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Research article

Limbal Stem Cell Damage Has a Pivotal Role in the Pathogenesis of Pterygium, Our Experience

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Abstract

Aim of the study: To find out that limbal stem cell damage has an important role in the pathogenesis of pterygium and replenishment of the damaged stem cells with healthy ones prevents recurrence.

Methods: This was a prospective interventional observational study of 30 cases of primary pterygium treated by a single surgeon in institutions and clinical practice from 2006 to 2023. Bare sclera excision with autologous conjunctival transplantation was done in all cases. In 2 cases, the tissue was from upper temporal bulbar conjunctiva without the limbal zone and was transplanted on the bare sclera. In rest 28 cases, upper limbal conjunctiva was transplanted in circumferential barrage fashion into the limbal area of excised pterygium. Follow up was done up to a year and results were assessed.

Results: All the cases were in the age groups of 15-35 years except one case of 65 years. All were male except one. In the first 2 cases, recurrence was seen in one case (50%). In the rest 28 cases, no recurrence was seen except in the 65 years' patient; where a conjunctival growth was observed in the lower part without encroaching the cornea.

Conclusion: This indicates that if the damaged limbal stem cells are replenished with healthy ones there is no recurrence. So, the ultra violet radiation damaged stem cells have a pivotal role in the pathogenesis of pterygium.

Keywords: Pterygium; Limbal stem cell; Autologous conjunctival transplantation; Autologous limbal conjunctival transplantation

Introduction

Pterygium is a raised fleshy wing shaped triangular growth that starts from the corner of the eye invading the avascular cornea in the interpalpebral fissure exposed to the environment. It is a subconjunctival elastotic degeneration which proliferates as a vascularized granular tissue by destroying the superficial stroma and Bowman's membrane, the whole being covered by conjunctiva [1].

The global incidence is 0.3 -29%. In India it is 9.5 -13%. It is highest in the equatorial zone, the pterygium belt, 370 north and south of the equator. It is predominant in males and in the

nasal corner of the eye [2,3]. The risk factors are possibly genetic predisposition, increasing age, male sex, outdoor job, low education, rural population, low income, darker skin complex, smoking, and prolonged habitual exposure to dry, dusty, sunny, and windy environment with exposure to ultraviolet radiation [3].

The exact aetiology is not clear. However habitual exposure to dusty, dry, windy, sunny environment with ultraviolet radiation, heredo- familial factors, viral agents such as human papilloma virus, and immunological and inflammatory agents are the possible causes [3,4].

3.1. Pathophysiology: Recent advances in the molecular tapestry of pterygium indicate that ultraviolet radiation produces genetic signals leading to disturbances of Matrix metalloproteinases (MMPs), especially MMP-2 and MMP-9 which contribute to extra cellular matrix (ECM) remodelling and angiogenesis. Elevated vascular endothelial growth factor plays a crucial role in angiogenesis. B-cell lymphoma-2, S-100 proteins, DNA repair genes (hOGG 1, XRCC 1), CYP mono-oxygenases, tumour suppressive gene (P 53, p 16) and other genes are implicated. A protein- protein interaction network analysis highlighted 28 edges between the afore mentioned proteins except VEGF indicating a high level of interaction. Gene ontology, micro-RNA and pathways analyses revealed the involvement of processes such as base excision repair, IL 17 and P 53 signalling disassembly, oxidative stress, hypoxia, metallopeptidase activity and others are essential for pterygium development. In addition, miR-29, miR-125, miR-126, miR-143, miR-200, miR-429, miR-451 microRNAs were shown to have a role in pterygium development and disease activity. Identification of these molecular mechanisms provides insights for potential diagnostic and therapeutic strategies to pterygium [5].

These molecular alterations lead to the damage of the limbal stem cells present in the palisade of Vogt leading to over expression of VEGF and vibrant fibroblast mitosis as angiogenesis which result in cell proliferation, migration, stromal changes with evidence of Bowman' layer dissolution. This induces inflammatory response which form pterygium cells resulting in disruption of limbal barrier, upregulation of inflammatory cytokines, imbalance of growth factors, MMPs, tear film changes and immunological disturbances. The limbal stem cells act as a barrier to the growth of conjunctival epithelium towards the clear cornea. When these are damaged partially or completely, conjunctivalization sets in with appearance of goblet cells and irregular unstable epithelium [6-12].

Surgery is the mainstay in management; but very often there is high recurrence (88%) after the classical bare sclera excision of pterygium. Newer surgical techniques are amniotic membrane transplantation, ologen transplantation, pterygium extended removal followed by extended conjunctival transplantation (P.E.R.F.E.C.T.). The procedure most advised is conjunctival limbal autograft with the use of intraoperative adjuvants like mitomycin-c, bevacizumab, cyclosporin-A,5-fluorouracil, dipyradimide and doxycycline [13]. In this study an innovative stem cell therapy in the form of autologous circumferential barrage fashioned limbal transplantation has been tried and evaluated.

