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Focus on oral pemphigus vulgaris's management

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Abstract

Pemphigus vulgaris is an intraepidermal autoimmune dermatosis characterized by autoantibodies directed against desmoglein 1 and / or 3, which are transmembrane proteins constituting desmosomes. It is a potentially fatal pathology, with very painful cutaneous and mucous manifestation. A reasoned and early management is of great interest. The European Dermatology Forum's (EDF) recommendations (October 2016), based on the High Authority for Health's (HAS) recommendations (April 2016), have established a precise care approach. Diagnosis is raised by clinical features; then confirmed by histological aspect and direct immunofluorescence. Treatment is based on general corticosteroid therapy for a prolonged period. The adjunction of immunosuppressants is often useful for cortisone sparing. The HAS also established recommendations for the oral management of patients with oral pemphigus vulgaris. These recommendations are intended to reduce the lesions's symptomatology and to improve the patient's quality of life.

Keywords: Pemphigus vulgaris, management, diagnosis, treatment, bucco-dental condition, autoimmune bulbous skin disease

Introduction

Pemphigus vulgaris is an autoimmune bullous dermatosis characterized by the formation of mucocutaneous bubbles. Indeed, the word pemphigus derives from the Greek word "pemphix", which means blister or bubble^[1]. A bubble consists of the accumulation of a liquid (serum or lymphatic exudate) within the cutaneous^[2] or mucosal structures.

In autoimmune bullous dermatoses (AIBD), the bubbles correspond to acantholyses or disjunctions caused by the deleterious action of autoantibodies. Within junctional AIBD or pemphigoides, auto antibodies are directed against the constituents ensuring the cohesion of the cutaneous epithelium to the underlying dermis. However when directed against interkeratinocyte junction systems (notably desmosomal cadherins such as desmogleine (dsg) 1 and 3), the lesion is intraepithelial AIBD or pemphigus.

There are two main types of pemphigus: superficial pemphigus and pemphigus vulgaris. For the first one, acantholysis occurs in the superficial granular layers of the epithelium with a strictly cutaneous presentation and dsg1's involvement. The second presentation is most common, the acantholysis occurs in the epithelium's deep layers, especially above the suprabasal layer with Dsg 1 and / or 3 involvements^[2-4].

Pemphigus vulgaris (PV) is a rare disease (global annual incidence estimated at 0.1-0.5 per 100,000), most common (more than 70% of cases), and potentially life-threatening^[1]. It has a slight female predominance, and has a predilection in 5th or 6th decade^[5]. It has an insidious onset with mucocutaneous manifestations. The first lesions are often mucosal, in which oral manifestations, very painful, are more common than genital and eye damage^[3-4]. The mucosal manifestation is followed, a few weeks later, by cutaneous manifestations. There are, however, cases of strictly mucosal PV^[3-4].

The prognosis depends partly on the extent of the cutaneous lesions. The adjunction of an acute infection, especially herpetic, is not uncommon and is life-threatening. Early and reasoned care is of great interest. The EDF's recommendations (October 2016), based on the French HAS's recommendations (April 2016), established a clear and precise care approach, both for diagnosis and therapeutic approach.

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Diagnostic work-up

The diagnostic approach of pemphigus consists first on, knowing how to raise the diagnosis based on the lesions's clinical aspect, second on performing a clinical assessment of the patient, before confirming the diagnosis by histological and immune complementary examinations [6-7].

The diagnosis of AIBD should be considered whenever there is intense painful symptomatology, preventing dental hygiene and nutrition, causing undernutrition and weight loss [8, 9]. This symptomatology is associated with mouth lesions presenting as bubbles, blisters filled with serosity [3, 4]. The flaccid and fleeting aspect of these bubbles causes most often erosions with jagged edges, dark red background, pseudomembranes and perilesional white slot of leucœdema [10].

Cutaneous involvement is characterized by Nikolsky's sign. The direct Nikolsky's sign is positive when a slight pressure on a bulb results in its extension to the adjacent skin. However Indirect Nikolsky's sign (fig 1) is positive when friction on clinically normal skin causes skin abrasion.

These signs are not always reliable for the diagnosis of PV, but they are suggestive when present [11].



Fig 1: Indirect Nikolsky signe [12]

Once the diagnosis is suspected, a clinical assessment must be performed. It aims to assess the dental and periodontal status of patients, to specify the location and extent of oral lesions and to classify them [8, 9].

