Direct Immunofluorescence of Uninvolved Non-Perilesional Mucosa: An Alternative for The Diagnosis of Mucous Membrane Pemphigoid

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Dear Editor,

Mucous membrane pemphigoid (MMP), is a heterogeneous group of autoantibody-mediated subepidermal bullous disorders of mucous membranes with different grades of severity. Many different autoantibodies directed against different structural components of the epidermal basement membrane zone (EBMZ) have been associated with MMP, including BP180[1,2] BP230, laminin 332, laminin 331, β4 integrin and type VII collagen. The oral mucosa is the most commonly affected site and usually the leading clinical manifestation, followed by the ocular, nasal, nasopharyngeal, anogenital, laryngeal, and esophageal mucosa. Skin may be affected but less frequently. Clinically, MMP is characterized by the presence of erythema, painful erosions, and blisters of mucosa with variable severity. Lesions tend to heal with scarring. Some HLA alleles, some single nucleotide polymorphisms, infections (HVB), vaccines and drugs have also been involved in the pathogenesis.[1,2] Consensus reference standard for diagnosis of MMP has been recently well detailed.[2] In accordance to Rashid H. *et al*,[1] and recent guidelines, the clinical diagnosis of MMP is based on clinical findings together with detection of anti-basement membrane zone (BMZ) autoantibodies detected by direct immunofluorescence (DIF) microscopy and/or direct immunoelectron microscopy, or indirect IF (IIF), ELISA or immunoblotting. (Table 1). Histopathology may be helpful in some cases when MMP, or another autoimmune blistering disease (AIBD), cannot be detected using these methods.[1,3] Immuno-serologic test and immunoglobulin deposition have prognostic and therapeutic value.[1] Recent research works have shown that DIF on a mucosal biopsy shows the highest sensitivity (41-100%) and predictive positive value for the diagnosis of MMP, being superior to serologic analysis,[1,3] moreover the sensitivity of DIF can be increased by obtaining multiple and repeated samples1 of the mucosa or skin. In addition, some authors have reported that DIF on perilesional mucosa biopsy from involved locations has been found to be equivalent to normal mucosa biopsy from spared locations for diagnosis of MMP (93.7% in uninvolved and 89.6% in perilesional oral mucosa).[1,3]

Table 1
Diagnosis criteria of MMP

CLINICAL DIAGNOSIS CRITERIA OF MMP[1]
A compatible clinical presentation and at least one of the following criteria:
1) a positive DIF biopsy result of the mucosa
2) a positive DIF biopsy result of the skin
3) a positive DIF biopsy result as well as a positive IIF SSS
4) a positive IIF on SSS as well as positivity in at least 1 other immunoserologic test (immunoblot, ELISA, or IIF on ME[2])

[1]*Mucous membrane pemphigoid (MMP)*
[2]*Microscopy electron (ME)*

On this topic an 88-year-old woman who was referred to our department for oral lesions and swallowing discomfort for 1 year was presented. She did not refer any other symptoms at the cutaneous, ocular, or anogenital level. She also denied a marked weight loss in the last year. No new drugs were prescribed before the beginning of the symptoms. The physical examination revealed erosive lesions, and blisters in the palate area with scarring in resolved areas (Figure 2). With the suspicion of autoimmune bullous disease, a biopsy was performed for hematoxylin eosin (HE), with another sample (perilesional mucosa) for DIF. Although no blisters were observed, a superficial neutrophilic ulcer was present, with a few eosinophils and scar changes in the superficial dermis. Lichenoid changes were not noticed. DIF was negative for IgG deposit, but showed linear deposit of IgA at the dermoepidermal junction. After that, an ELISA was requested

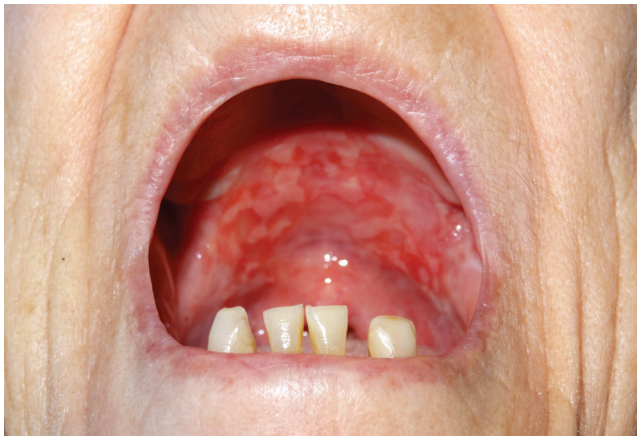

Figure 1
Erosive lesions, and blisters in the palate area with scarring in resolved areas.

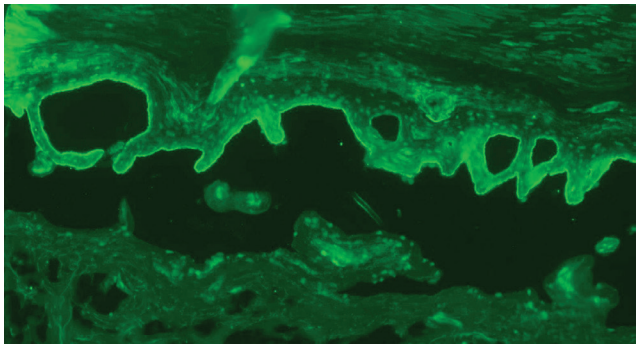

Figure 2
Positive IIF showing IgA deposit in the epidermal side using monkey salt-split skin as substrate.

(Dermatology profile, EA 1490-1208-1, Euroimmun) which includes desmoglein 1 and 3, collagen VII, envoplaquin, BP 180 and BP230. ELISA was negative for all auto antibodies using IgG targets, but positive for BP 180 (5.39) and BP 230 (4.04) using IgA conjugate (cutoff=1), confirming the diagnosis of IgA-type MMP. Laminin 332 determination was also negative. To reinforce the diagnosis, an IFI was performed, and it showed IgA deposition on the epidermal side. (Figure 3) A gastroscopy was requested. Although the esophageal mucosa was spared, we took advantage of the endoscopy to take a DIF sample of healthy mucosa, which show a linear IgA deposit at the junction, as in the perilesional mucosal sample taken from the oral cavity. Differential diagnosis was made mainly with linear IgA dermatosis, but it is extremely uncommon the isolated mucosal involvement in this bullous disease, and according to first international consensus on MMP, in that case, it must be comprised under the term MMP.5 Tumor markers, LDH and a body CT were normal. Otorhinolaryngological and ophthalmological examinations were also normal. Dapsone 50 mg daily was prescribed, withdrawing it in less than a month due to anemia (hemoglobin levels below 8 g / dl) and being replaced by prednisone 5 milligrams, doxycycline 100 mg twice daily and topical 0,01% tacrolimus achieving symptomatic relief and improvement of the lesions. In conclusion, and according to previous reports[1,5], DIF from uninvolved mucosa could be a very interesting tool for diagnosis, especially for patients with great pain in the affected area, patients with isolated ocular involvement where biopsy could cause scar or synechiae.

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