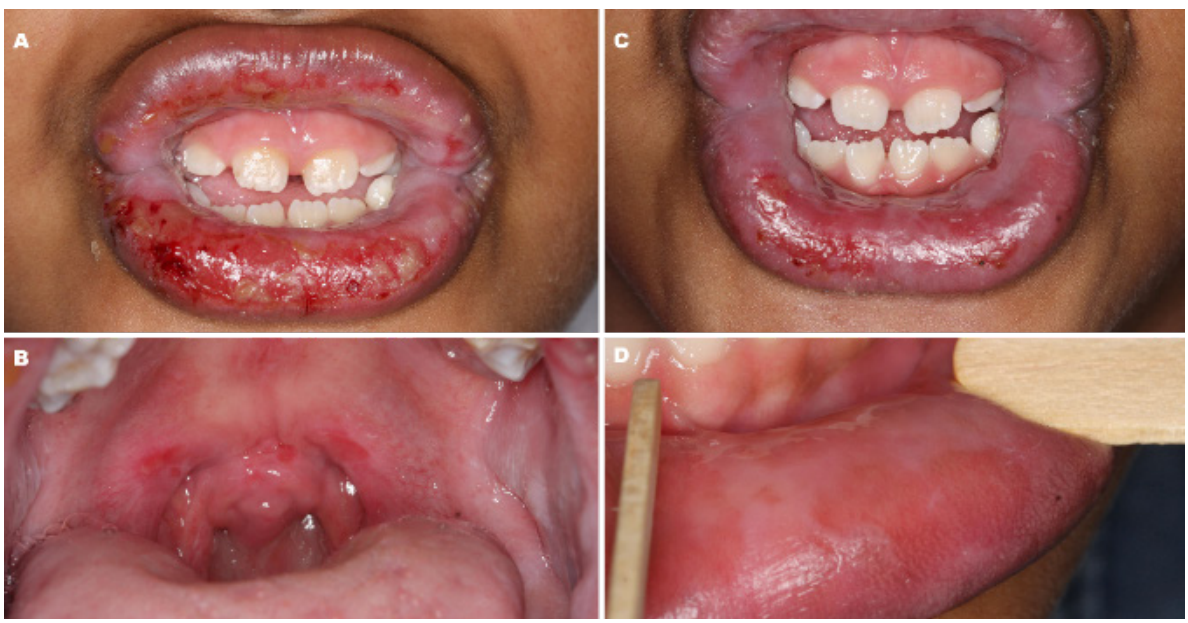

Figure 4. Patient presenting with multiple diffuse ulcerated and crusted oral lesions on upper and lower labial mucosa, and erythematous plaques on soft palate, uvula and pharynx (A and B). Observe regression of the lesions after treatment day 5 (C). And at the end of treatment (D).

The diagnosis of EM was made, based on the clinical findings of hemorrhagic crusts and ulcerations on lips and tunica mucosa of the oral cavity, as well as by the recurrence of the lesions, possibly associated with herpes simplex. Treatment consisted of acyclovir 200 mg, and oral cephalexin. Four sessions of photodynamic therapy were also performed, and regression of the lesions was observed after 18 days of treatment (Figure 4). The child guardian was contacted by phone and reported no recurrence of the lesions in the past three years.

Discussion

The epidemiology of EM is not fully understood. Most studies show that the age of incidence ranges from 20 to 40 years, and the prevalence rate between men and women is controversial[19]. Skin lesions in EM are usually erythematous macules or papules that evolve into classic target- or iris-shape lesions with an erythematous periphery and central area of necrosis with symmetrical distribution[7,8]. The central area may or may not present blisters. Lesions on the dorsal surfaces of the hands and limb extremities are more characteristic. Patients may present fever, malaise, headache, and nausea associated with EM, which usually occurs 7 to 14 days before the development of the skin lesion[14,18-20].

In Case 1, the patient presented lesions on the back of the hand and skin of the back, on one side of the body, with an appearance resembling a target. These were well-defined round erythematous patches, which had a small ulcerated portion. Some authors say that target-shape lesions may not be apparent until several days after the onset of the EM, when lesions of various clinical morphologies are usually present[7,8,14,18] and atypical lesions with only 2 different zones and/or an ill-defined border may also exist[21]. Studies show that 40% of patients with EM have lesions confined to the oral mucosa and lips, and have no skin involvement[22,23]. In a study by Lozada *et al.*[24] they observed that patients with oral involvement alone tended to predominate over those with oral and cutaneous disease[24]. In Cases 2 and 3, we observed only oral mucosal involvement without cutaneous lesions, as is seen in the literature and reported in other cases[2,19,24].

