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REVIEW ARTICLE
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Update on overview of pterygium and its surgical management

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ABSTRACT

Pterygium is a bulbar conjunctival fibrovascular growth that crosses the limbus and extends onto the peripheral cornea, and in some cases leads to significant visual complications. The prevalence of this disease has been reported to be from 1.2% to about 40% in different parts of the world. Although there are various risk factors for pterygium, which include ultraviolet (UV) radiation, viral infection, hereditary factors, immune factors, aseptic inflammation, and environmental irritation, the pathogenesis of pterygium is mainly related to exposure to UV light. In addition to cosmetic problems, pterygium can lead to eye irritation, disrupt the transparency of cornea on the pupil area, and cause disorders such as corneal astigmatism and damage to the visual axis leading to vision impairment. In the last few years, the treatment of pterygium has been developed and various new solutions have been used. Surgery is the main treatment for pterygium. Various techniques such as Bare Sclera, Rotational Conjunctival Flap, Limbal Conjunctival Autograft, Amniotic Membrane Graft, and Free Conjunctival Autograft are used for the removal of pterygium. It also seems that the worrisome problem of recurrence has been significantly reduced with newer treatment methods. On the contrary, the use of auxiliary treatments such as mitomycin C, b-radiation, 5-fluorouracil, topical use of interferons, and Avastin are also effective in reducing the recurrence rate.

Keywords: *Pterygium; risk factors; UV radiation; surgery; recurrence*

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INTRODUCTION

Pterygium is a common eye disorder, which is clinically described as a wing-shaped, fleshy, triangular fibrovascular conjunctival growth that extends over the cornea of the eye and is mostly located on the nasal side of the conjunctiva.[1–4] The pterygium consists of a body part that is located on the sclera, a head-like part that attacks the cornea, and a neck part that includes the superficial limbus. Stocker's line, an epithelial iron deposit at the leading edge of the pterygium, is a common clinical feature of pterygium.[1,5] The main components of pterygium include proliferative clusters of limbal stem cells (LSCs), epithelial metaplasia, active fibrovascular tissue, and inflammation and disruption of Bowman's layer along the invasive apex of pterygium.[6] Although the exact cause of pterygium is unknown, there appears to be an association between outdoor work and the formation of pterygium, particularly with ultraviolet (UV) radiation.[7] Also, various factors, such as viruses, oxidative stress, DNA methylation, apoptotic and oncogene proteins, loss of heterozygosity, microsatellite instability, inflammatory mediators, extracellular matrix modifiers, lymphangiogenesis, epithelial-mesenchymal cell transition, and changes in cholesterol metabolism, play a role in the development of pterygium.[8] In addition to cosmetic problems, pterygium can lead to eye irritation, disrupt the transparency of the pupil area, and cause disorders such as corneal astigmatism; in addition, it may rarely lead to visual impairment due to damage to the visual axis, which in severe cases requires surgery.[6,9–11] Due to the importance of this disease, this review provides a major review on etiologies, risk factors, complications, and surgical management of pterygium, focusing on the updates and the new features of the literature. Since new methods and medications are constantly developed to further reduce the recurrence of the pterygium after excision, different methods of pterygium surgery and recent adjuvant therapies are discussed in this review article. Articles were searched in databases of PubMed, Embase, Web of Science, Scopus, and Cochrane using the keywords of pterygium, complications, causes, pathophysiology, classification, and treatment. Studies published in English that were conducted from 1953 to 2022 were analyzed and included in this review.

MATERIALS AND METHODS

A comprehensive search in the online databases, including PubMed, MEDLINE, Science Direct, Scopus, Scielo, and Google Scholar, was performed using different keywords, including "pterygium" or "pterygium surgery" combined with "eye" or "ocular" or "ophthalmology." Considering the rapidly growing body of the literature, only peer-reviewed reviews and original research articles were included in this study, and case reports, letters, poster presentations, and editorials were not. Human studies were of priority, but when needed, animal studies were also included. Articles with English full text published since 1st January 2021 was evaluated for their appropriateness. Because of the high number of articles on this issue, we attempted to include the most important and unique articles in this review.

