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Title: White looking eye. What is your diagnosis?

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CASE REPORT
A 73-year-old woman with a medical history of non-rheumatogenic mitral valve disease. Regarding her ophthalmological history, the patient received treatment with hypotensive drops for many years and underwent glaucoma surgery.
She began experiencing trichiasis in both eyelids and underwent cryotherapy and electrolysis on multiple occasions, which caused significant discomfort to the ocular surface. She also presented inferior symblepharon, predominantly in the right eye, and mild peripheral vascularization in the right eye (upper limbic). Her eyes appeared rather whitish.
The patient came for a visit noting a "white spot" in the right eye and presenting keratinization of the inferior fornix and inferior cornea area that had appeared a few days earlier. A month later, a biopsy of the entire keratinized tissue was performed to rule out carcinoma or ocular pemphigoid.
The slide corresponds to a sample of the right bulbar conjunctiva received in the pathology department

Microscopic findings:
Conjunctival tissue showing hyperplastic epithelium with orthokeratotic hyperkeratosis and hypergranulosis, as well as spongiosis. Isolated images suggestive of dyskeratosis are identified. At the basal layer, isolated mitotic figures are observed, along with the formation of microcysts and occasional subepithelial bullae that do not present an inflammatory infiltrate within. No Civatte bodies are observed. Areas with subepithelial linear thickening of an amorphous material confirmed to be basement membrane (PAS positive) are identified. At the subepithelial level, a mild (focally moderate) lymphoplasmacytic inflammatory infiltrate with a band-like distribution is observed, with occasional dilated vascular structures.
No criteria for cytological atypia or malignancy are observed in the sections examined.
Direct immunofluorescence study has not demonstrated the presence of subepithelial linear deposits of immunoglobulins (IgA, IgG, IgM) or complement, so the diagnosis of cicatricial ocular pemphigoid cannot be confirmed.

DIAGNOSIS:
- *Inflammatory process with a lichenoid pattern, basement membrane-like subepithelial thickening, and subepithelial lymphocytic inflammation.*
- *No evidence of atypia or malignancy.*
- *Direct immunofluorescence study: negative.*

Follow up:
Treatment was started with oral Myfortic 1 tablet every 12 hours, and the dose was increased to 2 tablets every 12 hours plus topical tacrolimus and topical corticosteroids.
Six months later, she had already been evaluated by the dermatologist and was undergoing follow-up. Dapsone treatment was started, but the patient developed significant anemia and was discontinued. Oral mucosal pigmented lesions were observed and biopsies were performed; the diagnosis was lichenoid dermatitis of the mucosa. One year later, the cornea was compromised, and a new deepening of the right eye was performed. The diagnosis of corneal surface tissue was again inflammatory changes with a lichenoid pattern and stromal cicatricial fibrosis. All direct immunofluorescence studies to date have been negative.
Currently, the patient has no vision in her right eye, and clinically, the diagnosis of lichen planus vs. lichen planus pemphigoid vs. mucosal pemphigoid has not yet been established.

COMMENT:
Lichen planus (LP) is a chronic inflammatory and immune-mediated disease that affects the skin, hair, nails and mucous membranes where the skin and oral cavity remain the major sites of involvement(1).Ocular LP is an extremely rare presentation and the first case was reported by Gaucher and Druelle in 1904 (2). Its exact prevalence is unknown; however, in different epidemiologic studies, reports were between 0.14% and 1,27% (1). The disease is equally distributed in genders except for oral mucosal LP in which womenpredominance of 1.4-2:1 has been reported. The typical age of patients is between 30 and 60 years old, and only 1–3% of patients are children (1, 3).

Pathogenetic mechanisms of LP still remainunclear; however, the present evidence supports that epithelial damage results from T-cell–mediated keratinocyte apoptosis triggered by a yet unidentified antigen on genetically predisposed individuals. Viruses, autoimmune phenomena, drugs, vaccines, and contact allergens have been reported as potential etiologic factors (4).

Regarding on clinical manifestations (Table 1): the cutaneous form of LP presents with a preference for the anterior aspect of the wrists and ankles and is characterized by violaceous, flat-topped polygonal papules with a superficial network of fine white lines. Mucous membranes involvement may be associated with the cutaneous form and is characterized as reticular, erosive whitish macules, most typically on the buccal mucosa, lips, and genitalia.Ocular involvement usually presents with other clinical manifestations of LP. Cicatrizing conjunctivitis, lacrimal drainage stenosis, and even corneal involvement are possible manifestations of LP in ocular surface disorders that can lead to severe scarring, being clinically indistinguishable from other causes of scarring (2).Nevertheless, LP is not always easy to diagnose, it can clinically resemble ocular surface squamous neoplasia (5) and other vesiculobullous lesions, such as pemphigus, mucous membrane pemphigoid, and even lupus erythematous plaques.

Although isolated conjunctival involvement is rare, has also been reported and usually presents as a chronic cicatricial conjunctivitis or keratoconjunctivitis (6).As a matter of fact, the differential diagnosis of conjunctival LP should be established with other clinically indistinguishable diseases manifested as cicatrizing conjunctivitis, such as mucous membrane pemphigoid, pemphigus vulgaris, graft-vs-host disease, Stevens-Johnson syndrome, and paraneoplastic pemphigus (2, 4) (Table 2). External causes of lichenoid reactions include medications, viral infections, and vaccines.

