Chronic Cicatrizing Conjunctivitis in a Patient With Epidermolysis Bullosa Acquisita

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Objective: To describe a nonconventional diagnostic technique used to diagnose a case of cicatrizing conjunctivitis associated with epidermolysis bullosa acquisita.

Methods: Direct immunofluorescence of a biopsy specimen of the patient’s conjunctiva was performed using fluorescein-conjugated rabbit antihuman antibodies against IgA, IgG, and IgM; complement C3; and fibrinogen. Immunoblot assay using healthy human skin as substrate was performed to investigate for the presence of antibodies in the patient’s serum. After the diagnosis of systemic autoimmune disease was established, intravenous immunoglobulin therapy was administered.

Results: Direct immunofluorescence of the conjunctiva revealed linear deposition of IgA and IgG, and C3 at the epithelial basement membrane zone. Immunoblot analysis demonstrated the presence of IgG antibodies in patient serum directed against a 290-kDa protein in human skin. A diagnosis of epidermolysis bullosa acquisita was established. All signs and symptoms improved dramatically 4 months after initiation of intravenous immunoglobulin therapy and remained stable during follow-up.

Conclusions: Epidermolysis bullosa acquisita can manifest in the eye as chronic cicatrizing conjunctivitis indistinguishable from ocular cicatricial pemphigoid. A nonconventional diagnostic tool (immunoblot assay) might be helpful in establishing the diagnosis of an underlying systemic autoimmune disease in patients with chronic cicatrizing conjunctivitis. Intravenous immunoglobulin therapy was effective against chronic cicatrizing conjunctivitis associated with epidermolysis bullosa acquisita.

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CHRONIC CICATRIZING CONJUNCTIVITIS (CCC) is a potentially blinding condition often associated with a systemic autoimmune mucocutaneous blistering disease such as ocular cicatricial pemphigoid (OCP),1 linear IgA bullous dermatitis,2 epidermolysis bullosa acquisita (EBA),3 or pemphigus vulgaris.4

We report findings in a patient who was referred with CCC associated with a mucocutaneous autoimmune disease that was undiagnosed before referral. The laboratory test used to confirm diagnosis of the systemic condition and the treatment used in this case were unconventional.

REPORT OF A CASE

A 22-year-old white man with bilateral CCC was referred to us in October 2000. The patient’s medical history was remarkable for a mucocutaneous blistering disease with skin (Figure 1A), nasal, oral (Figure 1B), and anal sores, and bilateral CCC. The symptoms began with skin involvement in October 1998, when the patient noticed blisters on his arms, gluteal area, and left leg. Initial treatment was with systemic antibiotic drugs, but produced no substantial improvement. In September 1999, the patient experienced episodes of nasal bleeding that was difficult to control. The patient underwent sinus surgery, but the procedure was aborted when intraoperative findings revealed extensive mucosal erosions and scarring. After surgery, treatment with systemic prednisone, 35 mg/d, was begun. Despite this therapy, the patient continued to develop blisters, particularly at sites of trauma, including hands, elbows, knees, and ankles. Moreover, the disease progressed to involve both eyes in May 2000, when the patient experienced excruciating eye pain and photophobia that confined him to a dark room at home. His ophthalmologist prescribed dapsone,
100 mg/d, to treat presumed OCP, and 0.1% fluorometholone eyedrops 4 times a day, artificial tears 8 times a day, and a combination of 0.1% dexamethasone–0.3% tobramycin ointment (TobraDex) at bedtime. Two months later, however, the patient developed oral lesions that prevented him from chewing solid food. The dosage of dapsone was increased to 150 mg/d. Despite this regimen, the patient’s signs and symptoms continued to worsen.

At his initial visit to us, the patient was disabled by extraordinary photophobia, with visual acuity of 20/60 OD and 20/50 OS. Slitlamp biomicroscopy revealed trichiasis, distichiasis, fornix foreshortening, and posterior eyelid margin keratinization in both eyes, with symblepharon formation in the right eye. Because of severe photophobia with blepharospasm, general anesthesia was required to open the eyelids to further examine the eyes. This examination revealed moderately severe (3+/H11001) conjunctival hyperemia with symblepharon formation and corneal pannus in both eyes (Figure 2).

METHODS

CONJUNCTIVAL BIOPSY

Biopsy of the inflamed conjunctiva was performed with the patient under general anesthesia. Specimens were fixed in Karnovsky solution (1% paraformaldehyde, 1.25% glutaraldehyde, 0.13% sucrose, and 25 mmol/L of sodium phosphate in 0.2M sodium cacodylate buffer, pH 7.2), dehydrated with ethanol, and embedded in glycol methacrylate (LKB Historesin; LKB Produkter, AB, Bromma, Sweden). Sections 2-μm thick were stained with standard hematoxylin-eosin, para-acetylsalicylic acid, and alkaline Giemsa. Similarly, biopsy specimens from the skin and nasal mucosa were obtained.

DIRECT IMMUNOFLUORESCENCE

Direct immunofluorescence of the conjunctiva was performed using fluorescein-conjugated rabbit antihuman antibodies against IgA, IgM, IgG, complement C3, complement C4, and fibrinogen (Cappel, Durham, NC), as previously described.1

IMMUNOBLOT ASSAY

A modified immunoblot assay, described elsewhere,3 was used to investigate the antigen to which the circulating IgG antibody bound. In brief, basement membrane protein was extracted from healthy human skin using a buffer containing 8 mmol/L of urea, 0.3 mmol/L of β-mercaptoethanol, 0.05 mmol/L of Tris-hydrochloride, and protease inhibitors. In another procedure, the proteins were treated with collagenase (Sigma Chemicals, Perth, Western Australia). Proteins were subjected to sodium dodecylsulfate–polyacrylamide gel electrophoresis using 6% polyacrylamide slab gels and then were transferred onto nitrocellulose membrane and used in immunoblot assay. Serum obtained from a healthy individual was used as control.

