

## Ocular Cicatricial Pemphigoid

by Roxanne Chan, M.D.

CC (6/20/96): Red, itchy eyes, whitish discharge x 6 weeks

HPI: A 74 year old retired policeman noticed red, itchy eyes associated with whitish discharge that worsened over the past six weeks. Two weeks later, the patient consulted his ophthalmologist, who treated him antibiotic eye drops without a favorable response.

The patient did not respond to the antibiotic and states he was biopsied. He was then placed on "two round white pills three times a day."

ROS: buccal mucosal ulcer, no cutaneous lesions.

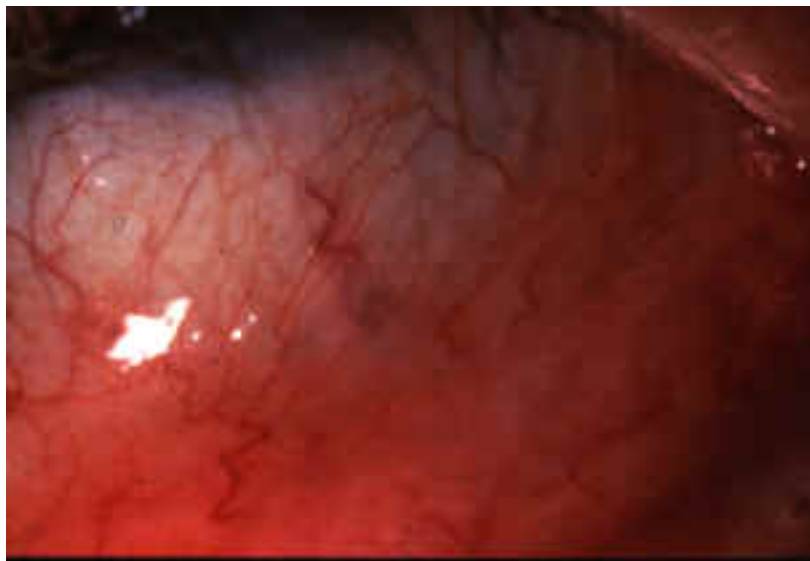
Examination

Visual acuity: 20/70 O.D. and 20/60 O.S.

IOP: normal

Neuromuscular: normal

SLE: poor tear film, 3+ conjunctival injection, meibomian gland disease, sub-conjunctival fibrosis (**Figure 1**)



**Figure 1**

Pathology

Immunofluorescence was negative. OCP perhaps? However, the definitive diagnosis of OCP requires the demonstration of immunoglobulin or complement deposition at the epithelial BMZ of the biopsied conjunctiva. What other entities could this patient have?

Many diseases from this differential diagnosis list can be excluded on the basis of the patient's history and physical examination.

## Differential

- ◆ Infections: trachoma, adenovirus, *Corynebacterium diphtheriae*, streptococcus
- ◆ Systemic disorders: sarcoidosis, progressive systemic sclerosis, Sjögrens, SLE
- ◆ Topical ocular drugs: epinephrine, pilocarpine, idoxuridine, echothiophate

## Differential

- ◆ Ocular trauma: chemical or thermal burn, multiple surgeries
- ◆ Skin and mucous membrane disorders: proctolol-induced eruption, SJS, TEN, atopic skin disease, rosacea blepharoconjunctivitis, porphyria cutanea tarda, OCP, erythroderma ichthyosiform congenita, lichen planus

Periodic-acid Schiff stain results reveal linear basement membrane staining. You call the patient's regular ophthalmologist, who is back from vacation, and HIS biopsy results are also consistent with OCP, with linear IgA, IgG and complement staining along the basement membrane zone (BMZ). **(Figure 2)** He had placed him on dapsone 25 mg PO tid and then increased the dose to 50 mg PO tid, without control of the patient's inflammation and thus referred the patient to MEEI.

