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Letter to the Editor

MUCOUS MEMBRANE PEMPHIGOID AFFECTING THE ORAL MUCOSAE: A BRIEF REVIEW

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ABSTRACT

A mucous membrane pemphigoid is a group of immune-mediated mucocutaneous diseases characterized by the formation of blisters whose rupture leaves an erosive area. It is classified as a rare disease with an unknown aetiology, although some agents may be considered causative. The pathogenesis consists of a subepithelial detachment caused by autoantibodies against basement membrane proteins. The diagnosis is made by integrating clinical appearance, histopathology, and direct immunofluorescence. Other diagnostic aids are indirect immunofluorescence and enzyme-linked immunosorbent assay. The main treatment is systemic and/or topical corticosteroids; in non-responsive patients, there are innovative alternative treatments with immunosuppressants and rituximab.

KEYWORDS: *Pemphigoid, oral, vesicle, disease, medicine, pathology*

INTRODUCTION

The term mucous membrane pemphigoid (MMP) refers to a variety of chronic, immune-mediated, vesiculobullous disorders that are heterogeneous in nature. They affect the skin and oral mucosa with vesicles, blisters, and erosion due to the formation of self-antibodies against the basal membrane and subsequent subepithelial attachment loss (1). MMP is the most common acquired autoimmune bullous dermatosis, with an incidence ranging from 6 to 14 new cases per year per million population (2). It occurs without gender predilection during the sixth decade of life, although rare cases of MMP in children and adolescents have been reported. The aetiology remains unknown, although several studies have shown a genetic predisposition with the involvement of the HLA-DQB1*0301 allele (3). Physical triggers (radiotherapy, ultraviolet radiation), burns, trauma, drugs such as vaccines, or even chronic use of spironolactone and phenothiazines have been found in 15% of patients diagnosed with MMP (4).

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Pathogenesis and the auto-antigens

MMP is characterized by antibodies directed against self-antigens of the hemidesmosome plaque known as BP180 (180 kDa) or BPAG2 and BP230 (230 kDa) or BPAG1. Both antigens are key hemidesmosome components responsible for the adhesion between epithelium and underlying connective tissue (1). Other target antigens are laminin 332, α6/β4 integrin subunits, laminin 311 and type VII collagen.

Antibodies directed against the α6 subunit are frequently associated with mucosal lesions, while autoantibodies against the β4 subunit are generally associated with ocular involvement. Antibodies directed against laminin 332 are associated with a more severe disease involving multiple mucosal sites (5). IgG (subtypes IgG1, IgG3, and IgG4), IgA and IgE (rarely) are the primary autoantibodies implicated. The binding of these autoantibodies to the basement membrane triggers complement activation that culminates in the release of metalloproteinases and cytokines responsible for dermal-epidermal detachment.

Clinical manifestations on the mucosal sites

Desquamative gingivitis, which occurs in 85% of instances of MMP, is the most common manifestation, followed by conjunctivitis in 65% of cases. Less frequently, the vaginal, nasal, pharyngeal, laryngeal, and oesophageal mucosa are affected. Less than 30% of patients develop skin lesions (6). In addition to the gingiva, lesions may involve the buccal mucosa, palate, and tongue. Sometimes vesicles may appear brownish-red in colour when blood extravasation is involved. However, the blisters quickly burst, resulting in an erosive area. The erosions are very painful and take a few weeks to heal with the simultaneous formation of other lesions, while ocular lesions are less frequent. They begin as chronic conjunctivitis of the sclera with fibrosis outcomes, which can lead to symblepharon (fusion of the sclera with the palpebral conjunctiva), entropion (inversion of the palpebral margins) or ankyloblepharon (fusion of the eyelids) up to blindness.

A challenging diagnosis

In most cases, the diagnosis of MMP is complex; the symptoms and signs are non-specific and vary from one form to another (7). The diagnosis is based on the evaluation of three criteria:

- Clinical manifestations
- Histological examinations: histological examination and direct immunofluorescence (IFD)
- Serological examinations: indirect immunofluorescence (IFI) and enzyme-linked immunosorbent assay (ELISA).

An examination is the starting point for making a diagnosis. The presence of vesiculobullous and erosive lesions at the level of the oral mucosa and/or the skin level are clinical findings shared by several autoimmune diseases. Nikolsky's sign (8) is helpful during the examination. It can be evocated directly or indirectly. The direct method consists in applying pressure, e.g. by blowing air, directly on an already present lesion; if it is a bullous lesion, this gesture will cause the lesion to expand.

On the other hand, the indirect method involves applying pressure, using a blunt instrument, directly on the healthy mucosa; in the case of a vesiculobullous pathology, this action results in the formation of a blister. Given its lack of specificity, this clinical examination is only helpful in directing the pathologist during the diagnostic procedure. It allows us to highlight an epithelial detachment but not its nature.

