CASE REPORT

Mucous Membrane Pemphigoid: A Case Report with Oral and Ocular Presentation

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Abstract

Aim: To describe the diagnosis and management of mucous membrane pemphigoid (MMP) with oral and ocular presentation.

Background: Mucous membrane pemphigoid constitutes a heterogeneous group of chronic, autoimmune vesiculobullous diseases characterized by blister formation that has a propensity to affect different mucous membranes of the body. The most commonly affected areas include the oral cavity, mucous membranes of the eyes, throat, genitalia, and nose. This disease usually affects elderly women with a peak incidence at around 50–70 years of age; however, rare cases have been diagnosed in children. The symptoms of MMP include recurrent blistering lesions which eventually rupture and occasionally heal with scarring that may lead to certain complications involving the eyes and throat regions.

Case description: In this report, we describe a 66-year-old female patient who complained of oral and ocular lesions for a period of 2 years. Pain, burning mouth, and gingival inflammation were present. Ocular examination showed mild conjunctivitis with scar formation at the lateral canthus of the left eye. The patient also noticed periods of water-filled balloon-like formation in the gingiva that rupture spontaneously leaving sore spots. A biopsy was obtained from perilesional tissue and sent for histopathological examination, correlation of clinical and histological features directed us toward the diagnosis of MMP. The patient was treated for both oral and ocular lesions using topical corticosteroid therapy in conjunction with antifungal and antibacterial drugs. The response to local treatment was augmented via effective periodontal therapy to control the concurrent plaque-induced gingival inflammation and via using a customized application tray to sustain the drug efficacy.

Conclusion: A multidisciplinary approach is often necessary in order to treat MMP lesions efficaciously.

Clinical significance: Early diagnosis and effective treatment protocol using systemic or topical corticosteroid therapy along with other therapeutic means including periodontal therapy, good oral hygiene practice, and timely follow-up are very useful in preventing long-term complications due to this disease.

Keywords: Autoimmune, Mucous membrane pemphigoid, Topical corticosteroids, Vesiculobullous disease.

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Introduction

Mucous membrane pemphigoid is an autoimmune vesiculobullous lesion predominantly affecting the oral mucosa. It causes mucosal blistering, which might ulcerate and heal with scarring. It is also known as "cicatricial pemphigoid," the subdivisions of which include vegetating cicatricial pemphigoid, localized cicatricial pemphigoid, and Brunsting–Perry syndrome, and vegetating cicatricial pemphigoid.[1]

Pathogenesis of MMP is attributed to the binding of autoimmune antibodies to bullous pemphigoid antigen, BP180, BP230, and laminin 332,[2] less often to bullous pemphigoid antigen 1 (BPAg1),[3] laminin 5 and 6, and collagen VII and collagen XVII[4] in the basement membrane zone (BMZ). Also, an association of MMP with immunoglobulin G (IgG), and IgA autoantibodies, human leukocyte antigen (HLA) major histocompatibility class II HLA-DQB1*0301, along the epithelial BMZ has been demonstrated. This triggers a cascade activating the complement system and the leukocytes damaging the subepithelial BMZ causing vesicle formation just beneath the epithelium.[5]

Demographics of MMP show that it usually affects elderly women with a female to male ratio of 2:1. It occurs initially in late adulthood with a variable prognosis. About 80–90% of the patients present with oral lesions, affecting the palate, gingiva, tongue, and buccal mucosa.[6] The exact incidence of MMP lacks clarity. Recently, showed that ocular MMP accounted for 61% of newly diagnosed cicatricial conjunctivitis with an incidence of 0.8 per million population. Although there is no known racial predilection mentioned in the literature.[4] A total of 50% of patients might develop ocular and esophageal lesions that heal with secondary atrophy leading to blindness and stenosis of the upper aerodigestive tract in severe cases.[7] Skin involvement occurs in the head and neck region.[8]

