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Learning Objectives

After reading this chapter, you should be able to recognize the different clinical features of MMP, know the target antigens and IF findings. You should also know potential complications in MMP and should be able to practice general treatment strategies.

Mucous Membrane Pemphigoid

Short Definition in Layman Terms

Mucous membrane pemphigoid (MMP) is the name for the whole group of patients with pemphigoid mainly affecting the mucous membranes (Table 15.1). The autoimmune disease targets components of the epidermal basement membrane zone (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. Patients clinically present with redness, erosions, vesicles or blisters or with redness of the gingiva. The intake of nutrition or fluids can be reduced because of pain. MMP with exclusively oral lesions is frequently unrecognized in the early stage and often misdiagnosed as oral lichen planus, oral aphthosis or other inflammatory oral diseases.

Table 15.1 Disease subtypes, target antigens and IF findings in mucous membrane pemphigoid

Disease type	Target antigens	IF findings	
		DIF	IIF SSS
MMP	BP180, BP230, α6β4 integrin	Linear n-serrated EBMZ IgG ± IgA, C3c	Epidermal
	Type 7 collagen	Linear u-serrated IgG ± IgA, C3c	Dermal
Ocular MMP	BP180	Linear (n-serrated) EBMZ IgG ± IgA	Epidermal
Localized vulvar pemphigoid	BP180	Linear n-serrated EBMZ IgG ± IgA, C3c	Epidermal
Anti-laminin-332 MMP	Laminin-332	Linear n-serrated EBMZ IgG ± C3c	Dermal

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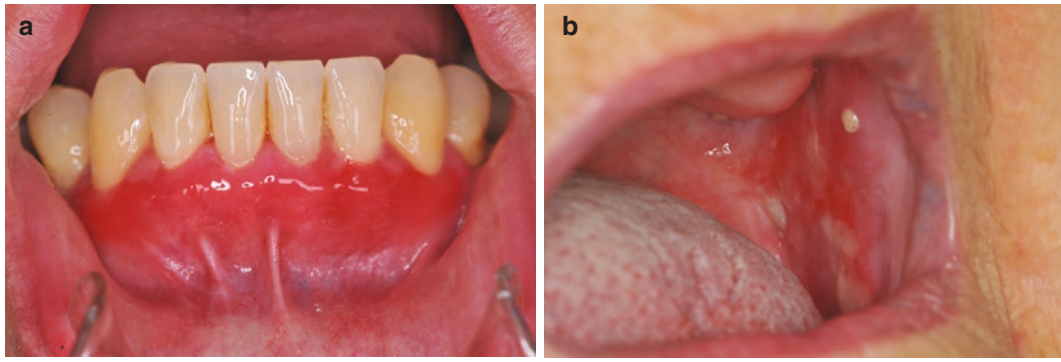

Fig. 15.1 (**a**) Clinical manifestations of a patient with monosite MMP limited to the oral mucosa with desquamative gingivitis, and (**b**) blistering on the buccal mucosa

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. 15.1a). More recently, blisters developed on the buccal mucosa (Fig. 15.1b). 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: Cross Section of Questions to Prime the Readers Interest

What are clinical differences between MMP and pemphigus vulgaris oris? How can you clinically differentiate between oral lichen planus and oral MMP? On which criteria is the diagnosis MMP based and where should you take a biopsy for DIF?

Facts and Figures

MMP is a heterogeneous group of chronic subepidermal autoimmune blistering diseases (sAIBD) with predominantly mucosal involvement and is characterized by autoreactivity mostly to BP180 (Table 15.1). 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 most often recognize the C-terminal epitopes of BP180. NC16A is the second immunodominant domain. In addition, autoantibodies may target BP230. Autoreactivity to the α6 and β4 integrin subunits have also been described. 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 and 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

Involvement of one or more mucosal sites may occur in MMP. Patients with involvement of only one mucosal site are termed monosite MMP (estimated 40%), such as monosite oral MMP or monosite ocular MMP, whereas patients with several affected mucosal sites are referred to as multisite MMP (estimated 60%). Patients with MMP clinically present with erosive or erythematous patches and small blisters of mucosa consisting of nonkeratinized stratified squamous

