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CASE REPORT

Cicatricial Pemphigoid in Accompany with Rheumatoid Arthritis: a Case Report

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CICATRICIAL pemphigoid (CP, also known as benign mucous membrane pemphigoid) is a rare chronic autoimmune subepithelial blistering disease, with an incidence of 1 per million, characterized by erosive lesions of mucous membranes and skin that result in scarring.^{1,2} Rheumatoid arthritis (RA) is a symmetric inflammatory arthritis that mainly affects the small joints of hands and feet, with a prevalence of 0.3% in China.³ In this case report we described the diagnosis of and treatment for a patient developing CP 18 years after the onset of RA, a combination rarely encountered or reported so far.

CASE DESCRIPTION

A 72-year old woman was admitted to our hospital because of polyarthritis, oral ulcers, and bilateral conjunctivitis. Nineteen years before, the patient developed insidious symmetric polyarthritis involving shoulders, proximal interphalangeal and metacarpophalangeal joints, knees, wrists, and elbows. Eight years later, deformities in hand joints developed. The patient had been treated with weekly oral methotrexate (MTX) and the polyarthritis subsided considerably after medication.

Seven months before admission, the patient noticed painful mucosal erosions and blisters in tongue, palate, and posterior pharyngeal wall, along with recurrent gingivitis. After one month, she began to experience burning, dryness, foreign body sensation, and marked conjunctival erythema in both eyes. Bilateral symblephara occurred in two months (Fig. 1). No skin lesions were noticed throughout the course.

One month before admission, the patient underwent a series of tests at the outpatient clinic. The test results showed an erythrocyte sedimentation rate (ESR) of 72 mm/h (reference range, <20 mm/h) and a rheumatoid factor (RF) level of 156 IU/mL (reference range, <20 IU/mL). The patient was diagnosed as RA and suspected with CP because of the characteristic scarring lesions involving oral mucosa and conjunctivae sparing the skin. Aggressive treatment for CP was prescribed considering the rapid progression of the ocular lesions. Oral cyclosporine A (50 mg three times a day), intravenous cyclophosphamide (cumulative dose, 1 g), and oral methylprednisolone in large dose were given in accompany with topical treatment in the eyes with tobramycin and dexamethasone. The patient was later hospitalized for further evaluation and management.

Upon admission, the physical examination detected oral and ocular lesions corresponding with the symptoms described above, found no skin lesions, ulnar deviation and swan-neck deformity in the digits, obvious joint swelling

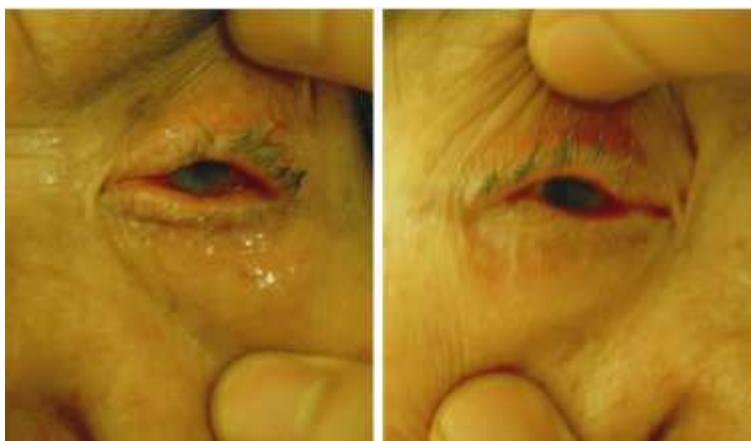


Figure 1. Bilateral symblephara in a rheumatoid arthritis patient concomitant with cicatricial pemphigoid.

and tenderness, or other abnormal signs. In the rheumatologic tests ordered after admission, ESR was found down to 33 mm/h, and the levels of serum C-reactive protein, immunoglobulins, and complements were normal. The test results for anti-nuclear antibodies, anti-dsDNA antibodies, anti-neutrophil cytoplasmic antibodies, RF, anti-perinuclear factor, and anti-keratin antibodies were all negative. However, her anti-cyclic citrullinated peptide antibody, a specific antibody in RA, was found at a level of 39 U/mL (reference range, <25 U/mL). Radiographs of her hands, wrists, and left elbow demonstrated osteoporosis and changes consistent with stage III RA. Cancer screening detected no obvious abnormalities. Serum anti-desmoglein 1, anti-desmoglein 3, and anti-BP180 autoantibodies were negative. Biopsy of the mucosal lesion was not performed as it was declined by the patient.

