Mucous membrane pemphigoid

Müköz membran pemfigoidi

Jorrit B. Terra[1], Joost M. Meijer[1], Marcel F. Jonkman[1]

[1]*Center for Blistering Diseases, Department of Dermatology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands*

Abstract

Mucous membrane pemphigoid (MMP) is the subgroup of pemphigoid which affects mucous membranes. Several sub-types are classified based on clinical symptoms and target antigens, such as ocular mucous membrane pemphigoid (OMMP), localized vulvar pemphigoid (LVP) and anti-laminin 332 MMP (anti-LN-332 MMP). Autoantibodies are directed against various structural proteins in the epidermal basement membrane zone (EBMZ), with the 180-kDa antigen (BP180) as the main target antigen. Other antigens, such as BP230, α6β4 integrin and laminin 332 can also be targeted by autoantibodies. Clinically MMP is characterized by erosions and blistering of the oral mucosa (85%), conjunctiva (65%), and less frequently, the nose (20-40%), esophagus (5-15%), pharynx (20%), larynx (5-10%) and genitals (20%). Clinical severity is highly variable in the different subtypes of MMP. Progressive scar formation is a severe complication in active disease in OMMP and anti-LN-332 MMP, resulting in blindness or upper airway obstruction when not treated accurately. Previously, the term cicatricial pemphigoid was used synonymously for MMP, however, at present the term refers to the rare clinical phenotype with scarring skin lesions. Patient and doctors delay is frequently seen in MMP because of its variation in clinical presentation and unfamiliarity among clinicians. For an accurate diagnosis, direct immunofluorescence microscopy (DIF) and detection of circulating autoantibodies in serum is mandatory. Management and prognosis of MMP depends on the severity and extent of the disease and involves a stepwise approach with first choice treatment with oral corticosteroids (CS), often used in combination with adjuvant to reduce the adverse effects caused by long-term CS use.

Key words: *hemidesmosome, basement membrane, autoimmune disease, desquamative gingivitis, pemphigoid, mucous membranes*

Özet

Müköz membran pemfigoidi (MMP), pemfigoidlerin müköz membranları etkileyen alt tipidir. Klinik semptomlar ve hedef antijenlere göre, oküler müköz membran pemfigoidi (OMMP) ve anti-laminin332 MMP(anti-LN-332 MMP) gibi çeşitli alt tiplere ayrılmıştır. Başlıca hedef antijen 180 kDa (BP180) olmakla birlikte, epidermal bazal membran bölgesindeki (EBMZ) çeşitli yapısal proteinlere karşı otoantikorlar mevcuttur. BP230, α6β4 integrin ve laminin 332 gibi diğer antijenler de, bu otoantikorlar tarafından hedef alınabilmektedir. MMP klinik olarak, oral mukozada (%85), konjunktivada (%65), daha az sıklıkta ise, burunda (%20-40), özefagusta (%5-15), farinkste (%20), larinkste (%5-10) ve genitallerde (%20) erozyon ve büllerle karakterizedir. MMP'nin klinik şiddeti, farklı klinik tiplerinde önemli farklılıklar gösterir. OMMP ve anti-LN-332 MMP klinik tiplerinde aktif hastalık uygun bir biçimde tedavi

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Correspondence: Marcel F. Jonkman, MD, Ph.D. Department of Dermatology University Medical Center Groningen Hanzeplein 1 9700 RB Groningen The Netherlands tel: +31-50-3612520 fax: +31-503612624 email: m.f.jonkman@umcg.nl

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edilmediğinde körlük veya üst havayolu obstrüksiyonu ile sonuçlanan ilerleyici skar gelişimi hastalığın ciddi bir komplikasyonudur.

Önceleri, MMP ile eş anlamlı olarak kullanılan skatrisyel pemfigoid, şimdi skarla seyreden deri lezyonlarına sahip nadir klinik fenotipi isimlendirmektedir. Klinik özelliklerdeki değişkenlikler ve klinisyenler arasında aşinalığın azlığı, MMP tanısında, hasta ve doktor kaynaklı gecikmelere yol açmaktadır. Doğru tanı için, direkt immünofloresan mikroskopik inceleme ve serumda otoantikorların gösterilmesi zorunludur. MMP'nin yönetimi ve prognozu hastalığın yaygınlığı ve şiddeti ile ilişkili olup basamaklı bir yaklaşım ile, ilk seçenek olarak oral kortikosteroidleri (KS) ve sıklıkla uzun dönem KS kullanımının yol açabileceği yan etkileri azaltmak için adjuvanlarla kombinasyonu içerir.