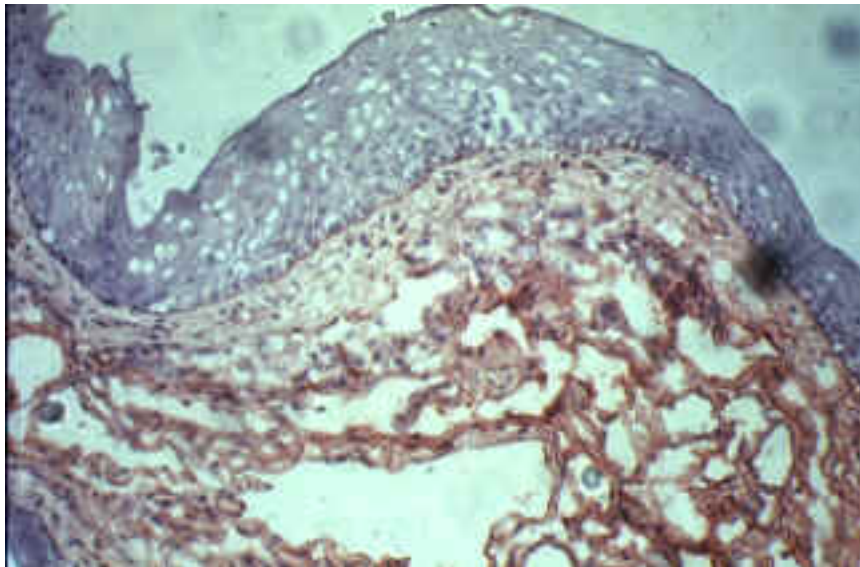


Figure 2

Dapsone was discontinued because the patient developed severe hemolytic anemia. He was placed on Livostin four times daily for pruritis then as needed and Vexol four times daily. Methotrexate 7.5 mg per week was initiated (8/22/96) and increased to 10 mg per week (9/12/96) and 15 mg per week (10/3/96) when the inflammation was still not controlled, along with folic acid 6 days per week and close follow-up of CBC and LFT's. However, despite the current level of medication, immunosuppression was not sufficient. Cytoxan 150 mg per day was initiated and methotrexate was discontinued on 10/24/96. The patient required an increased level of cytoxan 200 mg per day (11/14/96), which was discontinued on 12/12/96 due to a hematocrit of 28. The patient then underwent three courses of cytosine arabinoside injections 3 mg/kg in one session every three weeks for three times beginning 1/97 since his inflammation remained active. Prograf (tacrolimus) 8 mg per day was initiated 4/3/97 which seems to have made some difference but with severe abdominal symptoms, notably bloating, diarrhea, and slight persistent nausea; therefore, the drug was discontinued.

The patient's problems were initially worse in the left than in the right eye. His left eye improved a little and now his right is worse. For a year, the patient has experienced significant irritation, redness, burning, increased watering and mild pain in both eyes.

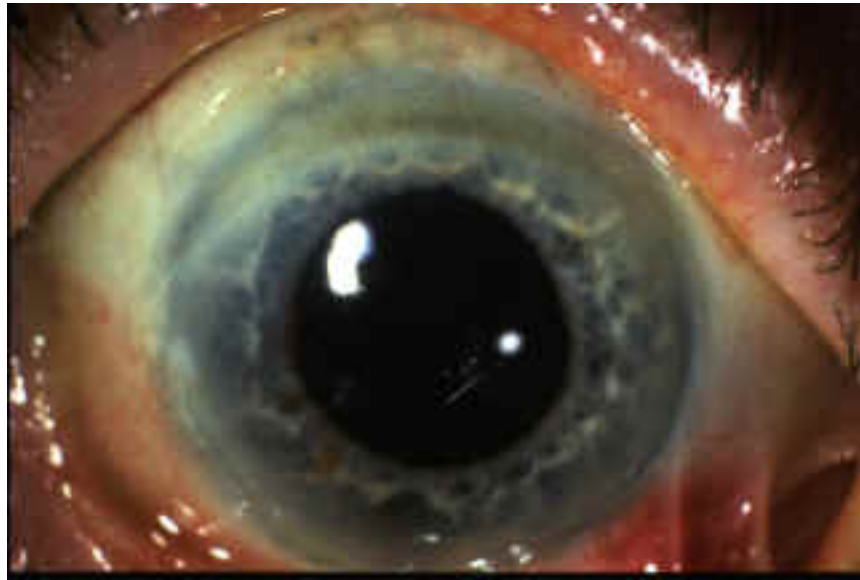
Since the disease was progressive and bothersome despite current therapy and since there was clinically significant inflammation, the patient was placed on intravenous immunoglobulin 50 g over a five day period every two weeks to be initiated around 4/24/97; by 8/5/97, he had a total of six treatments. The patient had significant immediate decreased conjunctiva and scleral erythema and congestion and over six weeks.

Since the patient's intraocular pressures were found to be elevated on subsequent visits, the patient was placed on timolol twice daily in both eyes.

