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Review Article

Histopathological Insights into Conjunctival Scarring

Omorodion NT[1]*, Iyare GI[3], Kiofi Barisuka[3], Ajanwanchukwu W[4] and Ehiremen S[2]

[1]*Department of Medical Laboratory Science, School of Basic Medical Sciences, University of Benin, Nigeria*

[2]*Department of Medical Laboratory Science, Faculty of Applied Sciences, Edo University Uzairue, Edo State, Nigeria*

[3]*Rivers state College of Health Sciences and Management Technology, Port Harcourt, River State, Nigeria*

[4]*Department of Medical Laboratory Science, Federal University, Otuoke, Nigeria*

***Corresponding Author:** Omorodion NT, Department of Medical Laboratory Science, School of Basic Medical Sciences, University of Benin, Nigeria.

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Abstract

Chronic cicatrizing conjunctivitis (CCC) refers to conditions causing inflammation and scarring of the conjunctiva, potentially resulting in impaired vision or blindness. Conditions such as trachoma, pemphigoid, and certain surgical procedures can exacerbate conjunctival scarring. Surgeries, particularly glaucoma filtration, often fail due to scarring at the subconjunctival level, especially at the bleb and sclerostomy sites. Antimetabolites like mitomycin C and 5-fluorouracil have shown effectiveness in reducing scarring in animal models. A thorough understanding of the pathophysiology of conjunctival scarring is essential for developing effective treatments. Both *in vivo* and *in vitro* experimental models are critical for studying the mechanisms and potential therapies for conjunctival scarring. This study aims to develop a simplified model to investigate conjunctival wound healing, emphasizing the importance of experimental approaches in translating basic research into clinical applications to improve patient outcomes.

Keywords: Conjunctival Scarring; Cicatrizing Conjunctivitis; Glaucoma Filtration Surgery; Antimetabolites; Experimental Models

Introduction

The term "cicatrix," originating from Latin, refers to the scar that forms after a wound heals. Chronic cicatrizing conjunctivitis (CCC) encompasses conditions characterized by inflammation and scarring of the conjunctiva [1]. Conjunctival scarring impacts the thin membrane covering the white part of the eye and the inner eyelids, often leading to impaired vision and, in severe cases, blindness. The extent of conjunctival scarring significantly affects visual prognosis and morbidity in various eye diseases, including cicatricial disorders like trachoma, pemphigoid, and chronic progressive conjunctival cicatrization [2,3]. Additionally, conjunctival scarring is crucial in surgeries where the healing response dictates treatment outcomes, such as in glaucoma, pterygium, and strabismus surgeries. Glaucoma filtration surgery often fails due to scarring at the subconjunctival level, especially at the bleb and sclerostomy sites [4-6]. Antimetabolites like mitomycin C and 5-fluorouracil have demonstrated significant antiscarring effects *in vitro* and *in vivo*, particularly in animal

models like rabbits and monkeys undergoing glaucoma filtration surgery [7,8]. Less commonly, models involving dogs, cats, and rats have been used to study wound healing in the sclera and conjunctiva [9,10]. The complex nature of fistulizing surgery, influenced by aqueous humor dynamics and the breakdown of the blood-aqueous barrier, presents challenges in assessing conjunctival wound healing independently [11]. Thus, this study aimed to develop a simplified model to investigate the conjunctival components of wound healing.

Understanding the pathophysiology of conjunctival scarring is crucial for developing effective therapies and improving patient outcomes. Conjunctival scarring can result from chronic inflammatory conditions, ocular surface diseases, and surgical procedures [12]. Surgeries like glaucoma filtration and pterygium excision can trigger fibrotic responses in the conjunctiva, leading to suboptimal outcomes and potential complications. The impact of conjunctival scarring on visual prognosis and morbidity is significant, especially in diseases where maintaining the ocular surface is vital for visual function [13]. For example, trachoma, a leading cause of infectious blindness, results in conjunctival scarring, corneal opacity, and visual impairment due to repeated chlamydial infections and inflammation. Autoimmune diseases like mucous membrane pemphigoid can lead to symblepharon formation, corneal scarring, and blindness if untreated. Conjunctival scarring complicates the management of these conditions, requiring a multidisciplinary approach involving ophthalmologists, immunologists, and corneal specialists to optimize outcomes and preserve vision [14].

