Case 1

Chronic scarring conjunctivitis with skin rash

Vipawee Ounsakul, M.D.
Kumutnart Chanprapaph, M.D.

Patient: A 32-year-old Thai male from Bangkok

Chief complaint: Generalized vesiculobullous eruptions for 1 month

Present illness:

6 mo: He developed conjunctival edema and redness, blurred vision and foreign-body sensation on his both eyes and was diagnosed severe conjunctivitis.

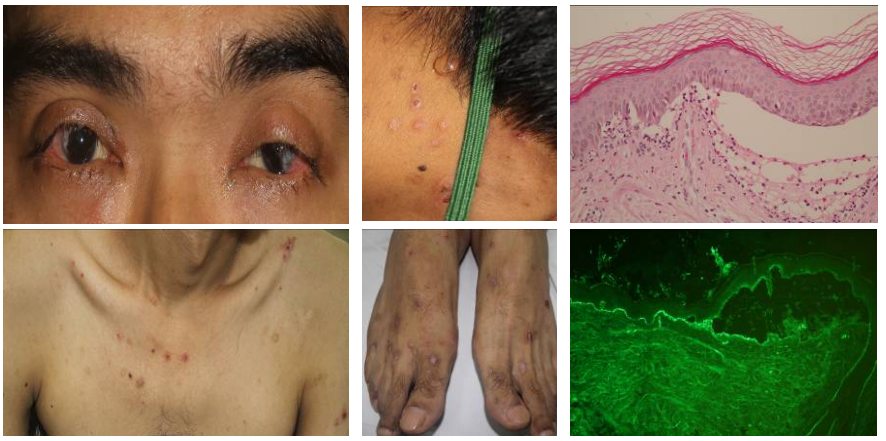
4 mo: He developed pruritis skin lesions on trunk and extremities, diagnosed as insect bite reaction.

3 mo: He developed nasal voice with hoarseness, diagnosed as acute on top chronic sinusitis.

1 mo: He developed vesiculobullous lesions with pruritus on trunk and extremities.

Past history:

Reactivation of pulmonary TB S/P IRZE for 1 month



Skin examination:

- Few vesicles and bullae on neck and dorsum of hands and foot
- Multiple discrete erythematous to brownish macules and crusted erosions and on trunk and extremities
- Conjunctival injection, symblepharon and purulent discharge both eyes
- Atrophic hemorrhagic crusted lesions and pus in nasal cavity

Histopathology: (S13-25824, right hand)

There is a subepidermal vesicle in association with inflammatory cell infiltrate of neutrophils admixed with a few eosinophils in the superficial dermis.

Direct immuofluorescence:

- Positive IgG 2+ linear pattern at floor
- Positive C3 linear and granular pattern at dermoepidermal junction
- Spitted skin showed combined epidermal and dermal IgG deposition

Diagnosis: Mucous membrane pemphigoid

Investigation:

- ANA: Positive homogeneous pattern 1:320
- ANA 12 profile: Negative
- C3 and C4 level: Normal
- ESR 26 mm/hr, CRP 11.52 mg/L
- BPAG 1 and BPAG2: Pending

Treatment:

- Intravenous immunoglobulin 2 g/kg/cycle at 4-week intervals x 3 cycles
- Oral prednisolone 30 mg/day (0.5 mg/kg/day)
- Mycofenolate mofetil 1 g/day since 4th August 2014
- 0.1% Betamethasone valerate apply lesions twice a day
- 1% Methyprednisolone apply both eyes four times a day
- 0.18% Sodium hyaluronate apply both eyes four times a day
- Cabomer gel apply both eyes at bedtime
- Calcium carbonate 1250 mg twice a day
- Vitamin D2 20000 IU once a week
- Omeprazole 20 mg twice a day

Discussion:

Mucous membrane pemphigoid (MMP) is a chronic autoimmune, mucous membrane-dominated, subepithelial blistering disease with or without skin involvement[1]. MMP is rare, with an annual incidence of 1 person per million in European country[2]. The mean age of onset is early to middle 60s[3]. Although there is no known racial or geographic predilection, several studies have shown an association with the HLADQB1*0301 alleles in MMP patients[3,4].

