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Response of Ocular Pemphigus Vulgaris to Therapy. Case Report and Review of Literature.

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Abstract

Background: Pemphigus vulgaris is an autoimmune bullous disease characterized by blistering and erosions within skin and mucous membranes. Lesions appear most commonly on mucosal surfaces of the oral cavity. Ocular involvement in patients with PV has rarely been reported.

Main Observation: A 47-year-old male patient with a 2 month history of oral erosions and dysphagia developed severe conjunctivitis with periodical presence of purulent discharge, photophobia and burning sensations. The diagnosis of pemphigus vulgaris was confirmed by histopathology, direct immunofluorescence and detection of anti-desmogelin 3 antibodies in patients' serum. Treatment was introduced with prednisone at a dose of 80 mg per day (1 mg/kg) and cyclophosphamide at a dose of 100 mg daily (1.25 mg/kg). After 7 days of therapy a significant reduction of eye symptoms was observed and after 4 weeks of treatment full clinical remission was achieved.

Conclusions: The grounds for rare involvement of conjunctiva in pemphigus vulgaris is unclear. We hypothesize that inactivation of conjunctival desmoglein 3 may be compensated by other desmosomal proteins. Severe conjunctivitis may be the dominating clinical manifestation in pemphigus vulgaris. This implies a need of establishing distinct severity criteria and therapeutic standards for ocular pemphigus. In our patient rapid clinical response was achieved after introducing combined treatment with prednisone and oral cyclophosphamide.

Introduction

Pemphigus vulgaris (PV) is an autoimmune bullous disease characterized by blistering of the skin and mucous membranes. Mucosal lesions usually precede cutaneous lesions or they are sole manifestation of the disease.[1] Erosions usually appear on mucous membranes of the oral cavity, but may be also observed within the nasopharynx, larynx, esophagus, urinary and reproductive mucosa or anus. Cases of simultaneous involvement of mucous membranes in multiple localizations were described.[2] Ocular involvement in patients with PV has rarely been reported.[3,4]

We report a case of a patient with PV in which severe ocular conjunctivitis was the dominating clinical manifestation of PV.

Case Report

A 47-year-old male patient, with a 2 month history of erosions of the oral cavity and dysphagia developed ocular symptoms. These included severe conjunctivitis with diffusely injected conjunctiva, edema, pain, lacrimation, periodical presence of purulent discharge, photophobia and burning sensations. Pterygium (a benign growth of the conjunctiva), which overlapped the cornea and a pigmentary naevus were additional ophtalmological findings. Endoscopic examination of the esophagus revealed congestion and swelling of the mucosa, contact bleeding and fragmentary detachment of epithelium. Few weeks later single blisters and erosions occurred on the glabrous skin of trunk and limbs.

Direct immunofluorescence of the perilesional skin showed intercellular deposits of IgG and C3 of pemphigus

type. Indirect immunofluorescence test on monkey esophagus as substrate revealed presence of pemphigus antibodies at a titer of 640 in serum. No antibodies were detected in immunofluorescence test with guinea pig esophagus as substrate. ELISA (enzyme-linked immunosorbent assay, MBL, Japan) demonstrated presence of serum anti-desmoglein 3 antibodies with an index of 97.4. The ELISA index for anti-desmoglein 1 antibodies was below threshold. These results confirmed the diagnosis of pemphigus vulgaris.

Treatment was introduced with prednisone at a dose of 80 mg per day (1mg/kg) and cyclophosphamide at a dose of 100 mg daily (1.25 mg/kg). Topical treatment consisted of repeated lubrication of the eyes and application of diclofenac, naphazolin and zinc sulphate solutions.

After 7 days of therapy a significant reduction of ocular symptoms was observed. Oral mucosal lesions and symptoms of dysphagia were markedly improved. Control ophtalmologic examination revealed significant reduction of conjunctival congestion. After 4 weeks of therapy full clinical remission was achieved. This was associated with a reduction of serum levels of pemphigus antibodies. Pemphigus antibody titer in indirect immunofluorescence was 320 on the monkey esophagus as substrate. Anti-desmoglein 3 antibody ELISA index was 41.7.

The dose of prednisone and cyclophosphamide was gradually reduced. No relapse was observed.

Discussion

The presence of circulating and in vivo bound antibodies to desmoglein 3 is specific for pemphigus vulgaris. It was shown that these antibodies trigger loss of cell-cell adhesion of keratinocytes and induce characteristic blisters or erosions in skin and mucous membranes.

Ocular involvement in pemphigus vulgaris may be explained by the presence of desmoglein 3 in ocular epithelium. Desmoglein 3 was found to be strongly expressed in the basal cells of the conjunctival epithelium, fading in the suprabasal layer.[5] The expression pattern of this antigen in the cornea and limbus is less prominent and mirrored by the expression pattern of desmocollin 3.[6] Other studies show that the conjunctiva is also rich in desmoplakin 1 and 2.[6]

Data about ocular expression of desmoglein 3 bring up the question, why ocular involvement in pemphigus vulgaris is relatively rare compared to the consistent presence of anti-desmoglein 3 antibodies in this disease. We hypothesize that inactication of desmoglein 3 in ocular epithelium may be compensated by the presence of non-desmoglein desmosomal proteins, similar to the desmoglein compensation mechanism described by John Stanley.[7] According to this controversial desmoglein compensation concept, anti-desmoglein 1 autoantibodies would only lead to epidermal splitting in those epidermal layers in which no desmoglein 3 is present to compensate for the functional loss of Dsg 1.[8]

Desmoglein 3 function loss in conjunctiva in most patients with pemphigus vulgaris may be compensated by the presence of other desmosomal proteins, responsible for epithelial cell attachment. Only a minority would develop ocular lesions.