3 phases are to distinguish

- Severe oral impairment (often initial disease's stage): numerous and / or extensive oral erosive lesions.
- Moderate oral impairment: few and small oral erosive lesions.
- Minimal oral impairment: healed lesions under treatment (disease controlled by treatment), but persistence of mouth sensitivity.

Confirmation of the diagnosis involves additional examinations. These are based on biopsies of the oral mucosa, or skin (if skin involvement is associated) [10].

A first biopsy is performed for standard histology. It's more accurate to take the specimen from a recent intact bubble's area or from an erythematous, erosive or ulcerated zone [13]. Fixture is insured by 10% formalin [8, 9].

Histopathological lecture shows, classically, (fig 2) intraepithelial, supra-basal cleavage with acantholysis and retention of a single layer of basal keratinocytes along the membrane base [7]. These histopathological features can also be observed in other oral diseases, such as oral lichen planus and erythema multiforme [13].

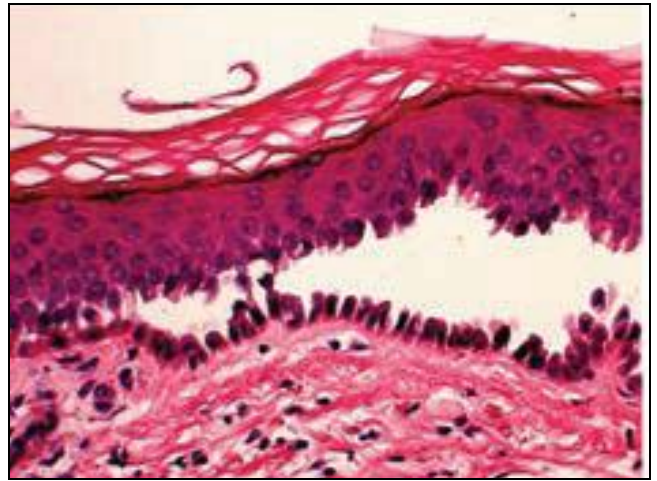


Fig 2: Standard histology: intraepithelial, supra-basal cleavage [14].

A second simultaneous biopsy is performed for direct immunofluorescence (DIF). The sample is taken from the lesion's nearby area (2 cm from an active bubble). For best results, it is transported in saline, and better of be delivered immediately to the laboratory. If necessary, it is transported in a bottle of Michel's liquid, [11] or in a bottle of liquid nitrogen [4].

The DIF objectify deposits of IgG and C3 (complement component) on the surface of keratinocytes presenting as "fishnet" or "mesh of net" appearance. The Labeling can be restricted to basal keratinocytes, [4] and confirms the disease's autoimmune nature.

Other complementary tests may be secondary requested, including assays for blood autoantibodies. They have especially a role in pathology's follow-up [8, 9].

Therapeutic approach

This part of treatment is ensured by the dermatologist. It aims to: [8, 9].

- Heal the bulbous eruption and eliminate the functional discomfort linked to the disease;
- Prevent or strictly limit the occurrence of recurrences;
- Improve the patients' quality of life;
- Limit common side effects associated to the usual extended treatment's duration.

Two phases of the treatment are to distinguish: initial phase and maintenance phase [9].

The initial phase aims to control the pathology. At present, the mainstay treatment remains systemic corticosteroid therapy [15, 16]: prednisone 1 to 1.5 mg / kg / day. [9] Although highly effective, the significant side effects of long-term corticosteroids' use must be taken under consideration, complication's manifestation may present on bones (cortisone osteoporosis), digestive tract (ulcer), or as neuropsychiatric, infectious, metaboli.

The immunosuppressive associated therapies could manage or at least decrease the required dose of corticosteroids [15] as the use of azathioprine, mycophenolate mofetil, rituximab, intravenous immunoglobulin, or methotrexate [9, 15].

Topical treatments, could be benefic if combined to systemic treatments as the application of clobetasol gel (dermoval®), mouthwashes (effervescent prednisone) or corticosteroid spray [8].

The maintenance phase is initiated once the pathology is controlled. In this phase, the treatment is maintained with a gradual reduction of corticosteroid doses. The goal is to reach a dose of 0.2 mg / kg / day or less, while maintaining the

remission state without relapse [9].