PREVALENCE

The prevalence of pterygium varies widely according to geography, age, and gender in different populations.[7] Although this disease occurs worldwide, its prevalence is higher in the "pterygium belt," which is between 30 degrees north and 30 degrees south of the equator.[3] In countries near the equator, the prevalence of this disease is higher, which is probably due to exposure to a higher level of UV radiation outdoors.[11] It usually occurs in people who live in hot and dry climates and may be a response to chronic dryness, tear film abnormalities, and exposure to sunlight.[12] Numerous studies have mentioned pterygium as one of the most common chronic eye diseases in Asia and other countries located in the pterygium belt.[10] The prevalence

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of pterygium has been reported from 1.2% to about 40% in different parts of the world.[10] The prevalence of pterygium has been reported to be 3% in Australians, 23% in African-Americans, 15% in Tibetans, 18% in Mongolia, 30% in Japan, and 7% in Chinese and Indian Singaporeans.[3] The difference in prevalence could be due to the age difference in the studied populations.[10] On the contrary, the prevalence of this disease is higher in people living in villages, which can be due to differences in employment conditions, lifestyles of urban and rural people, seasonal conditions, poverty, and limited access to health services.[10]

HISTOLOGICAL FEATURES

Understanding the histopathological changes and clinical features of pterygium may lead to a better understanding of its pathogenesis and provide more clues for its management strategies (surgical or nonsurgical) in order to reduce recurrence, severity of inflammation, tissue invasion, and proliferation.[13] The pterygium consists of three separate parts including cap, head, and body/tail.[14] The cap or front edge is a smooth area on the cornea that is mainly composed of fibroblasts that attack and destroy Bowman's membrane. The head is a vascular area located behind the cap and firmly attached to the cornea. The body and tail are mobile areas of bulbar conjunctiva that are easily separated from the underlying tissue. Stocker's line, which is iron deposition in the basal layer of the corneal epithelium in front of the cap, indicates the chronicity of pterygium.[1,14] Squamous metaplasia has also been observed in samples obtained from pterygium.[14] Histopathologically, pterygium is a collection of altered LSCs with centripetal growth, which is associated with metaplastic and hyperplastic epithelium, squamous goblet cells, disruption of Bowman's membrane with abundant active fibroblasts, stromal inflammation, neovascularization, and extracellular matrix metalloproteinases (MMPs) activities.[15–18] Many histopathological features of chronic inflammation are also observed in pterygium. The presence of chronic inflammation in the pterygium is also caused by factors such as the presence of lymphocyte purification consisting of T lymphocytes, plasma cells, and mast cells; the increase of newly formed blood vessels and fibroblasts; the presence of degenerative collagen fibers; and the presence of abnormal elastic fibers.[14] The destructive effect of UV rays leads to the reduction of corneal LSCs, and subsequently causes limbal failure and activates tissue growth factors that cause angiogenesis and cell proliferation. The pterygium consists of fibrovascular tissue and its collagen fibers often show elastosis. Except for the top of the pterygium, the rest of its parts are covered by conjunctival epithelium. Above the pterygium, a wedge-like extension of fibrous tissue is visible microscopically, and the head of the pterygium penetrates the cornea, thus the Bowman's membrane is invaded and fragmented.[19,20]

Although the pathogenesis of pterygium is not fully understood, it is believed that in the development of pterygium, corneal epithelial cells acquire an altered balance between proliferation and apoptosis.[21,22] The cellular origin of fibroblasts is not only remnants of embryonic origin but may arise from tissue-specific epithelial cells.[23] The phenomenon in which epithelial cells change their phenotype to fibroblastic cells following morphogenic pressure from damaged tissue is called Epithelial-Mesenchymal Transition (EMT), and it is a common feature of cancer cells.[8] EMT is a well-known mechanism that plays a role in the dispersion of cells during vertebrate embryogenesis and is also observed in adults during the repair of damaged tissue and also in the early stages of cancer metastasis.[23] EMT plays an important role in the pathogenesis of several eye diseases and is probably involved in cataracts in humans and mice and subretinal fibrosis after retinal detachment. On the contrary, it has been found that limbal epithelial corneal cells (LECs) also undergo EMT following exposure to air in vitro.[21] Also, there is a significant difference in the epithelium

