• Perspective •

Current approaches and future directions in the management of pterygium

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Abstract

• Pterygium, a common ocular surface disorder, has a complex pathophysiology that may mimic tumorigenesis. There is altered expression of cell cycle/proliferation-related factors in pterygium tissues. Therefore, similar to cancer treatments, the management of pterygium ought to be multifactorial based on the patient's condition. Current therapeutic methods for pterygium are focused on surgical resection in conjunction with antimetabolite use, in addition tissue graft is usually performed in the context of the avoidance of bare sclera. However, future directions in the management of pterygia will likely focus on genetic approaches. This perspective views the pathogenesis of pterygium, its existing therapies as well as current and future challenges in its treatment.

• **KEYWORDS:** pterygium; tumor; recurrence; future directions
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INTRODUCTION

Pterygium is a common ocular surface disorder that is characterized by hypertrophy of the subconjunctival connective tissue and overlying epithelium. Chronic ultraviolet (UV) light exposure is a known cause of degenerative deposition of subepithelial collagen fibers, which eventually leads to pterygium development. Pterygium may only cause cosmetic complaints, severe subconjunctival hypertrophic scarring, and subsequent symblepharon, ocular motility restriction, and significant vision loss (Figure 1). These severe complications can impair quality of life and psychosocial function.

PROLIFERATIVE FEATURES OF PTERYGIUM

Pterygium has the propensity to grow and recurs frequently. Therefore, some have suggested that it is actually a tumor-like proliferative disorder, rather than a degenerative process. Pterygium does not have malignant features in that it does not spread to distant organs. However, several prior studies have described its other characteristics that mimic cancer, including unlimited growth and local tissue invasion. Microsatellite instability and loss of heterozygosity have been found to be clinically correlated with pterygia[1]. Thereafter, the development and growth of pterygium is significantly related to aberrancy of cell cycle progression, and ultimately uninhibited proliferation[2]. In addition, several studies have identified carcinoma *in situ* and dysplasia, and some have analyzed the expression of cell cycle/proliferation-related factors (*e.g.* p27, Ki-67, cyclin D1, p63, p16 and p53) in pterygium epithelium[3-5]. Based on these prior findings, it is conceivable that pterygium management should parallel that of cancer.

PREOPERATIVE EVALUATION TO PREDICT POST-SURGICAL RECURRENCE

The most significant concern for both patients with pterygium and surgeons is post-surgical recurrence. Unfortunately, the fibrovascular growth propensity of pterygium during recurrence is often more rapid and extensive than it is during its initial development. Therefore, it is difficult to establish a surgical strategy for recurrent cases. Recurrence and its severity vary depending on the preoperative conditions of

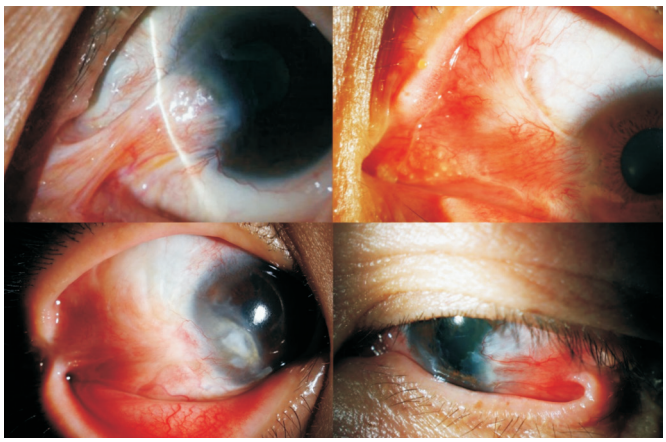

Figure 1 Severe cases of pterygium complicated by symblepharon, severe hypervascularization, motility restriction-related diplopia and impaired vision.

pterygium. Thus, to perform intervention with which less likely to cause postsurgical recurrence, especially in pterygium which is more likely to recur, is an essential prerequisite to a successful surgical outcome of pterygium. The excessive cautery of episcleral vessels or the improper use of mitomycin C (MMC) in pterygium treatment can cause devastating necrotizing scleritis. In contrast, the limited removal of pterygium tissue may lead to rapid recurrence. Therefore, there are two important main concepts in pterygium research: 1) preoperatively identifying the risk factors for recurrence; 2) selecting and devising a suitable intervention to prevent recurrence.

