CASE STUDY

CONTENTS

Mucous membrane pemphigoid with oral involvement: Two cases reports

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ABSTRACT

These cases present a fifty-four- and sixty-four-year-old females, one of whom had the second episode of the disease. Clinical and cytological examinations of the oral lesions were performed, and the Oral Health Impact Profile-14 (OHIP-14) questionnaire was administered. Additionally, histopathological examination and direct immunofluorescence microscopy were conducted on the patient's biopsied lesions.

This article presents two case reports of patients with mucous membrane pemphigoid involving the oral cavity. As an autoimmune bullous disease, mucous membrane pemphigoid is often characterized by oral manifestations without skin lesions and typically follows a chronic course. In addition to standard clinical and cytological observations, histopathology and direct immunofluorescence are essential for confirming the diagnosis. Because recurrence is common, identifying potential triggers is vital to minimizing flare-ups. Clinical management includes meticulous oral hygiene, topical anesthetics, corticosteroids, and antimicrobial mouthwashes.

The authors believe these cases will provide valuable insights for dentists and encourage the early diagnosis and treatment of this condition in routine practice.

KEY WORDS: oral mucosa, pemphigoid, direct immunofluorescence, oral health

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INTRODUCTION

Autoimmune bullous diseases can be localized on the skin and mucous membranes of various organs or exclusively on the oral mucosa. In this regard, these pathologies are collectively referred to as dermatostomatitis or dermatostomatosis. Diagnosis of oral mucosa lesions is complicated due to the low prevalence of bullous lesions worldwide (0.3–13%) [1]; different clinical manifestations, course of disease, and similarities to lesions of other origins, posing a challenge for both dentists and family physicians. Systemic autoimmune bullous disorders can be dangerous not only to health but also to life; therefore, early diagnosis of their clinical manifestations in the oral cavity facilitates the timely initiation of treatment.

One of the bullous diseases is pemphigoid, which is classified into gestational, bullous, and mucous membrane pemphigoid (MMP). The oral mucosa is usually the initial site of MMP, with gingivitis being the most common oral manifestation [2]. In the International Classification of Diseases (ICD-11), MMP of the oral cavity is coded as EB41.1: Mucous membrane pemphigoid with oral or esophageal involvement [3].

The aim of this study is to present two cases of MMP with oral involvement. Written informed consent for the publication of these case reports was obtained from the patients.

CASE REPORT

CASE 1

A 54-year-old female presented to the to the Communal Enterprise "Poltava Regional Center of Dentistry – Dental Clinical Polyclinic" of the Poltava Regional Council with mildly painful lesions on oral mucosa. The discomfort is interfering with her eating and general well-being. The patient's score on the OHIP-14 (Oral Health Impact Profile-14) questionnaire was 25, indicating a negative impact of oral health issues on daily activities and quality of life (Table 1).

The oral mucosal lesions first appeared one month ago (Fig. 1, Fig.2, Fig.3), and self-treatment provided no relief. The patient initially consulted a family physician, but the prescribed treatment was ineffective. Subsequently, she was referred to an oncology center,

Table.1. Impact of oral health status on quality of life

No	Category	Symptom/Impacts	Sum of scores of the first patient	Sum of scores of the second patient
1	Functional restrications	Trouble pronouncing words Worsened sense of taste	3 -	4 2
2	Physical pain	Aching pain (in the mouth) Discomfort when eating any food	2 4	4 4
3	Psychological discomfort	Feeling self-conscious Feeling tense	- 3	- 4
4	Physical disability	Unsatisfied with your diet Having to interrupt meals	2 2	4 4
5	Psychological disability	Difficulty relaxing Feeling slightly embarrassed	- 2	4 4
6	Social disability	Irritability with people or situations Difficulty performing usual jobs/tasks	- 3	- 3
7	Handicaps	Life in general is less satisfying Total inability to function	4 -	4 -
	In total		25	41

