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Chapter 45

DESQUAMATIVE GINGIVITIS AS AN ORAL MANIFESTATION OF MUCOUS MEMBRANE PEMPHIGOID: DIAGNOSIS AND TREATMENT

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ABSTRACT

Mucous membrane pemphigoid (MMP) is one of a group of autoimmune, subepithelial blistering diseases that predominantly affect mucous membranes. Desquamative gingivitis (DG) is a common manifestation of MMP. Both histopathological examination and direct immunofluorescence testing are essential to establish a final diagnosis. Early recognition and treatment of MMP can improve the prognosis, but diagnostic delays are common in DG because obtaining a diagnostic biopsy is technically challenging. The stab-and-roll biopsy technique is designed to prevent the epithelium from being removed from the biopsy specimen. The complications caused by scarring and associated loss of function often require surgical intervention in MMP patients. Early diagnosis of MMP is critical, and immunosuppressive treatment may prevent serious complications in mucous membranes.

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INTRODUCTION

Mucous membrane pemphigoid (MMP) is a group of putative autoimmune, chronic inflammatory, subepithelial blistering diseases that predominantly affect mucous membranes [1]. MMP is characterized by linear deposition of IgG, IgA, IgM or C3 along the epithelial basement membrane zone in direct immunofluorescence testing [1, 2]. Most patients with MMP are between 60 and 80 years of age. However, on relatively rare occasions, blistering disorders such as MMP have been reported in children, adolescents or young adults [3]. It affects women at a greater ratio of at least 2:1 compared to men [1, 4, 5]. Oral lesions are observed in 85-90% cases, and the primary lesions often appear in the oral cavity [1, 4, 5]. MMP can involve any oral mucosal site: gingival, buccal or labial mucosa, hard or soft palate, alveolar ridge, or tongue, although the gingiva is affected far more often than other oral tissues. In more than half of early cases, the gingiva is the only site of lesions [4, 6, 7]. Patients with MMP often initially report only oral symptoms of pain and discomfort (Table 1) and therefore often visit the dentist before other health care workers. Desquamative gingivitis (DG) is a common manifestation of MMP, probably because the usual mouth functions such as chewing, exposure to hot foods and liquids, and oral hygiene measures traumatize the gingiva, resulting in tissue sloughing [4, 7, 8]. This chapter presents the clinical and diagnostic features of DG, as a common oral manifestation of MMP. The current literature on the diagnostic and therapeutic modalities of DG associated with MMP is reviewed.

Table 1. Reported oral symptoms in patients with MMP

gingival pain
burning sensation, particularly after eating salty or spicy foods
easy bleeding
blister formation
redness of gum
gingival desquamation

Modified from Endo et al. [4], Endo and Rees [9], Nisengard and Levine [10]

DESQUAMATIVE GINGIVITIS

DG is a clinical manifestation that is common to several diseases or disorders [9-11]. It is characterized by localized or generalized epithelial desquamation, erythema, erosion of the gingival epithelium, and/or blister formation on the gingiva (Figure 1). Nikolsky's sign often shows a positive reaction in patients with DG (Figure 2). This sign involves the application of a shearing force on normal-appearing gingiva, producing epithelial desquamation [12]. Most cases of DG are caused by mucocutaneous diseases [9, 11, 13]. The differential diagnoses include MMP, oral lichen planus, and pemphigus vulgaris [9, 11, 13]. Contact allergic reactions to various oral hygiene products have also been reported in the differential diagnosis of DG [14, 15]. It is impossible to diagnose MMP from the clinical presence of DG lesions alone. The appropriate use of biopsies to perform histopathologic and direct immunofluorescence examination of lesional and peri-lesional tissues is required to establish the final diagnosis [9, 11]. Obtaining diagnostic gingival biopsies from MMP patients is

technically challenging. The excised gingival tissue tends to be fragile because disruption of the epithelial cell-to-basement membrane adhesion components is likely to occur. This situation may often result in detachment of the gingival epithelium from the underlying connective tissue, causing a failure in biopsy diagnosis. This tissue friability, coupled with an inadequate surgical technique, surgical site selection or improper tissue handling, may easily lead to the loss of the gingival epithelium, causing a failure in histopathologic and direct immunofluorescence diagnosis. Because of this, some authors have stated that if lesions are present at several mucosal sites, including the gingiva, it is usually best not to use the gingiva for biopsies [16-18]. However, in approximately 60% of the MMP patients, the gingiva was the only site of involvement [6] and in these cases, the gingiva should be selected as the biopsy site. Recently the authors developed and validated a biopsy technique (the stab-and-roll technique) to maintain the gingival epithelium/connective tissue union in DG patients [19] (Figure 3).