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and stroma of the connective tissue compared to the pterygium in the normal bulbar conjunctiva. Pterygium has similarities with tumors due to cell proliferation, corneal invasion, and recurrence after removal. Epithelial proliferation is also important in pterygium growth and development. This excessive cell proliferation occurs in the fibrovascular layer of the pterygium. Fractalkine (CX3CL1) is a member of chemokines that consists of low molecular weight proteins and has two isoforms, a soluble form (related to the cytoplasm) and a form bound to the cell membrane (CX3CL1 bound to the membrane). In many inflammatory conditions, such as atherosclerosis, rheumatoid arthritis, asthma, osteoarthritis, diabetes and pterygium, fractalkine expression is increased. Fractalkine is involved in the transfer of T cells, natural killer cells, leukocytes, and monocytes from the blood to inflammatory sites in the presence of inflammation. It also plays a role in controlling angiogenesis. Through the interaction of a specific receptor (CX3CR1), fractalkine increases the migration of inflammatory cells and tissue destruction by increasing the secretion of tumor necrosis factor-alpha (TNF-α), MMPs, and interferon-gamma (IFN-γ).[24] Solar basophilic elastoid degeneration has also been observed in the pterygium stroma. The presence of stromal vessels is both a cosmetic and a therapeutic goal in the management of pterygium. These vessels are associated with stromal fibrosis, in which the vessels are usually more prominent than the fibrosis. A mild chronic inflammatory response, either in the stroma or in the epithelium, has been present in most cases of pterygium.[6]

RISK FACTORS

Studies have shown that pterygium is associated with several risk factors, including UV radiation, viral infection, hereditary factors, immune factors, aseptic inflammation, and environmental irritation caused by wind, dust or impact, smoke, and dry eye.[25] In this section, we examine some of the most important factors.

UV RADIATION

Pterygium occurs due to a wide range of factors such as sunlight and UV rays, which is why pterygium is more common in tropical regions.[10] The prevalence of pterygium in these areas is estimated to be 22% and outside of them, this rate is less than 2%, which indicates that UV rays may be related to the pathogenesis of pterygium.[26,27] Ultraviolet-A (UVA) and Ultraviolet-B (UVB) are the primary subtypes of UV rays that reach the surface of the eye.[6] UVA is an important driver of pigmentation and contributes to premature skin aging, immune system suppression, and carcinogenesis. Unlike UVA, UVB is absorbed by the ozone layer and makes up about 1–10% of the total UV radiation that reaches the earth's surface. UVB acts as an erythema stimulant and, like UVA, is responsible for various biological events, including sunburn, immunosuppression, and carcinogenesis.[25,28] Although early studies focused on the role of UVB in DNA damage and altered intracellular signaling in ocular surface diseases, epidemiological studies have shown that both UVB and UVA play a role in the development of pterygium.[6] One of the crucial components of pterygium is abnormal synthesis and secondary degeneration of elastic fibers. This response has similarities with skin changes caused by the sun. It is believed that the changes caused by Ultraviolet radiation (UVR) in the corneal epithelial stem cells are the driving force for the subsequent destruction of Bowman's membrane and elastosis.[29] The transformation of LSCs is recognized as the first biological event in pterygium formation.[25] On the other hand, UV radiation can damage LSCs, change the function of stromal fibroblasts, or induce inflammatory responses.[6] It reaches the LSCs in the basal layer of the limbus through a transit pathway and can render them ineffective or degenerate. As a result of chronic UV light radiation, initially, focal LSCs are gradually changed by this radiation. Then, progressive corneal "conjunctivitis" occurs due to focal limbal barrier dysfunction.[25] Light entering

