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Histopathological diagnosis of pterygium, recurrent pterygium and pyogenic granuloma of the conjunctiva

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Abstract
Pterygium, recurrent pterygium, and pyogenic granuloma share similar etiologic factors and overlapping clinical and histopathological features, may result in impaired vision, induced astigmatism, and recurrent inflammation. This study aims to provide valuable insights into the risk factors, pathogenesis, and histopathological diagnosis and differentiation of these conditions, enhancing their understanding and management. The etiopathology of these conditions is multifactorial, including mechanical irritation, inflammation, genetic factors, and environmental influences. Pterygium affects over 10% of the population and is characterized by abnormal growth of epithelial and fibrovascular tissue involving the conjunctiva. Risk factors include prolonged ultraviolet (UV) exposure, sunlight exposure, dry eye disease, and aging. Additional risk factors for recurrent pterygium are postoperative inflammation, excessive suturing, and incomplete primary pterygium removal. The role of humoral and cell-mediated immune responses in these lesions is critical. Pterygium, histopathologically displays abnormal bulbal conjunctival epithelium and submucosal fibrovascular connective tissue that migrates to and involve cornea. Elastosis is the key morphological finding in pterygia. Histopathologically, pyogenic granuloma shows vascular proliferation, acute and chronic cellular infiltrates, and mucosal thickening. Recurrent pterygium and pyogenic granuloma after surgical trauma are common and can cause significant morbidity. While all these can be clinically diagnosed; histopathological investigations aid confirmation. Accurate diagnosis and appropriate management are crucial to prevent ocular surface damage, visual impairment, and pterygium recurrence.

Keywords: Pterygium, pyogenic granuloma, histopathology

Introduction
Pterygium is an abnormal growth of epithelial and fibrovascular tissue of cornea, leading to impaired vision, induced astigmatism, and recurrent inflammation [1]. Although pterygium management is primarily surgical, postoperative recurrence of pterygium is a significant concern [1]. Pyogenic granuloma, a relatively uncommon eye condition, causes notable morbidity with similar etiology to pterygium. Conjunctival pyogenic granuloma, a benign vascular tumor, can result from trauma, inflammation, or infection, causing ocular surface irritation, bleeding, and cosmetic disfigurement.
This study aims to provide insights into the risk factors, pathogenesis, histopathological diagnosis of pterygium, recurrent pterygium, and pyogenic granuloma, enhancing their diagnosis and management.

Materials and Methods
All ophthalmic tissues material submitted to histopathological section of our hospital, were retrospectively evaluated for six months. A total of four histopathological material from inpatient hospital admissions and outpatient clinics of ophthalmologists were submitted. Patients' ages ranged from 28 to 42 years, primarily females, except for one male patient. Surgical interventions varied in duration, with the longest being six months ago and the shortest less than a month.
All tissue samples were processed and embedded in paraffin blocks and stained with hematoxylin and eosin for routine histopathological screening. Histopathological diagnoses were inferred and analyzed, considering demographic, clinical, and relevant historical data.

Results

Most patients were females (except one), aged 28 to 42 years, with clinical presentations of foreign body sensation, eye redness, and lacrimation. Histopathological diagnoses included pterygium (2 cases), recurrent pterygium (1 case), and pyogenic granuloma (1 case).

Two patients were histopathologically diagnosed with pterygium through microscopic examination. One patient had a clinical suspicion, while the other presented with eye irritation and swelling without a specific clinical diagnosis. Recurrent pterygium was diagnosed in a patient with a history of surgical intervention six months prior, showing clinical suspicion and relevant symptoms. The fourth patient had a history of recurrence within a month of surgery, with histopathological findings consistent with pyogenic granuloma.