Anahtar Kelimeler: *hemidezmozom, bazal membran, otoimmün hastalık, deskuamatif gingivit, pemfigoid, müköz membranlar*

List of abbreviations:
BMZ : **basement membrane zone**
CS : **corticosteroids**
DIF : **direct immunofluorescence microscopy**

Short overview

Mucous membrane pemphigoid (MMP) is the nomenclature for the whole group of patients with pemphigoid affecting the mucous membranes (Table 1). Circulating autoantibodies target components of the EBMZ. In MMP the oral mucosa is mostly affected (85%), but all mucous membranes can be involved. In a minority of patients also the skin is affected. It is not clear yet whether MMP with lesions limited to the oral mucosa is only a stage of MMP or a distinct clinical entity. Patients clinically present with erosions or in case of limited oral lesions, with desquamative gingivitis (Fg. 1a). The intake of nutrition or fluids can be reduced because of pain. MMP with exclusively oral lesions is frequently unrecognized in the early inflammatory stage and often misdiagnosed as oral lichen planus, oral aphthosis or other inflammatory oral diseases.

Table 1. Target antigens, IF findings and clinical symptoms in subtypes of mucous membrane pemphigoid.

Disease type	Target antigens	IF Findings		Clinical symptoms
		DIF	IIF SSS	
MMP	BP180, BP230, α6β4 integrin	n-serrated EBMZ IgG ± IgA, C3c	epidermal	Erosions and blisters of the oral, nasal, eyes, pharyngeal, laryngeal, esophagus and anogenital mucosa
Ocular MMP	BP180	n-serrated EBMZ IgG ± IgA	epidermal	Dry eye, conjunctivitis, trichiasis, fornix shortening, symblepharon, ankyloblepharon
Localized vulvar pemphigoid	BP180	n-serrated EBMZ IgG ± IgA, C3c	epidermal	Vulval itching, burning sensation, pain, dyspareunia and dysuria
Anti-laminin-332 MMP	Laminin-332	n-serrated EBMZ IgG ± C3c	dermal	Erosions and ulcerations of the supraglottic area, nose, eyes, oesophagus and anogenital region, aphonia, dyspnoe

MMP : mucous membrane pemphigoid;
EBMZ : epidermal basement membrane zone;
IF : immunofluorescence microscopy;
DIF : direct IF;
IIF SSS : indirect IF salt-split-skin;
IgG/IgA : immunoglobuline G/A;
C3c : complement C3;

Case study: Part 1

A 62-year old man presents with desquamative gingivitis of the oral mucosa, diagnosed as oral lichen planus for several years (Fig. 1). No other mucosal surfaces are affected, but the patient does complain of itch. His oral lesions were treated with superpotent topical corticosteroids, that did not relieve the symptoms. Because of failure of treatment he was referred to our clinic.

Didactical questions

How can you clinically differentiate between oral lichen planus and oral MMP? On which three criteria is the diagnosis MMP based? MMP can resemble pemphigus vulgaris oris; name the clinical differences between these two diseases. A mucosal biopsy for direct immunofluorescence (DIF) will confirm the diagnosis of MMP. What is the additional value of also taking a biopsy for DIF of normal healthy skin?

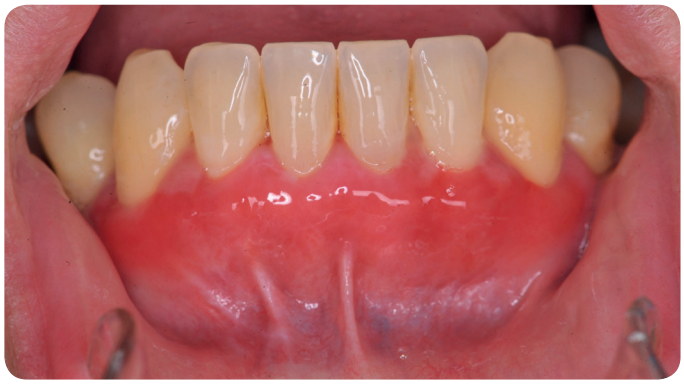

Fig. 1a. Clinical manifestations of a patient with MMP limited to oral mucosa with desquamative gingivitis, and blisters located on the attached gingival mucosa proximal of the lateral incisors

