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A 57-year-old woman presented with a 1-year history of blisters and erosions on her oral mucosa with bilateral conjunctivitis and symblephara formation. A diagnosis of cicatricial pemphigoid was made based on the clinical features and immunohistological findings. A multidisciplinary team managed her with different topical and systemic immunosuppressive agents but she finally succumbed due to multi-organ failure secondary to sepsis.

Introduction

Cicatricial pemphigoid (CP) is an autoimmune blistering disorder affecting primarily the mucous membranes and the skin. This disease is extremely difficult to treat despite the use of aggressive combination immunosuppressive regimens. Cicatricial pemphigoid with multiple mucosal site involvement has the worst prognosis due to its high resistance to medical therapy resulting in loss of function through scarring. In CP, autoantibodies are directed against the hemidesmosomal adhesion complex within the basement membrane zone, leading to blisters and erosions. In this condition, standard haematoxylin and eosin (H&E) staining shows a subepidermal blister with a mixed inflammatory infiltrate. Direct immunofluorescence demonstrates linear deposits of immunoglobulin G (IgG) and C3 at the dermal-epidermal junction.

Case report

A 57-year-old Chinese woman presented to Yaumatei Dermatology Clinic in March 2005 with a 1-year history of erosions on her oral mucous membranes, conjunctivitis, and blisters on her hands and feet. She had been treated with systemic steroids by a private dermatologist but defaulted follow-up due to financial constraint.

On examination, she had several flaccid blisters on her fingers with erosions and post-inflammatory hyperpigmentation. No milia were seen. There were erosions on her gingiva and palate with one intact blister on her left buccal mucosa. She also had bilateral conjunctivitis with symblepharon formation (Fig 1). A clinical diagnosis of CP was made and a skin biopsy was performed. Differential diagnoses included CP, bullous pemphigoid, pemphigus vulgaris, epidermolysis bullosa acquisita, linear IgA disease, paraneoplastic pemphigus, bullous systemic lupus erythematosus, and Behçet's syndrome.

Standard H&E staining of the biopsied materials showed a subepidermal blister with a mixed eosinophilic and lymphocytic infiltrate (Fig 2a). A periodic acid-Schiff reaction after diastase digestion demonstrated that the basement membrane was in the floor of the blister but there was no dermal scarring (Fig 2b). A direct immunofluorescence study showed linear IgG and C3 deposits along the dermal-epidermal junction. A diagnosis of CP was made.

Blood tests, including a full blood count, electrolytes, liver functions, fasting glucose, glucose-6-phosphate dehydrogenase (G6PD), hepatitis B serology, anti-nuclear antibody and anti-skin antibody were all within normal limits. The patient was referred to the ophthalmologist and she was started on oral prednisolone (1.5 mg/kg/day) and dapsone (50 mg daily) for the management of her eye disease. However, her clinical condition continued to progress and she developed a hoarse voice and extensive skin erosions. She was referred to the otolaryngologist and upon direct laryngoscopy, subglottic mucosal inflammation was seen with partial stenosis of the glottic and supraglottic laryngeal regions. Despite the combined use of prednisolone and dapsone for 3 months, her condition deteriorated and she was admitted to Queen Elizabeth Hospital (QEH) in October 2005.

Cyclophosphamide was considered but not started at this juncture because she had severe anaemia with a haemoglobin level of around 80 g/L and was in poor general condition. She was screened for any underlying malignancy because of marked emaciation and weight loss of 8 kg over 6 months but no malignancy was found.

She was given oral prednisolone (2 mg/kg/day) but dapsone was stopped. She was also

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一宗難治的癩痕性類天疱瘡個案

一名57歲婦人於診症一年前出現口腔黏膜糜爛及有疱，兩側有結膜炎，以及瞼球黏連。根據臨床徵狀及免疫組織化學的結果，診斷為患上癩痕性類天疱瘡。跨專科小組利用各種局部性及系統性的免疫抑制劑治療，但病人最終因膿毒引致多器官衰竭而死亡。

