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Isolated oral pemphigus vulgaris: Case series of 15 patients

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Abstract
Pemphigus is a chronic inflammatory autoimmune bullous disease that affects the oral mucosa and is sometimes difficult to diagnose when only mucosal involvement is present. We performed a retrospective descriptive study including 15 cases of isolated mucosal pemphigus (mPV). We noticed that this rare form is characterized by it slow healing, a female predominance with frequent relapses.

Keywords: pemphigus vulgaris, oral mucosa, mouth disease, desmoglein 3, erosions

1. Introduction
Pemphigus is the most frequent autoimmune bullous disease in the Maghreb, it represents the leading cause of hospitalization in our center with 15 new cases / year [1]. Depending on the antibody profile (desmoglein 1 or 3) and the level of cleavage (acantholysis): several forms of pemphigus exist; the deep form or pemphigus vulgaris (PV) can be subdivided into 2 subtypes: mucocutaneous (mcPV) and pure mucous PV (mPV). Given the rarity of isolated oral mucosa involvement, it seemed interesting to us to carry out a case study in order to determine the epidemiological and clinical peculiarities of this form.

2. Materials and methods
We performed a descriptive and unicentric retrospective study carried out over a period of 30 years from november 1990 to July 2020 in the dermatology department of the Ibn Sina University hospital in Rabat (Morocco), collecting 125 cases of pemphigus vulgaris, of which 15 had isolated disease of the oral mucosa without skin involvement at the time of diagnosis confirmed by mucosal biopsy, direct and indirect immunofluorescency (DIF, IIF). Data extracted from medical records included: age, sex, median time before consultation, site of lesions, IIF rate, course and treatment. The disease activity was retrospectively scored using the Japanese Pemphigus Disease Area Index (PDAI). We excluded from our study patients who developed skin involvement subsequent to diagnosis. Data collection and analysis were conducted using Microsoft Excel 2018 and. Descriptive statistical methods were applied. Data are presented as median and range.

3. Results & Discussion
3.1 Results
The median age of consultation was 53 year-old, the female to male ratio was 4 (12 females and 3 males). The mean consultation time was 13.16 months, the PDAI was severe in all our cases, 4 patients had an IIF rate at baseline 1280 ui/l, 4 others at 320 ui/l, 4 patients between 20-80 ui/l, the IFI was negative in 3 cases. The site of the lesions was as follows: inner part of the cheeks (4/15), gingiva (3/15), lower lip (4/15), palate (10/15) (figure 1). Koebner phenomenon was found in 8 cases. Oral steroids (2mg/kg per day) combined with azathioprine was initiated in 11 patients, prednisone and rituximab in a single patient, and steroids alone 3 cases. In order to accelerate the healing process 35% of TCA (tricholoroacetic acid) was applied topically in perilesional mucosal lesions in 4 patients.

The evolution of the patients was as follow: complete remission (4/15) after a complete remission of 3 months, clinical and immunological relapse (8/15), treatment failure (1/15), death (1/15), 1 patient was lost to follow-up. 8 patients developed oral candidiasis, 4 others developed herpes infection (figure2), and one patient developed Sars-Cov2 infection.

3.2 Discussion

Pemphigus is a life threatening disease defined as an acquired autoimmune bullous dermatosis, where blisters are due to a loss of interkeratinocyte adhesion (acantholysis) in the epidermis and the mucous membranes secondary to the production of anti-inflammatory antibodies against various desmosomal proteins. Depending on the level of cleavage (supra-basal or sub-cornea) and the anti-desmoglein profile (anti-DSG 1 or 3 or both): different types of existing pemphigus:

- Superficial pemphigus (foliaceous and seborrheic also called erythematosus)
- Deep pemphigus (vulgar and vegetans)
- Other types of pemphigus: paraneoplastic pemphigus and IgA pemphigus, pemphigus herpetiformis and induced pemphigus.

The diagnosis is made based on: clinical arguments (superficial blisters, erosions and positive Nikolsky's sign), histological finding (acantholtic cells, blisters and intraepidermal cleavage with positive direct immunofluorescency) and immunological profile (a positive deposit of antibodies in the intercellular substance, positive rates of anti DSG 1 and/or DSG3).

The involvement of oral mucosa in pemphigus vulgaris is caused by a supra-basal interkeratinocytic cleavage secondary to the development of anti-desmoglein 3 autoantibodies. The prevalence of isolated erosions of the mucosa varies according to HLA phenotype and ethnicity. One recent multicenter study in several countries showed that Bulgarian patients had less frequently oral mucous membrane lesions (66%) compared with Italian (83%) and Israeli (92%) patients [2].

In pemphigus vulgaris, oral lesions are common, they appear one or two months before the onset of the disease in 50–75% of cases [3], they are typically seen in adults (rarely during childhood [4, 5].

Clinically, the erosions are bordered with a yellowish white pseudomembrane, they are painful and interfere with eating, which can be responsible for weight loss, dehydration and severe undernutrition. The lesions can involve the entire oral cavity, However, the most common sites are the palate, lips, buccal mucosa, tongue [6], gingival lesions are less common they include: severe desquamative and erosive gingivitis characterized by red erosions and deep ulcerative craters [7]. Koebner's phenomenon is one of the triggering factor that maintain the persistence of the lesions. Some severe cases with extension to the pharynx and the esophageal mucosa have been described with a possible evolution into an oesophagal cancer.