Source: compiled by the authors of this study

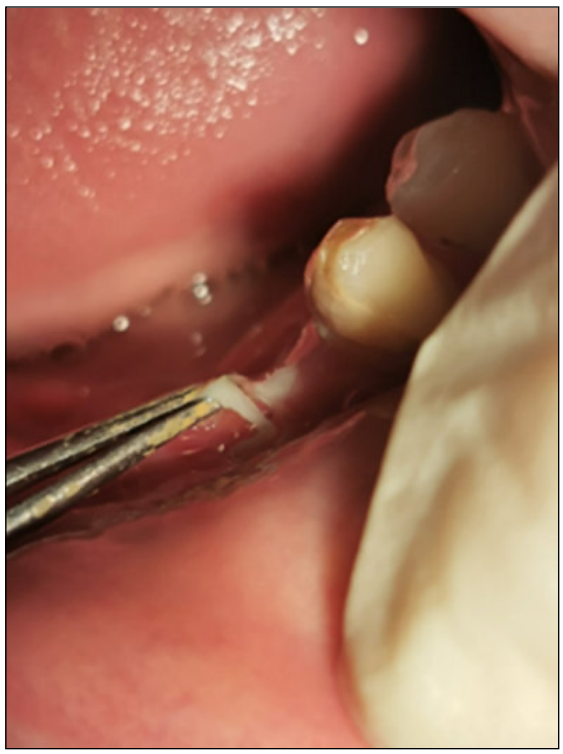

Fig. 1. Erosion on the mucosa of the lower alveolar process; above it, the roof of a bulla is lifted with tweezers (Case 1)
Picture taken by the authors

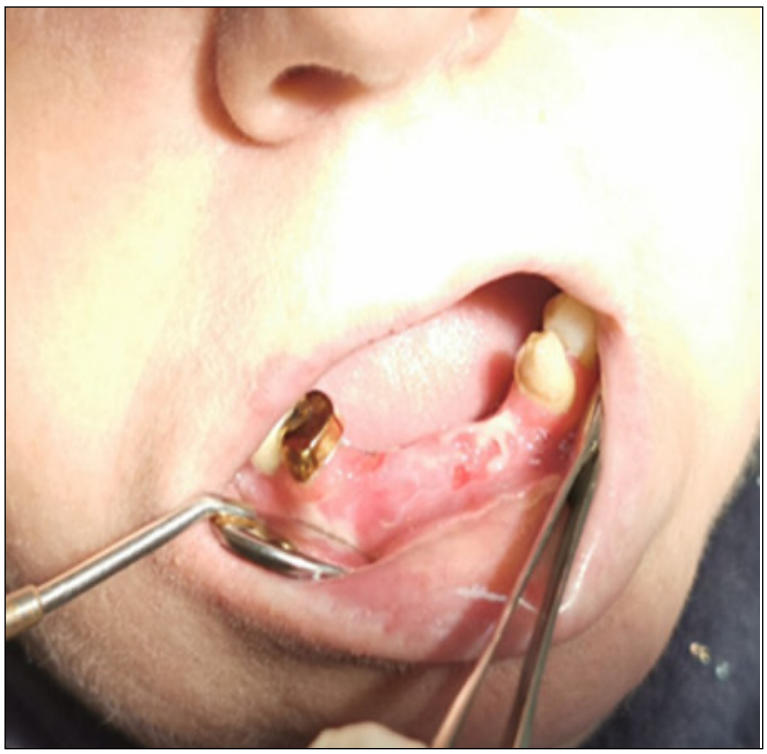

Fig. 2. Erosions on the mucosa of the lower alveolar process, covered with fibrin exudate and bullae roofs (Case 1)
Picture taken by the authors

where additional diagnostic tests ruled out oncological pathology. The patient had a comorbid condition – hypothyroidism.

The skin was pale pink with decreased turgor and no loss of integrity. The patient's general condition was satisfactory. The corners of the mouth were downturned, and the lower third of the face was reduced due to tooth loss. No visible lesions were found on the skin, eyes, or the vermilion border of the lips. Regional lymph nodes were not palpable. Mouth opening was unrestricted. Body temperature was 36,5°C. Examination of the oral mucosa revealed eight erosions and ulcers of various sizes on the lips, low alveolar process, and sublingual area. These were situated on a bright erythematous,