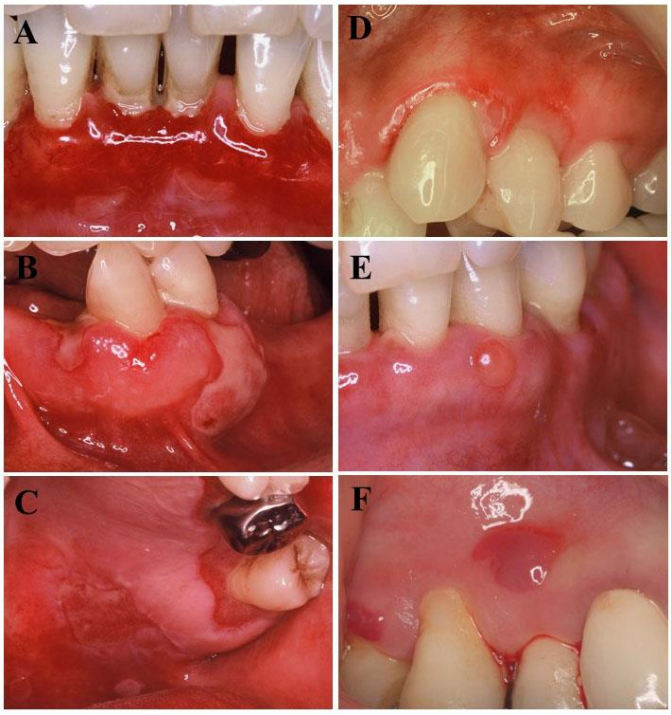

Figure 1. Clinical presentation of DG associated with MMP. (A) Erythema. (B) Pseudomembrane-covered erosion. (C) Erosion. (D) Ulceration. (E) Blister formation. (F) Localized blood-filled blister formation.

In this technique, the operator applies gentle pressure on the gingiva with the tip of a #15 blade until the bone surface is reached, and then the blade is rolled from the tip along the entire cutting edge. If a larger specimen is needed the tip of the blade can be repositioned and the rolling stroke extended. This stab-and-roll biopsy technique prevents the occurrence of lateral shear forces. In contrast in the conventional gingival biopsy technique, the scalpel blade is pulled across the biopsy site while the tip of the blade is against the bone surface. This potentially creates a lateral shear force potentially causing the epithelium to be displaced

from the biopsy specimen. A total lack of epithelium has been reported in 40% [20] - 41.2% [21] of gingival biopsy samples using the conventional biopsy technique whereas in a series of 52 gingival biopsies only 1.9% of the samples obtained using the stab-and-roll biopsy technique resulted in epithelium-connective tissue separation [19]. Some authors are concerned that gingival biopsies may result in permanent periodontal defects [20, 21]. Indeed, since many DG lesions develop in the anterior facial area, resultant periodontal defects could be an esthetic problem. To prevent this difficulty, stab-and-roll biopsies are often taken from perilesional tissues apical to the free gingival margin. This site selection also prevents the biopsy tissue from being obscured by gingival inflammation (Figure 4).

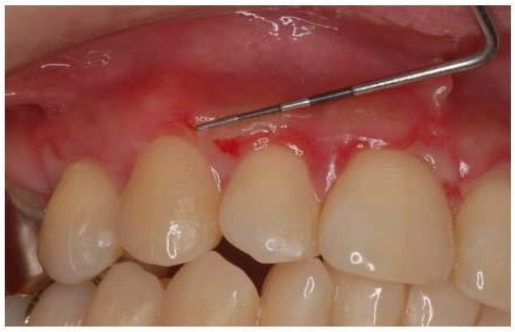

Figure 2. Positive Nikolsky's sign in a patient with MMP. Gentle palpation with the periodontal probe elicited some desquamation of the gingival surface.