Facts & Figures

MMP is a subepidermal autoimmune blistering disease (sAIBD) with predominantly mucosal involvement and is characterized by autoreactivity mostly to BP180. BP180 is a 180-kDa transmembrane glycoprotein that ultrastructurally spans the lamina lucida and curves back from the lamina densa into the lamina lucida. In MMP autoantibodies predominantly recognize the C-terminal epitopes of BP180. NC16A is the second immunodominant domain. In addition, autoantibodies may target BP230. Auto-reactivity to the α6 and β4 integrin subunits have been associated with oral and ocular MMP respectively. The main autoantibody isotype is IgG, predominantly of the IgG1 and IgG4 subclass, but deposits of IgA and complement C3 may be found.[1,2] The incidence of MMP as a group has been estimated at 1.3–2.0 per million per year in France and Germany, respectively. MMP often occurs earlier in life than BP, with age of onset commonly observed between 60-70 years.[2] Women are affected almost two times more often than men. MMP is rare in children. No racial differences have been seen.

Diagnosis paths

History and physical examination

Patients with MMP clinically present with erosive or erythematous patches and small blisters of mucosa consisting of nonkeratinized stratified squamous epithelium. Oral lesions occur predominantly on gingival and palatal mucosae and less often on the tongue or buccal mucosa (Fig. 1). Other mucosae can be affected, such as the conjunctiva (65%), and less frequently, the nose (20-40%), esophagus (5-15%), pharynx (20%), larynx (5-10%) and genitals (20%). MMP patients often present with complaints of bleeding, pain, dysphagia, and erosions or blister of the mucosa. Blisters of the mucosa are frequently seen, but often rupture rather quickly as a result of mechanical and traumatic forces. The majority of MMP patients with lesions limited to oral mucosa have gingival lesions resulting in the so called "des-

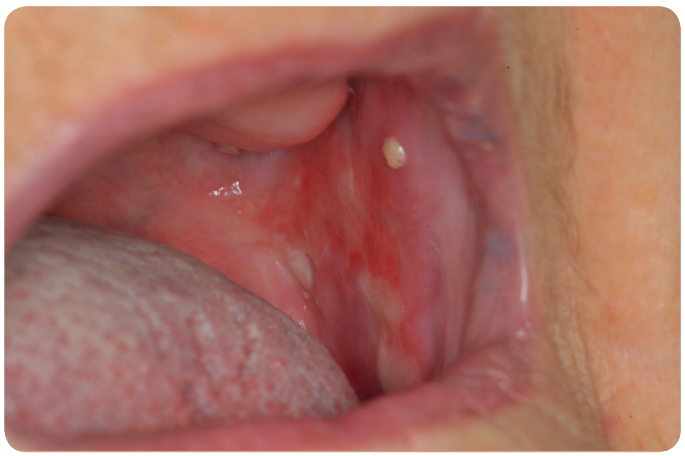

Fig. 1b. Another patient with MMP with blistering on the buccal mucosa

quamative gingivitis". The gingival erythema may be confused with non-specific gingivitis as part of chronic periodontal disease. The intake of nutrition or fluids can be reduced because of pain. In other forms of MMP lesions tend to heal with scar formation, however in oral lesions re-epithelisation without scarring may occur. Furthermore, the extent of (milder forms of) MMP should be assessed, for example with the MMP Disease Area Index (MMPDAI).

Desquamative gingivitis in MMP may be seen as non-specific gingivitis

Diagnostics

MMP should be differentiated from other diseases with involvement of the (oral) mucosa, such as (erosive) oral lichen planus, pemphigus vulgaris, erythema multiforme, oral aphthosis, and dermatitis herpetiformis. Diagnosis of MMP is based on clinical presentation with oral mucosal lesions and DIF of intact buccal mucosa that shows a linear deposition of IgG and/or complement C3 and IgA along the EBMZ. Serration pattern analysis is often not possible on mucosal biopsies. Therefore, an additional biopsy of healthy skin (for example on medial side of upper arm) may be required. IIF performed on 1 M NaCl-split skin substrate shows binding of autoantibodies on the epidermal side of the artificial split. The titer of circulating autoantibodies in serum is frequently low and often not detectable. Immunoblot is of additional value in diagnostics of MMP. The IF findings of MMP are identical to BP, the distinction should be made based on clinical symptoms.

An additional biopsy of healthy skin is required for DIF serration pattern analysis in MMP

Treatment tricks

Initial treatment and treatment ladder

Mild lesions of the oral mucosa can be treated effectively with moderate to superpotent topical corticosteroids, or alternatively tetracyclines combined with nicotinamide. Another treatment option in more severe lesions is dapsone (25mg to 200mg/day), or systemic CS (0,5mg/kg/day) with azathioprine (100-150mg/day).[1] Refractory cases may require high dose systemic CS, cyclophosphamide, intravenous immunoglobulin (IVIG) or anti-CD20 antibody rituximab.