The pathogenesis, which held responsible for the majority of MMP patients, is autoantibodies to autoantigens in basement membrane zone. Many different autoantigens are recognized by autoantibodies from patients including bullous pemphigoid antigen 2(BPAG2), laminin 332, integrin subunit β4 and α6, type VII collagen and bullous pemphigoid antigen 1(BPAG1), suggesting that MMP is not a single entity but rather a disease phenotype[1,5]. Although autoantigens are vary, subsets of patients with exclusive involvement of oral and ocular mucosae have autoantibodies targeting α-6 and β-4 integrins, respectively[6].

Clinically, MMP has various clinical spectrums ranging from minimal localized to severe with significant scarring which may affect any or all of the mucous membranes with the highest frequency of the oral site followed by the ocular, nasopharyngeal, anogenital, laryngeal and esophageal in descending order of involvement[1]. Oral involvement commonly manifests as desquamative gingivitis, others include erythematous patches, blisters and erosions in any oral lolations[3,6]. Ocular involvement typically manifests as conjunctivitis, although

may present early with subtle and nonspecific complaints of dryness, burning or foreign body sensation which can be detected only by slit-lamp examination. A chronic conjunctival inflammation results in subepithelial fibrosis that leads to fornix shortening, symblepharon, and ankyloblepharon formation. Then, subsequently, trichiasis and entropion may result in corneal irritation, corneal ulceration or blindness[3,6]. Nasopharyngeal involvement can result in discharge, epistaxis and chronic sinusitis. Laryngeal involvement may present as hoarseness, sore throat. Chronic laryngeal erosions, edema and scarring may result in supraglottic stenosis and airway compromise. Esophageal involvement may present with dysphagia, odynophagia, weight loss, and/or aspiration. Although anogenital involvement is rare, scarring in these sites can cause substantial pain and morbidity[3]. The skin is involved in 25%–35% of MMP patients with the most frequently affected areas of head, neck, and upper trunk. Cutaneous lesions typically present as erythematous plaques, blister formation and erosions with subsequent atrophic scarring, but occasionally present as BP-like clinical presentations[3].

The diagnosis of MMP is based on clinical, histological and immunopathological studies. Although, an international consensus considered direct immunofluorescence (DIF) examination with consistent clinical findings are sufficient for the diagnosis of MMP[1].

Histopathology from the lesions may be nonspecific. Typically, they demonstrate a subepidermal blister with dermal lymphocytes and histiocytes infiltration as well as variable numbers of neutrophils and eosinophils in skin lesions and plasma cells in mucosal lesions[1,3].

DIF examination on perilesional biopsies detects linear deposits along epithelial BMZ of 1 or combination of IgG, IgA and C3[1]. The most commonly detected immunoreactants are IgG and C3, but IgA, IgM, and/or fibrin are also found in some patients[3].

IIF using the patient's sera on a 1 M NaCl-split skin may perform to identify the presence and characteristics of autoantibodies. The patterns of autoantibodies binding allow physicians to subdivide patients with autoantibodies targeting upper lamina lucida antigens (bullous pemphigoid antigen 2, α6β4 integrins) or lower lamina lucida/sublamina densa antigens (laminin-5, laminin-6, type VII collagen), respectively[1,6].

The prognosis of patients who have restricted oral disease are excellent, they tend to have a mild to moderate disease, while patients with ocular disease generally have a progressive disease resulted in scarring or blindness[6]. Patients with anti- laminin 332 autoantibodies, also known as anti-epiligrin cicatricial pemphigoid have been reported an increased relative cancer risk for solid organ carcinomas[7] while patients with autoantibodies to β4 or α6 integrin showed a lower than expected relative cancer risk[8,9].