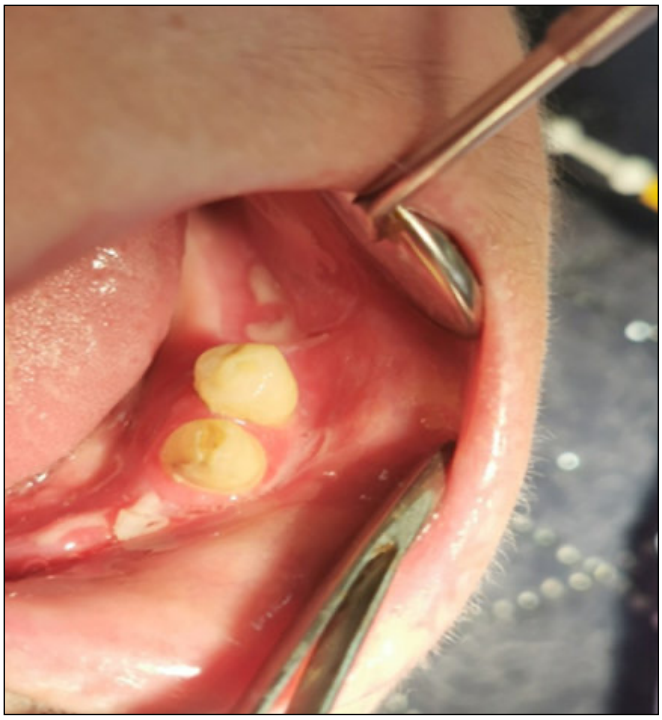

Fig. 3. Erosions on the mucosa of the lower alveolar process, covered with dense fibrin exudate and bullae roofs (Case 1)
Picture taken by the authors

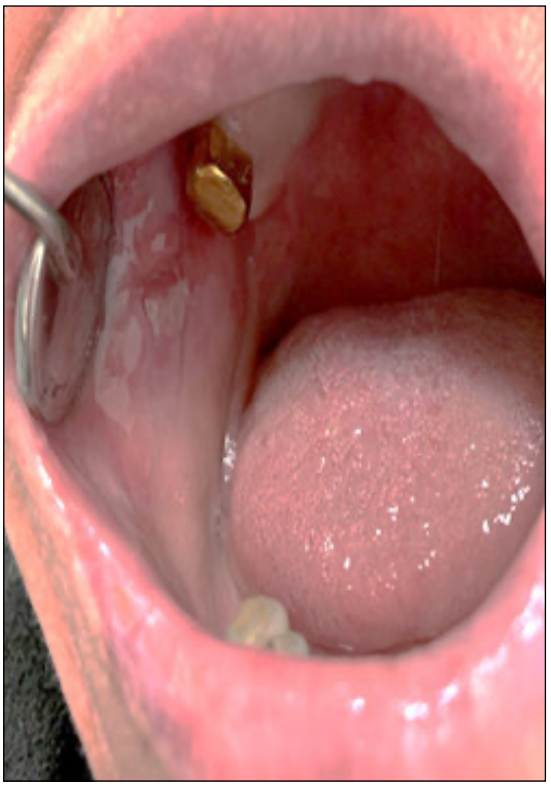

Fig. 4. Erosions on the buccal mucosa, covered with dense fibrin exudate and bullae remnants (Case 2)
Picture taken by the authors

mildly painful base and were covered with a dense fibrinous coating and blister roofs. Nikolsky's sign was negative. No other cutaneous or mucosal sites were involved, such as the conjunctiva or genital or nasopharyngeal mucosae.

The results of the complete blood count (CBC), urinalysis, and blood glucose levels were within normal limits. Cytological examination showed negative Tzanck test. We biopsied the patient's buccal mucosal erosion lesions and nearby normal mucosa tissue. Histopathological examination revealed signs of subepithelial splitting without evidence of acantholysis. The underlying connective tissue showed moderate inflammation, characterized by the presence of eosinophils, neutrophils, lymphocytes, and histiocytes. Direct immunofluorescence (IF) microscopy showed linear deposits of IgG and C3 along the epithelial basement membrane.

Differential diagnosis was performed with Bechet's disease, lichen planus, erosive-ulcerative leukoplakia, erythema multiforme, chronic recurrent herpetic stomatitis, pemphigus vulgaris, and bullous pemphigoid. Bullous Pemphigoid Disease Area Index (BPDA) was used for the assessment of pemphigoid severity. The final diagnosis was mucous membrane pemphigoid with oral involvement, mild degree.

Careful tooth brushing with a soft toothbrush and 0.0015% benzydamine hydrochloride spray for painful erosions were recommended. We also administered 0,12% chlorhexidine gluconate oral rinses followed by topical applications of 0.064% betamethasone cream. This therapy resulted in the gradual healing of the oral mucosal erosions. The patient's oral lesions had not recurred at the most recent follow-up (4 months).

CASE 2

A 64-year-old female patient presented to the same clinic complaining of painful oral ulcers that made eating impossible, sleep disturbances, deterioration of general well-being, anxiety, and a weight loss of 7 kg. The total OHIP score was 41 (Table 1), indicating a significant negative impact of oral health problems on daily activities and overall quality of life.

