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Not All Conjunctival Scarring is Due to Trachoma A Focus on Ocular Cicatricial Pemphigoid and Chronic trachoma

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Abstract:

Introduction: Cicatrizing conjunctivitis is a chronic, often progressive inflammatory disease the hallmark of which is conjunctival fibrosis and scarring that may negatively impact the functional and structural integrity of the ocular surface e.g. conjunctiva, cornea, tear film as well as eyelid mechanics resulting in a wide range of ocular complications of variable severity.

Aim of the study: The objective of this study is to investigate the clinical features in patients with cicatrizing conjunctivitis attributed to OCP and chronic trachoma.

Subjects and Methods: The study was a prospective observational comparative study, encompassing 30 eyes of biopsy-proven OCP patients, and 30 eyes of chronic trachoma patients. Detailed histories regarding autoimmune diseases, eye trauma, eyelid surgery, and topical eyedrop usage were collected from all participants. Each patient underwent a comprehensive eye examination, including assessment of the lid margin, tarsal and bulbar conjunctiva, and cornea using a slit lamp. Photographic documentation of the findings was performed.

Results: In our study, we observed a female predominance among patients with ocular cicatricial pemphigoid (OCP). Clinical indicators of OCP included a history of eye redness, burning sensation, gritty sensation, and watery eyes. OCP primarily affects the lower lid and lower bulbar conjunctiva, particularly the nasal region. Typical manifestations of OCP encompass lower lid metaplastic trichiasis, loss of the plica semilunaris, caruncle effacement, shortening in the lower fornix, symblepharon between the lower bulbar and palpebral conjunctiva, ankyloblepharon, and corneal epithelial erosion, occasionally accompanied by ocular surface keratinization. On the other hand, clinical findings suggestive of chronic trachoma include a history of eye redness, burning sensation, watery eyes, and prominent gritty sensation. Chronic trachoma primarily affects the upper palpebral conjunctiva and is characterized by post-trachomatous degenerations (PTDs), Arlt's line, upper lid entropion, and entropic trichiasis, with a tendency towards metaplastic trichiasis. Corneal epithelial defects are more prevalent than erosion, and ocular surface keratinization is typically absent in chronic trachoma cases.

Conclusion: The distinctive clinical offers valuable insights into the differential diagnosis and management of OCP and chronic trachoma, aiding in the development of targeted and effective therapeutic strategies for affected patients.

Keywords: Conjunctiva; Cicatricial Conjunctivitis; Chronic Trachoma; Ocular Cicatricial Pemphigoid.

1. Introduction

Cicatrizing conjunctivitis is a chronic, often progressive inflammatory disease the hallmark of which is conjunctival fibrosis and scarring that may negatively impact the functional and structural integrity of the ocular surface e.g. conjunctiva, cornea, tear film as well as eyelid mechanics resulting in a wide range of ocular complications of variable severity [1].

Cicatrizing conjunctivitis is etiologically heterogeneous. Some are caused by infectious agents such as chlamydia trachomatis, adenovirus while others result from allergic autoimmune inflammatory reactions to assumed exogenous antigens e.g. rosacea, atopic keratoconjunctivitis, Steven Johnson Syndrome or endogenous antigens e.g. ocular cicatricial pemphigoid (OCP), linear immunoglobulin A disease, Graft Versus Host Disease (GVHD). Furthermore, physically-induced inflammation, as in traumatic, chemical and irradiation injuries, can result in conjunctival scarring. [1] Trachoma is the most infectious cause of blindness worldwide. The culprit organism is chlamydia trachomatis with often multiple reinfection cycles resulting in progressively more intense inflammatory response and scarring. Trachoma has long been endemic in Egypt with reports tracing the history of the disease to Ancient Egypt in 1500 BC [2]. Repeated episodes of infection, the conjunctiva is scarred and shortened leading to rubbing lashes and corneal opacity [3]. Ocular cicatricial pemphigoid (OCP) is a chronic, immune-mediated, bullous, cicatricial disease within the spectrum of mucocutaneous membranous pemphigoids (MMP). OCP is the leading cause of cicatrizing conjunctivitis in most developed countries as opposed to developing countries where trachoma predominates. The diagnosis of ocular cicatricial pemphigoid (OCP) is challenging, especially in its early stages where no pathognomonic clinically evident signs can be detected by conventional slit lamp examination [4]. However, OCP is a largely underestimated clinical presentation with many cases misdiagnosed as trachoma, particularly in endemic regions. Therefore, it has become a clinical imperative to reliably differentiate between them. Such a task is as arduous as it is necessary given their striking similarities. The importance of accurate diagnosis is compounded by the completely different treatment strategies for each. While