The intraoral features of MMP include pain, burning sensation while eating spicy food, gingival inflammation, tenderness, bleeding, erosion, bullae formation, and fetor oris.[9] Nikolsky's sign is positive in most cases, which is demonstrated when lateral pressure is applied on the border of an intact bulla, resulting in the dislodgement of normal epithelium causing the extension of the blister.[10] It is elicited by palpation with a mouth mirror, or periodontal probe and finger.[11] The blisters rupture leading to the formation of a pseudomembrane, which are irregularly shaped erosions with a yellowish slough in the center surrounded by an erythematous halo. Commonly involved areas include gingivae,

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hard palate, buccal mucosa, tongue, and soft palate. Oral lesions that scar rarely can be painful resulting in poor nutrition and hygiene.

Case Description

A 66-year-old female patient presented to the clinics of Periodontology at the College of Dentistry, Jazan University, Saudi Arabia in June 2020, with a chief complaint of pain and burning sensation of the oral cavity for the past 2 years. The patient reported that pain became intense while eating or when performing oral hygiene practices. She also noticed periods of water-filled balloon-like formation in the gingiva that rupture spontaneously leaving sore spots.

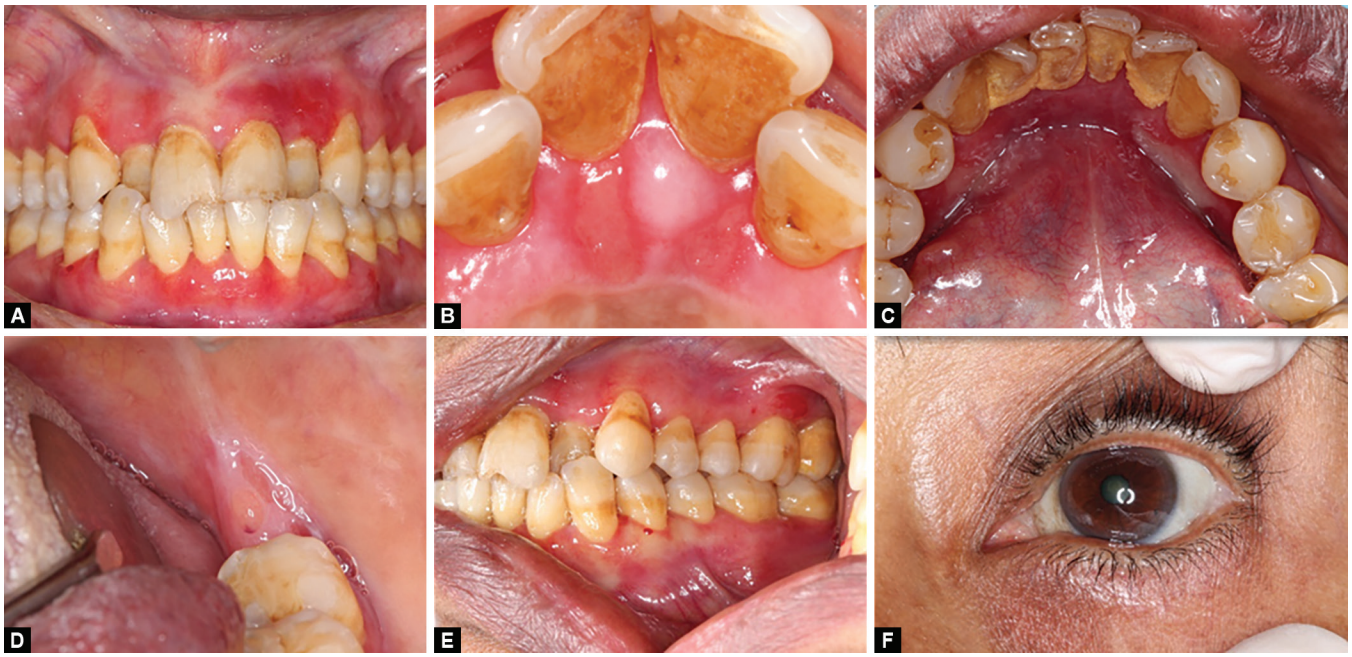
The patient revealed a significant medical history of having hyperlipidemia, hypertension, and hyperuricemia for which she was on medication; taking atorvastatin, atenolol, and allopurinol respectively. In addition, the patient indicated using lubricant eye drops for her eye irritation that lasted for more than a year. The initial diagnosis was made by the patient's general dentist who had misdiagnosed the case at an early stage. The patient was treated through multiple scaling sessions and a prescription for an antiseptic mouthwash. No improvement was observed. After the failure of multiple treatments, the patient was referred to the Periodontics clinic, where the final diagnosis was given after proper clinical and histopathological examination.