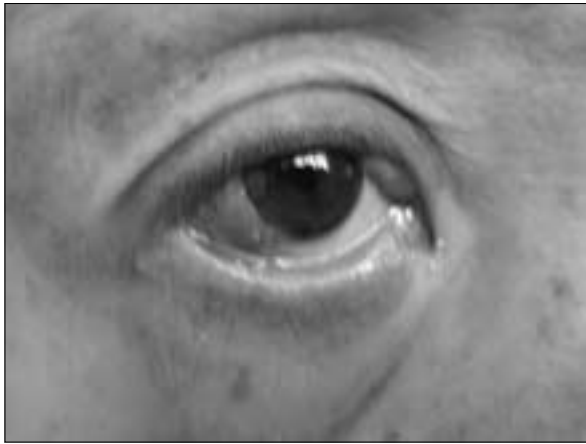


FIG 1. Ocular inflammation revealing conjunctival injection, early symblepharon formation and forniceal shortening

treated with an intravenous infusion of immunoglobulins (IVIg) of 1g/kg daily for 2 consecutive days and her skin and mucosal erosions improved significantly within 1 week. However, her skin and mucosal disease began to deteriorate again soon afterwards so 1 month later a second cycle of IVIg was given. The patient received a total of five monthly cycles of IVIg but the clinical response to each cycle of IVIg was getting weaker. In February 2006, cyclophosphamide (1.5 mg/kg/day) was added but she developed significant bone marrow suppression and the cyclophosphamide had to be stopped after 4 weeks.

During her stay in QEH, she was jointly managed by a dermatologist, ophthalmologist, otolaryngologist, and gastroenterologist. Antibacterial and lubricating eye drops were given. Regular laryngoscopy was performed to detect any life-threatening stenosis and at one point a prophylactic tracheostomy was offered but declined by the patient. Despite the combination of prednisolone, cyclophosphamide, and IVIg, she developed further conjunctival adhesions and severe oral and pharyngeal mucosal ulcerations causing pain, dysphagia, and malnutrition. As a result of the combined effect of immunosuppression, extensive skin and mucosal erosions and poor nutritional status, the patient died from overwhelming sepsis and multi-organ failure in April 2006.

Discussion

Cicatricial pemphigoid is a rare autoimmune blistering disorder that affects the mucous membranes and skin. It was first described by Thost in 1911.¹ Recent studies conducted in Europe estimated an incidence of 1.16 cases per million per year with a female-to-male ratio of 2:1 and a mean age of 64 years at diagnosis.² There is no racial predilection.

Immunosuppressive therapy forms the mainstay of treatment. Patients likely to develop therapeutic resistance are those with lesions in any of the following sites: ocular, genital, nasopharyngeal, oesophageal, and laryngeal mucosae. So early, aggressive treatment using a multidisciplinary approach is vital.³ A definitive diagnosis of CP can only be made by a combination of clinical, histological, and immunofluorescence studies. The best characterised autoantigens in patients with CP are BP180, BP230, laminin 5, laminin 6, type VII collagen, and integrin β_4 subunit.³

Oral lesions are the most common presentation in CP⁴ and are associated with the best prognosis. In mild cases, it is characterised by gingival erythema and oedema. Moderate to severe involvement is manifested by pain and desquamation with blisters, erosions, and ulcers.

The conjunctiva is the second most frequent site of involvement and can be the only site affected. Ocular CP begins as a non-specific conjunctivitis and patients often complain of burning and tearing. Periods of exacerbation and remission are typical, with eventual progression to subepithelial conjunctival fibrosis and symblephara formation if not treated aggressively.

Two types of skin lesions have been described in CP. The first type consists of recurrent tense bullae, similar to those seen in bullous pemphigoid, which rupture and heal without significant scarring. The second type consists of flaccid blisters surrounded by patches of erythema in which significant scarring can occur and is known as the Brunsting-Perry type.⁵

Nasal lesions have been associated with extensive involvement of the upper aerodigestive tract in most cases of CP. In patients with laryngeal involvement, the earliest manifestation is hoarseness. Once scarring of the larynx occurs, it is permanent. Life-threatening obstruction requiring tracheostomy may result.

As highlighted by our case, CP is a systemic autoimmune disease involving multiple mucosal surfaces and the skin. Therefore, it is crucial that a multidisciplinary team including a dermatologist, ophthalmologist, otolaryngologist, and gastroenterologist manages such patients. Aggressive treatment should be given early to prevent scarring and other complications. Surgical intervention may also be required but it is crucial that this is undertaken only when disease activity is well-controlled or this will lead to further scarring.⁶

Systemic corticosteroids such as prednisolone at 1-2 mg/kg/day are the first-line medications in CP because of their potent anti-inflammatory and immunosuppressive effects.⁷ However, long-term systemic steroids commonly have side-effects including osteoporosis, avascular necrosis, hypertension, diabetes mellitus, peptic ulcer disease, cataract formation and infection. Due to the aggressive nature of CP, a second immunosuppressive agent is often required. Dapsone was chosen as the second immunosuppressive agent for our patient because there was only limited conjunctival and skin involvement during her initial presentation. However, dapsone has a moderate anti-inflammatory activity⁸ and a more potent immunosuppressive agent such as cyclophosphamide may have been a better choice for our patient. Before the use of dapsone, patients should have evaluation of their G6PD and methaemoglobin levels. Side-effects include reversible haemolytic anaemia and leukopaenia.