tangentially at the temporal limbus travels across the anterior chamber of the eye and is focused on the contralateral cornea near the nasal limbus.[29] Theses rays damage the LSCs and fibroblasts residing in the nasal limbus, and these changed LSCs (pterygium cells) migrate centrally toward the cornea to form a migratory limbus, and a certain number of these cells infiltrate the epithelium surrounding the limbal and local conjunctiva.[25] In addition to interfering with the onset of pterygium, UV radiation plays a role in the development of pterygium through the positive regulation of numerous proinflammatory cytokines, growth factors, and MMPs. These factors are involved in inflammation, fibrosis, angiogenesis, and ECM regeneration, which are the characteristics of pterygium.[25] Exposure of cells to UVR induces the activation of epidermal growth factor receptors and subsequent signaling through mitogen-activated protein kinase pathways, which are partially responsible for the expression of proinflammatory cytokines and MMPs in pterygium cells. Expression of MMP-2 and MMP-9 by pterygium fibroblasts is significantly increased after pterygium progression, suggesting their role in disease progression.[29] In addition, UVR induces mutations in p53 tumor suppressor genes. These genes are involved in DNA repair or apoptosis of cells that have a lot of DNA damage. Therefore, if the p53 genes are mutated, they can no longer contribute to the DNA repair process.[29] It has been found that UV-induced p53 gene mutations may also be involved in the development of pterygium cells. Therefore, p53 mutations occur in primary basal LSCs under the influence of chronic focal UV radiation. Due to the lack of p53-dependent programmed cell death, mutations in other genes are gradually acquired by altered LSCs, which eventually transform into pterygium cells.[25] On the other hand, exposure to UV rays is also responsible for the abnormal behavior of pterygium fibroblasts. It has been found that these fibroblasts have a higher proliferative capacity compared to normal conjunctival stromal cells.[6] UV radiation induces multiple DNA changes in pterygium fibroblasts and may therefore be responsible for their abnormal biological behavior.[25] UV-altered LSCs may activate underlying fibroblasts through transforming growth factor-β (TGF-β) and a fibroblast growth factor-dependent mechanism (b-FGF), or the injury of conjunctival epithelial cells may result in changes in the metabolism of stromal fibroblasts, which is revealed by changing the expression of elastin and collagen fibers.[6]

INHERITANCE

Pterygium has previously been considered a degenerative disease. However, this hypothesis has been challenged in recent years by the detection of critical genetic alterations in pterygium, including loss of DNA heterozygosity, microsatellites, or overexpression of mutant versions of poorly functioning p53, which can promote tumor growth.[30] The role of family history can indicate the association of inheritance with the incidence of pterygium.[5] The familial occurrence of pterygium was first reported in 1893 by Gutierrez-Ponce, who identified five affected men in three generations of the same family.[6] Therefore, it seems that there is a hereditary potential for pterygium. Some pedigrees have shown clear transmission over several generations, indicating a probable autosomal dominant mode of inheritance.[31] However, the exact mode of inheritance of pterygium and its genetic basis are not fully understood. Identifying the genetic basis of familial pterygium facilitates knowledge about the pathological mechanisms of pterygium development.[25] There are various reports of familial occurrence of pterygium.[32,33] It is reported that genetic factors probably lead to abnormalities in the control of proliferation of fibrovascular vessels, and UV light also causes the growth of pterygium by inducing growth factors that stimulate fibrovascular proliferation in susceptible individuals.[32] Reproduction between cousins increases the risk of hereditary diseases in a large family. The ratio between pterygium-affected and nonafflicted

individuals in the combined family of pterygium probands is 9:7, which indicates double inheritance (the simplest form of multifactorial inheritance).[34] Several genes and familial pathways have been proposed for pterygium inheritance, and one of the proposed genes is MMP-1. It is believed that a certain polymorphism of the MMP-1 promoter can predispose the carriers to develop pterygium through the loss of heterozygosity process.[6] In a certain number of families, there may be a dominant mode of pterygium inheritance. However, this assumption does not mean that every pterygium occurs as a result of hereditary factors. Pterygium can also develop as an acquired pathological condition that is provoked by external factors. It seems that the hereditary potential of pterygium is revealed only if exogenous conditions exist and contribute to its growth.[26]

VIRAL INFECTION

Some reports show the presence of the herpes simplex virus and human papillomavirus (HPV) in pterygium samples.[35,36] Viruses encode proteins that inactivate p53, leading to chromosomal instability and increasing the likelihood of cell progression to malignancy. HPV is often found in the pterygium with different rates of prevalence. Although its involvement as a cofactor in the pathogenesis of pterygium has been suggested, there are debates in this field. If HPV is indeed involved in the pathogenesis or recurrence of pterygium, antiviral drugs or vaccination may be new options in the treatment of pterygium.[37] HPV types 16 and 18, which are considered high-risk strains for causing cancer, are the most common genotypes reported to be associated with pterygium.[6] These strains encode E6 and E7 proteins and interfere with p53 function.[30] A multistage pathogenetic process, involving genetic inheritance, UV radiation, and oncogenic viral infection has been proposed for the pathogenesis of pterygium. Based on this hypothesis, inherited genetic changes or exposure to environmental factors such as UVR can predispose individuals to this benign neoplastic disease. Oncogenic viruses or additional UVR exposure that adds further damage to a susceptible genetic material may trigger the development or recurrence of pterygium[30].