A joint consultation participated by specialists in dermatology, dentistry, ophthalmology, and rheumatology concluded that the patient's RA was in late stage but stable, CP could be clinically diagnosed with confidence, and the progression had been halted by previous treatment. Ongoing MTX therapy was continued in the treatment for her RA; as for CP, oral and topical cyclosporine A were used, oral methylprednisolone tapered off over six months, and the topical use of dexamethasone stopped immediately. The patient was advised to keep good oral hygiene. In addition to medication, the ophthalmologist suggested that her symblephara be relieved by surgery, but only after CP was fully controlled, which is usually around 1 year after onset. The possibility of relapse in this patient entails long-term follow-up.

DISCUSSION

CP is a chronic and progressive disorder, which rarely mitigates spontaneously. It typically affects elderly people

(aged 60-80 years), and more females than males (female to male ratio, 1.5 : 1-2 : 1). The commonly involved sites are oral mucosa (85%), conjunctiva (64%), skin (24%), pharynx (19%), external genitalia (17%), nasal mucosa (15%), larynx (8%), anus (4%), and esophagus (4%).¹ Desquamative gingivitis, tense blisters, and mucosal erosions are common types of oral lesions. Ocular lesions usually manifest as conjunctivitis progressing to scarring which could lead to trichiasis, symblephara, ankyloblephara, corneal ulceration, and blindness. Other major complications may include supraglottic stenosis, dysphagia, and anal stenosis. Skin lesions, including scattered erosions or blisters, are present in only 25%-35% of patients.² The patient in this report presented with the typical clinical characteristics of CP.

Ultrastructurally, lesions develop within the epithelial basement membranes (EBM).^{1,2} Circulating anti-EBM autoantibodies can be detected in the sera of some but not all patients. The differentiation of CP from other autoimmune bullous diseases may sometimes require immunopathologic studies and immunoelectron microscopy, when clinical findings are atypical. On the other hand, CP patients with anti-laminin-5 autoantibodies appear to have a high risk of adenocarcinoma that approximates the risk in dermatomyositis patients, and the time between onset of CP and cancer diagnosis is reported to be about a year,⁴ therefore cancer screening was conducted in this case.

Mild lesions in this disease can be treated with topical glucocorticoids, tacrolimus, or cyclosporine A. Oral administration of dapsone may be effective as well. For severe CP conditions, a combination of systemic glucocorticoids and immunosuppressive drugs is recommended. Intravenous immunoglobulin and etanercept have also produced good results,⁵ providing alternatives in cases where first-line therapy fails. Surgical intervention may exacerbate the disease,¹ therefore should not be consi-

dered until full control by medication.

The association between CP and RA has been reported in several case series since 1978,^{6,7} the largest to date reported by Olsen et al.⁷ In their report, charts from a period of 26 years were retrospectively analyzed, and 8 patients were found having RA concomitant with ocular CP, including 7 females and 1 male. Those patients developed RA 19 years on average before CP diagnosis. The mechanism underlying this association has not been fully understood yet. Genetic factors, especially class II major histocompatibility complex molecules, may have important effects in it. For instance, both RA and CP have been shown to be strongly associated with HLA-DR4.^{1,3} RA and CP may also be linked *via* an immunologically mediated process. In RA, the abnormal activation of T cells is the initiation of pathogenesis, and in CP, apart from humoral immunity, cellular immunity and cytokines may also play a role, particularly in inducing collagen production and fibrosis.⁸ Further studies on their association might shed some new light on the pathogenesis of both diseases.

REFERENCES

1. Bruch-Gerharz D, Hertl M, Ruzicka T. Mucous membrane pemphigoid: clinical aspects, immunopathological features and therapy. *Eur J Dermatol* 2007; 17:191-200.
2. Fleming TE, Korman NJ. Cicatricial pemphigoid. *J Am Acad Dermatol* 2000; 43:571-91.
3. Harris ED Jr, Firestein GS. Clinical features of rheumatoid arthritis. In: Firestein GS, Budd RC, Harris ED, et al, editors. *Kelley's textbook of rheumatology*. 8th ed. Philadelphia: Saunders; 2008 .p.1043-78.
4. Egan CA, Lazarova Z, Darling TN, et al. Anti-epiligrin cicatricial pemphigoid and relative risk for cancer. *Lancet* 2001; 357:1850-1.
5. Canizares MJ, Smith DI, Conners MS, et al. Successful treatment of mucous membrane pemphigoid with etanercept in 3 patients. *Arch Dermatol* 2006; 142:1457-61.
6. Spigel GT, Winkelmann RK. Cicatricial pemphigoid and rheumatoid arthritis. *Arch Dermatol* 1978; 114:415-7.
7. Olsen KE, Holland EJ. The association between ocular cicatricial pemphigoid and rheumatoid arthritis. *Cornea* 1998; 17:504-7.
8. Lee SJ, Li Z, Sherman B, et al. Serum levels of tumor necrosis factor-alpha and interleukin-6 in ocular cicatricial pemphigoid. *Invest Ophthalmol Vis Sci* 1993; 34:3522-5.
1. Bruch-Gerharz D, Hertl M, Ruzicka T. Mucous membrane