Intraoral examination revealed generalized diffuse erythema on buccal and lingual/palatal mucosa (Fig. 1), specifically, diffuse gingival inflammation (Fig. 1A), inflamed gingival margins seen around the incisive papilla region (Fig. 1B), epithelial sloughing at lingual mucosa (Fig. 1C), localized gingival bleeding in maxillary and mandibular arches with areas of bullae (Fig. 1D), and ulcer formation. A positive Nickolsky sign was also evident as surface epithelium detached from the underlying connective tissue upon applying gentle pressure to the intact epithelial surface (Fig. 1E). Oral hygiene was assessed as less than optimum due to significant plaque accumulation. Ocular examination showed mild conjunctivitis with scar formation at the lateral canthus of the left eye (Fig. 1F).

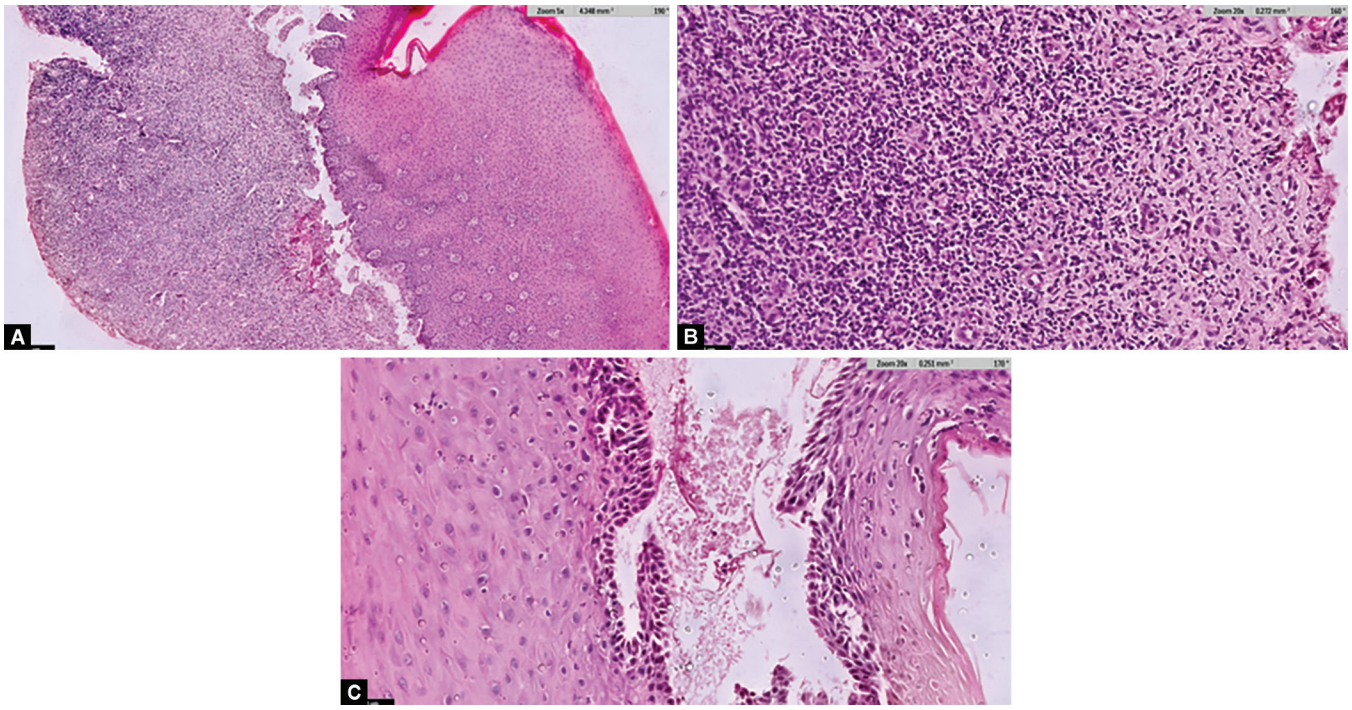
In this case, a perilesional biopsy was obtained from the palatal gingival, and a histopathological examination was done. The hematoxylin and eosin-stained (H&E) section revealed subepithelial split, that is, detachment of surface epithelium from the underlying connective tissue at the point of the BMZ (Fig. 2A). The lamina propria was infiltrated mainly by plasma cells with scattered neutrophils and chronic inflammatory cells of lymphocytes (Fig. 2B). Erythrocytes were seen in the subepithelial space (Fig. 2C).