TREATMENT OF PTERYGIUM

The treatment of pterygium is still a controversial issue. In the past, different materials, such as romania, akebia, licorice, ginseng, acacia gum, vinegar, sweet wood, aloe extract, and salt, have been used to remove pterygium.[38] Another safe and effective treatment in the past was to use a material such as thread or horse hair as a Gigli saw to remove the pterygium. Later, agents, such as lead-acid, mercury lanolin, radiotherapy, thiotepa, 5-fluorouracil, and, recently, mitomycin C, have been used for its treatment. The Food and Drug Administration (FDA)[2] also considers the administration of mitomycin C in pterygium surgery. The Greeks believed that when the pterygium is small, it should be treated with purgatives, but when it is advanced or hardened, surgery is needed.[38] Nonsurgical treatment of pterygium includes the use of topical lubricating solutions, occasional use of vasoconstrictors or mild anti-inflammatory agents for flare-ups, and protection from UV rays with sunglasses.[2] Nonsurgical treatments may provide relief, foreign body sensations, and reduction of inflammation.[39] On the other hand, pterygium surgery is one of the most common eye surgeries performed. However, the reality is that the procedures differ widely. Several techniques have been proposed with significant variations among them in terms of recurrence rate, required surgical time, and patient comfort. This review shows that the current preference of ophthalmologists is to completely remove the pterygium, including its base, along with removing the mid-posterior Tenon's capsule.[40]

PTERYGIUM SURGERY AND RECURRENCE

Surgery is the main treatment for pterygium disease.[3] The first documentation of surgical removal

dates back to about 500–1000 BC (by Susruta), which is similar to today's bare sclera technique.[41] By the 1930s, several surgical techniques were proposed, but none had significant success or efficacy. These techniques included resection, incision, cauterization, grafting, surgical division, inversion, radiation, coagulation, rotation, and chemotherapy.[42] The incision method with simple conjunctival closure was the most common. The pterygium was shaved from the cornea, the damaged conjunctiva was removed from the limbus to the caruncle, and the defect was closed with sutures. By the mid-1900s, the bare sclera technique had evolved. In this method, the head of the pterygium, along with some abnormal bulbar conjunctiva adjacent to the nose and Tenon's tissue that is located under the abnormal bulbar conjunctiva, was cut entirely.[42] Depending on the preference of the patient and the surgeon and the complexity of the case, pterygium surgery can be performed in an operating room using local anesthesia.[2] An ideal surgical procedure for pterygium should be a simple technique with the aim of optimizing aesthetics as much as possible and minimizing adverse consequences.[43] There is still no consensus on the ideal way to remove the pterygium with the lowest rate of recurrence.[3] When the pterygium is removed, astigmatism and topographical irregularity are often reversed and visual acuity improves. While surgical removal can often effectively reduce or eliminate symptoms, there are complications in achieving safe, aesthetically pleasing, and permanent removal of the pterygium. The possibility of recurrence of pterygium after surgical removal is frustrating for both patients and surgeons. In this regard, many studies have evaluated the risk factors of recurrence.[44] Recurrence of pterygium is defined as the primary complication of surgery, with the regrowth of fibrovascular tissue throughout the limbus and on the cornea.[3] This usually excludes the continuation of deeper corneal vessels and corneal scarring that may remain even after adequate pterygium resection. Conjunctivochalasis and the formation of parallel rings of vessels, pointing almost like an arrowhead toward the limbus, usually indicate conjunctival recurrence.[45] Fibroblast proliferation and invasion adequately explain the clinical appearance and behavior of pterygium with histological support.[34] Most recurrences occur in the first 6 months after surgery and are attributed to the positive regulation of the inflammatory process.[46] Surgical trauma and postoperative inflammation cause the activation of subconjunctival fibroblasts, the proliferation of fibroblast and vascular cells, and the deposition of extracellular matrix proteins, which in turn contributes to the recurrence of pterygium.[47] The reported recurrence rate ranges from 2% for removal with conjunctival autograft technique to 89% for bare sclera technique. Differences in study methodology, patient characteristics, nature of pterygium, geographic region, definition of recurrence, length of follow-up, and loss to follow-up are some of the factors responsible for the widely varying rates of recurrence.[48] Also, recurrence is affected by various factors, which include geographic location, race, age, and pterygium morphology.[42,48] Also, pre-existing lacrimal caruncle deformity, ocular motility restriction, concurrent inflammation of the ocular surface, fibrogenic structure, and family history are among the patient characteristics associated with recurrence.[49] Pterygium recurrence cannot be successfully predicted based on histological or immunohistological parameters alone, and several biological characteristics are associated with recurrence; thus, related biomarkers should be further evaluated as predictors of recurrence.[42] Recurrence after pterygium surgery can occur in the cornea or conjunctiva. Corneal relapses, such as primary pterygium, manifest as fibrovascular tissue growth across the limbus and on the cornea, and conjunctival relapses manifest as conjunctival retraction.[50] Kamiya et al. also suggested that a significant myopic shift can occur postoperatively, postulating corneal thickening after pterygium removal as the cause and the degree of myopic shift is related to pterygium size.[51] Gulani and Dastur reported that 63% of the studied patients achieved a distance-corrected