## Case Summary

- **OCP is a systemic autoimmune disease.**
- **Despite systemic immunosuppression, there was continued inflammation.**
  - progressive cicatrization**
  - anatomic al disorganization**
  - glaucoma (10%)**
- **Intravenous immunoglobulin controlled the disease.**

The progression of the disease, although usually slow, may be punctuated by periods of explosive exacerbation with rapid progression of conjunctival scarring (such as in this patient) and associated keratopathy. (**Figure 3**)



**Figure 3**

### Ocular Cicatricial Pemphigoid

#### **Discussion**

Ocular cicatricial pemphigoid is a systemic autoimmune disease. Mounting evidence supports the concept of immunoregulatory dysfunction: (1) Antibodies are directed against the basement membrane zone (BMZ) of the conjunctiva and other mucous membranes derived from stratified squamous epithelia and occasionally the skin. (2) Antinuclear antibodies and other autoantibodies are found in the serum of many patients. (3) Immunosuppressive techniques are effective.

#### Incidence

Different figures are found in the literature regarding incidence, which usually estimate relatively advanced CP since diagnosis during earlier stages is difficult (stage III). It is likely that stages I and II are not included in these estimates. The estimated incidence of this disease ranges from 1 in 8,000 (Bedell) to 1 in 46,000 (Smith).

#### **Epidemiology**

In the majority of publications, the average age of onset of OCP is 60 to 70 years old, with patients who usually present that are already in stage III. Although OCP is typically a disease of the elderly, patients as young as 19 (Mauriello 1994) and 12 (Iglesias 1992) have been reported. This disease has a slight female preponderance, with a female to male ratio of 2:1. The distribution is worldwide and all races are affected.

#### Clinical Manifestations

Stage I is characterized by chronic conjunctivitis with mild conjunctival or corneal epitheliopathy and subepithelial conjunctiva fibrosis, which is best seen at the tarsal conjunctiva as fine, white striae.

As the disease progresses, there is cicatrization with conjunctival shrinkage, distorted anatomy and foreshortening of fornices (Stage II).

Symblepharon appears in Stage III. Subepithelial fibrosis alters normal eyelid anatomy and adnexal components, disturbing the lid architecture and normal lid/globe relationship. If severe enough, fibrosis may cause cicatricial entropion.

Stage IV is the end stage, which consists of dry eye with keratinization of the cornea and ankyloblepharon, which immobilizes the globe. Profound keratopathy can develop secondary to eyelid disorders, tear insufficiency, and corneal exposure. There is corneal epitheliopathy, persistent epithelial defects, stromal ulceration, and neovascularization, all developing with astonishing rapidity. Secondary microbial keratitis is common, with perforation and endophthalmitis complicating the disease. (**Figure 4**)





**Figure 4**

#### Clinical Course

The course of OCP is characterized by chronic relapsing and remitting cicatrizing conjunctivitis and progressive conjunctival subepithelial fibrosis causing distorted anatomy, such as trichiasis and entropion, tear film abnormalities (exposure and MGD), and limbal stem cell deficiency, results in severe corneal epitheliopathy, persistent epithelial defect, corneal stromal ulceration, secondary infection, corneal neovascularization, and blindness. In the end, the cornea is fully scarred, vascularized, and keratinized. It may take 10 to 30 years to reach this endstage.

Of 111 patients, 26% had glaucoma, most with advanced, with a long history of medication use, optic nerve damage, and visual field loss (Tauber 1989).

#### Differential

Cicatricial pemphigoid (CP) has a wide spectrum to disease presentations; thus, the name OCP is misleading. The nonocular manifestations of CP may include skin, scalp, oral mucosa, pharynx, larynx, trachea, esophagus, vagina, urethra, and anus. The desquamative gingivitis presents in nearly all patients. There may be esophageal or tracheal stricture formation, risking suffocation. Oral mucosal presentation is quite variable from chronic, erythematous lesions to erosions covered by a fibrinous slough produced by bullae rupture involving gingiva, buccal mucosa and palate.

Scarring of the skin and mucosa is usual. The skin lesions are of two types: recurrent vesiculobullous lesions similar to but smaller than those of bullous pemphigoid (these rupture and heal without much scarring) or erythematous plaques of the head and neck that evolve into pruritic blisters which rupture and leave atrophic scars, called Brusting-Perry CP, which shares immunopathologic features with both pure mucosal CP and bullous pemphigoid (BP) of the skin.