Case study: Part 2

Mucosal biopsy for DIF showed IgG 1+ and complement C3 1+ along the EBMZ, the serration pattern was undeterminable in this mucosal biopsy. Indirect IF on monkey-esophagus and salt-split skin was negative for IgG and IgA. Immunoblot showed positive staining for BP180 IgG, but was negative for BP230. BP180 NC16A index was 39 (positive). The diagnosis of MMP was made, based on clinical symptoms of affected oral mucosa and a positive DIF.

Follow-up and tapering

It has been suggested that MMP with lesions limited to the oral mucosa has a better prognosis compared to other subtypes of MMP. However, the clinical symptoms are highly variable and the number of reports in literature regarding follow-up and treatment is limited. An otolaryngologist should examine patients with nasal or laryngeal symptoms, whereas an oral and maxillofacial surgeon is expert on oral lesions.

Case study: Part 3

Treatment was started with dapsone 50mg/day and, after a G6PD deficiency was excluded, increased to 100mg/day. Because of increasing fatigueness and loss of appetite, treatment was switched to cyclophosphamide up to 2mg/kg/day. Unfortunately, the disease was not controlled. The patient therefore received an intravenous cycle of anti-CD20 antibody 2x1000mg which reduced the blister frequency and subjective complaints.

Ocular mucous membrane pemphigoid

Short overview

Ocular mucous membrane pemphigoid (OMMP), previously named ocular cicatricial pemphigoid (OCP), is

defined as MMP with lesions of the conjunctiva. If the lesions are confined to the eyes than the term is pure OMMP. Clinical severity is variable and can range from burning sensation of the eyes to scarring resulting in blindness. Early recognition of OMMP is of utmost importance because of the scarring potential phenotype.

Clinical symptoms

OMMP usually starts unilaterally with a recurrent inflammatory process resulting in clinical features of dry eye, conjunctivitis, trichiasis, fornix shortening, symblepharon and ankyloblepharon formation (Fig. 2a-b). In the final stage of the disease pannus occurs: total keratinization of the entire ocular surface, resulting in blindness when not treated accurately. In most cases the disease is bilateral within two years.

Diagnosis paths

The target antigen in OMMP is the 180-kDa antigen. In patients with OMMP, DIF (conjunctiva) is frequently the only positive assay, and shows IgG and/or IgA in linear n-serrated pattern along the epidermal BMZ. These biopsies can be performed by the dermatologist or ophthalmologist. With high suspicion of OMMP and negative DIF conjunctiva, DIF of oral mucosa and IIF are recommended for diagnosis. IIF performed on 1 M NaCl-split skin substrate showing binding of antibodies to the epidermal site (roof) of the blister and by immunoblot analysis revealing immunoglobulin binding to the 180-kDa antigen.

Treatment tricks

Mild OMMP is treated with dapsone, mycophenolate mofetil or mycophenolic acid. Blepharitis should be treated with eye lid hygiene and topical tetracycline cream. In rapidly progressive OMMP with impending blindness, dexamethasone pulse therapy or systemic CS (1.0mg/kg/day) in combination with cyclophoshamide should be first choice of treatment. Consultation of the ophthalmologist is needed to evaluate the effect of treatment with slit-lamp examination. In refractory cases of OMMP the anti-CD20 antibody rituximab, a single cycle of 2 infusions of 1000 mg or intravenous immunoglobulin (IVIG) may induce remission. Surgical intervention like eye lash ablation or amniotic membrane transplantation can be performed when OMMP is in clinical remission.

In rapidly progressive OMMP aggressive therapy is needed to prevent cicatrisation