Based on the clinical and histopathological findings, the patient was diagnosed with MMP. A gentle supragingival scaling was started to eliminate the plaque and calculus build-up at the gingival margins. The patient was then provided with a topical corticosteroid (clobetasol propionate 0.05%, dermovate cream) to be applied for 20 minutes, 3 times a day by applying a thin layer to the internal surface of the acrylic tray. The tray was custom made to fit the patient's dentition and the gingiva extending to the mucogingival line and served as a carrier for the medication. The prescription was given for 4 weeks and the patient was instructed to spit any excess saliva after the application and not to swallow, eat, or drink for at least one hour. In addition, the patient was prescribed antifungal prophylaxis (Nystatin 100,000 units) 2 times a day to avoid secondary infection by *Candida albicans* during the course of corticosteroid treatment. Oral hygiene instructions were given to maintain good oral health.

Treatment progress was assessed after 2 weeks at which the patient reported less pain upon chewing and when performing oral hygiene. Clinically, the gingiva showed significant improvement in ulcers and areas of inflammation. On the same visit, the second round of thorough subgingival scaling was performed as the patient's



Figs 1A to F: Clinical features of MMP representing the following: (A) Diffuse gingival inflammation; (B) Inflamed gingival margins seen around the incisive papilla region; (C) Epithelial sloughing at lingual mucosa; (D) Bullae at retromolar area; (E) Exposed connective tissue with hemorrhagic surface following gentle pressure on the attached gingiva of the maxillary first molar (positive Nikolsky's sign) at first molar area; (F) Scarring at lateral canthus of the eye



Figs 2A to C: Histopathological section of MMP representing the following: (A) Subepithelial cleft (H & E magnification; 5×); (B) Diffuse inflammatory cell infiltrates in the lamina propria constituted mainly of lymphocytes and plasma cells with scattered neutrophils; (H & E magnification; 20×); (C) Erythrocytes were seen in the subepithelial space (H & E magnification; 20×)

tolerance level was improved since the lesions had crossed the acute phase. The patient was also instructed to use a non-alcoholic chlorhexidine mouth rinse and to keep optimal oral hygiene practices.