Oral pemphigoid (OP) patients usually have a benign self-limited disease in which pathological changes are restricted to the oral mucosa, unlike patients with OCP, who may have involvement of other mucous membranes. Patients may also have skin involvement.

Immune-mediated subepidermal bullous dermatoses that are characterized by in vivo-bound linear IgG or IgA and complement deposition at the cutaneous BMZ include pseudo-ocular cicatricial pemphigoid (P-OCP), epidermolysis bullosa acquisita (EBA), BP, and linear IgA disease. CP reveals subepidermal, large, tense, non-scarring blisters on erythematous urticarial like lesions.

Since its first description in the 1970's, numerous substances, such as antiglaucomatous drugs have been reported as potential causes for drug-induced pseudopemphigoid.

EBA is an acquired systemic bullous disease characterized by IgG autoantibodies directed against type VII collagen, the major component of anchoring fibrils. The classical phenotype of EBA is a non-inflammatory, mechanobullous disease resembling BP. Mucous membrane involvement is frequent but usually mild. Direct immunofluorescence may reveal linear IgA and C3 at the BMZ, with IgA anti-BMZ autoantibodies stained on the dermal side of salt-split skin by indirect immunofluorescence and recognized a 290-kDa protein comigrating with type VII collagen by immunoblotting (Caux 1997).

Dermatitis herpetiformis is characterized by clusters of vesicles on residual hyperpigmentation, is pruritic, associated with GI disease, gluten sensitive enteropathy, younger patients, and is treated with dapsone.

Lever, a Boston dermatologist, was the first to make the clinical and histopathologic distinction between pemphigoid and pemphigus in 1953. The predominance of mucosal lesions or lack of skin lesions distinguish CP from BP. Bullous pemphigoid is an autoimmune subepidermal blistering disease seen primarily in elderly persons, characterized by the development of tense bullae and by the presence of linear antibasement membrane antibody staining (Frith 1989). In BP, the antigens involved in the autoimmunity are epidermal basement membrane peptides BPAg1 and BPAg2.

PV is an immune-mediated vesiculobullous disease of the skin and mucous membranes, but antibody deposition is intercellular. Generally, patients present first with oral lesions, which may precede the cutaneous lesions, such as bullae and erosions, by several months. PV has extensive lesions, mostly erosions and crusts. There are no intact bullae. Nikolsky's sign is positive. Ocular manifestations are unusual. The most common ophthalmologic involvement in



PV is conjunctivitis, but without progressive scarring such as occurs in OCP. Corneal involvement is rare. PV can be differentiated on the basis of clinical findings and histopathological and immunohistochemical features. Pemphigus-like antibodies were found in a patient on indirect immunofluorescence (Kuman 1980). Generally, PV can be treated with steroids or with a combination of an immunosuppressant and corticosteroids.

Chronic progressive conjunctival cicatrization is found in other mucocutaneous disorders, such as linear IgA disease that also has complement C3 deposition. Linear IgA disease resembles DH, differentiated by DIF findings. It appears like bullous impetigo and has large blisters arranged in a rosette pattern.

## Diagnosis

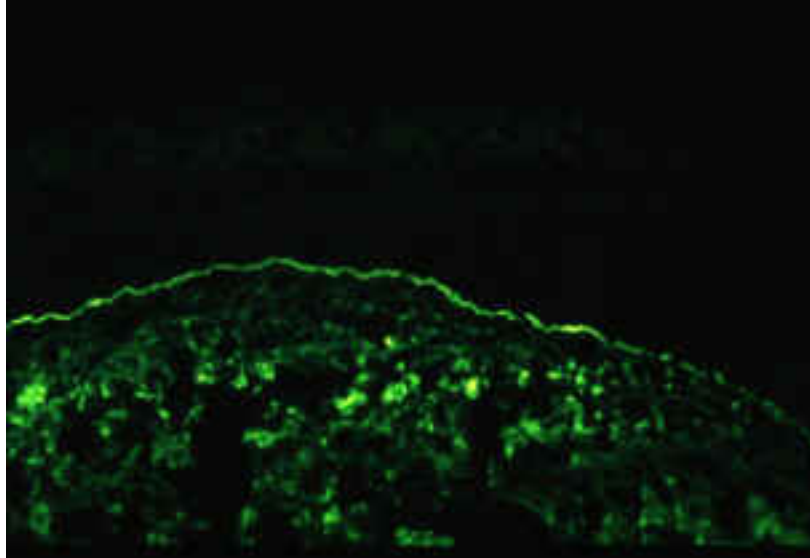
Diagnosis of OCP is difficult in the early stages of the disease. It is of critical importance to make the diagnosis as early as possible to allow early treatment. Conjunctival biopsy facilitates the early diagnosis of OCP. The routine use of immunoperoxidase in immunofluorescence-negative biopsies increases the sensitivity from 52% to 83% in 166 patients with clinically suspect OCP (Power and Foster 1995).