Oral mucosal lesions appeared 3 weeks ago. She initially consulted a family physician, but the prescribed treatment was ineffective. Subsequently, she was referred to an oncologist, whose evaluation ruled out oncological pathology. Medical history and comorbidities: a severe course of acute respiratory viral infection two months ago, and esophageal reflux, for which she periodically takes Omeprazole.

The patient's general condition was poor, with noted weakness and fatigue. Similar symptoms had been observed in the patient 7 years ago. Body temperature was 36.7°C. The skin was pale pink with decreased tur-

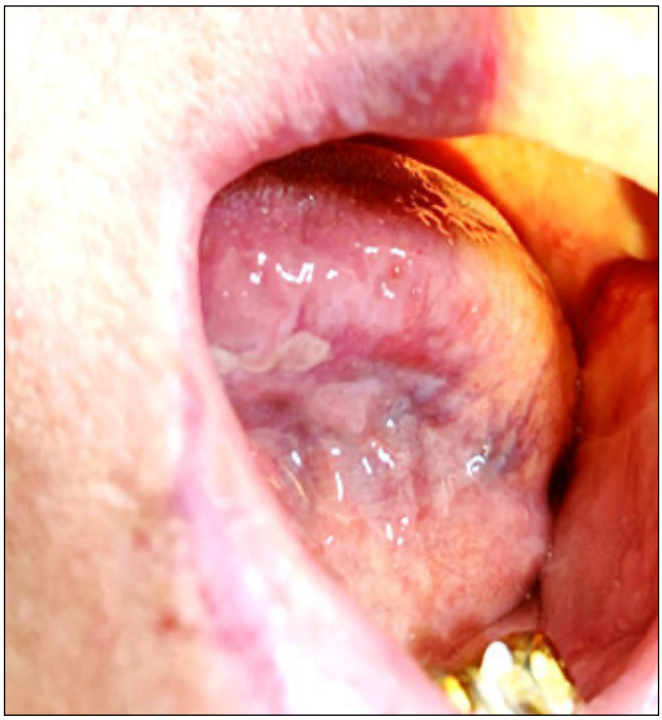

Fig. 5. Erosions on the mucosa of the lateral surface of the tongue, covered with dense fibrin exudate, bullae remnants, and bullae roofs (Case 2)
Picture taken by the authors

gor and no loss of integrity. The corners of the mouth were downturned, and the lower third of the face was reduced due to tooth loss. No visible lesions were detected on the skin, eyes, or the vermilion border of the lips. Regional lymph nodes were not palpable. Mouth opening was unrestricted. Examination of the oral mucosa revealed approximately 20 erosions and ulcers of various sizes on a bright erythematous, painful base, covered with a dense fibrinous coating and blister roofs (Fig. 4, Fig. 5). Nikolsky's sign was negative. No other cutaneous or mucosal sites were involved, such as the conjunctiva or genital or nasopharyngeal mucosae.

The CBC revealed thrombocytopenia. Urinalysis results and blood glucose levels were within normal limits. The Tzanck test was negative. Histological examination showed subepithelial splitting (formation of a bulla beneath the epithelium) with no signs of acantholysis. Direct immunofluorescence indicated the linear basement membrane zone deposition of IgG and C3, while IgA and IgM were rarely found.

Differential diagnosis was performed with lichen planus, erosive-ulcerative leukoplakia, erythema multiforme, chronic recurrent herpetic stomatitis, pemphigus vulgaris, and bullous pemphigoid.

The final diagnosis was MMP with oral involvement, moderate degree with BPDA index.

Careful tooth brushing with a soft toothbrush and 0.0015% benzydamine hydrochloride spray for painful erosions were recommended. We also administered 0,12% chlorhexidine gluconate oral rinses followed by topical applications of 0.064% betamethasone cream. Given the fact that this patient was experiencing a second episode in the oral mucosa after a long remission, the authors focused on the medications she was taking. We noted from the literature [4] that omeprazole is associated with pemphigus; therefore, we speculated that this medicine might be a trigger for MMP due to its short-term use. Consequently, we consulted with the family physician and agreed to discontinue omeprazole for three weeks, replacing it with pantoprazole tablets. Topical therapy gradually healed the oral mucosal erosions. The patient's oral lesions had not recurred at the most recent follow-up (4 months).