trachoma management is based principally on the SAFE strategy supported by WHO (S, surgery for trichiasis, A, antibiotic, F, Facial hygiene, E, environment improvement), OCP treatment relies heavily on long-term immunomodulation [3,4]. Trachoma and OCP are essentially clinical diagnoses with a marked overlap of signs. Therefore, adjuvant investigative tools could be of great help to elucidate otherwise clinically undetectable differences. Anterior segment optical coherence tomography is a recent promising imaging modality. It is non-invasive, non-contact and provides high spatial resolution with reasonable tissue penetration depth. These advantages, among others, make it a suitable candidate to assess conjunctival histopathological characteristics in both trachoma and OCP in vivo without the need for biopsies (optical biopsy) [5, 6].

2. Subjects & Methods

2.1. Study design

A prospective observational comparative study included 30 eyes of OCP patients and 30 eyes of trachoma patients to find characteristic conjunctival features.

Inclusion criteria

That included:

- Patients having biopsy-proven OCP.
- Patients having a clinical diagnosis of chronic trachoma by an experienced ophthalmologist.

Exclusion criteria

Other causes of cicatrizing conjunctivitis include:

- Autoimmune/allergic inflammatory conditions other than OCP e.g. Steven Johnson syndrome, linear IgA disease, Graft Versus Host Disease (GVHD), atopic keratoconjunctivitis, rosacea, …
- Physically-induced cicatrizing conjunctivitis e.g. conjunctival trauma, chemical burns, medicamentosa, radiation.
- Conjunctival neoplasia.

- History of eye or eyelid surgery or trauma involving the conjunctiva. Biopsy-negative clinical OCP.
- Mixed cases of chronic trachoma and OCP.

2.2. Subjects

Recruited patients were separated into two groups:

- Group A: Patients were diagnosed with chronic trachoma, based on clinical examination by an experienced ophthalmologist.
- Group B: Patients susceptible to having OCP underwent biopsy. Only biopsy-proven cases were included.

2.3. Methods

All patients underwent a comprehensive eye examination and photographic documentation in a standard format.

History taking

That included demographic histories such as age, gender, and district, general medical histories such as DM, HTN, and autoimmune disease, history of mucosal ulcers, skin lesions, and previous ocular surgery or trauma.

Full ophthalmological examination

That included the best corrected visual acuity with lindolt chart and eyelid examination as follows:

- Trichiasis: number of trichiatic lashes.
- Type: entropic: rubbing against the ocular surface due to rolling in the lid margin.
- Misdirected: the direction of the lash toward the ocular surface with normal origin (lash line).
- Metastatic: the roots of the lashes are from the Meibomian line. The lid margin: Meibomian gland dysfunction.
- Entropion:
  - Grade 0: none, the mucocutaneous junction is posterior to the meibomian gland openings, which lie within the lid margin skin.
  - Grade 1: The mucocutaneous junction is anterior to its normal position; the junction is very close to the meibomian gland openings, which lie just within the lid margin skin.

- Grade 2: mucocutaneous junction is located anterior to the line of the meibomian gland orifices for < 50% lid.
- Grade 3: mucocutaneous junction is located anterior to the line of the meibomian gland orifices for > 50% lid.

Slit lamp examination

The upper eyelid was everted and examined for subconjunctival scaring (pattern and severity) and tarsal conjunctival inflammation. In chronic Trachoma: tarsal conjunctival findings were graded as the WHO trachoma grading system. The patients were asked to look up and the lower lid was distracted inferiorly and examined for subconjunctival scaring (pattern and severity) and tarsal conjunctival inflammation. Lower fornix shorting was graded as:

- A: 0–25% loss of inferior fornix depth.
- B: 25–50% loss of inferior fornix depth.
- C: 50–75% loss of inferior fornix depth.
- D: 75–100% loss of inferior fornix depth.