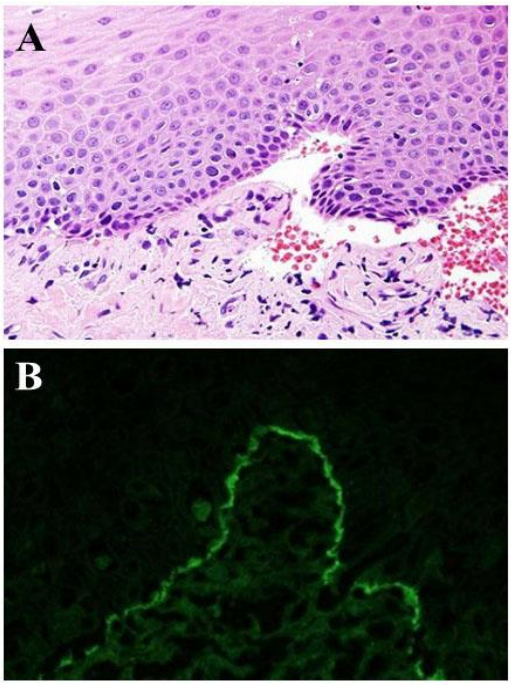

Figure 3. Histopathologic and direct immunofluorescence features of MMP. Gingival biopsies were performed using the stab-and-roll technique. (A) Hematoxylin- and eosin-stained section (Original magnification x400). Subepithelial bulla formation. (B) Direct immunofluorescence section (Original magnification x200). A linear deposition of IgG along the basement membrane zone.

SPECIFIC SITE CONSIDERATION

Extraoral MMP lesions have been reported on skin including the external genitalia and perianal skin as well as on the mucous membranes of the eye, nose, pharynx, larynx, esophagus, and anus [1, 22]. Although scarring is rarely a feature of oral MMP, in extraoral sites scar formation may lead to an irreversible loss of function of the affected areas. Sight-threatening ocular scarring [23-25] and life-threatening upper airway obstruction [26-28] have been reported. In contrast, only one case report has described oral scarring. Sato et al. [29] reported microstomia associated with MMP exhibiting anti-laminin 332 autoantibodies. Scar contracture was ring-shaped and localized on the oral mucosa. A commissuroplasty was performed in treatment using 5-flap Z-plasty on the upper lip and 2-flap Z-plasty on the lower lip. The patient was reported to be satisfied with the postoperative esthetics and the size of the oral aperture.

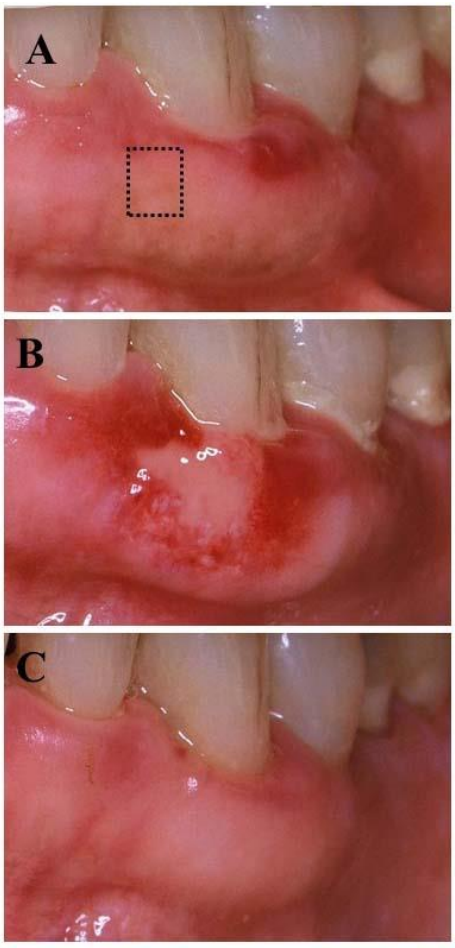

Figure 4. Periodontal conditions after gingival biopsy. The periodontal defects or recessions did not occur after the gingival biopsy using the stab-and-roll technique. (A) Before biopsy. The gingival sample was removed from the dotted-line area. (B) 1 week after biopsy. (C) 6 months after biopsy.

In a previous study, an incidence of only 10.4% (10/96) ocular lesions was reported in MMP associated DG patients [30]. Consequently, patients with exclusively intraoral MMP were thought to have a less severe disease that might not be associated with ocular involvement [7, 31]. However, a recent study indicated 30% (9/30) of patients with oral MMP had ocular involvement at presentation to an opthalmologist [24]. Another study of 25 patients who initially had only oral involvement reported that 4 (16%) developed ocular lesions within 5 years [25]. These studies indicate that MMP patients with initial oral lesions have a risk of developing ocular involvement with a calculated incidence rate from 0.03 [24] to 0.05 [25] person per year. Some specific oral symptoms are common in individuals likely to have oral MMP (Table 1). The presence of these symptoms should increase the healthcare provider's level of suspicion of a mucocutaneous disease such as MMP. Symptoms suggestive of possible ocular involvement in patients with MMP are shown in Table 2. MMP patients with oral involvement, however, frequently have asymptomatic ocular lesions, especially in the early stages of ocular disease [24, 25]. These observations indicate that all patients diagnosed with intraoral or extraoral MMP should undergo ophthalmic examination by an ophthalmologist (Figure 5). Patients with oral MMP should have regular opthalmologic monitoring every 6 to 12 months, even if no ocular involvement is identified at initial diagnosis [24].