In a previous study, the flesh-like morphology of pterygium (grade T3) was well correlated with a higher recurrence rate after bare sclera surgery[6]. While searching for biomarkers that predict uninhibited proliferation, a recent study showed that the expression of stromal cell-derived factor 1 (SDF-1) in pterygium body fibroblasts increased the subsequent expression of transforming growth factor beta (TGF-β), a well-known pan-organic key fibrogenic stimulant[7]. It has also been reported that stromal fibroblasts from more severe pterygia (with thick body morphology) (grade T3 by Tan *et al*[6]) overexpressed angiogenin[8] and SDF-1[9] more than did the mild form of pterygia. The expression levels of both angiogenin and SDF-1 were positively correlated with that of alpha-smooth muscle actin, a marker of myofibroblast characteristics. Myofibroblasts are the activated and transformed cells of fibroblasts. Myofibroblasts are resistant to programmed cell death, and may perpetuate the synthesis of extracellular matrix for fibrotic tissue remodeling. In this study, we assumed there were diverse factors also associated with the propensity for post-surgical recurrence, including young age, current active growth, pre-existing disfiguration of lacrimal caruncle, ocular motility restriction; concurrent ocular surface inflammation, fibrogenic constitution (*e.g.* keloid tendency) and the genetic predisposition to recur (*e.g.* family history). At out institution, the variables are now used in the development of differential surgical strategies. Ideally, we expect that whole-genome sequencing may one day help to catalogue the characteristics and spectrum of germline alterations, enabling researchers to fully understand the genetic aspect of pterygium and its malignant mimicry. Similarly, there has been a recent effort to scan the proliferation-driving factor through microRNA arrays and to confirm such a regulator in pterygium fibroblasts[10].

OPTIONS TO LOWER POST-SURGICAL RECURRENCES

The undisputed operative strategy to minimize the risk of pterygium recurrence is to maximize residual fibroblast ablation at the surgical wound area through thorough removal of subconjunctival fibrovascular tissue. There are several adjuvant options to reduce the proliferative activity of stromal fibroblasts during the postoperative recovery phase. These adjuvant therapies include: application of an antimetabolite such as MMC or 5-fluorouracil, intralesional steroid injection and insertion of multimicroporous expanded polytetrafluoroethylene (e-PTFE) in multirecurrent pterygia[11]. In addition, the intraoperative uncovered wound area should be minimized using a conjunctival flap, amniotic membrane graft, or conjunctivo-limbal autograft to allow for rapid epithelial wound healing. The bare sclera technique, for example, has relatively high and variable recurrence rates from 33% to 88%[6]. A large open wound after pterygium excision inevitably results in severe pain. Based on our experience, severe pain induces exaggerated wound hypertrophy, leading to pterygium recurrence. This hypothesis is in line with our previous report, in which substance P, a neuropeptide famous for nociception, drove the mobilization of injury-inducible stromal-like cells from the bone marrow to participate in wound healing[12]. Therefore, we do not support perioperative pain-provoking surgical methods such as bare sclera excision. In addition, delayed epithelial wound healing may induce alternative and prolonged stromal overgrowth, most likely due to a lack of contact inhibition with the overlying epithelial cells. In challenging cases of keloid constitution or repeated recurrence, we carefully avoid loss of the adjacent normal conjunctival epithelium. In addition, in these cases, we undoubtedly cover the large wound area by sliding or rotating the flap tissue of the nearby conjunctiva or conjunctivo-limbal allograft onto the base of the amniotic membrane graft. This process is followed by meticulous excision of the stromal pterygium tissue and gentle application of MMC with occasional temporary e-PTFE insertion.

In conclusion, the most appropriate initial step in the management of pterygium is to determine the risk of recurrence using clinical information. Next, the pterygium tissue is removed with appropriate adjuvant options. In the future, it will be important to identify the molecular/genetic biomarkers of recurrence, as well as patient-individualized therapeutic methods in order to maximize therapeutic effectiveness overcoming the complicated problems in pterygia. Furthermore, the CRISPR-Cas9 system or "gene scissors", declared the "Breakthrough of the Year 2015" by the journal *Science*, is cautiously predicted to be a therapeutic option in pterygium using gene-targeted fundamental techniques.

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