Caruncle effacement was graded as:

- A: 0-25% with less superficial characters.
- B: 25-50%.
- C: 50-75% without ankyloblepharon.
- D: 75-100% with ankyloblepharon.

The number and size of the symblepharon, loss of the plica semilunaris, conjunctival hyperemia and limbitis were documented. Corneal opacity was graded as Grade 0: clear cornea. Grade 1: mild corneal opacity visible only with slit lamp examination. Grade 2: mild corneal haze, iris details visible. Grade 3: moderate corneal haze, iris details not visible. Grade 4: severe corneal haze, anterior chamber structures not visible. Corneal vascularization was graded as:

- Peripheral.
- Paracentral.
- Central.

The corneal epithelial defect was described as:

- Corneal epithelial erosion.
- Corneal ulcers.

3. Results

The present study included a total of 60 patients (30 eyes of ocular cicatricial pemphigoid (OCP) patients and 30 eyes of chronic trachoma patients). There was female predominance among patients having OCP compared to patients having chronic trachoma (p = 0.011). As shown in the **Table 1.**

Table 1. Demographic characteristics of the study population.

		Eye disorder		***P*-value**
		OCP	**Trachoma**	
Sex	Male	1 (3.3%)	10 (33.3%)	0.011*
	Female	29 (96.7%)	20 (66.7%)	
Age (years)		61.57 +11.03	55.9 +15.98	0.052

* significant as $P \leq 0.05$.

UL trichiasis; entropic UL trichiasis was prevalent in 26 (86%) eyes, but absent in both the OCP and normal eye groups. Mis-directed UL trichiasis was present in four (13.3%) eyes with chronic trachoma, while two eyes (6.7%) having OCP exhibited this condition. Metaplastic UL trichiasis was observed in 15 (50.0%) eyes with OCP, but none in the chronic trachoma. These differences were found to be statistically significant ($p < 0.001$).

Metaplastic LL trichiasis was present in 21 eyes (70%) of the OCP group, while no eyes were found in the chronic trachoma ($p < 0.001$). Regarding inferior Forniceal shorting, ten eyes (33%) in the OCP group had 50-75% inferior fornix loss, compared to none eyes in the other group. Similarly, ten eyes (33%) in the OCP group had 75-100% inferior fornix loss, compared to none eyes in the other group ($p < 0.001$) (**Figure 1**).