In normal conjunctiva, the epithelium is nonkeratinized and about 5 layers thick. There are scattered individual secretory cells (goblet cells), whose function is to secrete mucin, a glycoprotein which upon hydration forms a lubricating solution (mucus). In the underlying substantia propria of dense connective tissue, a small number of mononuclear cells are seen. The normal localization of the mast cells is beneath the epithelium.

CP is characterized by a separation of the basal epithelium from the underlying basement membrane, forming a subepithelial bleb that tends to form a scar. The histopathological conjunctival finding in OCP patients reveals submucosal scarring with aberrant type IV and VII collagen (Dutt 1996), chronic inflammation, perivasculitis, and squamous metaplasia of the epithelium with loss of goblet cells. In CP, there are enormous inflammatory cell infiltrate into the substantia propria with neutrophil margination. Plasma cells predominate in the infiltration. Eosinophils stain inside vessels prominently. Neutrophils are present in the epithelium with occasional eosinophils. Mast cells are prominent in the stroma.

## Pathophysiology

The pathophysiology of fibrosis is incompletely understood. OCP and other clinical subsets are all histologically characterized by the definitive immunoglobulin and complement deposition at the conjunctival BMZ (Foster 1986, Fine 1984), separation of the epithelium from the underlying tissues within the BMZ, and initiation of a type II hypersensitivity reaction. There is striking IgA and IgG along the BMZ with immunofluorescence. (**Figure 5**) Linear IgA deposition at the BMZ correlates with primary subepidermal bullous disease in a high percentage of patients, but reflects a heterogeneous group of blistering disorders (adult linear IgA bullous dermatosis, chronic bullous disease of childhood, CP, BP, EBA). with or without IgG deposition (Peters 1989).



**Figure 5**

Antibodies are also found in the serum, as detected by radioimmunoassay and the immunopathologic abnormalities deposition are not limited to the conjunctiva.

In PAS, goblet cells are decreased or absent in advanced OCP. Decreased numbers of conjunctival goblet cells, coupled with decreased tear stability and eventual tear insufficiency in CP patients have led some to characterize CP as a mucin deficient dry eye. However, patients with active CP have excess mucous production and strands of mucous-like material in the inferior fornix. Observations with scanning and transmission electron microscopy indicate that mucous is present on the surface of the conjunctiva, even though goblet cells are not seen.

Biochemical studies of patients with active OCP have shown that patients have measurable amounts of mucin glycoprotein. The source of these mucins could be the lacrimal apparatus or nongoblet conjunctival epithelium. Histologic studies have indicated that the main accessory lacrimal gland tissues contain PAS positive granules. With Mucomyst treatment, or with chemotherapy control of inflammation, the thick sheet of mucous is significantly decreased.

In giemsa staining, there is an overrepresentation of mast cells in the stroma and none in the epithelium.

Genetics: An isolated family study did not support a single-gene theory for the development of OCP (Bhol 1995). There is an increased association with DQB1\*0301 (Haider 1992). 16/21 (76%) Caucasian patients with OCP carried the class II MHC gene DQB1\*0301 compared to 14/42 (33%) of race-, age-, and geography-matched normal individuals; however, this allele is not significantly increased in patients without ocular involvement (Chan 1997). In another study, BP, OCP, and OP patients had increased association with DQB1\*0301, a common marker for enhanced susceptibility and that T-cells recognized this class II region bound to a peptide from the basement membrane of conjunctiva, oral mucosa, and skin (Delgado 1996, Ahmed 1991). Patients with OP (38.6%) and OCP (52.6%) had increased association with this allele than controls (17.8%) (Yunis 1994); OCP (90%) and controls (52%) (Chan 1994). An increased association with HLA-DR4 was found (Zaltas 1989). The environmental trigger that stimulates the

individual to develop OCP may be microbial or chemical, for example drugs such as practolol, pilocarpine, timolol, echothiophate iodide, or epinephrine.

**Antigens:** It should be recognized that multiple antigens in the BMZ of squamous epithelia may serve as targets for a wide spectrum of autoantibodies observed in vesiculobullous diseases. Molecular definition of these autoantigens will facilitate the classification and characterization of subsets of CP and help distinguish OCP from BP.