The treatment recommendation are based on site of involvement, severity and rapidity of progression[1,10]. Low-risk patients defined as those who have only oral disease or oral plus skin involvement. In mild cases, topical corticosteroid of moderate to high potency should be tried. In moderate to severe cases, dapsone (25-200 mg/d) and a low dose of prednisone (0.5 mg/kg/d) with or without immunosuppressive, such as azathioprine (100-150 mg/d) should be initiated. High-risk patients defined as those who have any of the ocular, genital, nasopharyngeal, esophageal and laryngeal involvement. In slow to moderate progressive cases, dapsone (50-200 mg/d), plus systemic corticosteroids and an immunosuppressive such as azathioprine or

mycophenolate mofetil should be initiated. In severe or rapid progressive cases, cyclophosphamide (1-2 mg/kg/d) plus systemic corticosteroids (1-1.5 mg/kg/d) is preferred due to a faster onset of action of cyclophosphamide. In patients with recalcitrant ocular disease, treatment with rituximab with or without combination of intravenous immunoglobulin have been reported to successfully arrest disease progression and prevent total blindness[10,11,12].

In our patient, vesiculobullous lesion together with mucous membrane involvement (ocular, nasopharynx and larynx) suggests the diagnosis of MMP. Histopathology confirms subepidermal separation and perilesion DIF show positive of IgG (linear pattern) and C3 (linear and granular) pattern at DEJ, which is consistent with the diagnosis of MMP. Oral prednisolone 0.5 mg/kg/day was commenced in our patient. Initially, the patient was diagnosed with pulmonary TB; therefore, we were reluctant to give high dose systemic steroid as well as any other immunosuppression. IVIG 2g/kg/cycle was given with satisfactory results. However, since recently pulmonary TB is now considered undercontrolled, MMF has been initiated for 3 weeks. Gradual increment of MMF to therapeutic dose is planned.

References:

1. 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: 370–79.
2. Bernard P, Vaillant L, Labeille B, et al. Incidence and distribution of subepidermal autoimmune bullous skin diseases in three French regions. Bullous Diseases French Study Group. Arch Dermatol. 1995; 131: 48–52.
3. Kim B.Yancey. Cicatricial Pemphigoid. Fitzpatrick 's Dermatology in general medicine 8th edition. 2012; 57: 617-23.
4. J.Setterfield, J.Theron, R.W.VaughanA, et al. Mucous membrane pemphigoid: HLA-DQB1*0301 is associated with all clinical sites of involvement and may be linked to antibasement membrane IgG production. Br J Dermatol. 2001; 145: 406-14.
5. Khwaja A. Rashid, Hakan M. Gürcan, A. Razzaque Ahmed. Antigen Specificity in Subsets of Mucous Membrane Pemphigoid. J Invest Dermatol. 2006; 126: 2631–36.
6. Lawrence S. Chan. Ocular and oral mucous membrane pemphigoid (cicatricial pemphigoid). Clin Dermatol. 2012; 30: 34–37.
7. Egan CA, Lazarova Z, Darling TN, Yee C, Cote T, Yancey KB. Anti-epiligrin cicatricial pemphigoid and relative risk for cancer. Lancet. 2001; 357: 1850–51.
8. E. Letko, H. M. Gürcan, G. N. Papaliodis. Relative risk for cancer in mucous membrane pemphigoid associated with antibodies to the b4 integrin subunit. Clin Exp Dermatol. 2007; 32: 637–41.
9. Malik M, Gürcan HM, Christen W, Ahmed AR. Relationship between cancer and oral pemphigoid patients with antibodies to alpha6-integrin. J Oral Path Med. 2007; 36: 1-5.
10. Schmidt E, Zillikens D. Pemphigoid diseases. Lancet. 2013; 381(9863): 320-332.
11. Jennifer E. Thorne, Fasika A. Woreta, Douglas A. Jabs, et al. Treatment of Ocular Mucous Membrane Pemphigoid with Immunosuppressive Drug Therapy. Ophthalmology. 2008; 115: 2146–52.
12. C. Stephen Foster, Peter Y. Chang, A. Razzaque Ahmed. Combination of Rituximab and Intravenous Immunoglobulin for Recalcitrant Ocular Cicatricial Pemphigoid. Ophthalmology 2010; 117: 861–9.