visual acuity of 6.12 postoperatively, but both astigmatism (ATR and with-the-rule) was greater than 1 diopter (D) in 6 months.[52] Kamiya et al. reported target correction in only 48% of patient eyes examined at G0.5 D (82% at G1.0 D).[51,52] Several surgical techniques have been described since the early 1960s, including the Bare Sclera technique, Rotational Conjunctival Flap, Limbal Conjunctival Autograft (LCAG), Amniotic Membrane (AM) Graft, and Conjunctival Autograft.[2,44,53]

BARE SCLERA TECHNIQUE

Complete removal of the pterygium from the cornea and sclera and subsequent exposure of the corneal scleral surface is a classic surgical procedure. This method, which is also known as the bare sclera technique, was first fully described by D'Ombrain in 1948.[54] This technique, which is the first technique used to remove the pterygium, is characterized by a simple incision, and allows the scleral bed to re-epithelialize.[49] In general, this technique involves removing a part of the bulbar conjunctiva through the nose, which causes this defect to heal from the surrounding conjunctiva.[38] In the bare sclera technique, the pterygium is removed from the cornea, conjunctiva, and underlying Tenon's tissue.[2] Sometimes, the conjunctiva is actually sutured to the sclera, leaving a defect, and sometimes the conjunctiva is left free to adhere to the underlying sclera.[38] For a long time, this treatment method was the method of choice for the treatment of pterygium, but the high frequency of its recurrence led to the search for adjuvant treatment options.[54] These adjuvant therapies included intraoperative mitomycin, postoperative mitomycin, beta radiation, 5-FU, anti-VEGF agents, and cyclosporine.[6,38] The advantages of this technique are that it is by far the fastest removal method with the least surgical intervention, and theoretically, it seems to be the easiest and cleanest removal method. However, this method is the least satisfactory for treatment due to the recurrence rate, which may vary up to 80%.[38]

CONJUNCTIVAL AUTOGRAFT TECHNIQUE

Kenyon et al. first described conjunctival autograft as a treatment for pterygium in 1985.[55,56] They reported a recurrence rate of 5.3% with rare and relatively minor complications.[47] Since then, this technique has gradually become a popular treatment for pterygium.[54] Conjunctival transplantation is based on the theory of differentiation of conjunctival epithelium into corneal epithelium.[57] This technique involves covering the scleral bed with a free graft taken from the adjacent conjunctiva after removing the pterygium.[6] The conjunctival autograft technique enables the reconstruction of the natural limbus structure.[58] The graft can be fixed to the adjacent tissue with sutures or adhesive products.[6] Compared to bare sclera alone, this method is associated with a lower recurrence rate and has greater long-term effectiveness. Even if the recurrence rate after conjunctival autograft varies in different clinical studies, this method is often considered the most effective method for the treatment of pterygium.[49] Although conjunctival autograft is effective in preventing pterygium recurrence, due to fixation, this technique requires technical expertise and longer surgical time, especially when sutures are used. In fact, due to the need to stabilize the graft, the surgical time required can be longer than that required for simple removal of the bare sclera. Also, the cost of the operation and the discomfort of the patients are among the disadvantages of this technique.[47,49,59] However, despite the need for more time and expertise, this method is associated with a lower recurrence rate compared to the bare sclera technique alone.[6] Tenon's tissue associated with the graft may act as a new reservoir for further proliferation of fibroblasts and inhibition of pterygium recurrence.[6] Also, complications caused by conjunctival autograft are rare and do not threaten vision.[55] The main side effects of this method are discomfort and burning of the eye after the operation, granuloma formation, and rarely displacement or rejection of