The OCP antigen is different than those of BP or P-OCP. Purified IgG from the sera of patients with active OCP identified a cDNA clone from a human keratinocyte cDNA library that had complete homology with the cytoplasmic domain of beta-4 integrin subunit. The sera recognized a 205-kDa protein in human epidermis, human conjunctiva, and tumor cell lysates that was identified as the beta-4 subunit by its reaction to monoclonal and polyclonal antibodies of human beta-4 integrin (Mohimen 1993). Sera from patients with BP, PV, and CP-like diseases did not recognize this 205-kDa protein, indicating the specificity of the binding to the beta-4 subunit. These data strongly implicate a role for beta-4 integrin in the pathogenesis of OCP (Tyagi 1996).

Some patients have antiepiligrin, a laminin isoform, IgG autoantibody deposition at the BMZ; indirect immunofluorescence shows IgG against the dermal side of salt-split skin. One patient reported had both oral cavity pemphigus vulgaris and OCP diagnosed by histopathology and direct/indirect immunofluorescence and confirmed by immunoblot analysis of serum; dapsone and sublesional corticosteroids were used (Buhac 1996).

**Cells:** There is a possible defect in immunoregulation, with decreased Ts and immunoglobulin production. Immunohistochemical staining reveals mainly CD4-helper T-lymphocytes in the inflammatory cell population in the substantia propria. There may be distinct T-cell subsets in the conjunctiva of healthy persons and of patients with OCP (Bialasiewicz 1997). Alpha/beta-TCR+ cells can be found in the non-infected epithelium and stroma of healthy and inflamed conjunctiva in patients with OCP, lye burns, and SJS, whereas gamma/delta-TCR+ cells are absent (Bialasiewicz 1996). There was an increased absolute number as a percentage of CD3+ TCR gamma/delta+ T-cells (Soukiasian 1992). In OCP patients, human mucosal lymphocyte antigen (HML-1) (mucosa-specific intraepithelial lymphocytes that correspond to the suppressor/cytotoxic subset and express HML-1) was normal CD8/HML-1+ cells but CD8/CD4+ cells was low (Dua 1995). Acutely, the conjunctiva is infiltrated with neutrophils, macrophages Langerhans cells and CD8+ and CD4+ T-cells while in chronic disease, the conjunctiva is infiltrated by CD8+ and CD4+ cells, the latter of which shows evidence of activation (increased IL2R and HLA class II expression) (Sacks 1989, Elder 1994, Mondino).

The total mast cell number and ratio of connective tissue mast cells to mucosal mast cells (MMC) were significantly higher in OCP than in normal conjunctiva (Hoang-Xuan 1989).

Limbal langerhans cell density (IIF on CD1a+) in OCP is significantly higher than in normal conjunctiva (Bodaghi 1997)

## **TREATMENT**

Persistent epithelial defects, limbal inflammation, ongoing conjunctival inflammation are important factors that lead to keratopathy and visual handicap. Systemic immunosuppression (Foster 1980, 1982, Mondino 1983) and aggressive management, in collaboration with the chemotherapist or rheumatologist is highly effective in controlling the disease, and may cure it in many instances.

Several randomized, controlled clinical trials done in the mid-eighties have demonstrated that systemic chemotherapeutic agents are both safe and effective when use properly in over 90% of the patients with CP and poses fewer long-term risks than does systemic corticosteroids. Systemic immunosuppressives should be used only in patients with progressive disease, not for those with quiescent or end stage disease.

