Acta Dermatovenerol Croat 2007;15(4):236-242 CASE REPORT

Unrecognized Cicatricial Pemphigoid with Oral Manifestations and Ocular Complications. A Case Report

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Received: April 16, 2007
Accepted: October 20, 2007

SUMMARY Cicatricial pemphigoid is an autoimmune bullous disease characterized by mucous membrane fibrosis with resulting scarring, predominantly in the conjunctival and oral mucosa, which rarely involves skin changes. The majority of patients present with painful erosions or desquamative scarring gingivitis, resulting in eating and drinking disorders. Typical ocular lesions include chronic scarring conjunctivitis with progressive subconjunctival fibrosis, fornix foreshortening and synechia formation between the bulbar and palpebral conjunctiva, occasionally resulting in blindness. A 69-year-old woman was admitted to our Department for intense pain and severe burning sensation in the oral cavity, induced by several erosions and solitary blisters, lasting for 3 years. She was also diagnosed with the right eye symblepharon, lid entropion, trichiasis, leukoma and blindness of the right eye. The diagnosis of cicatricial pemphigoid was based on clinical picture and histopathology combined with immunofluorescence methods, with therapy initiated thereupon. Systemic corticosteroid (methylprednisolone) therapy in combination with azathioprine proved successful in the treatment of oral lesions as well as for stabilization of ocular lesions. Unfortunately, the patient was diagnosed in the advanced stage when scarring had already occurred. Prompt recognition of cicatricial pemphigoid and close patient monitoring are an imperative for the future prognosis of the disease.

KEY WORDS: cicatricial pemphigoid, oral lesions, ocular lesions, complications

INTRODUCTION

Cicatricial pemphigoid (Lever 1942, benign mucous membrane pemphigoid, scarring pemphigoid) (CP) is a chronic autoimmune subepidermal bullous disease, which primarily involves mucous membranes, predominantly in the oral cavity and eyes, but rarely the skin (1-4). In some patients, oral blisters may present as the only manifestation, but extension of lesions into the pharynx and esophagus may cause sore throat and dysphagia. Ocular involvement is believed to occur in

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approximately 70% of patients; progressive ocular lesions may cause blindness (5).

Recent studies have demonstrated that CP is not a single entity but a complex disease (2). The etiopathology of CP has not yet been completely understood but is considered as an autoimmune disease, with participation of basement membrane-directed antibodies, thus leading to subepithelial blistering, granulation tissue and inflammatory infiltrate formation in the substantia propria. Eosinophils and increased proportion of type I and type III collagen have also been demonstrated in CP patients (6). Various antibodies have been found, such as antibodies against BPAg2 carboxy terminal domains, NC16A domain (in proximity to the keratinocyte membrane), laminin 5 (adhesion molecule which interconnects lamina lucida and lamina densa, demonstrable on the dermal portion of a salt-split skin), hemidesmosomal integrins α6 and β4 (7-9).

Increased susceptibility for the CP development may also be related to human leukocyte antigens HLA-DR2, HLA-DR4 and DQw7 genotypes (6). There is some evidence that ophthalmic medications, especially those used for glaucoma, may cause CP, or possibly the glaucoma reflects early ocular lesions in the course of CP (2).

Clinical presentation of CP patients may vary; it primarily affects the elderly, predominantly women. Generally, oral lesions have been reported in more than 90% and ocular lesions in 60%-70% of cases (2). The majority of patients with CP do not present with skin lesions; 25% of CP patients present with cutaneous lesions.