The lack of awareness of the mucosal involvement in pemphigus patients and the confusion with canker sores, oral lichen, drug eruption (Lyell syndrome or erythema multiform) or even post traumatic erosions are the main causes of diagnostic delay. Thus, patients can develop severe forms of pemphigus with high PDAI> 45 score.

According to recent studies, mucosal involvement is correlated with severity of the disease (PDAI) but also with the risk of relapse. In fact, in the study by Cho *et al.* [8], the risk of relapse was 4.626 times higher in patients with mucosal lesions than patients without mucosal involvement. In addition, patients with isolated oral disease responded less to treatment with rituximab and relapsed more frequently, moreover, the risk of relapse in these patients was equivocal in both sexes, concluding that pemphigus vulgaris would be more likely to relapse than pemphigus foliaceous, in addition to a higher risk of relapse as the disease begins with mucosal involvement.

The main aim of the treatment is to maintain a long term remission. Oral pemphigus vulgaris is generally managed by strict hygienic measures: for instance, dental care should be gentle and performed as much as possible outside of the disease's outbreaks. According to the Haute autorité de la santé (HAS) French guidelines [9]: when the lesions are accessible; topical steroids (clobetasol gel) are preferred, mouthwash with effervescent prednisolone and injection of triamcinolone are possible in case of refractory lesions. The association with antiseptic and anesthetic mouthwashs or xylocaine can be used for their analgesic effect. Mycostatin is used for prophylaxis against candidiasis infections especially if patients are under steroids or other immunosuppressive therapy. Once the erosions start to heal, a gentle tooth brushing can be prescribed 3 times per day (after each meal, before mouthwashes) with an ultra-soft 7 / 100th toothbrush using 0.12% chlorhexidine gel. In case of poor tolerance: the use of water or children's toothpaste is an alternative. It is very important to educate the patient toward the mechanical action of brushing that should be gentle in order to avoid any damage of the gum tissue. In case of persistent refractory lesions, Mahmoudi and al recommend the use of topical trichloroacetic acid (TCA) 33% using a cotton-tipped swab at the periphery of the lesions two times per week [10].

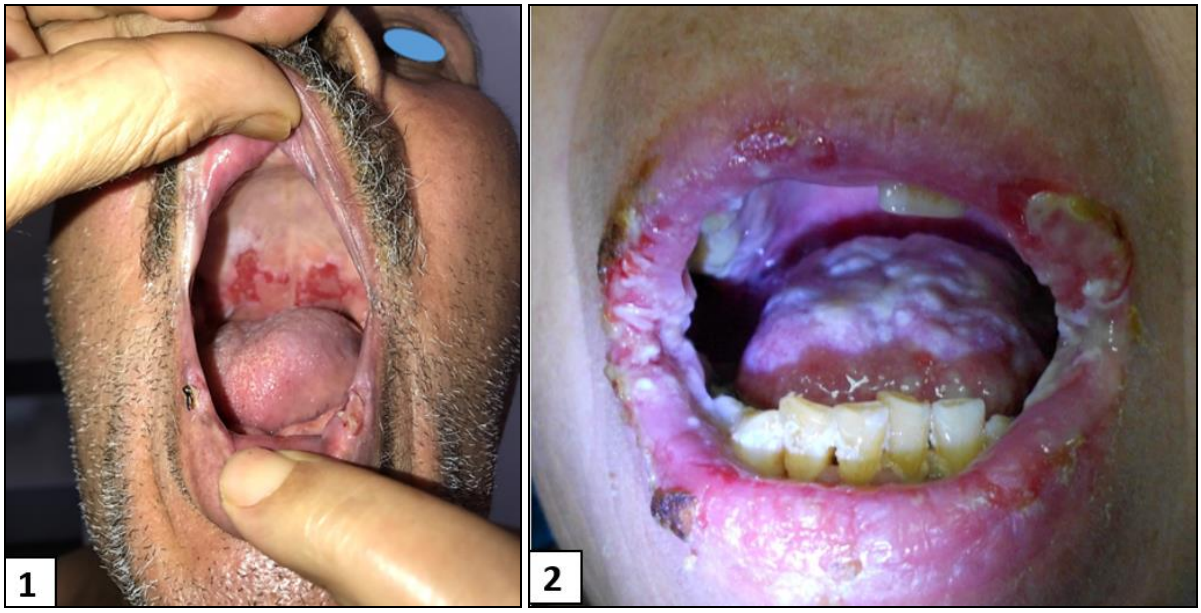

Fig 1 and 2: Involvement of oral mucosa (soft palate and labial mucosa) in Moroccan patients with isolated mucous pemphigus vulgaris (Mpv)

4. Conclusions

To conclude, isolated mucous pemphigus is a rare entity characterized by: a female predominance, a severe PDAI, a slow healing and frequent relapses which often requires systemic treatment and long-term follow-up. According to our literature research, our study is the first one with a largest sample of strictly mucous pemphigus. The main limitations remain the lack of dosage of anti DSG3 antibodies. Training and awareness of dentists and general practitioners is essential to make the correct diagnosis at an early stage in order to improve the quality of life of patients. Multicenter studies involving: dermatologists, dentists and maxillofacial surgeons are therefore required to better understand the role and the physiopathology of the oral mucosa involvement in pemphigus patients.

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