It is very important to point out that it is strictly contraindicated to prescribe systemic or even topical corticosteroid therapy immediately after the diagnosis's suspicion, before carrying out the immunological complementary examinations, at risk of obtaining false negatives [9].

Oral management [8]

The HAS's (April 2016) managed to simplify and codify the recommendations of pemphigus vulgaris's oral management. 3 steps are to respect: first patient's motivation to daily oral hygiene, then carry out the dental and periodontal care and finally ensure follow up.

Daily oral hygiene procedures depend on the progression stage of pemphigus vulgaris's oral lesions.

Table 1: daily oral hygiene procedures of the patient depend on the progressive oral involvement's stage pemphigus vulgaris.

Severe oral impairment	Moderate oral impairment	Minimal oral impairment
<p>Composite mouthwashes (MW) : Eludril® 4% 90ml + Mycostatin® 24ml + Xylocaine® 5% 24ml + Bicarbonates 14 % 362ml</p> <p><u>Dosage:</u> 1 glass (80 cc) 6 X / day (before and after meals), leave in the mouth at least 1 minute, then spit out, without rinsing the mouth afterwards.</p> <p>As soon as possible: gentle teeth brushing (cervical dental regions ++) 3 X / day (after each meal, before BDB) 7 / 100th ultrasoft toothbrush and 0.12% chlorhexidine gel. At this stage no interdental brushing is needed</p> <p>On painful lesions, before meals and / or before toothbrushing: Xylocaine viscous 2% gel (Prevent patients from the risk of false routes with Xylocaine.)</p>	<p>Stop composite MW, use non-alcoholic BDB based on chlorhexidine 0.12% after teeth brushing 3X / day.</p> <p>Teeth brushing : 3X / day, after each meal, standard toothbrush 15 / 100th (or maintain a 7 / 100th toothbrush at the level of cervical dental regions if gingival sensitivities persist) and toothpaste for children or chlorhexidine gel at 0.12%</p>	<p>Stop MW</p> <p>Teeth brushing 3X / day standard toothbrush 15 / 100th and fluoride toothpaste without menthol nor lauryl sulfate</p> <p>Interdental brushes.</p>

When performing dental and periodontal care, the high degree of mucosal fragility must be kept in mind, therefore the need to respect specific rules is common to all treatments:

- Slow local anesthesia (drip), pricking away any lesions. Loco regional anesthesia should be preferred.
- Salivary cottons should not be placed on gums (replace with soaked compresses in 0.12% chlorhexidine or physiological saline).
- No contact salivary aspiration / oral mucosa should be tolerated: aspirate through a compress
- Treatments should be as "conservative" as possible in order to maintain dental prosthetic supports as long as removable dentures are often uncomfortable.
- Conduct conservative dental care if possible "under rubber dam" (or by applying vaseline on the instruments that touch the oral mucosa in case of inability to lay the rubber dam).

The accessibility to dental care depends on oral impairment's stage.

During severe oral impairment, dental or periodontal care other than the following types should be avoided:

- Manual removal (curette) of supra-gingival dental plaque (at the cervical region), without carrying out a scaling.
- Management of emergency situations: acute pulpitis, acute apical periodontitis, terminal alveolysis, periodontal abscess, pericoronitis and cellulitis of dental origin.

During mild or moderate oral impairment, gentle, progressive manual descaling along with infectious lesions' treatment (juxta-pulpal caries or apical periodontitis) should be performed as soon as possible.

The accomplishment of non-urgent dental extractions, fixed

(ideally) and removable prostheses, establishment of orthodontic devices as well as root planing and periodontal surgery (access surgery) must await the complete or almost complete oral lesions' remission.

Dental and periodontal follow-up is an essential and necessary step after obtaining clinical remission, with a frequency of 2 to 3 times a year, at least for the first years following diagnosis.

Conclusion

PV is an insidious pathology. The early and effective management is the prime measure. Since oral lesions are often the first in line, the dentist must respect the treatment approach, as described by the EDF European recommendations (October 2016), as well as the HAS's recommendations (April 2016), especially by avoiding to initiate corticosteroids' treatment before a confirmed diagnosis. The dentist must also ensure oral lesion's management by motivation to oral hygiene and removal of irritants; this will ensure improvement in the patient's quality of life.

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