Table 15.2 Clinical symptoms of affected mucosal sites in mucous membrane pemphigoid

Affected mucosal site	Clinical features
Oral	Oral discomfort, burning sensation, gingival bleeding, mucosal peeling and difficulty in eating. Clinical features of erythematous patches, blisters and erosions/ulceration of the oral mucosa. Desquamative gingivitis
Nasal	Hemmorhagic nasal crusts, erosions and frequent nose bleeding
Ocular	Redness, tearing, burning, decreased vision, foreign body sensation or dry eyes. Clinical features of (chronic) conjunctivitis, trichiasis, fornix shortening, symblepharon, ankyloblepharon and blindness. Infrequently conjunctival ulceration
Genital and urological	Anogenital pain and/or pruritus, burning sensation, dyspareunia and dysuria. Clinical features of erythema, vesicles, blisters or erosions with potential mucosal adhesion and scarring or stenosis
Laryngeal/ pharyngeal	Dyspnea and dysphonia, dysphagia, strictures or stenosis or laryngeal obstructions. Clinical features of erosions and ulcerations of the larynx, supraglottic area, potential esophageal involvement

epithelium (Table 15.2). Oral lesions occur most frequently (85%) and are mainly located on the gingival, buccal and palatal mucosa and less often on tongue or lip (Fig. 15.1). Other mucosa can be affected, such as the conjunctiva (30–60%), and less frequently the nasal mucosa (20–40%), esophagus (5–15%), pharynx (20%), larynx (5–10%) and genital mucosa (25%). 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 desquamative gingivitis. The gingival erythema may be confused with non-specific gingivitis as part of chronic periodontal disease or oral lichen planus. The intake of nutrition or fluids can be reduced because of pain. In oral lesions re-epithelisation occurs without scarring, while in other forms of MMP lesions tend to heal with scar formation. The severity of MMP depends on the affected mucosal site. Patients with mild and moderate MMP often present with lesions limited to the oral mucosa, while patients with severe MMP usually have additional affected sites such as ocular, nasopharyngeal, laryngeal, esophageal, genital mucosa, or skin. An ophthalmologist or otolaryngologist should examine patients with ocular, nasal or laryngeal symptoms, whereas an oral and maxillofacial surgeon is expert on oral lesions. Furthermore, the extent of disease should be assessed, for example with the MMP Disease Area Index (MMPDAI, see Chap. 2).

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

A multidisciplinary approach is recommended to prevent disease progression and complications

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 predominant mucosal lesions and DIF of normal or perilesional buccal mucosa that shows a linear deposition of IgG and/or complement C3 and IgA along the EBMZ [3]. The n-serrated or u-serrated pattern is only observed in approximately 40% of mucosal biopsies. In case of negative DIF findings, a sequential biopsy from a different mucosal site may be performed if clinical suspicion of MMP persists. In addition, patients with MMP may show positive DIF findings of affected or unaffected skin. Therefore, an additional DIF skin biopsy of unaffected skin (for example on medial side of upper arm) or affected skin is recommended for diagnosis and serration pattern analysis. 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 of the predominant mucosal phenotype.

In case of initially negative DIF findings, it is recommended to take a sequential biopsy from mucosa and/or skin

Case Study: Part 2
A perilesional mucosal biopsy from buccal mucosa for DIF showed IgG 2+ and complement C3 1+ along the EBMZ, the serration pattern was undeterminable in this mucosal biopsy. Although skin was not affected, a simultaneously performed skin biopsy for DIF showed n-serrated IgG 2+ depositions along the EBMZ. Indirect IF on monkey-esophagus and salt-split skin was negative for IgG and IgA. Immunoblot showed positivity 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.