Experimental models of conjunctival scarring are vital for advancing our understanding of the underlying mechanisms and evaluating potential treatments. Animal models, particularly those involving rabbits and monkeys in glaucoma filtration surgery, have been essential in studying the antiscarring effects of pharmacological agents like mitomycin C and 5-fluorouracil. These models allow simulation of the conjunctival wound healing process and evaluation of novel treatments' efficacy and safety. Additionally, innovative *in vitro* models using human conjunctival epithelial cells and fibroblasts offer valuable tools for screening potential therapies and understanding the molecular pathways involved in conjunctival scarring. These models bridge basic science research with clinical applications, holding promise for developing targeted therapies to prevent or reverse conjunctival scarring, ultimately improving visual outcomes for patients [15,16].

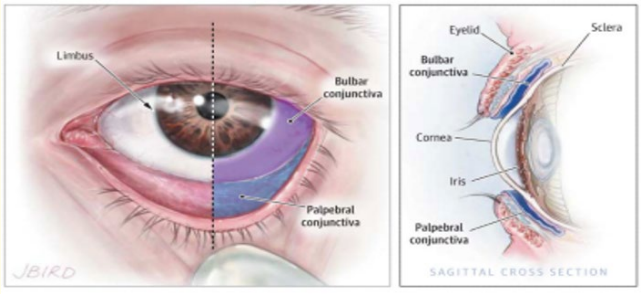

Figure 1: Normal Conjunctival Anatomy.

The conjunctiva is a delicate membrane that covers the sclera (referred to as the bulbar conjunctiva and indicated in purple) and lines the inside of the eyelids (known as the palpebral conjunctiva and indicated in blue) [2].

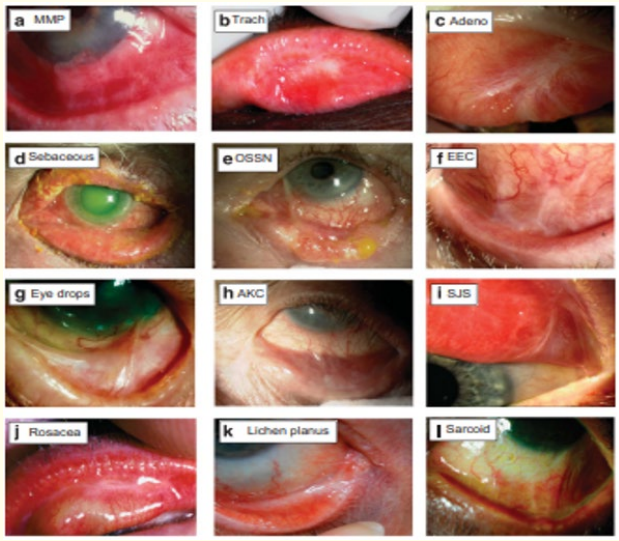

Figure 2: Illustrations of various causes of cicatrizing conjunctivitis include (a) mucous membrane pemphigoid, (b) trachoma, (c) adenovirus, (d) sebaceous carcinoma, (e) ocular surface squamous neoplasia, (f) ectrodactyly ectodermal dysplasia cleft lip/palate, (g) glaucoma drops, (h) atopic keratoconjunctivitis, (i) Stevens-Johnson syndrome, (j) ocular rosacea, (k) lichen planus, and (l) sarcoidosis [1-12].