Ocular cicatricial pemphigoid (OCP) is characterized by a chronic scarring conjunctivitis with progressive subconjunctival fibrosis, fornix foreshortening and synechia formation between the bulbar and palpebral conjunctiva (2,6). The disease may initially involve only one eye, with initial unspecific symptoms, often localized for up to 1-2 years, but frequently followed by conjunctival fibrosis, sometimes with severe entropion, trichiasis, symblepharon, dry eye syndrome, corneal epithelial erosions or ulcerations, keratitis and even blindness (4,6). Thus, OCP may present as a chronic, acute or subacute disease with periodic exacerbations of conjunctival inflammation, sometimes with lacrimal duct and meibomian duct obstruction and goblet cell decay, leading to the development of dry eye due to the tear film deficiency. Secondary glaucoma is one of the most frequent complications, coincident in up to 25% of patients (2).

Oral lesions mostly manifest as scattered painful erosions or desquamative gingivitis with smooth erosions along the fixed gingival or rarely mucosal detachment. Scars may be present, but oral blisters are rare (2). Buccal mucosa scarring results in chewing and swallowing difficulties (oral scarring is less significant than in the OCP). Oral alterations may affect the frenulum and the tongue or vegetating lesions are occasionally localized in the mouth. Other mucosal surfaces such as the larynx, esophagus, or genitalia may also be involved with possible adhesion and stricture formation (2).

The diagnosis of CP is supported by histopathologic analysis of mucosal or skin lesions, which typically show marked inflammation with various inflammatory cells, followed by fibrosis and vascular proliferation in a later stage, as expected in a scar (2). Histopathologic examination of an intact blister shows subepidermal separation resembling a bullous pemphigoid blister. Immunofluorescent examination is beneficial only in some patients. Moreover, direct immunofluorescence has shown to be positive in 50%-60% of cases, displaying IgG, C3 and occasionally IgA deposits on the basement membrane zone. Routine indirect immunofluorescence is positive in less than 50% of cases. Therefore, more sophisticated methods such as salt-split skin or electron immunomicroscopy may occasionally prove useful (2).

Recommended treatment includes systemic immunosuppressants and corticosteroids, aiming to suppress active inflammation. Therapy is predominantly successful for cutaneous lesions, but less effective in the treatment of ocular and oral lesions (2). Alternative systemic CP treatment includes azathioprine (usually in combination with corticosteroids), cyclophosphamide (the most effective systemic immunosuppressive agent), dapsone (suitable for oral lesions and mild OCP), retinoids, cyclosporine, etc. (2,10,11).

Topical therapy usually includes local corticosteroids, often in the form of special oral adhesive pastes or intralesional triamcinolone acetonide. The management of ocular lesions is preferentially conducted by an ophthalmologist. Surgical treatment is sometimes indicated, such as for lysis or removal of skin adhesions, for correction of scars, entropion, trichiasis and other complications (2).

Since OCP is a distressing chronic disease, its treatment is often difficult, with blindness as a feared complication occurring in 20%-60% of cases. Unfortunately, most patients are diagnosed

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in the advanced stage when scarring has already occurred.

The purpose of this case report is to present our patient suffering from CP, and to evaluate clinical features, diagnostic and therapeutic difficulties in CP.

CASE REPORT

A 69-year-old woman was admitted to our Department for intense pain and severe burning sensation in the oral cavity induced by several erosions and solitary blisters, lasting for 3 years. She was also diagnosed with the right eye symblepharon, lid entropion, trichiasis, leukoma and blindness of the right eye. Personal history indicated that the patient had noticed lesions on the right eye five years before, demonstrating progressive course; therefore, she was under constant care of an ophthalmologist and was treated surgically on several occasions. Azathioprine (Imuran) therapy was initiated two years before for a two-year period, however, without any significant improvement. Oral lesions including erosions with subsequent scar formation occurred in the oral mucosa and bilaterally buccally three years before, resulting in severe burning sensation and difficult swallowing. The patient had no skin changes whatsoever.

On admission, clinical features on the right eye suggested an advanced phase of CP. The patient came to our Department for advanced lesions of the oral mucosa and eyes (Figures 1 and 2). The patient had several erosions on the buccal mucosa bilaterally and on the hard palate. Ocular status showed amaurosis of the right eye in addition to symblepharon. There were several oral erosions, partly covered with fibrin deposits on buccal and palatine mucous membranes with gingival cicatricial formations.