PATHOGENESIS OF MMP

The basis of the disease is an autoimmune aggression against proteins of the basement membrane zone (BMZ), leading to subepithelial detachment of the mucosa. In cases of isolated oral involvement, the primary targets for autoantibodies are BP180 (type XVII collagen) and laminin 332. A distinctive feature is that antibodies more frequently attack the C-terminal domain of BP180, whereas in classic bullous pemphigoid, they target the NC16A domain. Autoantibodies (primarily IgG and IgA) bind to antigens within the hemidesmosomes.

This binding directly disrupts protein-protein interactions (e.g., the bond between collagen XVII and collagen IV), which weakens epithelial adhesion to the underlying tissue without necessarily requiring protein internalization. An inflammatory cascade is then triggered. The binding of antibodies activates the complement system and recruits inflammatory cells (neutrophils, eosinophils). This leads to the release of proteolytic enzymes that destroy the outer basement membrane, resulting in the formation of a subepithelial bulla [2,5,6]. A significant infiltration of T-lymphocytes is observed at the lesion sites, which also participate in the pathogenetic chain.

IL-26 was considered as a perspective marker to detect the inflammation level in lung tissue of COPD patients [7]. IL-26–DNA complexes enhanced the production of inflammatory cytokines in monocytes and neutrophils, and augmented the production and activity of proteases from co-cultured monocytes and neutrophils, which induced BP180 cleavage in keratinocytes and dermal-epidermal separation in a modified human cryosection model [8]. Complement activation begins when IgG autoantibodies bind to target antigens, such as BP180. This binding activates both the classical and alternative pathways, leading to the release of anaphylatoxins C3a and C5a. These

mediators recruit neutrophils to the site, ultimately resulting in proteolytic tissue damage and subepidermal separation.

DIAGNOSIS OF MMP

Clinically, MMP is divided into "low-risk" and "high-risk" progression subtypes based on the anatomical distribution of lesions. Low-risk cases involve lesions limited to the oral mucosa, with or without skin involvement. High-risk cases involve critical mucous membranes, such as the ocular, genital, nasopharyngeal, esophageal, or laryngeal epithelium [2]. Therefore, MMP in our patients presented a low risk of progression.

MMP with oral involvement primarily affects patients over 50 years of age, predominantly women. The disease course, duration of remission, lesion area, and epithelialization period vary and depend on the patient's overall health. Our patients exhibited increased oncological alertness and anxiety, seeking consultation after seeing an oncologist; however, such patients typically first present to a dentist with oral lesions. MMP is significantly associated with hypothyroidism [9]. Medications such as Captopril, Enalapril, Furosemide, Ibuprofen, and Omeprazole have been implicated in inducing bullous pemphigoid [4,10]. Thus, the first case might be associated with hypothyroidism, while the second was likely induced by omeprazole, triggering a recurrent episode after 7 years.

The most common manifestation of MMP with oral involvement is desquamative gingivitis (up to 97%), characterized by marked erythema and gingival desquamation. In the oral cavity, the gingiva is most frequently affected (70%), followed by the buccal mucosa (60%), palate (27%), and the tongue and lips (13%) [5].

The diagnosis of oral MMP is based on clinical and laboratory data. Clinical methods include subjective assessment (complaints, medical and life history, questionnaires) and objective examination (inspection, palpation, laboratory tests, and photo protocols). To assess the clinical and psycho-emotional state of patients, questionnaires are utilized as key tools to measure the impact of bullous diseases on daily life, such as the ABQOL (Autoimmune Bullous Disease Quality of Life), TABQOL, or OHIP-14 (Oral Health Impact Profile-14) [11]. Assessment of quality of life in these patients aids in prescribing patient-oriented therapy [1].

The BPDAI (Bullous Pemphigoid Disease Area Index) is used for the objective assessment of bullous pemphigoid severity [12]. One component of the BPDAI evaluates mucosal severity based on the total number of erosions/blisters: mild (<10), moderate (10–24), and severe (>24 lesions).

Direct immunofluorescence (DIF) and serological testing are critical for confirming the diagnosis. Laboratory methods include cytological, histological, and direct immunofluorescence studies. Punch biopsy is considered the most effective sampling method compared to scalpel biopsy for oral bullous lesions. The gingiva has been established as the optimal site for sampling. Histological analysis typically shows subepithelial splitting with a non-specific mixed infiltrate consisting of lymphocytes, histiocytes, plasma cells, neutrophils, and eosinophils. To confirm the diagnosis, DIF of the mucosal biopsy is used to detect fixed autoantibodies (IgG, IgA, IgM) and complement components (C3) directly in the patient's tissues [13,14].