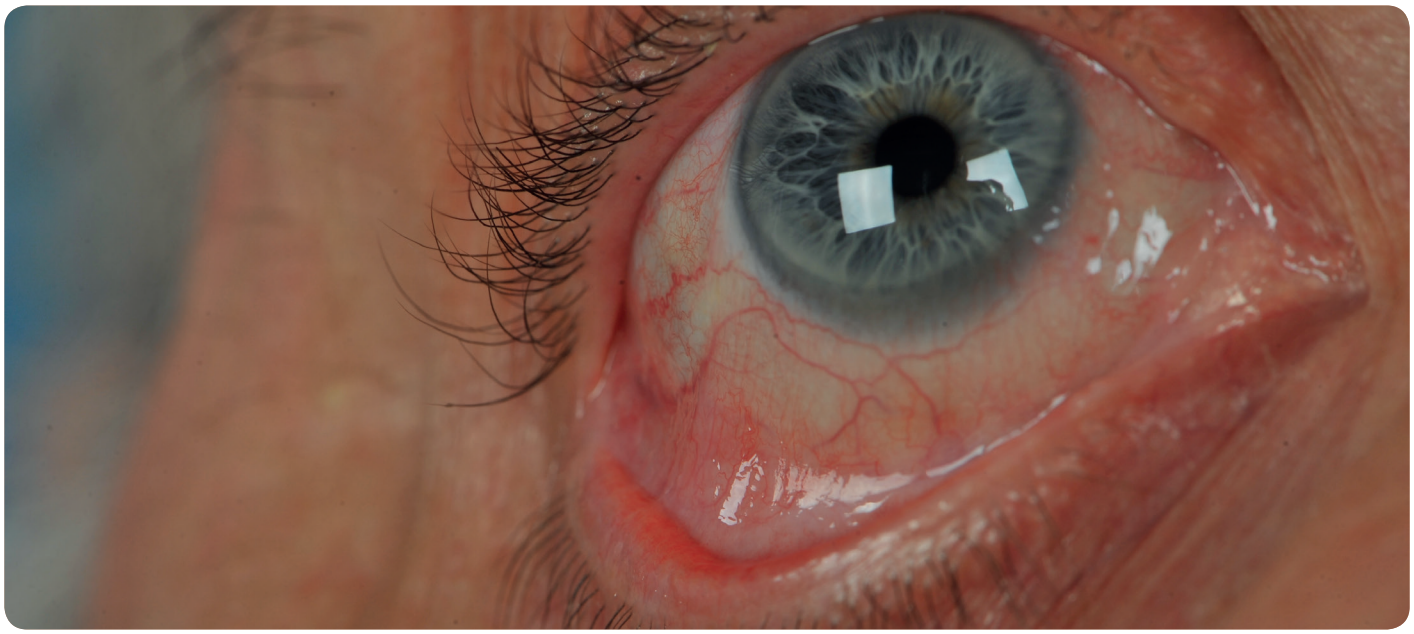

Fig. 2a. Clinical clues of ocular MMP: conjunctivitis and fornix shortening

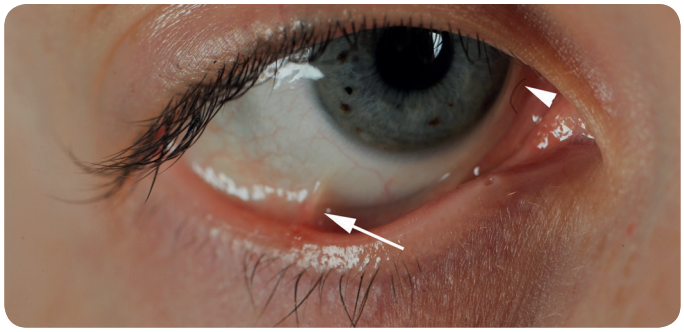

Fig. 2b. Clinical clues of ocular MMP: symblepharon (arrow) and trichiasis (arrow head)

Localized vulvar pemphigoid

Short overview

Localized vulvar pemphigoid (LVP) is a rare subtype of pemphigoid with solitary lesions in the genital region. Findings at vulva inspection can be very similar to lichen sclerosus and lichen planus. Full examination of skin, mouth, eyes and nasal mucosa is essential for adequate diagnosis.

Definitions and classification

In classic MMP woman can present with erosions and blisters at any mucosal surfaces. LVP is defined as pemphigoid limited to the cornified epithelium (skin) of the vulva and perineum. LVP can present at two different episodes in life: i) in childhood, around ten years, called juvenile or childhood LVP (Fig. 3) and ii) at postmenopausal age, called adult LVP. Because of the similarity with lichen sclerosus and lichen planus doctor's delay is frequently seen. On occasion the disease is erroneously confused with sexual abuse.

Clinical symptoms

Patients may complain of vulvar itch, burning sensation, pain, dysuria, and in adults dyspareunia. Upon inspection of the vulva erosions and ulceration with structural architectural changes (scarring), labial fusion and clitoral burial can be seen.

LVP clinically resembles lichen sclerosus and lichen planus

Diagnosis paths

Histopathology in the early phase shows similarities with lichen sclerosus like subepidermal oedema. At a latter phase a subepidermal blister underneath with an infiltrate existing from lymphocytes eosinophils and / or neutrophils, with or without fibrosis is seen. DIF shows IgG, IgA and C3 depositions in the n-serrated pattern along the epidermal BMZ. IIF on monkey esophagus is often negative because the circulating autoantibodies usually have a low titre. IIF performed on 1 M NaCl-split skin substrate showing binding of antibodies to the epidermal site (roof) of the blister.