Excisional biopsy of oral lesions with direct immunofluorescence microscopy of skin biopsies and indirect immunofluorescence analysis were performed. Histopathologic analysis of mucous membranes was nonspecific; there were no elements to confirm the diagnosis, while direct immunofluorescence showed neither IgG nor C3 deposits. Indirect immunofluorescence showed no circulating antibodies.

Three weeks later, biopsy was repeated due to uncertain findings. Repeat histopathologic analyses of oral mucous membrane lesions showed acantholytic cells, and the underlying dermis showed loose neutrophilic infiltrates with erythrocyte extravasation. Stratified squamous keratinized epithelium samples were separated at the basal and suprabasal keratinocyte level with few detached acantholytic cells marginally, which could histologically contribute to the diagnosis of CP (Figure 3).

The following diagnostic and laboratory tests were performed during hospital stay: complete blood count (CBC) was within the physiological range except for slightly increased neutrophil and lymphocyte counts; glucose, transaminases, electrophoresis, C3, C4, ANA, total bilirubin, total protein, creatinine and electrolytes showed normal findings; cholesterol and triglyceride levels were increased, iron decreased and urine analysis abnormal. Urine analysis verified bacterial infection (*Escherichia coli* 10^6/mL), sensitive to cephalexin. Other laboratory findings were also normal (pharyngeal and nasal swabs, oral cavity mycology, PPD, hemoccult test); ECG showed left ventricular strain; abdominal ultrasound was free from significant changes.

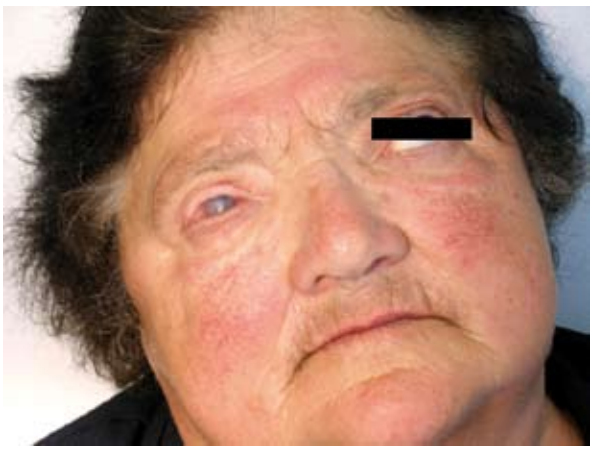

Figure 1. Ocular manifestations in the patient with cicatricial pemphigoid.

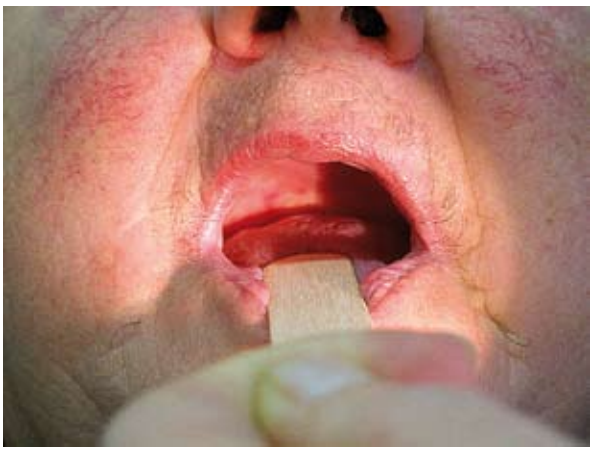

Figure 2. Oral lesions in the patient with cicatricial pemphigoid.