The variability in disease course–severity, duration, and epithelialization time–requires a multidisciplinary approach involving consultations with specialists from other fields. Such patients require dynamic and long-term follow-up.

DIFFERENTIAL DIAGNOSIS

Pemphigus vulgaris is characterized by acantholysis and the presence of Tzanck cells. In pemphigoid patients, Nikolsky's sign is negative and Tzanck cells are absent. Bechet's syndrome and lichen planus are typically characterized by extraoral manifestations. Erythema multiforme may present only in the oral cavity but primarily affects younger individuals; erosions are located on erythematous, edematous mucosa, covered with a difficult-to-remove fibrinous coating, are highly painful, and bleed upon trauma. Hemorrhagic crusts on the lips and enlarged regional lymph nodes are also common for erythema multiform. In chronic recurrent herpetic stomatitis, regional lymph nodes are enlarged, and cytological examination in the first 5–7 days reveals giant multinucleated herpes cells (ballooning degeneration). In our patients, the erosions were only mildly painful, with no lip involvement or lymphadenopathy.

Mucosal involvement can occur in 10% to 30% of bullous pemphigoid patients, most commonly affecting the oral mucosa, including the buccal mucosa or soft palate, followed by the gingival or labial mucosa. These patients are usually younger, have more extensive skin disease, and require more intensive therapy [15]. In contrast to the more commonly multifocal MMP, mucosal involvement in bullous pemphigoid is typically limited to the oral mucosa and associated with more extensive cutaneous involvement. In standard indirect immunofluorescence (IIF), oral pemphigoid typically shows lower antibody titers compared to cutaneous forms [16].

PROPOSED CLASSIFICATION BY LOCALIZATION

Based on clinical experience, the authors suggest categorizing MMP with oral involvement into the following forms: localized-fixed, generalized, and gingival.

I – Localized-fixed. Symptoms are mild and do not affect the patient's general condition. Small, painless, solitary vesicles/bullae (3–10 mm) with transparent content appear and persist for 2–3 days. They have a firm consistency and do not rupture under instrument pressure. Eventually, they burst to form erosions covered by a dense roof, located on a mildly erythematous or unchanged base, usually epithelializing within 6–10 days. Recurrence may occur after weeks or years at the same site.

II – Generalized. Numerous bullae are distributed across the entire oral mucosa. They rupture, forming erosions on a mildly erythematous base; pain arises due to the large surface area of the lesions. Blister remnants remain tightly adherent to the erosion. Patients often have a long history of the disease. While epithelialization may initially occur spontaneously, medical intervention eventually becomes necessary. Treatment is prolonged, and relapses are possible. At this stage, oral hygiene, nutrition, denture use, and dental treatment are severely compromised. Secondary infection of erosions often leads to anxiety and decreased quality of life.

III – Gingival. This form occurs predominantly in women. Patients complain about pain during eating (especially firm foods). Difficulties arise with oral hygiene and dental procedures. Examination reveals painful areas of desquamation on a mildly erythematous gingival base.

Our patients presented with the generalized form, with mild to moderate severity and a low risk of progression.

TREATMENT

Mild disease may respond to high-potency topical corticosteroids (clobetasol or betamethasone). Treatment of chronic lesions may include triamcinolone acetonide [2,7]. Considering the risk of secondary candidiasis, the authors recommend antifungal agents, so our patients were advised to use chlorhexidine mouthwashes. Since MMP is a low-risk bullous lesion, the appearance of new erosions or recurrence requires a search for potential triggers (medications, comorbidities). Alternatively, a dermatologist or family physician may prescribe systemic corticosteroids or immunosuppressants for moderate to severe cases to achieve remission. The efficacy of doxycycline [7,17] and monoclonal antibodies [7,18] in treating bullous pemphigoid has also been established.

CONCLUSIONS

The described cases emphasize that a definitive diagnosis of MMP with oral involvement should be established through a combination of histopathology and DIF. Because recurrence is common, identifying potential triggers is vital to minimizing flare-ups. Clinical management includes meticulous oral hygiene, topical anesthetics, corticosteroids, and antimicrobial mouthwashes. Systemic medications are prescribed in cases of severe manifestations or recurrent episodes of MMP under the supervision of a dermatologist or family physician. The authors believe these cases will provide valuable insights for dentists and encourage the early diagnosis and treatment of this condition in routine practice.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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