Treatment tricks

Topical tetracycline cream is first-line therapy. Superpotent topical corticosteroids (TC) can be used after failure of treatment. Dapsone is treatment of choice when systemic treatment is needed.

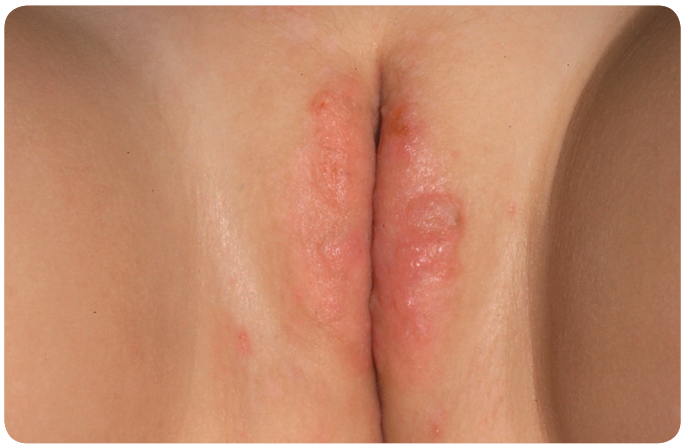

Fig. 3. A young girl with juvenile LVP, presenting with vulvar erosions

Anti-laminin-332 mucous membrane pemphigoid

Short overview

Anti-laminin 332 MMP (anti-LN-332 MMP) is a rare subtype of MMP that is difficult to distinguish from other forms of MMP at first sight. It is known for the scarring phenotype with airway obstruction due to pharyngeal and laryngeal involvement or loss of vision because of subconjunctival fibrosis and cicatrisation.

Furthermore patients have an increased relative risk for malignancy, especially adenocarcinoma.[3] Because of this clinical aggressive behavior it is important to diagnose patients in an early phase of the disease.

Definitions and classification

Domloge-Hultsch et al. were the first to describe an sAIBD with autoantibodies that bind epiligrin: anti-epiligrin cicatricial pemphigoid.[4] Epiligrin appeared to be a mixture of laminin 5, now named laminin 332 (LN-332), laminin-6 (LN-311), and laminin-7 (LN-321). LN-332 is a heterotrimeric protein consisting of α3, β3 and γ2 laminin subunits. Approximately 5 to 20% of all MMP patients show circulating IgG autoantibodies against LN-332.[3]

Anti-laminin-332 MMP is previously known as anti-epiligrin cicatricial pemphigoid

Pathogenesis

Anti-LN-332 MMP is a form of MMP with circulating autoantibodies targeting LN-332. This protein is present in the lamina lucida of the basement membrane zone of keratinizing and nonkeratinizing stratified squamous epithelia, and connects hemidesmosomes to anchoring fibrils by interlinking integrin α6β4 and BP180 to type VII collagen. In most patients the IgG autoantibodies predominantly target the laminin α3 subunit, although IgG autoantibodies targeting the β3 or γ2 subunits have also been described[3].

Clinical symptoms

Anti-LN-332 MMP mimics other forms of MMP and presents with involvement of the mucosal surfaces of the mouth, eyes, nasopharynx, oropharynx, larynx and anogenital region (Fig. 4a-d). In most patients the skin is also involved, but usually less severe. In some cases the pharynx and larynx are the only regions involved (Fig. 5). Patients may present with aphonia (loss of voice) due to edema, erosions and ulcerations of the supraglottic area. This is followed by scarring of the larynx, and acute upper airway obstruction due to initial laryngeal edema may occur, necessitating tracheotomy. In these patients a doctor delay is frequently seen because of ignorance of this autoimmune blistering disease.

Diagnosis paths

We developed a new algorithm (Table 2) to diagnose anti-LN-332 MMP based on the combination of clinical symptoms, state-of-the-art laboratory diagnostics and multidisciplinary cooperation.[5] Patients with anti-LN-332 MMP should be screened for neoplasia. This occurs in approximately 20% of the patients, mostly ad-