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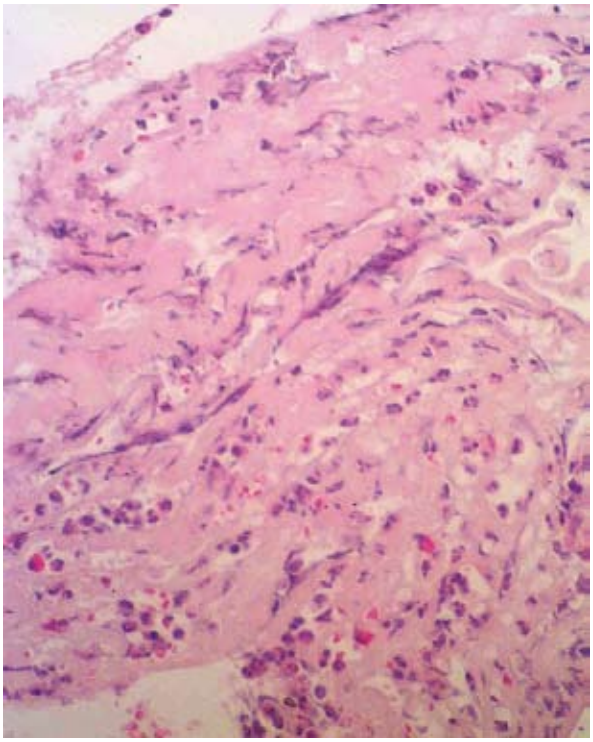

Figure 3. Detached stratified squamous epithelium at the level of dermoepidermal junction; H&E staining, X100).

Ophthalmologist consultation confirmed amaurosis of the right eye, VOS +1.0, dsph 1.0, the upper and lower fornix of the right eye affected by symblepharon, with total corneal keratinization. Ocular clinical features suggested an advanced stage of CP. As results of the biopsy of oral lesions were crucial and supported the diagnosis of CP, the disease was diagnosed according to clinical and histopathological appearance (immunofluorescence analysis was nonspecific).

After consulting an internal medicine specialist, administration of cyclophosphamide was planned following treatment for urinary tract infection (due to the indication and imminent blindness) with continuous monitoring of leukocyte count (due to the possibility of the most common side effects of cyclophosphamide therapy including bone marrow suppression, hemorrhagic cystitis as a dose-dependent adverse effect). Methylprednisolone (Medrol) was administered during hospital stay at a dose of 60 mg initially, tapered to 48 mg daily at discharge. The patient used sage tea and prednisone solution topically for oral cavity lesions. In continuation as before hospitalization, antihypertensives and cardiac medications were administered *per os*, in addition to oral antibiotic therapy for urinary tract infection (cephalexin for 10 days), according to the antibiotic sensitivity report obtained.

Following discharge from the hospital, the patient continued taking methylprednisolone (Medrol) 48 mg daily *per os* with gradual dose reduction, along with therapy prescribed by the internist, used sage tea, triamcinolone acetonide (Volon A haftsalbe®), and an oral antimycotic agent (miconazole gel, Dactarin) topically for oral cavity lesions. Systemic corticosteroid therapy showed no side effects. Oral lesions completely resolved with time and the eye condition became stable, with the patient using low doses of systemic corticosteroids (methylprednisolone) with azathioprine (Imuran, 100 mg daily). She has been under constant dermatologist and ophthalmologist care.

Due to significant clinical and subjective improvement with methylprednisolone and azathioprine therapy, we decided not to include cyclophosphamide.

DISSCUSION

The diagnosis of CP is based particularly on clinical features and histopathologic examination, immunofluorescence methods, or sometimes electron immunomicroscopy (which enables distinguishing CP from other autoimmune diseases of the dermoepidermal junction). It is sometimes difficult to make a diagnose of CP, especially when histopathology results, direct immunofluorescence and indirect immunofluorescence are negative, as found in approximately half of the patients. Careful evaluation of a patient with CP is essential and often requires a multidisciplinary approach, involving a dermatologist, an ophthalmologist, otorhinolaryngologist, etc. However, histopathologic examination, direct immunofluorescence microscopy of skin biopsies and indirect immunofluorescence are mandatory in all patients (13).