Table 2. Symptoms possibly related to ocular involvement in patients with MMP

burning sensation
dryness
foreign body sensation
irritation
excess tearing
mucus production
photophobia
blurry vision
decreased visual acuity

Modified from Fleming and Korman [5], Kourosh and Yancey [22]

Patients with MMP restricted to the upper airway tract are rarely observed [26, 27]. More than 84% of MMP patients with upper airway involvement had oral lesions [26, 27]. Despite this, reports of the upper airway involvement in DG patients are scarce. One report described a case of MMP in a young patient presenting with DG and laryngeal manifestations that resulted in severe life-threatening sequels of events [32]. Symptoms that should raise suspicion regarding the presence of upper airway involvement in patients with MMP are shown in Table 3. When DG patients complain of these symptoms, they should be seen by an otolaryngologist for evaluation and possible endoscopic examination of the upper airway tract (Figure 6).

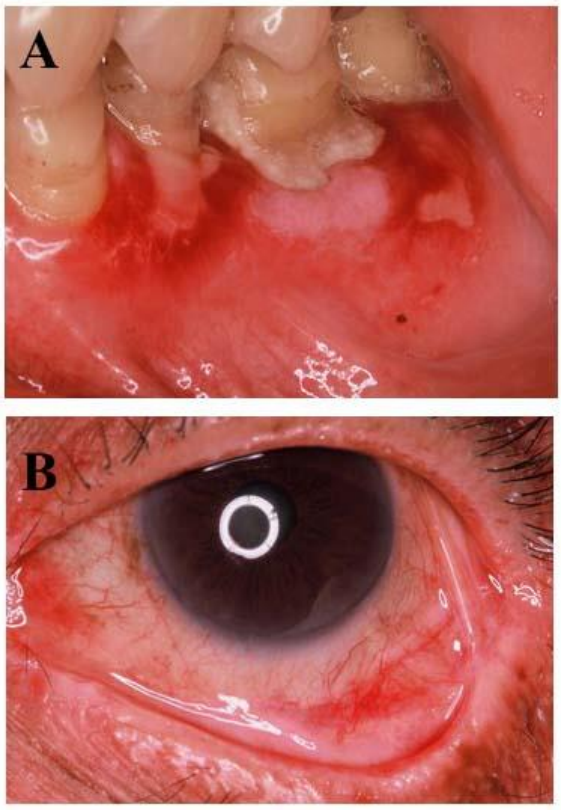

Figure 5. Ocular involvement in a DG patient with MMP. (A) Desquamative lesions featuring gingival erythema. (B) Ophthalmic examination by an opthalmologist revealed lower conjunctiva symblepharon in the same patient.

Table 3. Symptoms suggestive of possible upper airway involvement in patients with MMP

nasal stuffiness
nasal bleeding or blood-tinged mucous discharge
cough
hoarseness
difficult or labored breath
continuous inspiratory musical sound of variable pitch
sore throat
pain on swallowing
dysphonia

Modified from Alexandre et al. [26], Higgins et al. [27]

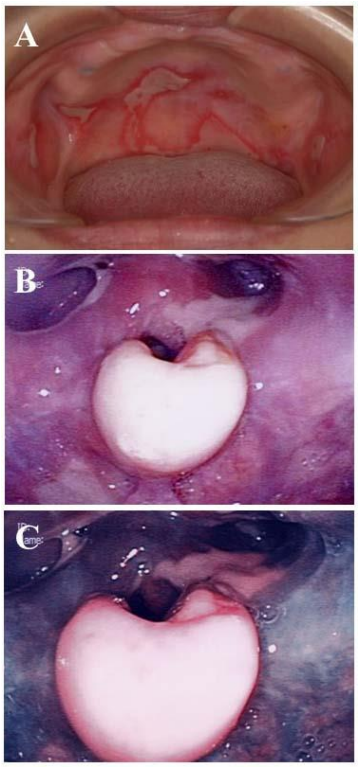

Figure 6. Laryngeal involvement in a DG patient with MMP. (A) Desquamative lesions of soft palate in addition to gingiva. The patient complained of chronic cough and sore throat. (B) Conventional endoscopic examination revealed white coat of the epiglottis and the aryepiglottic fold. The involvements are consistent with MMP early lesions. (C) Narrow band image (NBI) enhanced and defined white coat MMP.