Treatment Tricks

Initial Treatment and Treatment Ladder

Mild to moderate MMP can be treated effectively with moderate to superpotent topical corticosteroids, and/or dapsone (25–200 m/day), methotrexate (7.5–25 mg/week) or tetracyclines. In refractory cases systemic corticosteroids (0.5 mg/kg/day) may be added and/or treatment changed to azathioprine (100–150 mg/day) or mycophenolic acid (500–2000 mg/day). Another treatment option in severe MMP is dapsone or cyclophosphamide (50–200 mg/day) with systemic corticosteroids. Refractory cases may require treatment with anti-CD20 antibody rituximab, intravenous immunoglobulin (IVIG) or TNF-α inhibitor.

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. Lesions on other mucosa may develop during follow-up, including ocular or largyngeal involvement. Therefore, the multidisciplinary approach is also advised during follow-up.

Case Study: Part 3
Treatment was started with dapsone 50 mg/day and, after a G6PD deficiency was excluded, increased to 100 mg/day. Because of increasing fatigueness and loss of appetite, treatment was switched oral corticosteroids and azathioprine up to 150 mg/day. Unfortunately, the disease was not controlled. Therefore, the patient received Rituximab treatment (see box # Chap. 8) which reduced the blister frequency and subjective complaints.

Ocular Mucous Membrane Pemphigoid

Short Definition in Layman Terms

Ocular mucous membrane pemphigoid, previously termed ocular cicatricial pemphigoid, is defined as MMP with lesions of the eyes. Ocular MMP may be present in monosite or multisite MMP. Clinical severity is variable and can range from burning sensation of the eyes to scarring resulting in blindness. Therefore, early recognition is important to prevent scarring.

Clinical Symptoms

Ocular MMP usually starts unilaterally with a recurrent inflammatory process resulting in clinical features of dry eye, conjunctivitis, trichiasis, fornix shortening, symblepharon and ankyloblepharon formation (Fig. 15.2). In the final stage of the disease pannus occurs: total keratinization of the entire ocular surface, resulting in blindness when not treated accurately. Although ocular

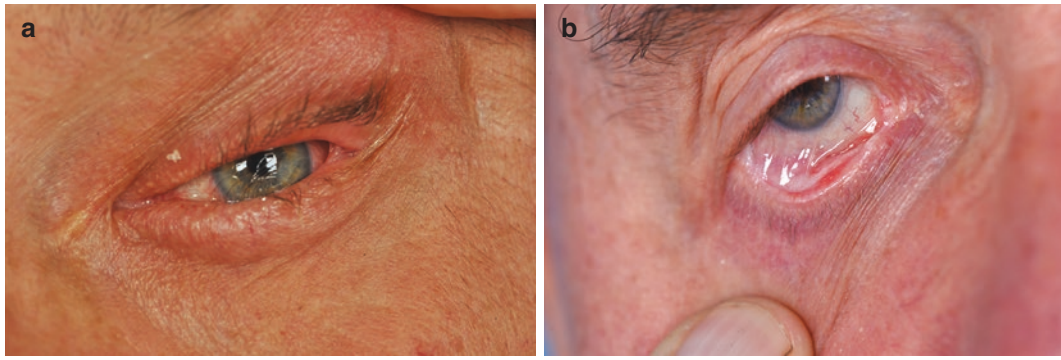

Fig. 15.2 Four clinical clues of ocular MMP: (**a**) conjunctivitis and trichiasis, (**b**) symblepharon and fornix shortening

MMP may initially start unilateral, in most cases the disease is bilateral within 2 years.

Diagnosis Paths

The target antigen in ocular MMP is the 180-kDa antigen (BP180). In patients with ocular MMP, a biopsy for DIF (of the conjunctiva) may show linear IgG and/or IgA depositions. These biopsies can be performed by the dermatologist or ophthalmologist (see Chap. 3 How to take a biopsy). However, up to 50% of ocular MMP patients show negative DIF and serology. With high suspicion of ocular MMP and negative DIF of the conjunctiva, repeated DIF of oral mucosa or skin and IIF are recommended for diagnosis. IIF performed on 1 M NaCl-split skin substrate showing binding of antibodies to the epidermal side (roof) of the blister and by immunoblot analysis revealing immunoglobulin binding to the 180-kDa antigen.