CP is primarily a disease affecting the elderly and the majority of CP patients are female (61%), as in our case report (5). In the study by Messmer *et al*., the mean age of patients with OCP was 73 years, similar as in the study by Baier *et al*., where the mean age at CP onset was 69 (50-76) years (5,13). The most prominent finding in CP is involvement of mucosal surfaces. Miziara *et al*. found mucosal bullous lesions in 85%-90%, ocular lesions in 66%, nasal lesions in 15%-23%, and laryngeal involvement in 8%-21% of CP patients (14). Baier *et al*. found oral lesions in 90.9% (10/11) and/or conjunctival lesions in 54.5% (6/11), less frequently lesions of the larynx (4/11), nasal

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mucosa (3/11), skin (3/11) or pharynx (1/11) (13). Agbo-Godeau *et al*. found variable skin lesions (sometimes involving the lower limb); ocular lesions (including two patients with severe lesions at onset); and nasal and/or laryngeal involvement in 35% (6/17) (frequently involving severe lesions with major functional impairment) of patients each (12).

It is sometimes difficult to obtain the correct diagnosis, as the histopathologic analysis may be nonspecific. Study results revealed specific histopathologic findings (subepidermal detachment) in 64.7% (11/17) and specific positive direct immunofluorescence in 64.7% (11/17) of patients each, and negative indirect immunofluorescence in 70% (12/17) of patients (12). Agbo-Godeau *et al*. found negative both histologic and immunofluorescence analyses in 11.7% (2/17) of patients; electron immunomicroscopy was useful in these cases and confirmed the diagnosis in 4 patients (12). Repeat biopsies are frequently required to obtain a positive result, as in case of our patient.

Oral manifestations of CP may be isolated or associated with skin or other mucosal lesions (12). Agbo-Godeau *et al*. found sole oral lesions in 35.3% (6/17) and coexisting oral and cutaneous, ocular, nasal or anal lesions in 64.7% (11/17) of patients, with gingival lesions in 88.2% (15/17) of patients. The most prominent oral difficulty is occasional pain in oral lesions, potentially interfering with eating and drinking. There is rarely a laryngeal or pharyngeal stenosis or life-threatening complications, potentially with squamous cell carcinoma in mucosal scarring. Sometimes, there is a severe periodontal disease with oral lesions (desquamative gingivitis), isolated or combined with lesions on the skin and eyes. Although isolated, oral manifestations are generally well controlled by topical corticosteroids, whereas ocular, nasal and laryngeal localizations often require more extensive treatment (12). Because of frequent painful oral lesions, patients are referred to dentists or periodontists; therefore, the diagnosis is often made by dentists. Thus, cooperation between dental specialists and dermatologists is essential to achieve rapid and definitive diagnosis of the disease (4). Skin lesions are troublesome, but not as significant as the OCP or oral changes (2).