For eye irritation, the patient was advised to see an ophthalmologist for further evaluation. The ophthalmologist prescribed an eye drop medication named (Loxtra). As per the manufacturing pharmaceutical company, each milliliter of Loxtra contains benzalkonium chloride 0.05 mg (as preservative), ofloxacin 3.0 mg, HPMC as a vehicle, tetrahydrozoline hydrochloride 0.4 mg, and prednisolone acetate 2.0 mg. This eye drop is indicated for corticosteroid-responsive conjunctival inflammations. The prescribed dose was one drop for each eye, 4 times a day for 1 week. At 4 weeks, healing of all ulcerative lesions was evident and the patient was able to function normally (Fig. 3); healing of inflammation on labial (Fig. 3A), palatal (Fig. 3B), and lingual mucosa (Fig. 3C), respectively. Regular follow-up visits at 6 months and 1 year were done in which the patient did not reveal any recurrence of the lesions.

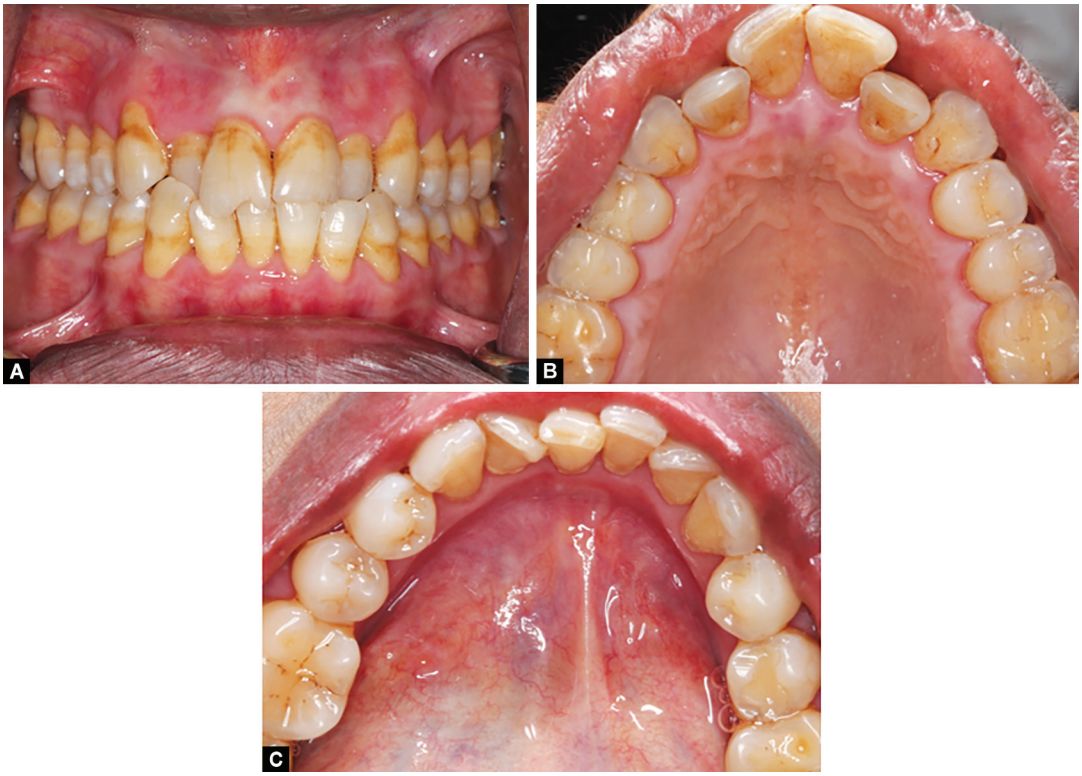
Discussion

Autoimmune subepidermal blistering disorders or immune-mediated subepithelial blistering diseases (IMSEBD), belong to a class of mucosal/dermal diseases, representing a common feature of subepithelial blistering.[12] The etiology of MMP is unclear. It can be attributed to genetic predisposition such as HLA-DQB1*0301,[13] severe inflammatory injury to the mucosa, drugs (clonidine, indomethacin, penicillamine-D, and atenolol),[2,14] viruses, and ultraviolet rays. Our case presented with an initial diagnosis of gingival inflammation given by a general dentist whom the patient had visited earlier. Clinical signs of plaque-induced gingival inflammation which led to this initial diagnosis include bleeding upon probing, changes in contour and consistency, redness, and edema of the gingival tissue, changes in tissue texture of gingiva manifested as smooth and shiny with loss of stippling, and presence of calculus and/or plaque. Therefore, a thorough clinical examination and a biopsy were considered at the first visit to arrive at a definitive diagnosis. Differential diagnoses to be considered when a biopsy of such lesions is advised to include allergic reaction, erythema multiforme, vesiculobullous diseases, etc.