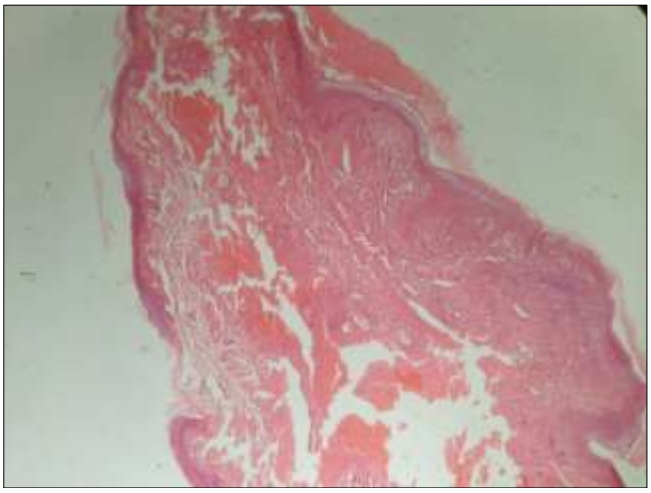

Fig 1: Pyogenic granuloma, conjunctiva (10x)

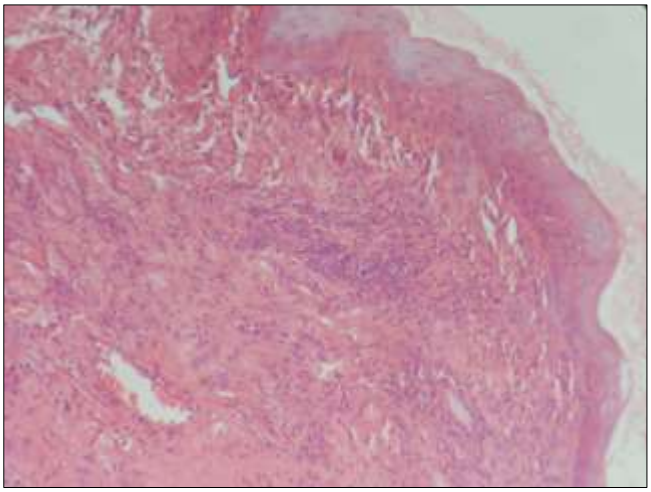

Fig 2: Pyogenic granuloma (40X)

Discussion

Clinically, pterygium typically presents with redness and eye irritation, displays abnormal epithelium and fibrovascular tissue growth involving the conjunctival stroma. Impaired vision, induced astigmatism, and recurrent inflammation commonly follow pterygium. While the management of pterygium is mainly surgical, the postoperative 'recurrent pterygium' remains a significant concern [1]. Recent history of surgical intervention for pterygium removal and the recurrence of small reddish, exophytic growths in the eye provided us a clue in one case that we might be dealing with a case of pyogenic granuloma [2]. The 'pyogenic granuloma' is a misnomer term, is neither associated with pus nor represent a true granuloma; instead, it is a reactive inflammatory response to constant stimuli or minor trauma, potentially related to hormonal changes [3] & and can be triggered by ophthalmic surgeries [4].

Risk factors for primary pterygium include prolonged ultraviolet (UV) or sunlight exposure, dry eye disease, aging, and male gender. Genetic factors like the p53 tumor suppressor gene and ethnicity have also been linked to recurrent pterygium [5-6]. Limbal stem cells and fibroblasts play roles in the pathogenesis of pterygium [7-8]. Postoperative inflammation, excessive suturing, and incomplete primary pterygium removal are additional risk factors for 'recurrent pterygium' [8-9]. The extent of fibrovascular tissue removal during initial surgery have significantly impact on pterygium recurrence and most recurrences occur within 3–6 months of primary eye surgery [10].

The etiopathology of both recurrent pterygium and pyogenic granuloma is multifactorial, involving mechanical irritation, inflammation, angiogenesis, genetic factors, and environmental influences. Conjunctival irritation and inflammation resulting from UV light/sunlight exposure, trauma, or infection may serve as common precipitating etiologic factors for pterygium, recurrent pterygium, and pyogenic granuloma [11, 4]. Although pyogenic granuloma occurrences on the lips, tongue, oral mucosa, palate, and fingers have been reported, they are relatively uncommon in the eye. Pyogenic granulomas are highly vascular due to their composition of hyperplastic granulation tissue with prominent capillaries. Consequently, even minor trauma to the lesion can result in significant bleeding due to its pronounced vascularity. While the lesion's clinical development is usually slow, it can occasionally grow rapidly [2, 11, 12].