As OCP involves chronic progressive cicatrizing alterations with complications, it is often difficult to treat (7). Mostly, OCP includes sight-endangering manifestations and potentially life-threatening extraocular CP manifestations. There are frequently various complications, such as entropion, recurrent epithelial erosions, corneal ulcers, keratitis or corneal perforations. Multiple surgical interventions are sometimes performed, e.g., entropion surgery, tarsorrhaphy, mucous membrane grafting, amniotic membrane transplantation, tectonic keratoplasty, keratoprosthesis and enucleation. Despite anti-inflammatory therapy, visual loss occurred in 53%, while reading visual acuity could only be maintained in 35% of patients (5). The crucial problem often lies in the late recognition of the disease. Messmer *et al*. presented 28 patients with OCP who had reached advanced stage of the disease, i.e. stage III (83%) or stage IV (17%) (5). Reduced vision at initial presentation was recorded in 38%, ocular lesions in 64% and glaucoma in 28% of these CP patients. Life-threatening extraocular manifestations of CP (laryngeal stricture, esophageal stricture) were manifested in 2/28 patients. Messmer *et al*. showed results of conjunctival or mucosal biopsies in OCP, revealing typical immune deposits at the basement membrane zone in 80% (12/15) of patients (5). High association of OCP with glaucoma and/or anti-glaucomatous treatment in patients may indicate an etiological factor that yet has to be confirmed. Various clinical symptoms often render the diagnosis of CP difficult, yet thorough history, direct and indirect immunofluorescence microscopy and sometimes HLA-genotyping are crucial for the accurate diagnosis. Whenever persistent conjunctival inflammation is present, biopsy and immunohistochemical analysis of conjunctival changes should be performed in the diagnosis of OCP (6).

With regard to advanced CP stages, which often result in irreversible visual loss despite administration of immunosuppressive therapy, early diagnosis and therapy are needed to prevent complications of OCP (5). OCP management requires a multidisciplinary approach intended to optimize the care for these patients (7). Treatment of OCP includes topical drops or ointments (lubricants, corticosteroids, antibiotics, antiglaucomatous medication) and local corticosteroids, with systemic immunosuppressive drugs necessary for activity control in progressive cases (cyclophosphamide, systemic corticosteroids, oral dapsone, azathioprine, methotrexate, rarely mycophenolate mofetil, daclizumab, intravenous immunoglobulin therapy, etc.). Due to the systemic nature of the disease and the poor efficacy of current local therapies, systemic immunomodulatory therapy is the treatment of choice for controlling the disease activity and limitation of its progression (7). Systemic cyclophosphamide with short-term adjunc-

tive high-dose prednisolone is the preferred treatment for severe and/or rapidly progressing OCP. Oral methotrexate therapy is the first-line systemic therapy for OCP, especially low-dose methotrexate weekly for mild-to-moderate OCP (7,15). It has been demonstrated that treatment of OCP patients with methotrexate monotherapy after a mean follow-up of 30.2 months results in conjunctival inflammation reduction in 89% to 100% of eyes (15). Prevention of conjunctival cicatrization progression was reported in 72% to 90% of patients, maintenance or improvement of visual acuity in 85% of patients (methotrexate monotherapy), and final visual acuity was achieved in 74% of the eyes (15). Methotrexate therapy is mostly tolerated well, although with the possibility of side effects (the most common are gastrointestinal (50%), mostly reversible upon dose reduction (78%)) (15). Low-dose oral methotrexate monotherapy is generally highly effective and well tolerated as the first-line treatment for OCP (15).

Oral manifestations in CP are often painful and may be isolated or associated with skin changes or other mucosal lesions (12). Treatment of patients with CP depends on the disease severity. Thus, isolated oral manifestations are generally well controlled by topical corticosteroids while ocular, nasal and laryngeal localizations often require more extensive treatment (12). Appropriate therapy should be initiated as soon as possible due to uncommon spontaneous remissions and treatment limitations in the advanced stages of the disease (13). Although mucosal and skin lesions responded well to the treatment, OCP frequently shows a progressive course despite therapy. Careful evaluation and diagnosis are essential and require a multidisciplinary approach.

CONCLUSION

Since definitive diagnosis of CP is sometimes difficult to make, it is essential to analyze the clinical presentation, histopathologic findings of the affected tissue, laboratory results, immunological findings, and sometimes electron immunomicroscopy or HLA-genotype. Treatment of our patient with systemic corticosteroids (methylprednisolone) in combination with azathioprine was successful for oral lesions as well as for stabilization of ocular lesions. Unfortunately, the patient was diagnosed at the advanced stage when scarring had already occurred. This indicates that the timely recognition of CP and close monitoring of the patient are imperative for the future prognosis of the disease.

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