Histopathology perspective

Trabeculectomy is a key surgical technique for managing glaucoma [17,18], but its success is highly dependent on the degree of fibrosis within the filtering bleb [19]. Activation of fibroblasts in the subconjunctival tissue plays a crucial role in fibrosis development. Histological studies reveal that eyes with previous ocular surgeries involving conjunctival incisions tend to have increased fibroblasts and lymphocytes, correlating with higher failure rates of trabeculectomy [20]. Cataract surgery, often performed in patients with glaucoma due to the prevalence of both conditions in older adults, has generally shown good outcomes [21,22]. However, a prospective study indicated a higher failure rate of trabeculectomy in eyes with open-angle glaucoma after transscleral phacoemulsification compared to phakic eyes with open-angle glaucoma [23]. This may be attributed to conjunctival scarring from transscleral phacoemulsification, leading to subconjunctival fibrosis and subsequent trabeculectomy failure. Although the temporal incision during transscleral phacoemulsification might not cause fibrosis in the superior conjunctiva where trabeculectomy is performed, conventional slit-lamp biomicroscopy has limitations in assessing subconjunctival scarring. Thus, direct conjunctival incision is needed for proper assessment. Recently, anterior segment optical coherence tomography (AS-OCT) has allowed for non-invasive imaging of conjunctival structures, including the epithelial layer, stroma, and Tenon's capsule, providing quantitative thickness measurements. However, no studies have yet used AS-OCT images to evaluate conjunctival scarring post-ocular surgery. Therefore, our study aimed to: (i) Assess AS-OCT's capability to quantify conjunctival structure damage after transscleral phacoemulsification; (ii) Determine if temporal conjunctival incisions affect AS-OCT imaging of the superior conjunctiva; and (iii) Correlate AS-OCT imaging findings with histological data from rabbit eyes undergoing transscleral phacoemulsification [24,25].

Tissue remodeling

Initially, it was believed that conjunctival tissue could transform into normal corneal epithelium. In 1977, Thoft described a technique for conjunctival transplantation, where conjunctival epithelium from a healthy eye was grafted onto eyes with alkali burns, showing damaged ocular surface epithelium and superficial vascularization. However, biochemical analyses later revealed differences between the transplanted and original corneal epithelium. The discovery of limbal stem cells as the source of corneal epithelial cells led to various limbal tissue transplantation techniques. Holland and Schwartz recently categorized these techniques [15] based on carrier tissue (conjunctiva or cornea) and tissue origin (autograft or allograft), defining four categories: conjunctival limbal autograft, living-relative conjunctival limbal allograft, cadaveric conjunctival limbal allograft, and cadaveric keratolimbal allograft. Kenyon and Tseng [16] pioneered conjunctival autografting, including limbal epithelium, showing greater effectiveness than conjunctival autograft transplantation in animal studies. This procedure involves creating a conjunctival peritomy posterior to the limbus of the injured eye, removing abnormal corneal epithelium and pannus. Donor limbal epithelium is harvested from the healthy eye and transplanted to the injured eye, extending onto the clear cornea and bulbar conjunctiva to include limbal stem cells. Postoperative care includes topical antibiotics, steroids, cycloplegics, non-preserved artificial tears, and a soft contact lens or tarsorrhaphy for graft protection.

Inflammation

Chronic conjunctival inflammation of autoimmune origin typically affects both eyes asymmetrically, often with acute flare-ups. Skin lesions (bullous dermatosis) are present in a minority of cases (10–43%). Deposition of immunoglobulin and complement along the basement membrane triggers inflammatory cascades, activating subepithelial fibroblasts and collagen synthesis. Histopathological findings show varying subepithelial inflammatory infiltrates in the conjunctiva, correlating with disease activity stages. Neutrophils and macrophages dominate during active stages, while T lymphocytes are present throughout. Conditions like pemphigus and bullous pemphigoid, characterized by autoantibodies to the epidermis and subepidermal basement membrane, can lead to ocular surface cicatrization. Linear IgA disease and dermatitis herpetiformis, marked by IgA and complement deposits at the epidermal basement membrane, occasionally involve the conjunctiva, contributing to inflammatory responses and potential scarring [12,13].

Epithelial changes during the spontaneous healing of adult conjunctival wounds involve a series of regenerative processes. Initially, inflammation occurs, followed by re-epithelialization

where cells migrate, proliferate, and differentiate at the wound edges. Concurrently, wound contraction reduces wound size through inward movement of wound edges. Despite the potential for spontaneous re-epithelialization, pathological healing often leads to subconjunctival fibrous scar formation.

Conclusion

Understanding the pathophysiology of conjunctival scarring is vital for developing effective treatments and improving patient outcomes. Chronic inflammatory conditions, ocular surface diseases, and surgical interventions can cause scarring, leading to severe complications. Experimental models, especially those using animals and *in vitro* systems, are essential for advancing our knowledge and evaluating potential therapies. These models play a critical role in translating basic scientific discoveries into clinical practices that can prevent or mitigate conjunctival scarring, ultimately enhancing visual outcomes and quality of life for affected patients.Top of FormBottom of Form

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