Treatment Tricks

Mild and moderate ocular MMP is treated with dapsone, methotrexate, azathioprine, mycophenolate mofetil or mycophenolic acid or cyclophosphamide. Blepharitis should be treated with eye lid hygiene and topical tetracycline cream. In rapidly progressive ocular MMP with impending blindness, methylprednisolone or systemic corticosteroids (1.0 mg/kg/day) in combination with cyclophoshamide is a recommended treatment. Consultation of the ophthalmologist is needed to evaluate the effect of treatment with slit-lamp examination. In refractory cases of ocular MMP rituximab treatment (see box # Chap. 8), intravenous immunoglobulin (IVIG) or TNF-α inhibitor may induce remission. Surgical intervention like eye lash ablation or amniotic membrane transplantation can be performed when ocular MMP is in clinical remission.

In rapidly progressive ocular MMP aggressive treatment is needed to prevent cicatrisation

Localized Vulvar Pemphigoid

Short Definition in Layman Terms

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

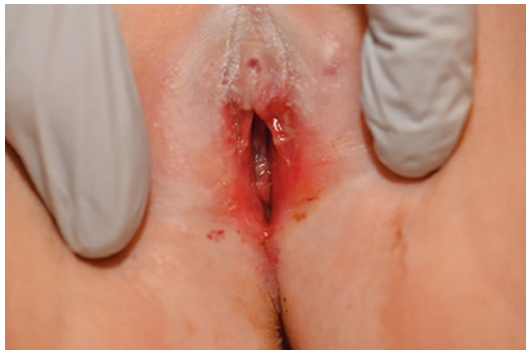

Fig. 15.3 A young girl with juvenile LVP, presenting with vulvar erosions, petechiae

defined as pemphigoid limited to the conified epithelium (skin) of the vulva and perineum. LVP can present at two different episodes in life: (1) in childhood, around 10 years, called juvenile or childhood LVP (Fig. 15.3) and (2) 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. Vaginal involvement is unknown in LVP.

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 C3c 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 side (roof) of the blister.

Treatment Tricks

Topical tetracycline cream is first-line therapy. Superpotent topical corticosteroids can be used after failure of treatment. Dapsone is treatment of choice when systemic treatment is needed. Refractory cases are treated following MMP recommendations.

Anti-laminin-332 Mucous Membrane Pemphigoid

Introduction

Short Definition in Layman Terms

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

Definitions and Classification

Anti-LN-332 MMP is previously known as anti-epiligrin cicatricial pemphigoid. Anti-epiligrin cicatricial pemphigoid with autoantibodies that bind epiligrin was first described in 2003. 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 5–20% of all MMP patients show circulating IgG autoantibodies against LN-332.

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.

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. 15.4). Complications of anti-LN-332 MMP are airway obstruction due to pharyngeal and laryngeal involvement or loss of vision because of subconjunctival fibrosis and cicatrisation. In most patients the skin is also involved, but usually less severe. In some cases the pharyngeal and laryngeal mucosa are the only regions involved (Fig. 15.5). 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 diagnostic delay is frequently seen.