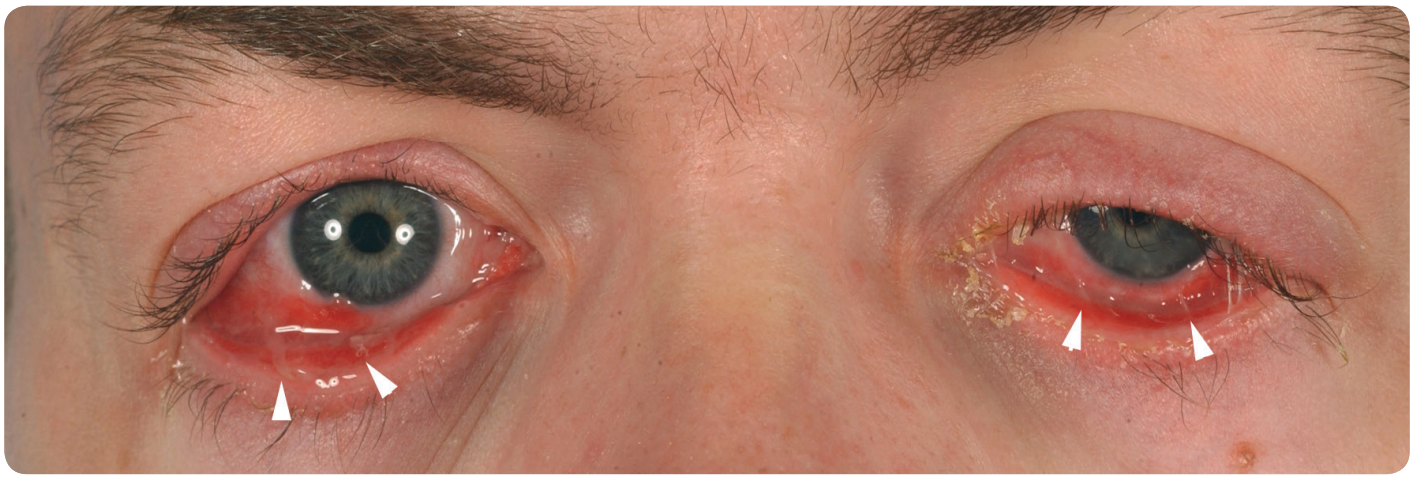

Fig. 4a. Clinical features in a patient with anti-LN-332 MMP: Conjunctivitis with symblepharon (arrow heads) and edema of the upper eyelid [Reprinted from Terra JB, Pas HH, Hertl M, Dikkers FG Kamminga N, Jonkman. Immunofluorescense serration pattern analysis as a diagnostic criterion in antilaminin-332 mucous membrane pemphigoid: immunopathological findings and clinical experience in 10 Dutch patients. British Journal of Dermatology 2011 Oct;165(4):815-22, with permission from Wiley.]