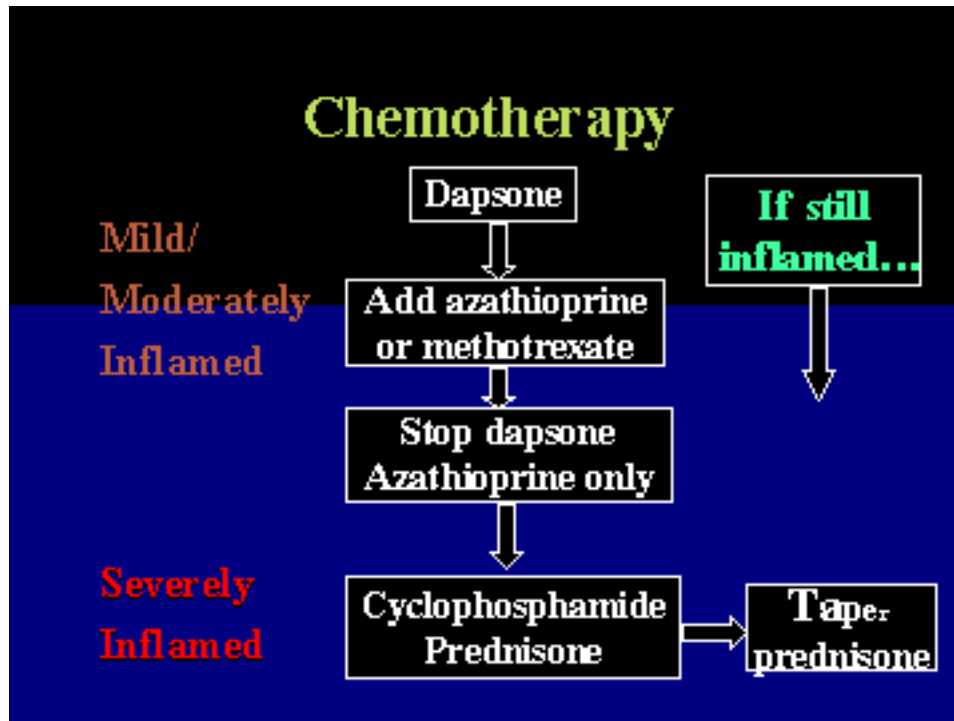
High dose prednisone can control the process, but the long-term consequences of moderate to high doses of systemic steroid required for control of CP are unacceptable. Therefore, along with evidence for immunoregulatory dysfunction, methotrexate, azathioprine, and cyclophosphamide were eventually employed for CP, after demonstrated success for PV and BP.

Dapsone is sulfone-derived, related to the sulfonamides, whose mechanism of action lies in interfering with neutrophil chemotaxis and inhibiting lysosomal enzyme release and neutrophil phagocytosis. Stratification of results revealed that dapsone, a drug widely used in treating dermatologic disorders (such as dermatitis herpetiformis, and BP) and leprosy, was the most effective initial agent for modestly active OCP (Tauber 1991). Hemolysis, such as was seen in our case presentation, is a well-known complication; rarely neutopenia or agranulocytosis may occur (Raizman 1994), especially 8 to 10 weeks after initiating therapy, resulting in a 50% mortality rate. Methemoglobinemia is common; anorexia, nausea, vomiting, and an infectious mononucleosis-like syndrome may be fatal. These hematologic abnormalities return to normal after cessation of dapsone. A safe dose is less than 100 mg/day in healthy and less than 50 mg/day in G6PD-deficient patients. Sulfapyridine is a good alternative (Elder 1996).

3/4 patients responded to azathioprine (Dave and Vickers 1974).

Cyclophosphamide was the most effective initial choice for highly active cases; a sequential approach is presented (Tauber 1991). Agents such as azathioprine and cyclophosphamide may be used if conventional therapy, such as dapsone or prednisone, are ineffective.

Cyclosporine (Palestine 1984) and high dose prednisolone are effective in severe inflammation caused by OCP but may not completely prevent cicatrization (Elder 1995).



For mild to moderate inflammation, the first drug of choice is dapsone. If an insufficient response is noted, then azathioprine should be added to the treatment regimen. If still no response, then the next step should be the substitution of dapsone by azathioprine.

If there is severe inflammation or rapidly progressive disease, the cyclophosphamide and systemic prednisone is recommended. The systemic steroids is gradually tapered after the inflammation is controlled (and not more than 2 months).

Methotrexate is also used occasionally.

Many of our patients respond to intravenous immunoglobulin.

## **Intravenous Immunoglobulin**

- ◆ **Indications:** chemotherapy resistant patients
- ◆ **Dose:** 2 to 3 g/kg/week
- ◆ **Interval:** 2 to 4 weeks
- ◆ **Precautions:** volume overload, vasoocclusion
- ◆ **Contraindications:** selective IgA deficiency, severe systemic reaction to IV or IM human Ig
- ◆ **Potential adverse effects:** headache (1%)
- ◆ **Advantages:** minimum or no side effects (99%)

## **IVIg: Mechanisms of Action**

- ◆ **Fc receptor blockage and modulation**
- ◆ **Inhibits B cell function**
- ◆ **Restoration of idiotypic network**
- ◆ **Induction of T<sub>s</sub> cell activity**
- ◆ **Modulation cytokine production to decrease antibody production (ie. IL-10)**
- ◆ **Modulate complement uptake on target cells**
- ◆ **Modulate T cell functions**