For many years it was believed that EM was an exclusive skin disease. However, involvement of the skin in association with the oral mucosa in patients with EM were described as well as patients with typical oral lesions of EM without any skin lesions[19,25,26]. It was also noted that skin involvement may not occur in the initial attacks. This condition gradually became known as oral erythema multiforme (OEM)[19,25,26]. Oral involvement is characterized by lesions that begin as erythematous plaques that undergo epithelial necrosis and evolve into large shallow erosions and ulcerations with irregular borders, usually more pronounced in the anterior parts of the mouth. Intact vesicles are rarely observed, as they rupture rapidly. The lips become swollen and cracked, with bleeding and crust formation[8,9,17,20], as we observed in Cases 1 and 3. The intraoral lesions observed in the three cases consisted mainly of ulcers, crusts and plaques, of varying sizes, found in different sites, but mainly on the lips, buccal mucosa and hard and soft palate. Usually, lips, labial mucosa, buccal mucosa, tongue, the floor of the mouth and the soft palate are the most common sites of involvement[2].

In the reported cases, serology for HSV was not requested, but in the third case, due to multiple recurrences and the report of an initial clinical presentation resembling herpes, as well as the clinical features of the disease, it was possible to associate HSV as a precipitating factor for EM episodes, since it is usual for this condition to develop after an episode of clinical or subclinical HSV[13]. In a study involving 63 EM patients, HSV DNA was detected (by polymerase chain reaction in skin biopsy samples) in 60% of patients with recurrent EM associated with clinically diagnosed herpes, and in 50% of patients with idiopathic recurrent EM (defined as erythema multiforme without a clinical history of HSV infection or drug intake), showing a large association between EM cases with HSV[14,27].

Although drug intake causes less than 10% of EM cases, many drugs have been associated with EM such as barbiturates, hydantoins, nonsteroidal anti-inflammatory drugs, penicillins, phenothiazines, sulfonamides, allopurinol, tetracyclines, and TNF-α inhibitors. There are also reports of vaccine-associated EM (diphtheria-tetanus, hepatitis B, smallpox)[6,10-14]. In Cases 1 and 2, no infection before the episode of EM lesions was reported. However, in Case 1, the patient stated that he was taking enalapril and puran T4, so far there are no reports in the literature of EM caused by these drugs, but this possibility cannot be ruled out, due to the wide variety of drugs that are described as triggering factors in the literature.

EM is a clinical diagnosis, based on the patient's history and physical examination. In these reports, the diagnosis was based primarily on the clinical appearance of the conditions and patient testimony, but also by analysis of cytopathological and histopathological examinations, and routine blood tests. Histopathological examination of the perilesional mucosa of EM exhibits a pattern that is characteristic, but not pathognomonic, and is useful for establishing the diagnosis, but mainly for ruling out other similar diseases[4,5,8,17,28]. The histopathological results depend on the clinical morphology and the time of existence of the lesions, as well as on the area of the lesion where the sample is obtained[14]. In general, a mixed inflammatory infiltrate is present, consisting of lymphocytes, neutrophils and eosinophils, which may be arranged in a perivascular orientation. Subepithelial or intraepithelial vesicles may be observed, along with necrotic basal keratinocytes[4,14]. The results of exfoliative cytology of the lesions in Case 1 revealed desquamative epithelial cells of different strata mixed with inflammatory infiltrate, and the incisional biopsy performed in the second case, revealed diffuse, mononuclear, perivascular inflammatory infiltrate, both consistent with the histopathological features of EM lesions.

The treatment of EM varies according to the severity of the disease and in many respects remains controversial[5]. Systemic or topical corticosteroids are typically used, despite the little scientific evidence. If a

drug is identified or suspected as a causative factor, it should be discontinued[8,17]. In cases of HSV-associated EM, the use of antiviral therapy is considered[10]. Some authors argue that the course of the disease is self-limited and that only supportive measures should be taken for symptom relief[8,17]. In Case 1, prednisone was prescribed, due to its anti-inflammatory effects, and Dexpanthenol, for moisturizing the lips, and the lesions regressed within a week. Literature reports show EM cases treated with prednisone, with a mean time of lesions healing of 3 to 20 days[19,29,30,31]. In Case 2, a topical corticosteroid was prescribed, and within 30 days there was a significant improvement in the lesions. In Case 3, because the association with HSV, Acyclovir was prescribed. In addition, four sessions of photodynamic therapy were performed, and regression of the lesions was observed after 18 days of treatment. When the disease is triggered by the HSV, continuous oral therapy with acyclovir or valacyclovir can prevent relapses[2,5,10].

Conclusion

The diagnosis of EM can be challenging because it usually presents with a variety of clinical manifestations and a self-limited clinical course. In the last 10 years, three patients with oral manifestations of erythema multiforme were treated at the Oral Diagnosis Center (NDB) and related disciplines of the Dentistry Course of the Federal University of Espírito Santo. The main characteristics observed in these patients were clinical manifestations of oral lesions, composed of shallow erosions and ulcerations with irregular margins, edematous and cracked/scaling lips, with bleeding and crusts. Treatment of EM involves determining the etiology, to subsequently treat the trigger infection or discontinue the causative drug. Corticosteroids have been the most commonly used drugs for treating EM.

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