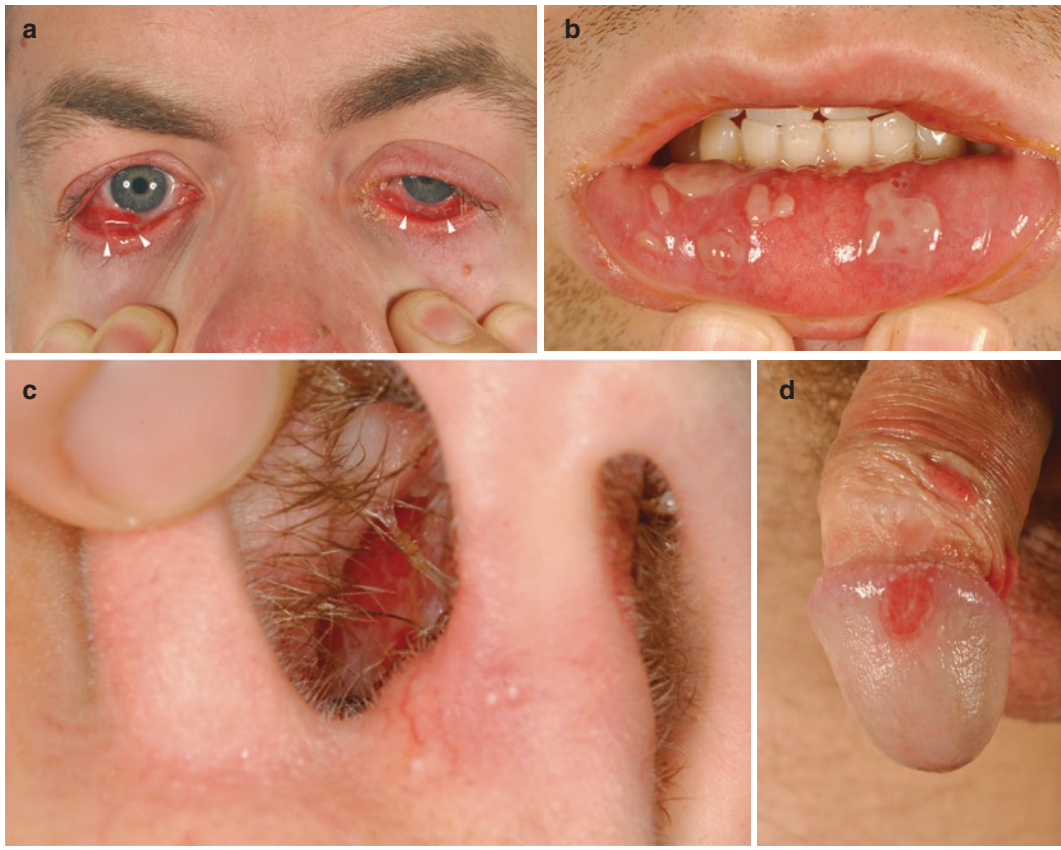

Fig. 15.4 Clinical features in a patient with anti-LN-332 MMP. (**a**) Conjunctivitis with symblepharon (arrow heads) and edema of the upper eyelid, (**b**) extensive blistering of the oral mucosa, (**c**) erosions on nasal mucosa, and (**d**) genital ulcers. (Reprinted from Terra et al. [4] with permission from Wiley)