In this case, the patient gave a significant medical history of hypertension, hyperlipidemia, and hyperuricemia, for which she was on medication. Kanjanabuch et al. in a case report stated a case of atenolol-induced MMP in which the patient showed generalized redness, inflammation, and desquamation of gingiva, large areas of gingival ulceration covered by a pseudomembranous slough.[15] Discontinuing the drug-inducing lesions could help us resolve such cases.

In 2016, Dharman et al. discussed two unique cases of oral MMP showing no ocular or cutaneous involvement. One case showed a generalized mucosal involvement of the oral cavity compared to the other case wherein the lesion was localized to the left upper posterior vestibular region. Clinical examination revealed the presence of inflammation, and localized ulceration, on the application of lateral pressure there was the formation of a new vesicle on adjacent mucosa eliciting positive Nikolsky's sign.[8]

Most autoimmune blistering diseases show an overlapping of clinical features which makes it difficult for the clinician to arrive at a definitive diagnosis. Gingival inflammation along with desquamation of gingiva is typically present in most autoimmune diseases showing mucosal involvement. Hence, a differential diagnosis of lesions such as pemphigus vulgaris, ulcerative lichen planus,[10] erythema multiforme, epidermolysis bullosa, and paraneoplastic pemphigus has to be considered.[16] In pemphigus vulgaris the bullae would be less tense and rupture easily when compared to MMP and also will not be associated with conjunctival symptoms. Ulcerative lichen planus could be distinguished by the



Figs 3A to C: Four weeks follow-up visit. (A) Healing of inflammation on labial; (B) Palatal; and (C) lingual mucosa, respectively

presence of white striae circumscribing the ulcers. In Erythema multiforme the lesions would have a characteristic "target or bull's eye" lesion. In epidermolysis bullosa, the blisters are usually induced by trauma. These lesions also show periods of remission and exacerbation.

The histopathologic features of MMP are characterized by subepithelial clefts showing separation of the superficial epithelium from underlying connective tissue. The underlying lamina propria shows a mixed inflammatory infiltrate comprising of plasma cells, eosinophils, neutrophils, and lymphocytes. The presence of erythematous areas showing red blood cells (RBCs), edema fluid, and histiocytes can also be noted.[17] Our case showed a similar histopathological picture where the surface epithelium was detached from the underlying connective tissue at the point of the BMZ. The lamina propria was infiltrated by lymphocytes and plasma cells with scattered neutrophils and erythrocytes seen in the subepithelial space. Further, lesions showing subepithelial blistering, that is, lichen planus, pemphigoid, linear IgA disease, and epidermolysis bullosa should be considered under the differential diagnosis of such cases.[11] In cases of lichen planus, hydropic degeneration of the basal layer along with lymphocytic infiltration is observed. Histopathology of pemphigoid reveals, subepidermal split with dermal infiltrate of plenty of eosinophils whereas, epidermolysis bullosa shows subepithelial space with luminal infiltration with eosinophils. Linear IgA disease has a characteristic subepidermal split along with numerous neutrophilic microabscess.[9]