The role of humoral and cell-mediated immune responses in lesion development is also crucial. Environmental irritants and ultraviolet radiation can lead to chronic inflammation and angiogenesis and contribute to the development of pterygium and pyogenic granuloma. Familial cases point to genetic factors' involvement in primary pterygium's pathogenesis [5]. Carriers of the genetic mutation BRAFV600 have an associated 8-fold increased risk of pterygium recurrence during the first year after surgery [13]. Viruses like HSV, EBV, CMV, and HPV have also been implicated as risk factors for pterygium recurrence [13].

Understanding of underlying molecular mechanisms of recurrent pterygium and pyogenic granuloma offers potential diagnostic and therapeutic advantages. Mutations in the "transforming growth factor-beta (TGF-β)" pathway and increased expression of "vascular endothelial growth factor (VEGF)" have been associated with the development of both pterygium and pyogenic granuloma. Targeted therapies inhibiting TGF-β signal and VEGF expression in patients hold promise for these conditions. Local pterygium lesions exhibit enhanced MMP-1 expression [1]. Various inflammatory cytokines, growth factors, elevated levels of stromal cell-derived factor 1, transcription factor specificity protein 1, and collagen I accelerate recurrence of pterygium [6, 14, 15, 16]. Excessive production of VEGF and bFGF, and decreased amounts of angiostatin, thrombospondin-1, and estrogen receptors contribute in development of pyogenic

granuloma [14]; and VEGF receptor-2 (VEGFR-2) expression may predict pterygium recurrence [15].

Pterygium and recurrent pterygium, histopathologically displays abnormal bulbal conjunctival epithelium and submucosal fibrovascular connective tissue that migrates to and involve cornea. Elastosis is the key morphological finding in pterygia. Corneal epithelium is focally atrophic and contains increased mucus secreting goblet cells. Epithelial atrophy with goblet cell loss is nonspecific and can be seen in dry eye syndrome. Most pterygia are benign however actinic induced conjunctival intraepithelial neoplasia and squamous cell carcinoma arising in pterygium have been documented [16].

The Stromal tissue in pyogenic granuloma shows vascular proliferation, acute and chronic cellular infiltrates in the stroma, and mucosal thickening. It exhibits marked vascular proliferation, composed of numerous small and larger endothelium-lined vessels filled with red blood cells and infiltrated with mixed cellular infiltrates of neutrophils, plasma cells and lymphocytes. Surface may be focally ulcerated [2]. A high incidence of pyogenic granuloma is seen in the young adults, in second decade of life, more in females, possibly due to the vascular effects of female hormones [2, 17].

Potential complications associated with pterygium, recurrent pterygium and pyogenic granuloma may be ocular surface damage, visual impairment, and recurrence after treatment. Surgical interventions, such as excision and conjunctival auto-graft, can treat pterygium, though recurrence remains a possibility. Pyogenic granuloma, although not common, may also recur after surgical excision and might necessitate further treatment. Although clinical diagnosis of pyogenic granuloma can be quite accurate, radiographic and histopathological investigations aid in confirming diagnosis and treatment. Radiographs are useful for ruling out bony destruction suggestive of malignancy or identifying foreign bodies

Conclusion

Clinical features of pterygium, recurrent pterygium, and pyogenic granuloma can appear similar. They can primarily be differentiated clinically, depending on the eye's location, corneal involvement, lesion severity, and history of previous eye surgery, inflammation, or irritation. Imaging studies can assist in accurate localization; however, histopathology will provide a definitive diagnosis and guide management.

This article is important because recurrent pterygium and pyogenic granuloma following surgical trauma are common conditions that can cause significant morbidity in affected eyes. Therefore, accurate diagnosis and appropriate management are crucial for preventing ocular surface damage, visual impairment, and recurrence.

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