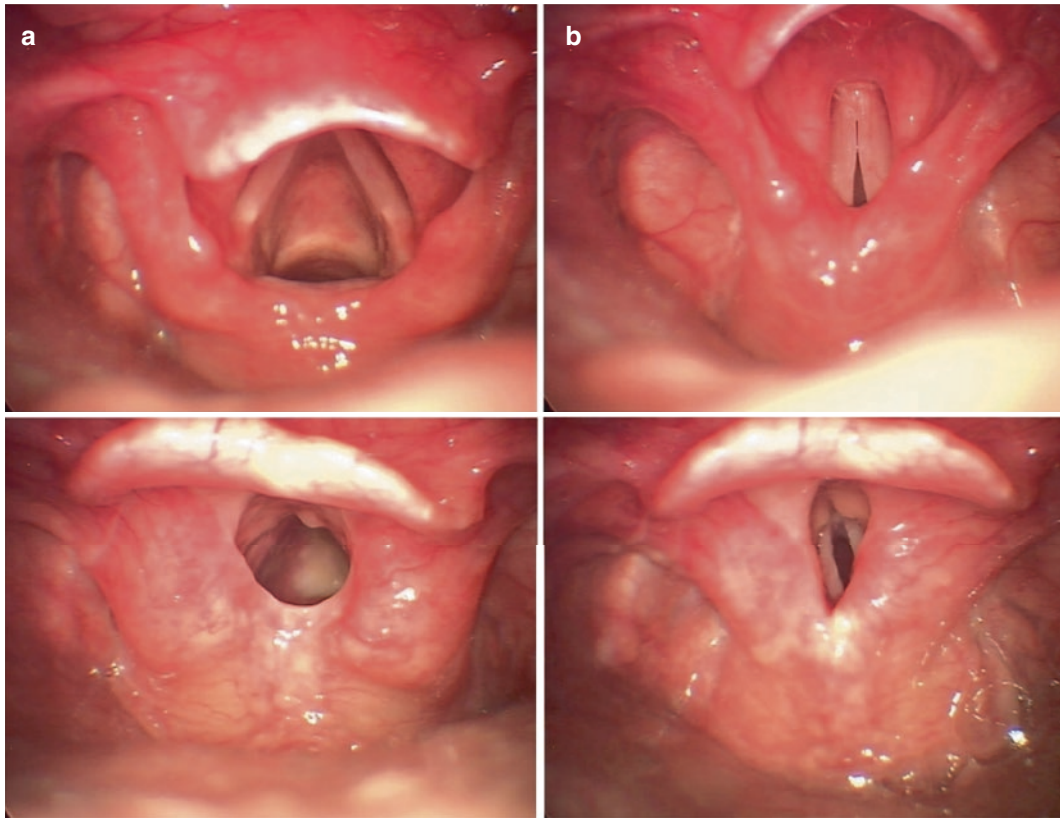

Fig. 15.5 Laryngeal cicatrisation of the ary-epiglottic folds with (**a**) supraglottic stenosis, and in healthy control. (**b**) Top is ventral side of patient. (Reprinted from Terra et al. [4] with permission from Wiley)

Diagnosis Paths

A biopsy for DIF shows an n-serrated linear deposition of IgG along the EBMZ. IIF performed on 1 M NaCl-split skin substrate reveals binding of antibodies to the dermal side (floor) of the blister in anti-LN-332 MMP, in contrast to MMP with BP180 reactivity and epidermal side staining of the blister. However, a substantial portion of patients require additional serological tests for antigen-specific detection of autoantibodies against laminin-332, such as the keratinocyte footprint assay (see Chap. 6 Immunoassays). Patients with anti-LN-332 MMP should be screened for malignancy, which is present in estimated 20–30% of the patients, mostly adenocarcinoma [1, 2, 5].

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

Treatment Tricks

Besides the screening and therapy of a potential underlying malignancy, treatment of patients with anti-LN-332 MMP follows the general MMP recommendations (see above). Prompt adequate treatment is advised to achieve control of disease and to delay disease progression of scarring.

Review Questions

1. What is the main target antigen in MMP?
   (a) BP180
   (b) BP230
   (c) Laminin 332
   (d) Type VII collagen
2. In rapidly progressive ocular MMP with impending blindness recommended treatment is:
   (a) Dapsone
   (b) Azathioprine
   (c) Cyclophosphamide and systemic corticosteroids
   (d) Mycophenolic acid

3. Specific diagnostics for anti-LN-332 MMP are:
   (a) DIF IgG u-serrated and SSS dermal binding
   (b) DIF IgG u-serrated and SSS epidermal binding
   (c) DIF IgG n-serrated and SSS dermal binding
   (d) DIF IgG n-serrated and SSS epidermal binding
4. First line therapy of juvenile LVP consists of:
   (a) Topical superpotent corticosteroids
   (b) Topical tetracycline cream
   (c) Oral corticosteroids (0.5 mg/kg/day)
   (d) Dapsone
5. Which statement about MMP is incorrect?
   (a) Oral mucosa is affected in the majority of the patients
   (b) Serration pattern analysis is less often possible on mucosal biopsies compared to skin biopsies
   (c) The titer of circulating autoantibodies in serum is frequently low and often not detectable
   (d) Patients with MMP do not have skin lesions, otherwise the diagnosis is bullous pemphigoid

Answers

1. (a)
2. (c)
3. (c)
4. (b)
5. (d)

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