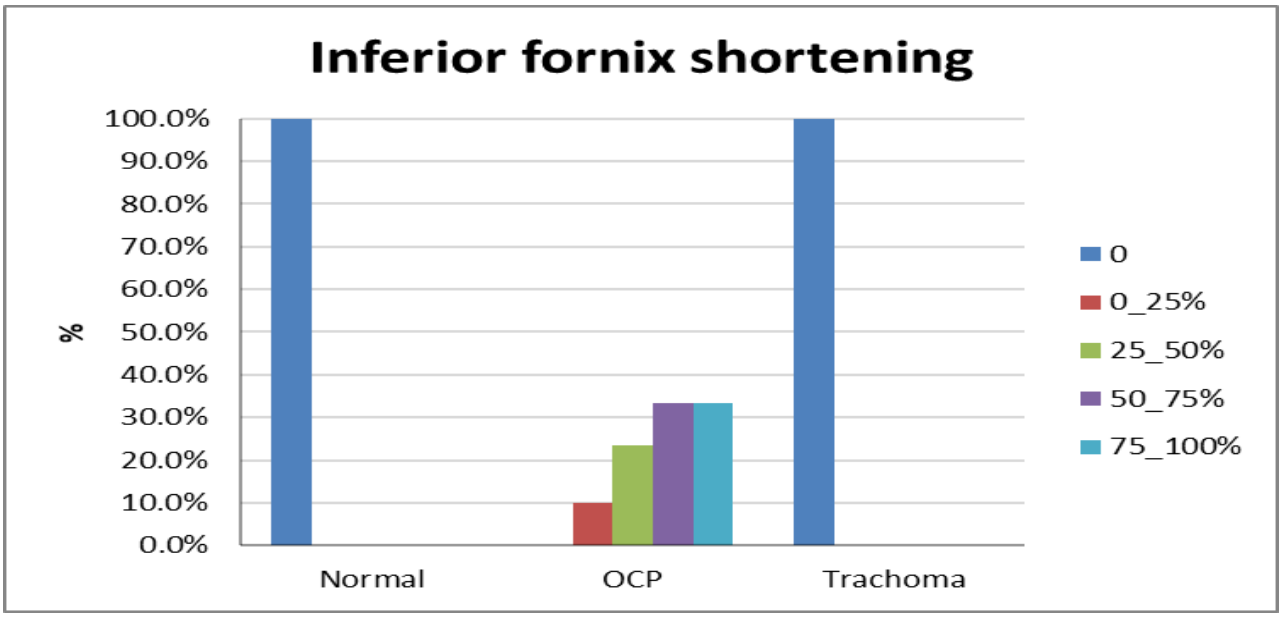

Figure 1: inferior fornix shortening details.

Concerning Symblepharon, 26 eyes (86.7%) in the OCP group had symblepharon, compared to no eyes observed in the other group (p <0.001). Twenty-one eyes (70%) of the OCP group displayed ankyloblepharon, while no eyes were observed in the other group (p <0.001). The Plica semilunaris was lost in all (100%) patients having OCP, whereas 11 eyes (36.7%) in the chronic trachoma group had obliterated plica semilunaris (p <0.001). Regarding caruncleulare effacement, in the OCP group, nine eyes (30%) had 25-50% caruncle effacement, five eyes (16.7%) had 50-75% caruncle effacement and 14 eyes (46.7%) had 75-100% caruncle effacement compared to none in the other group (p <0.001).

4. Discussion

In the present study, OCP cases are mostly females except for one case with an average age of 61.57 ±11.03, while the percentage of females with chronic trachoma cases is 66.7% higher than males of 33.3% and the average age of 55.9 ±15.98.

Both OCP and trachoma showed subconjunctival fibrosis. OCP affects mainly

the lower fornix and causes symblepharon between the lower bulbar and palpebral conjunctiva. The lower eyelid trichiasis and entropion are complications of subconjunctival fibrosis. In early of the disease, it causes flattening of the caruncle and loss of the plica semilunaris [7-9].

Trachoma affects mainly the upper eyelid. in ~ 10% of patients, it also affects the lower lid but rarely without upper eyelid affection [10]. The fibrosis ranges from fine subconjunctival lines to intensive scaring and Arlets lines (thick and dense horizontal lines of scarring). In trachoma, lashes come in contact with the ocular surface by entropion as a sequel of tarsal conjunctival scarring that results in migration of the squamous epithelium from anterior to the grey line to posterior to it. It gives the appearance of anteriorization of the mucocutaneous junction to be in front of the white line (Meibomian glands). In another cicatrizing inflammatory disease, which affects the conjunctival the trichiasis is caused by misdirection and metaplasia of the eyelashes [11].

Upper eyelid entropic trichiasis and entropion were predominantly observed in cases of trachoma, whereas lower eyelid misdirected and metaplastic trichiasis were more commonly seen in patients with OCP. These differences in clinical presentation highlight the importance of careful clinical evaluation and differential diagnosis when managing patients with chronic cicatricial conjunctivitis.

Flattening of the caruncle, shortening of the lower fornix, ankyloblepharon, and symblepharon between the lower bulbar and palpebral conjunctiva have been observed exclusively in OCP cases. Additionally, while loss of the plica semilunaris has been observed in both diseases, it was more frequently observed in OCP cases compared to trachoma cases.

Limbitis was present in approximately half of the cases of ocular cicatricial pemphigoid (OCP), while it was absent in cases of trachoma. Ocular surface keratinization and corneal conjunctivalization were noted in a small number of severely affected OCP cases and none in chronic trachoma patients.

5. Conclusion

In our study, OCP cases are more common in females and older age groups than chronic trachoma. OCP affects mainly the lower lid and causes subconjunctival

fibrosis, metaplastic trichiasis and symblepharon between the lower bulbar and bulbar conjunctiva. On the other hand, trachoma is a disease that affects the upper lid and manifests with upper palpebral conjunctiva fibrosis, Arlets line, PTDs, and entropic trichiasis. Flattening of the caruncle, shortening of the inferior fornix, limbitis, and ocular surface keratinization are characteristics of OCP that are not noticed in trachoma cases. Subepithelial fibrosis, conjunctival hyperemia, corneal epithelium erosion, vascularization and opacity are common in both diseases.

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