Cicatricial pemphigoid can be rapidly progressive, as in our case, and the early combined use of oral prednisolone and oral cyclophosphamide (1-2 mg/kg/day) may prevent disease progression and complications.⁹ However, there are significant risks with this therapy including infections, haemorrhagic cystitis, and bone marrow suppression, as occurred in our patient.

In a study of 10 patients with treatment-resistant ocular CP, IVIg therapy was found to be a safe and effective therapy.¹⁰ The drug is given at a dose of 2-3 g/kg/cycle over a 4-hour infusion for 2 consecutive days and repeated every month. Side-effects include volume overload and IVIg is also contra-indicated in patients with selective IgA deficiency. It was interesting to note that our patient initially had an excellent clinical response to IVIg but her response to subsequent doses lessened. This phenomenon has been reported previously in the treatment of myositis.¹¹ A possible explanation for the tachyphylaxis of IVIg in the treatment of our patient was that IVIg could only remove some of the autoantibodies produced but not all of them. Further studies are needed to investigate the sustained efficacy of IVIg.

Other therapies reported to be of value in the treatment of CP include azathioprine,¹² methotrexate,¹³ mycophenolate mofetil,¹⁴ and plasmapheresis.¹⁵

In summary, CP is a chronic systemic autoimmune disease that has potentially life-threatening extracutaneous manifestations. Optimal management of such patients is a challenge and requires good communication between a multidisciplinary team. Use of early aggressive systemic