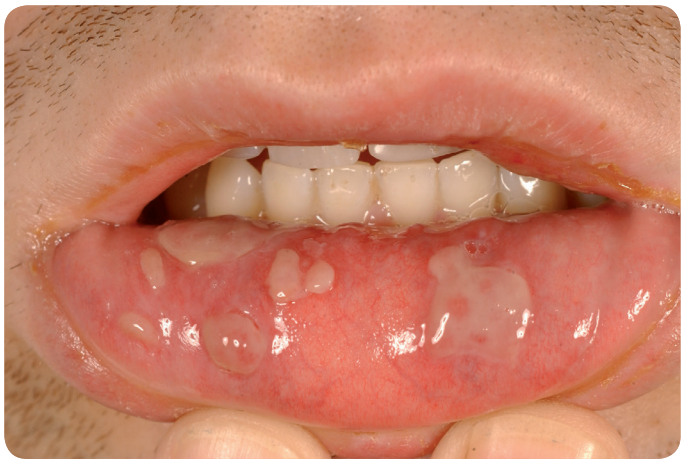

Fig. 4b. Extensive blistering of the oral mucosa, anti-LN-332 MMP*

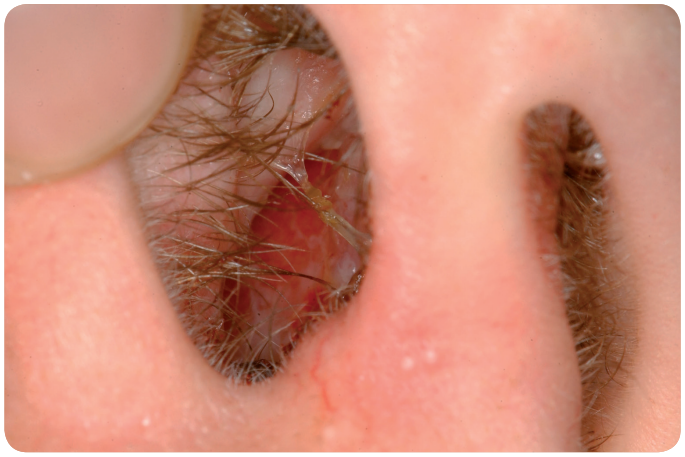

Fig. 4c. Erosions on nasal mucosa, anti-LN-332 MMP*

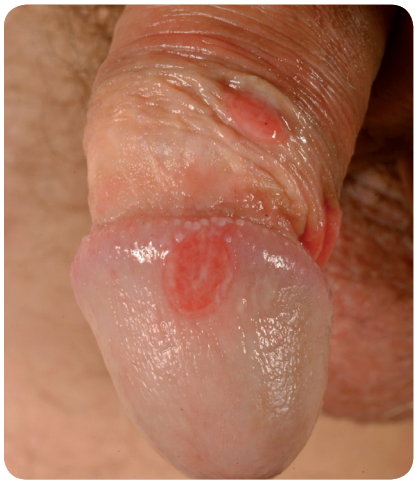

Fig. 4d. Genital ulcers, anti-LN-332 MMP*

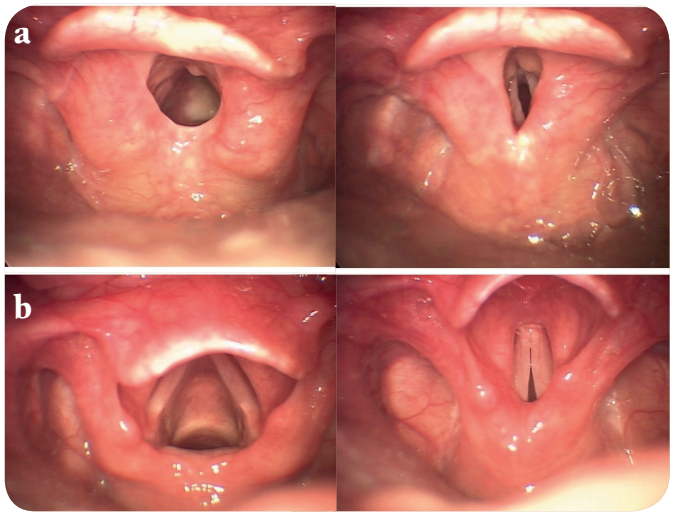

Fig. 5. Laryngeal cicatrization of the aryepiglottic folds with supraglottic stenosis (a), compared with healthy control (b). The ventral side is shown at the top*

enocarcinoma.

Because of the increased risk for malignancy patients with anti-LN-332 MMP should be thoroughly oncologically screened

Treatment tricks

Patients with anti-LN-332 MMP must be treated promptly and adequately to achieve control of disease and to delay progression. A multidisciplinary approach is a necessity when multiple mucosal sites are affected. An intense standard cooperation with the ophthalmologist and otolaryngologist for these patients is needed. Treatment used is always a combination of oral corticosteroids (prednisolone) and a steroid sparing adjuvant. For acute crisis management, dexamethasone pulse therapy can be started. Dapsone and cyclophosphamide are preferred choice when ocular involvement is present. Other immunosuppressant drugs given include mycophenolate mofetil, mycophenolic acid, intravenous immunoglobulins and rituximab.

*[Reprinted from Terra JB, Pas HH, Hertl M, Dikkers FG Kamminga N, Jonkman. Immunofluorescense serration pattern analysis as a diagnostic criterion in antilaminin-332 mucous membrane pemphigoid: immunopathological findings and clinical experience in 10 Dutch patients. British Journal of Dermatology 2011 Oct;165(4):815-22, with permission from Wiley.]

Table 2. Diagnostic criteria for anti-laminin 332 (anti-LN-332) mucous membrane pemphigoid

#	Criterium*
	Major criteria
1	Subepithelial erosions or blisters on mucous membranes frequently associated with scarring phenotype
2	Immunodepositions along the EBMZ in an n-serrated pattern by DIF
3	IgG bound to the dermal side of 1.0 M NaCl-split human skin by IIF
	Minor criteria
1	Anti-LN α3, β3, or γ2 IgG binding by immunoblot analysis on keratinocyte cell extract
2	IgG reactivity to native LN-332 by ELISA
3	Serum immunoprecipitation of LN-332 trimer
4	Negative IIF on LN-332 knockout skin, while positive IIF on type VII collagen knockout skin
5	IgG deposits in EBMZ overlay LN-332 by FOAM

EBMZ : epidermal basement membrane zone;
DIF : direct IF;
FOAM : fluorescence overlay antigen mapping
IIF : indirect IF;
IgG : immunoglobuline G

* To diagnose anti-LN-332 MMP at least three major criteria, or two major criteria and one minor criterion must be obtained.

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