Methods

This is a prospective interventional case series study done in institutional and clinical practice approved by institutional ethics committee. 30 cases of pterygium of various age and sex undergoing surgery by the author from 2006 to 2023 have been included with informed consent. Detail ophthalmological examination was done in each case. Bare sclera excision along with auto conjunctivoplasty was done in all cases. In 2 cases, bulbar conjunctiva was retrieved from upper temporal area without the limbal zone and transplanted into the bare sclera with fixation by 10-0 nylon sutures. In rest 28 cases, limbal conjunctiva from the upper part extending two clock hours in length and 3 mm. wide (2 mm. behind and 1 mm. in front of the limbal line) was retrieved and transplanted circumferentially in barrage fashion in the excised limbal area with 10-0 nylon sutures. The bare sclera was left as such uncovered. The upper limbal conjunctiva in the retrieved area was left as such with a subconjunctival injection of gentamycin with decadron. The patients were discharged on the third post operative day with protective goggles and the advice to use local antibiotic and steroid drops for three weeks. They were evaluated at frequent intervals after a week, fort night, one month, three months, six months and one year. Some were evaluated even after a year.

Results

Thirty cases of pterygium, undergone surgery by the author from 2006 to 2023 were evaluated for one year and more. Majority were in the age group from 15 -35 years except a case of 65 years. This patient was having cystoid degeneration of the pterygium since last 30 years or so. Only one case was a female, a labourer by profession. In 2 cases, who had undergone auto conjunctivoplasty from the upper temporal quadrant without the limbal zone had recurrence in one case (50%), habitually exposed to dry, dusty, and sunny environment due to his profession. In the rest 28 cases there was smooth post operative recovery without any spectacular event. The bare sclera was covered by healthy conjunctiva with no recurrence. In the elderly case with cystoid degeneration, the excised tissue was found to be benign in nature by histopathological study. There was some type of conjunctival growth from the lower side without encroaching the cornea after a period of one year.

Discussion

Pterygium can be congenital and acquired. The latter variety appears to occur in persons frequently exposed to sunny, dry, dusty and windy environment for a prolonged period, probably due to exposure to ultra violet radiation. Surgical excision is the main stay of management. However very often there is recurrence with conventional surgery. It is presumed that corneal stem cells are present in the limbal zone in the palisade of Vogt. The main function of these cells is to replenish the old and damaged corneal epithelium. Besides this, it prevents conjunctivalization by not allowing neovascularization from the limbal vessels into healthy cornea. The altered stem cells damaged by ultra violet radiation initiate the pathogenesis. Replenishment of damaged stem cells with healthy ones by autologous transplantation can prevent

recurrence.

In this study two types of autologous conjunctival transplantation were done. In the first type, bulbar conjunctiva retrieved from the upper temporal area without limbal tissue was transplanted into the bare sclera following simple excision. There was recurrence in one case (50%). This may be due to further exposure to dry, sunny, dusty and windy climate or as there are no stem cells in the upper bulbar conjunctiva. In the second type, after bare sclera excision of pterygium, autologous limbal conjunctival transplantation in circumferential barrage fashion was done. There was no recurrence (0%) after a period of one year. Probably this was due to the replenishment of damaged stem cells with healthy ones and taking the precautionary measures like wearing protective glasses outside.

Mathew Caldwell et al. in their study on pterygium reveal that increased prevalence in hot and dry climate and regions nearer to the equator suggest a role of environmental factors such as ultra violet radiation and dryness. Actinic changes seen in histopathology similar to actinic keratoses on the skin also support the role of ultra violet radiation. It has been suggested that radiation activated fibroblasts may result in excessive production of materials resulting in pterygium [14].

Sanjay Kumar Singh has found that amniotic membrane transplantation following pterygium excision has the recurrence rate of 4%-7.6%. Bare sclera technique with adjuvant therapy has reduced the recurrence rate (2%-15%) [7].

Toktam Shahraki, et al. opine that as the altered stem cells are mainly located in the head of the pterygium, complete removal of the apex is critical during surgery. The procedure most advised for repair is conjunctival and conjunctivo-limbal autografting with the use of intraoperative adjuvants of mitomycin-C, bevacizumab, cyclosporin-A [8].

Mathias Fuest et al. in their study on New Treatment options for pterygium opines that conjunctival autografting represents the current gold standard treatment for pterygium. Limbal conjunctival autograft is more effective than conjunctival autograft in recurrent pterygium [15]. Elizabeth Clearfield et al. have found that conjunctival autograft is associated with a lower risk of recurrence at six months after surgery than amniotic membrane transplant [16].

B Paganelli et al. in their study of Conjunctival and Limbal Autograft versus Amniotic membrane graft in primary pterygium surgery, have observed a recurrence of 7.6% in conjunctival autograft, 5.50% in limbal conjunctival autograft, and 9.0% in amniotic membrane graft. It was 8.99%,6.03% and 23% respectively in the above groups receiving sutures. Surgical techniques combining conjunctival autograft or limbal conjunctival autograft with amniotic membrane graft yielded even lower recurrence rate (1.83) [17].

K.P.S. Malik et al. studied the efficacy of suture less and glue free limbal conjunctival autograft for primary pterygium surgery and found a recurrence in one (2.5%), graft dehiscence in 2 eyes (5%), graft retraction in 3 eyes (7.5%) [18]. It appears that ultra violet radiation altered limbal stem cells initiates the pathogenesis of pterygium by conjunctivalization in to the compromised limbal barrier resulting in elastotic degeneration and fibrotic proliferation invading the clear cornea. Replenishment of altered stem cells with healthy ones prevents recurrence.

Conclusion

It appears that ultraviolet radiation alters the limbal stem cells leading to the pathogenesis of pterygium. If these are replenished with healthy ones, there is no recurrence. This indirectly proves that damaged stem cells have a pivotal role in the pathogenesis of pterygium.

Conflict of Interest

None.

Acknowledgement

None.

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