## Treatment

- ◆ inflammation
- ◆ posterior lid keratinization
- ◆ trichiasis/distichiasis
- ◆ dry eye
- ◆ exposure
- ◆ meibomian gland disease
- ◆ limbal cell deficiency
- ◆ poor substrate
- ◆ hypesthesia

The most common indications for PK are corneal perforation and extensive corneal scarring (Tugal-Tutkun 1995). However, the outcome of successful PK is poor in eyes with end-stage chronic cicatrizing conjunctival diseases such as OCP, SJS, and toxic epidermal necrolysis due to immunologically-driven conjunctival inflammation, trichiasis/distichiasis (Wells 1988), severe dry eye and extensive corneal neovascularization. The major causes of graft failure are immunologically-driven inflammation, trichiasis/distichiasis, epithelial defect formation/persistence, stromal ulceration, dry eye, poor substrate, meibomian gland disease, posterior lid margin keratinization, hypesthesia, perforation, limbal stem cell deficiency and graft rejection. A combination of techniques, such as cryotherapy (Elder 1994) or epilation, mucous membrane grafting (Heiligenhaus 1993, Shore 1992), limbal stem cell and amniotic membrane transplantation, mucous membrane grafting, anterior segment reconstruction can be used to reconstruct the ocular surface (Tsubota 1996) and increases the prognosis for visual rehabilitation.

Corneal epithelial defects (18%) and limbitis (32%) were associated with a worse visual prognosis (Elder 1996). After withdrawal of immunosuppressive therapy for OCP, one-third of patients remained in remission for an average of 4 years and 22% relapsed, who regained control readily upon reinstatement of therapy (Neumann 1991). Since relapse may be slow to develop, the disease can be controlled with reinstatement of therapy, even with less aggressive treatment, patients (active and inactive) must be monitored for possible relapse life.

## Conclusion

- ◆ OCP is a potentially blinding systemic disease.
- ◆ Biopsy results are characteristic.
- ◆ Treatment is a challenge.
  - systemic immunosuppressives
  - intravenous immunoglobulin
  - anti-glaucomatous medication
  - correct disorganized anatomy and dry eye

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## **Review Questions for Ocular Cicatricial Pemphigoid**

**by Erik Letko, M.D.**

1. All of the following statements about OCP are true EXCEPT:
  - a. average age of onset is 60-70 years, but younger patients can be affected as well
  - b. diagnosis during early stages is difficult
  - c. the course is characterized by chronic relapsing and remitting cicatrizing conjunctivitis
  - d. male to female ratio is 2:1
  
2. The site of antibody deposition in conjunctiva in patients with OCP is:
  - a. epithelium
  - b. stroma
  - c. epithelial basement membrane
  - d. all above
  
3. Cicatricial pemphigoid can affect:
  - a. scalp
  - b. urethra
  - c. oral mucosa
  - d. all above
  
4. All of these findings can be secondary to OCP EXCEPT:
  - a. iritis
  - b. corneal defects
  - c. glaucoma
  - d. limbal stem cell deficiency
  
5. Cicatrizing conjunctivitis can be caused by all the following conditions EXCEPT:
  - a. adenovirus
  - b. superior limbal keratoconjunctivitis
  - c. rosacea
  - d. multiple eye surgeries
  
6. Stage II OCP is characterized by:

- a. persistent epithelial defect
- b. cicatricial entropion
- c. ankyloblepharon
- d. fornix foreshortening

7. Dry eye in OCP patients can be caused by all of the following EXCEPT:

- a. Meibomian gland dysfunction
- b. loss of Goblet cells
- c. trichiasis
- d. exposure

8. The target antigen found in the conjunctiva of OCP patients is:

- a. beta-4 integrin
- b. alpha-6 integrin
- c. type IV collagen
- d. type VII collagen

9. The first choice of initial treatment of a patient with mild to moderate inflammation secondary to OCP is/are:

- a. topical steroids
- b. systemic steroids
- c. Dapsone
- d. Cytoxan

10. The most common indication for corneal grafting in patients with OCP is:

- a. corneal perforation
- b. vision 20/40 or worse
- c. limbal stem cell deficiency
- d. persistent epithelial defect

Answers: 1-d 3-d 5-b 7-c 9-c

2-c 4-a 6-d 8-a 10-a