The mucosal examination is fundamental for an early differential diagnosis; a negative Nikolsky's sign and the absence of white reticular lesions can be helpful to differentiate pemphigoid from lichen planus; the clinical way the ulcerative lesions appear can lead to the differentiation of the pemphigoid from recurrent aphthous stomatitis or ulcerative cancer lesions. Thus, an accurate physical examination and a highly experienced and trained clinician are essential for an adequate second-tier analysis.

Biopsy: a crucial exam

The histological examination provides an incisional biopsy (9). In order to perform an adequate histological analysis, it is crucial to take a sample of perilesional tissue, i.e. at the edge of the lesion, where healthy tissue is present. Biopsy sampling in cases of suspected bullous pathology is extremely delicate and complicated, as simple tweezing or mishandling of the surgical specimen carries the risk of iatrogenic epithelial detachment, thus preventing adequate anatomopathological evaluation.

The technique currently used to perform the biopsy is the stab-and-roll technique (10). It involves inserting the scalpel

blade perpendicularly to the gingival mucosa; the blade is rotated within the cutting margins before reaching the bone surface. This way, the forces are directed in a single direction without causing epithelial detachment of the specimen, unlike the direct technique. However, the latter requires a deeper incision resulting in a more significant movement of the scalpel blade.

Sampling can also be performed using a 6-mm diameter punch, which makes the size of the piece homogenous and standardized and allows for less handling of the surgical piece. After sampling, the surgical piece is fixed in formalin to avoid tissue alterations that could affect the microscopic analysis. Moreover, it is not sufficient to assess the presence of an epithelial detachment, which is common in different vesiculobullous diseases.

The pathological mark in MMP is the presence of sub-epithelial vesicles with an inflammatory infiltrate represented by lymphocytes, eosinophils, and neutrophils. There are no Tzank cells, and the epithelium does not have a tombstone pattern. Sometimes, however, a reparative process at the level of the basement membrane can make it difficult to differentiate between intraepithelial and subepithelial detachment, making the histological exam not diriment. For this reason, a histological examination is completed with immunofluorescence analyses to confirm the diagnosis.

Direct immunofluorescence represents the diagnostic gold standard in the context of vesiculobullous pathologies and is essential for diagnosis in doubtful cases. Moreover, immunofluorescence can be considered more sensitive than conventional histological examination because autoimmune deposits generally precede the appearance of epithelial detachment. This diagnostic method involves a biopsy of perilesional tissue, performed simultaneously with the histological examination. According to Gilvetti et al. (11), the optimal sampling site for direct immunofluorescence analysis is the gingiva, which is thus optimal in the case of patients with desquamative gingivitis. It also appears that the optimal technique is punch sampling.

Direct immunofluorescence provides quantitative information about target antigens, immunoglobulin subclass and binding type. In pemphigoid, direct immunofluorescence microscopy reveals the intercellular binding of immunoglobulins within the epithelium giving the typical linear deposition of immunoglobulins at the basement membrane.

Indirect immunofluorescence is a serological method that tests for autoantibodies in the patient's serum. Indirect immunofluorescence microscopy uses a substrate of various kinds, including monkey skin, rabbit, and human oesophagus, which is incubated with the patient's serum (12). Then fluorochrome-labelled antibodies are added and directed against the patient's autoantibodies. Indirect immunofluorescence, although performed during the diagnostic procedure for bullous disorders, is not considered sufficient to make a definitive or differential diagnosis.

Enzyme-Linked Immunosorbent Assay (ELISA) is an enzyme immunoassay that identifies and quantifies autoantibodies directed against specific antigens in each sample. ELISA is a method used for diagnosing and monitoring disease following therapy. This method involves a primary binding between the antibody in the patient's serum and a specific antigen, thus forming a primary complex. Next, a specific antibody conjugated with an enzyme is introduced, which binds to the primary complex, resulting in a coloured product. Finally, analysis by spectrophotometer allows evaluation of the response, which correlates with the intensity of the signal.

For the diagnosis of pemphigoid, currently marketed kits use recombinant forms of the NC16A portion of BP180, the C-terminal and N-terminal sequence of BP230, and type VII collagen (13). The ELISA method is performed on serum; recent studies also apply this method to the patient's saliva. Such studies aim to use saliva as a diagnostic method, as it is less invasive and troublesome for the patient than a blood sample.

Treatment

The severity of MMP has a significant impact on how it is treated. Patients with modest risk factors may initially need topical treatment, but high-risk patients may also need effective systemic therapy. Systemic corticosteroids have been proven to have an effective result in treating MMP, yet they have adverse effects when used long-term. Therefore, other medications, such as immunosuppressants, biological agents, inflammatory-reducing medications, and antibiotics, are also used (14).

CONCLUSIONS

MMP is a defined nosological entity which needs an clinical and laboratory diagnosis. It is caused by several factors and therapy is mainly based on the use of an immuno-suppressant agent.

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