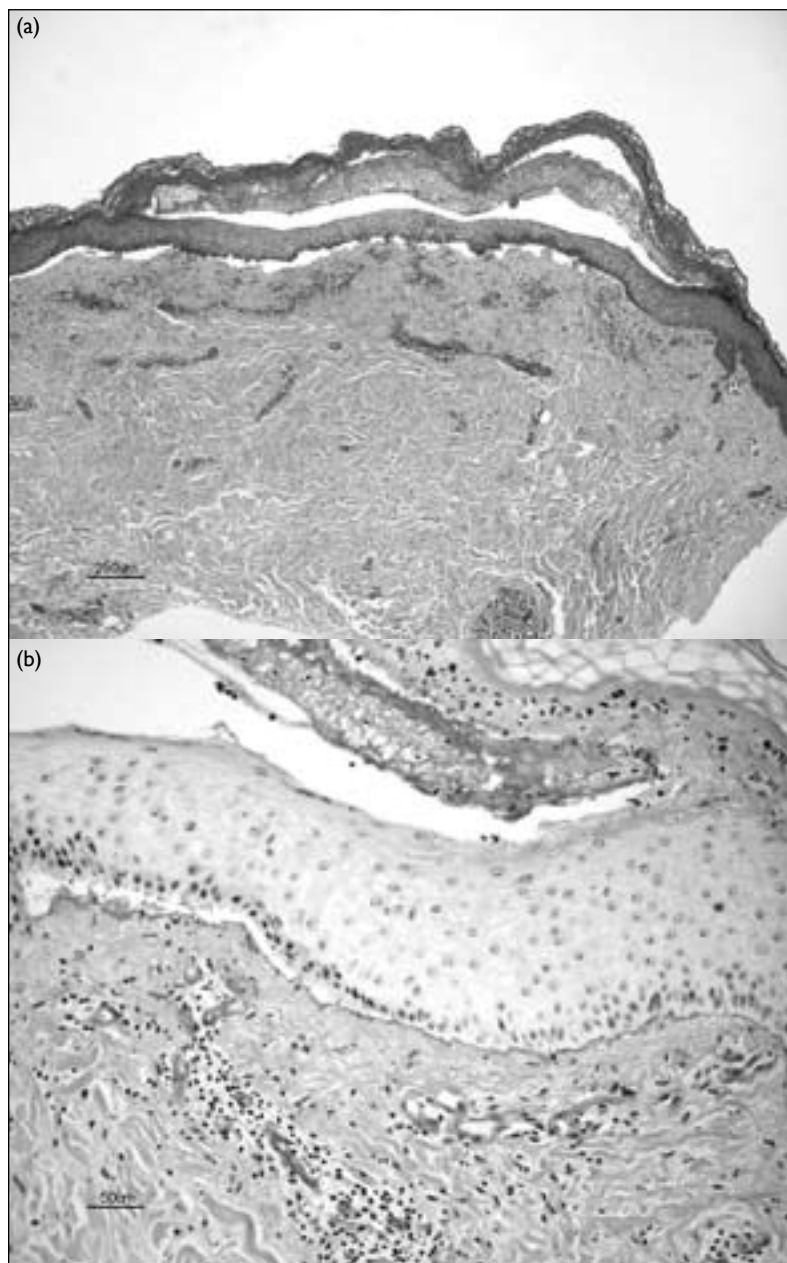


FIG 2. Skin biopsy: (a) there is a subepidermal blister with re-epithelialisation and re-blistering. A mixed infiltrate consisting of lymphocytes and eosinophils is found in the base of the blister. There is, however, no obvious dermal scarring (H&E), and (b) periodic acid-Schiff reaction after diastase digestion staining highlights the basement membrane in the floor of the blister

immunomodulatory agents is the treatment of choice for controlling disease activity and progression.

References

1. Thost A. Der chronische schleimhaut-pemphigus der oberen luftwege. Arch Laryng Rhinol 1911;25:459-78.
2. Zillikens D, Wever S, Roth A, Weidenthaler-Barth B, Hashimoto T, Brocker EB. Incidence of autoimmune

- subepidermal blistering dermatoses in a region of central Germany. *Arch Dermatol* 1995;131:957-8.
3. Chan LS, Ahmed AR, Anhalt GJ, et al. The first international consensus on mucous membrane pemphigoid: definition, diagnostic criteria, pathogenic factors, medical treatment, and prognostic indicators. *Arch Dermatol* 2002;138:370-9.
 4. Chang JH, McCluskey PJ. Ocular cicatricial pemphigoid: manifestations and management. *Curr Allergy Asthma Rep* 2005;5:333-8.
 5. Brunsting LA, Perry HO. Benign pemphigoid; a report of seven cases with chronic, scarring, herpetiform plaques about the head and neck. *AMA Arch Derm* 1957;75:489-501.
 6. Tseng SC, Di Pascuale MA, Liu DT, Gao YY, Baradaran-Rafii A. Intraoperative mitomycin C and amniotic membrane transplantation for fornix reconstruction in severe cicatricial ocular surface diseases. *Ophthalmology* 2005;112:896-903.
 7. Mondino BJ, Brown SI. Ocular cicatricial pemphigoid. *Ophthalmology* 1981;88:95-100.
 8. Tauber J, Sainz de la Maza M, Foster CS. Systemic chemotherapy for ocular cicatricial pemphigoid. *Cornea* 1991;10:185-95.
 9. Foster CS. Cicatricial pemphigoid. *Trans Am Ophthalmol Soc* 1986;84:527-663.
 10. Foster CS, Ahmed AR. Intravenous immunoglobulin therapy for ocular cicatricial pemphigoid: a preliminary study. *Ophthalmol* 1999;106:2136-43.
 11. Reimold AM, Weinblatt ME. Tachyphylaxis of intravenous immunoglobulin in refractory inflammatory myopathy. *J Rheumatol* 1994;21:1144-6.
 12. Dave VK, Vickers CF. Azathioprine in the treatment of mucocutaneous pemphigoid. *Br J Dermatol* 1974;90:183-6.
 13. McCluskey P, Chang JH, Singh R, Wakefield D. Methotrexate therapy for ocular cicatricial pemphigoid. *Ophthalmology* 2004;111:796-801.
 14. Ingen-Housz-Oro S, Prost-Squarcioni C, Pascal F, et al. Cicatricial pemphigoid: treatment with mycophenolate mofetil [in French]. *Ann Dermatol Venereol* 2005;132:13-6.
 15. Hashimoto Y, Suga Y, Yoshiike T, Hashimoto T, Takamori K. A case of antiepileptic cicatricial pemphigoid successfully treated by plasmapheresis. *Dermatology* 2000;201:58-60.

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