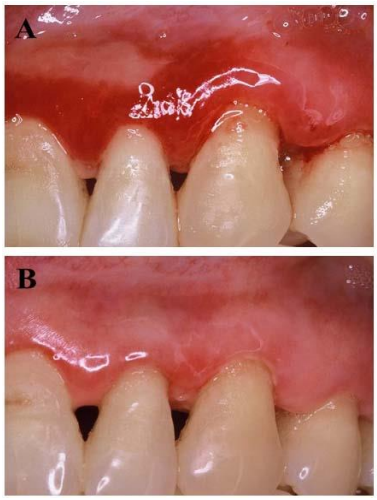

Figure 7. Topical corticosteroid therapy in a DG patient with MMP. (A) The initial examination revealed localized erythematous gingiva. (B) The gingival lesions went into remission with the topical corticosteroid therapy.

MANAGING PATIENTS WITH DESQUAMATIVE GINGIVITIS

The therapeutic goal for DG lesions is the remission or suppression of the clinical signs and symptoms. The severity of the DG lesions, the presence or absence of extraoral lesions, and the medical history of the patient are key factors in determining the selection of a topical or systemic treatment. In most cases, topical therapy alone is sufficient to achieve resolution of lesions when MMP is diagnosed and treated in its early stages. When MMP affects the oral cavity as the sole involvement, moderate to very high-potency topical corticosteroids are effective and widely used for treatment [6, 9] (Figure 7). The absorption of topical corticosteroids may increase in the presence of DG, since the continuity of intact epithelium may be disrupted. In 1990, Plemons et al. [33] studied the systemic uptake of high-potency topical corticosteroid gel (0.05% fluocinonide gel) applied to oral desquamative diseases three times daily for 3 weeks. They found no evidence of adrenal suppression in the study population. Occlusive steroid therapy using a plastic stent may be used to enhance the effect of topical corticosteroid therapy by maximizing the contact between the corticosteroids applied on the gingiva [34, 35] (Figure 8). In this therapy, the topical corticosteroid is in contact with the gingiva for a longer time period and the systemic absorption is probably increased thus enhancing the effect of the topical agent. To date there are no studies documenting medical complications related to the intraoral use of very high potency topical corticosteroids, but caution should be used when providing occlusive steroid therapy for patients afflicted with hypertension, gastrointestinal ulcers or diabetes mellitus, pending further study. Secondary candidosis is the most common side effect from topical corticosteroid therapy (Figure 9). Oral candidosis should be suspected in patients that continue to complain of oral symptoms despite several days or weeks of topical therapy.

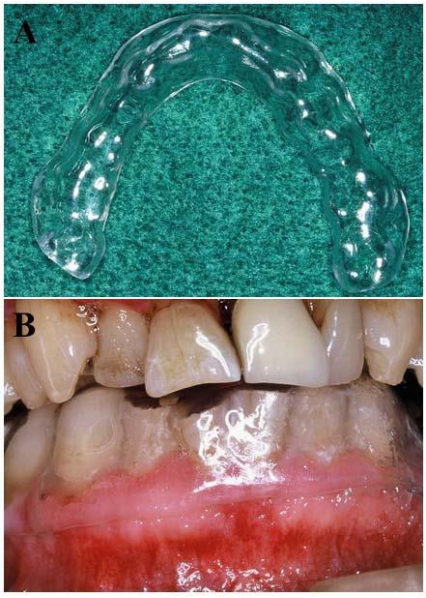

Figure 8. Occlusive steroid therapy using a plastic stent in a DG patient with MMP. (A) Plastic stent for mandibular arch. (B) Stent in place.