In fact, our patient was treated for glaucoma with hypotensive drops for many years. Is well-known that ocular surface disease isa complication of topical glaucoma therapy that affects not only the lacrimal and meibomian glands but also the corneal and conjunctival epithelium. After exposure to any antiglaucoma medication, although β-blockers are the most frequently reported, conjunctival involvement is in the form of drug-induced cicatricial conjunctivitis (DICC) (pseudo pemphigoid) (7). The most frequent presumed causes of pseudo pemphigoid are topical glaucoma medications (28.3%), rosacea blepharoconjunctivitis (20.0%), atopic keratoconjunctivitis (8.3%), and conjunctival lichen planus (8.3%) (8).

The histopathological findings of DICC can be very similar to those found in other scarring conditions such as ocular cicatricial pemphigoid (OCP).Conjunctival biopsy with direct immunofluorescence is the gold standard in OCP diagnosis confirmationandis characterized by increased proliferation of conjunctival epithelial basal cells, marked infiltration of inflammatory cells (macrophages, neutrophils, and T cells) in the acute phase, and fibroblasts and fibrosis in the chronic phase.Still, 20-40% of patients have a negative biopsy result that does not rule out the diagnosis (9). Distinction between DICC and OCP can be made with direct immunofluorescence (DIF). While DIF from a patient with OCP shows linear deposition of IgA, IgG, IgM, and complement C3 in the conjunctival epithelial basement membrane zone (7, 9), in pseudo pemphigoid cases such as DICC is usually negative for these findings and requires clinical diagnoses (7).

The histologic diagnosis of LP is made by the triad of irregular acanthosis, band-like infiltrates (made of lymphoid surrounding the basal cell layer), and basal cell vacuolation with scattered

apoptotic cells (Civatte bodies). Finally, irregular acanthosis with rete ridges forms a sawtooth pattern at the dermo-epidermal junction. Small clefts may be present at the dermoepidermal junction. Melanin incontinence with melanophages is usually variable but prominent onlyin hyperpigmented clinical variants. Eosinophils may be seen indrug-induced lesions (1). Histology can be inconclusive without evident characteristic features, when it happens, DIF can be helpful. The main findings in DIF patterns include shaggy anti-fibrinogen staining with weak anti-C3 staining in the basement membrane zone and positive antiIgM staining of Civatte bodies in the papillary dermis.

A definitive diagnosis is crucial because persistent and chronic inflammation may lead to progressive subepithelial fibrosis, synechiae, secondary ocular dryness, entropion, trichiasis, and corneal opacification, which are invariably associated with a severe loss of visual acuity and blindness(4).

As far as treatment is concerned,first-line treatment includes topical corticosteroid and cyclosporine. Aggressive use of preservative-free artificial tears is also important. If there is not a good response from topical treatments, systemic corticosteroids and immunosuppresants, such as cyclosporine, azathioprine, or mycophenolate mofetil can be used. For severe disease state, amniotic membrane transplantation can be used (6).

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ANNEXES:

Table 1. Clinical variants of LP (1)

Cutaneous LP	Localized cutaneous lesions of LP Generalized cutaneous LP Palmoplantar LP with localized erythematous scaly plaques Hypertrophic LP Atrophic LP Vesiculobullous LP Erosive and ulcerative LP Annular LP LP pigmentosus Lichen planus pemphigoides
Appendageal LP	Lichen planopilaris LP lesions of the nails
Mucosal LP	LP plaque-like or erosive Atrophic LP lesions of the oral mucosa Bullous LP of the mucosa Papular genital LP. Hypertrophic genital LP Chronic erosive LP lesions in genitalia lichen planus of the oesophagus
Other forms of LP	Invisible LP Overlap syndromes: LP erythematosus Lichenoid reaction of graft-versus-host disease Lichenoid keratosis Drug-induced lichen planus Ocular LP Aural and urethral LP

Table2. Common cause of cicatricial conjunctivitis (2)

1. Infectious
   a. Trachoma
   b. Adenovirus
2. Allergic
   a. Stevens-Johnson Syndrome (24% have ocular manifestations during the acute phase)
   b. Atopic keratoconjuctivitis
   c. Drug-induced cicatrizing conjunctivitis
3. Autoimmune
   a. Cicatricial pemphigoid
   b. Sarcoidosis
   c. Linear IgA disease
   d. Lupus
   e. Scleroderma
   f. Lichen planus
4. Miscellaneous
   a. Rosacea
   b. Chemical thermal burns
   c. Trauma
   d. Neoplasia

This case illustrates the diagnostic and therapeutic complexity of chronic cicatrizing conjunctivitis with a lichenoid pattern. The overlapping clinical and histopathological features between ocular lichen planus (LP), mucous membrane pemphigoid, and drug-induced cicatricial conjunctivitis (pseudo-pemphigoid) complicate definitive diagnosis—especially with persistently negative direct immunofluorescence studies. Long-term use of antiglaucoma medications is a significant risk factor for DICC, which must be considered. Despite aggressive systemic and topical immunosuppressive therapy, the patient progressed to corneal opacification and vision loss, highlighting the importance of early diagnosis and intervention in preventing irreversible ocular damage.