This hypothesis might be supported by the frequent ocular involvement in paraneoplastic pemphigus (paraneoplastic autoimmune multiorgan syndrome), which is characterized by the presence of autoantibodies to a wide spectrum of antigens, including members of the plakin family (desmoplakin I, II, BPAG1, envoplakin, periplakin, and HD1/plectin as well as desmogleins and desmocollins.[9]

Ocular involvement in patients with PV has been rarely reported.[4,10,11,12,13] According to our literature search results, 26 cases of immunologically confirmed (by either direct immunofluorescence or detection of circulating autoantibodies) ocular pemphigus were described. These were 14 females and 12 males (1.16:1 ratio). Mean age at disease onset in these patients was 49.6 (range 15-80) years, which appears to be slightly younger than in patients with pemphigus vulgaris in general.[14] This however might be misleading. When not taking into consideration pediatric patients, aged 15, the average age at disease onset is 52.5 years. Ocular symptoms developed few days to many months after onset of other symptoms of pemphigus. Their severity does not correlate with general disease severity.[13]

Most commonly ophthalmologic examination reveals bilateral conjunctivitis, conjunctiva congestion, inflammation of eyelid margin, occasionally accompanied by blisters and erosions of the bulbar/palpebral conjunctiva or eyelid margin.[15,16] Most patients with ocular PV have full recovery without sequelae. Ocular pemphigus does not appear to affect visual acuity but one case of corneal perforation has been reported.[4, 17]

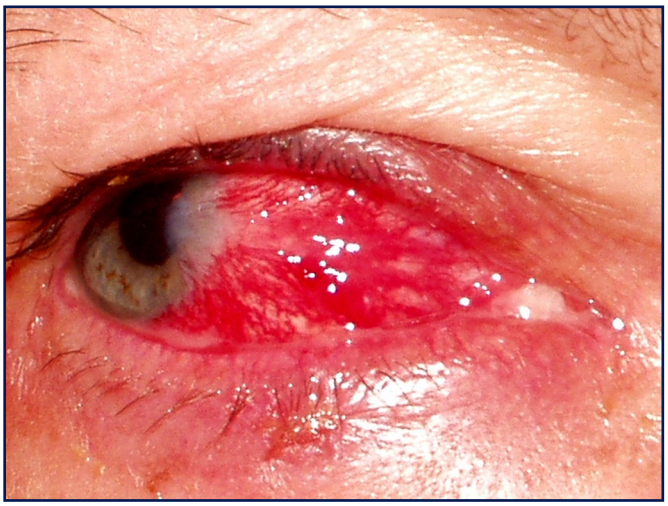

Figure 1

Diffusely injected conjunctiva as dominating clinical manifestation in patient with pemphigus vulgaris.

Histological examination of the conjunctiva is usually not specific.[12] The typical pemphigus histology picture of acantholysis has been rarely observed. Only in some cases suprabasal acantholysis was detected on routine histological examination of the conjunctiva and skin of the eyelid.

In all published cases of ocular pemphigus patients received oral prednisone. In 7/26 published cases prednisone was used in monotherapy. Not in all cases information about prednisone dose is provided in publications. In 19/26 cases one or more adjuvant drugs were added to corticosteroids. Most commonly, in 9/26 cases (52.9%) intravenous immunoglobulins were applied. Other patients received: 6/26 (35.3%) azathioprine, 6/26 (35.3%) dapsone, 5/26 (29.4%) cyclophosphamide, 4/26 (23.5%) methotrexate, 3/26 (17.6%) cyclosporin A and 3/26 (17.6%) mycophenolate mofetil. Taken into consideration that some patients received more than one adjuvant drug and that information in some cases was not provided by authors, time required to achieve clinical remission was 10,5 months in patients receiving prednisone in monotherapy. In patients receiving additionaly adjuvant drugs the time required to achieve remission was 13.3 months for intravenous immunoglobulins, 12.2 months for azathioprine, 12.0 months for cyclosporine A and cyclophosphamide, 11.7 for dapsone, 10.0 months for mycophenolate mofetil and 9.5 for methotrexate. A single case of rapid response to topical treatment with tacrolimus has been reported.[18] Many authors apply supplementary prophylactic topical or systemic antibacterial and antifungal treatment.

The number of patients in each group was to low to perform statistical analysis, but these results indicate that no single treatment modality has a significant benefit over other methods. This may indicate that there is a need for elucidating whether ocular pemphigus requires different treatment approach as compared to regular mucocutaneous or mucosal pemphigus vulgaris.

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