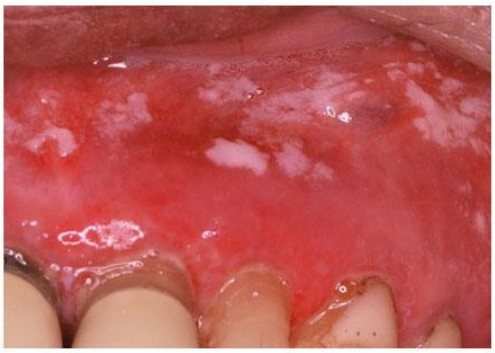

Figure 9. Secondary candidosis in a DG patient with MMP. During the topical steroid therapy period, gingival candidosis occurred. The symptoms disappeared after an antifungal medication was administered.

Patients with severe and/or multiple oral lesions, or recalcitrant lesions, may need aggressive systemic treatment [36]. The presence of extraoral lesions also may require systemic corticosteroids and/or immunosuppressive drugs for effective MMP management. Careful medical management is necessary to monitor the patient for adverse effects of systemic drugs and to manage concomitant systemic diseases. Although extraoral MMP lesions involving erythema, erosion, ulceration, or blister formation will respond well to medical immunosuppressive therapy, the treatment will be highly resistant if fibrosis and scarring has occurred [22]. The complications caused by scarring and associated loss of function often require surgical and/or medical intervention. Airway obstruction is the most serious complication and may necessitate an emergency tracheotomy [26-28]. Ocular lesions occur most often in association with DG and may induce inflammation, loss of tear film, progressive scarring and adherence of the eyelid to the eyeball (symblepharon), inward turning of the eyelashes (triachiasis), and inward turning of the eyelids (entropion) [5, 22]. Unless treated aggressively, these lesions can lead to loss of vision in one or both eyes [37]. Early diagnosis of MMP is critical and immunosuppressive treatment may prevent scar formation in mucous membrane.

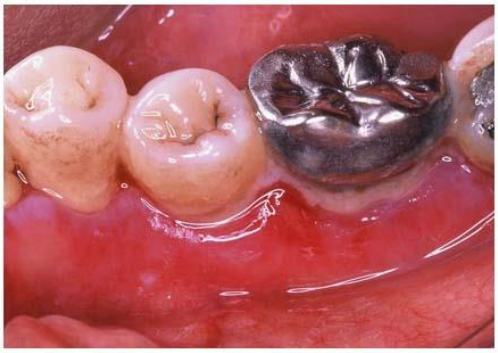

Figure 10. Poor oral hygiene status in a DG patient with MMP. Dental plaque and calculus deposits were recognized around teeth.

PERIODONTAL CONSIDERATIONS

It is often very difficult for DG patients to clean their teeth due to pain and bleeding, and patients often fear to create new lesions on the gingiva. Therefore, their oral hygiene is likely to be ineffective, making it difficult to treat this condition (Figure 10). For this reason, some authorities have stated that desquamative lesion of the gingiva could lead to periodontal destruction and bone loss, necessitating tooth extractions [5, 37]. However, little information is available regarding the periodontal conditions of patients with DG associated with MMP. The relationship between the existence of MMP lesions and progression of periodontal diseases is inconclusive. Arduino et al. [38] demonstrated that periodontal status is worse in MMP patients compared with healthy controls because of substantial differences in oral hygiene. Conversely, Tricamo et al. [39] and Schellinck et al. [40] suggested that MMP patients demonstrate higher levels of gingival inflammation, but not chronic periodontitis compared to healthy age and sex matched controls even after at least a 5 year history of MMP. Plaque accumulation may be an aggravation factor to make DG worse. Plaque-related gingivitis is almost universal in patients with painful gingival lesions and an effective therapeutic protocol should include non-surgical periodontal therapy consisting of oral hygiene instruction, scaling, and root planing [41]. Orrico et al. [42] affirmed that plaque control performed by a professional and the application of 0.12% chlorhexidine digluconate resulted in 90% improvement of gingival lesions in MMP patients. Professional oral hygiene treatment and detailed oral hygiene instructions are connected with improvement of gingival status and a decrease in gingival-related pain in patients affected by MMP with DG lesions [43]. Combined treatment and long-term maintenance of MMP and periodontal disease are effective at improving and stabilizing the gingival conditions in MMP patients [44-46].

CONCLUSION

Early signs and symptoms of MMP develop in the oral cavity in almost all cases, and DG is a common manifestation. After MMP is diagnosed from DG or concomitant lesions, patients should undergo examination by medical specialists including an opthalmologist and an otolaryngologist, and the presence or absence of extraoral mucosal lesions should be determined. Scarring may lead to an irreversible loss of function of the affected extraoral mucous membranes in some MMP cases. Early recognition and treatment of the diseases is very important and can significantly improve the prognosis.

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