Direct Immunofluorescence studies are proven to be one of the most important diagnostic aids in the investigation of vesiculobullous lesions. The pemphigoid family (herpes gestations, cicatricial pemphigoid, and bullous pemphigoid), a bullous variant of systemic lupus erythematosus, and epidermolysis bullosa acquisita are characterized by the linear deposition of Ig's along the BMZ.[18] Cicatricial and bullous pemphigoid show deposition of C3 and IgG at the basement membrane. Bullous variant of systemic lupus erythematosus and epidermolysis bullosa acquisita usually have multiple classes of immunoreactions. Indirect immunofluorescence (IIF) is generally performed to identify circulating autoantibodies to the BMZ, but it shows positivity in about 17–53% of cases. Moreover, 1-M NaCl-split skin indirect immunofluorescence IIF (ssIIF) is more sensitive than IIF. The staining of ssIIF with MMP sera produces linear IgG deposits in 58–82% of MMP cases which is determined by the binding of circulating IgG and IgA to target antigens in the epithelial BMZ such as antigen BP180, BP230, and laminin 5.[4] This technique helps us to differentiate between epidermal and dermal binders and hence useful in the identification of subepithelial blistering diseases. Immunoblotting using epidermal or dermal extracts and recombinant antigenic polypeptides is also considered to be one of the recent diagnostic modalities. Goletz et al. performed a specific IIF assay using laminin 332-expressing human HEK293 cells for the detection of anti-laminin 332 autoantibodies.[19] Correlation of clinical features, medical history, and histopathologic findings including immunofluorescence, antibody titer provides a valuable data and aids in arriving at a proper diagnosis.[20]

In this case, we did not perform any of the special diagnostic procedures since it was a straight forward case. Histopathology being the gold standard, our case was diagnosed based on the microscopic findings alone.

The treatment modality for MMP changes based on the disease severity, site involved, and the patient's age, as there is no standard protocol for treatment.[17] In mild cases, topical corticosteroids, tacrolimus, and intralesional corticosteroids can be given. In moderate-to-severe disease immunosuppressive drugs come in four different categories, namely, antimetabolites (methotrexate and mycophenolate), T-cell inhibitors (cyclosporine and daclizumab),

B-cell inhibitors, and cytotoxic agents (cyclophosphamide and chlorambucil) can be prescribed. Severe and refractory disease can be managed with biologic therapies such as CD-20 monoclonal antibody (rituximab), tumor necrosis factor (TNFα) antagonist (etanercept), and intravenous Ig. Systemic and topical corticosteroids with or without immunosuppressive drugs, tetracycline,[20] and dapsone[21] are used widely as treatment alternatives.

In this case, we prescribed a topical corticosteroid (clobetasol propionate 0.05%, dermovate cream) and an antifungal agent (Nystatin 100,000 units) 2 times a day to avoid secondary infection.[22] The course of the disease might be aggravated by the concurrent presence of plaque-induced gingival inflammation, hence it is of prime importance to perform effective periodontal therapy and reinforce the proper oral hygiene practices in order to eliminate etiological factors that can elicit gingival inflammation and delay the response to treatment.[23,24] Periodic follow-up with the maintenance of proper oral hygiene can help the patient in improving the pain and associated symptoms.[25]

Conclusion

Mucous membrane pemphigoid is a chronic disease that does not follow a definitive pattern, it shows periods of remission and exacerbation posing a challenge in diagnosis. Clinicians should correlate clinical features, medical history, histopathology, and immunologic techniques to arrive at a final diagnosis. A multidisciplinary approach is often necessary in order to treat these lesions efficaciously. This case showed oral and ocular involvement of MMP which was treated effectively with topical corticosteroids, and adjuvant antibacterial and antifungal therapy. The response to local treatment was augmented via effective periodontal therapy to control the concurrent plaque-induced gingival inflammation and via using a customized application tray to sustain the drug efficacy. Dental professionals along with other health care workers should recognize the lesions at the earliest and help the patient to aid in the proper management of the disease.

Clinical Significance

Early diagnosis and effective treatment protocol using systemic or topical corticosteroid therapy along with other therapeutic means including periodontal therapy, good oral hygiene practice, and timely follow-up are very useful in preventing long-term complications due to this disease.

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