INTRAVENTOUS IMMUNOGLOBULIN THERAPY

Given the severity of EBA in this patient, along with failure of previous therapy with prednisone and dapsone, the next choice of treatment was a challenge. The use of an alkylating agent in this 22-year-old patient was considered but was rejected because of the high risk for sterility. Therefore, we initiated intravenous immunoglobulin (IVIg) therapy following previously described protocol.6

In brief, IVIg was initially given at monthly intervals at a dose of 2 g/kg. Each dose was divided into 3 intravenous infusions administered during 3 consecutive days. As clinical improvement was observed, the interval between the infusion cycles was increased, but the dosage of IVIg remained the same for each session. In addition to IVIg, the patient used preservative-free artificial tears in both eyes.
RESULTS

HISTOPATHOLOGIC FINDINGS

Hematoxylin-eosin staining of the conjunctiva biopsy specimen revealed an inflammatory infiltrate in the epithelium and substantia propria consisting of neutrophils, lymphocytes, and plasma cells. Keratinization of the superficial layer and cellular hyperplasia of the basal layers were dominant morphologic changes in the epithelium (Figure 3A). Staining with periodic acid-Schiff showed mucin in the epithelium but no formed goblet cells. Mast cells, visualized at alkaline Giemsa staining, were present in large numbers in the substantia propria and epithelium.

DIRECT IMMUNOFLOUORESCENCE

Direct immunofluorescence of the conjunctival biopsy specimen disclosed deposition of IgA, IgG, and C3 at the epithelial basement membrane zone (Figure 3B). No deposition of immunoreactants in the intercellular spaces of the epithelium or in blood vessels of the substantia propria was detected. Similar findings were seen in the skin and nasal mucosa biopsy specimens.

DIRECT IMMUNOFLUORESCENCE

IMMUNOBLOT ASSAY

We observed binding of IgG in the patient’s serum to 290- and 145-kDa proteins in a lysate of normal human dermis, previously identified as collagen VII (Figure 4). No binding of IgM from the patient’s serum was detected. Neither IgG nor IgM from normal human serum bound to the lysate proteins.

IVIG THERAPY

At a follow-up visit 4 months after the initiation of IVIG therapy, the patient’s symptoms had improved dramatically. He was comfortable, without photophobia, and nasal and oral lesions had improved remarkably. The skin lesions had healed, leaving atrophic scars. The ocular examination disclosed improvement in visual acuity to 20/25 OD and 20/20 OS; conjunctival hyperemia was mild (1+) in both eyes (Figure 5).

COMMENT

We describe a 22-year-old patient who became disabled as a result of CCC associated with an autoimmune mucocutaneous blistering disease that remained undiagnosed and treated ineffectively for 2 years before his initial visit to our clinic. Immunohistochemistry of a conjunctival biopsy specimen disclosed deposition of immunoglobulin at the basement membrane zone. This pattern of staining can be observed in patients with OCP, EBA, or linear IgA bullous dermatitis. In such cases, particularly in the context of limited or equivocal clinical manifestations, nonconventional diagnostic methods must be used to establish or confirm the diagnosis. We used immunoblot assay, which disclosed the presence of IgG autoantibodies in the patient’s serum that bound to a 290-
kDa protein from a lysate of normal human dermis. This protein has been previously identified as type VII collagen, the primary target autoantigen in EBA. Hence, the diagnosis of EBA was confirmed. Immunoblot assay can be used to help establish a diagnosis in a spectrum of patients with CCC associated with deposition of immunoglobulin components at the basement membrane zone. Our previous report described patients with CCC secondary to OCP whose serum bound to a 205-kDa antigen in bovine gingival lysate, identified as the β4 subunit of α6β4-integrin. Furthermore, we have recently established the diagnosis of linear IgA bullous dermatitis in another patient with CCC using an immunoblot assay with normal human epidermis as substrate. The assay disclosed the presence of autoantibodies to a 95-kDa antigen in the serum. Hoang-Xuan et al reported use of direct immunofluorescence electron microscopy of the conjunctiva to confirm the diagnosis of EBA in 2 patients with CCC. The authors observed the presence of immune deposits in the anchoring fibril zone beneath the lamina densa of the basement membrane zone, a finding specific for EBA.

Epidermolysis bullosa acquisita is a systemic autoimmune mucocutaneous blistering disease characterized by blister formation and chronic progressive scarring of the skin and mucous membranes. Skin blisters can be induced spontaneously or after mechanical injury, predominantly at sites predisposed to trauma such as the gluteal area and elbows. In addition, EBA can cause progressive scarring of mucous membranes that can be complicated by blindness, esophageal strictures, and anal stenosis.

Several immunosuppressive agents, including methotrexate, azathioprine, and cyclophosphamide, have been shown to be effective in controlling the inflammation and inducing long-term remission in patients with CCC associated with deposition of autoantibodies at the basement membrane zone. IVlg therapy is effective and safe in patients with OCP and linear IgA bullous dermatitis in whom immunosuppressive therapy failed to control conjunctival inflammation or produced major adverse effects that necessitated discontinuation of immunosuppressive agents. Our patient represents yet another case of successful use of IVlg to treat CCC.

**CONCLUSIONS**

Chronic cicatrizng conjunctivitis is frequently associated with a systemic autoimmune disease that can result in debilitating consequences including blindness. Conventional diagnostic methods may fail to establish the diagnosis and usual therapeutic approaches may not control the inflammation. Early referral to an appropriately equipped center may result in diagnosis of underlying systemic disease and preservation of sight.

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