the transplant.[6] However, this method avoids the unacceptable serious side effects of a single dose of mitomycin C, such as melting of the sclera and the destruction of corneal endothelial cells, and provides a lower recurrence rate and a better aesthetic result than AM transplantation.[60] This technique can be fixed on the level of the scleral bed by different methods. Fibrin glue is an alternative synthetic glue (made from donor plasma) that is used for this purpose. Although fixation with fibrin glue requires a shorter operation time, it has a possible risk of infection, hypersensitivity reactions, potential risk of graft tissue loss, and higher costs.[49] In the study conducted by Wanzeler, the results showed that removal of pterygium using conjunctival autograft and fibrin glue improves symptoms with a high satisfaction rate.[61] Covering the bare sclera using autologous conjunctival tissue can be done with primary direct closure, sliding conjunctival flap, or free conjunctival autograft. The free graft is usually removed from the upper bulbar conjunctiva and sutured, or after cutting the pterygium, it is attached to the bare scleral defect. It seems that sliding and free grafts are equally effective, but direct conjunctival closure alone is not as effective as sliding or free grafts.[54]

ROTATIONAL CONJUNCTIVAL FLAP TECHNIQUE

Recently, rotational flaps have been proposed as an alternative to conjunctival autograft in pterygium surgery. They are also used to treat tube erosion with glaucoma drainage devices.[62] In the conjunctival flap technique, instead of completely removing the conjunctiva at the donor site, a part of the conjunctiva remains attached and the surgeon rotates or slides the flap in its position.[44] In this technique, a rectangular conjunctival flap, related to the bare scleral area, is removed from the upper conjunctiva and then rotated through the nose around a limbal anchor point and sutured to the bare scleral area using polyglactin sutures.[63] The conjunctival flap technique has less twisting effects on the tissues and has better aesthetic results compared to the conjunctival autograft in the early and late postoperative periods. This method can be used as an acceptable method for pterygium surgery, especially in patients with insufficient conjunctiva.[49] The rotational conjunctival flap has been performed since the 1940s with varying recurrence rates.[55,64] Reported recurrence rates range from less than 1% to more than 5% for this technique. Also, this technique has minimal complications; although complications such as flap retraction and cyst formation have been reported.[55] The key feature of this technique is that by extensive resection of Tenon's capsule beyond the border of the conjunctival resection (up to 2 mm at the nasal margin), the source of fibrovascular tissue for future recurrence can be reduced. Also, the partial preservation of the vascular network in the limbal anchoring area may play a role in increasing the survival of the flap and reducing its contraction.[63] In general, this technique is a more challenging surgical procedure than the conjunctival autograft, but once mastered, it requires less surgical time compared to the conjunctival autograft. The reason for this is the difficulty of separating the fibrovascular tissue from a small graft, the smaller size of the graft in relation to the bare sclera, and the need for more sutures to hold the graft in the rotational method.[49] Although there is a consensus that flap is better than grafting for reconstructive surgery,[65] more clinical trials are needed to confirm the superiority of flap methods over conjunctival autograft treatment.[44] In a study conducted by Hassanen et al., the results showed that after a long period of follow-up for autograft and conjunctival flap surgery, there was no statistically significant difference in terms of the recurrence rate, but the flap technique was associated with less postoperative edema and was a faster and easier technique.[66] A study by BİLGİN and ŞİMŞEK also showed that autograft and conjunctival flap have advantages and disadvantages and both are effective in preventing recurrence.[67] Also, a study by Abul Naga et al. on the two

techniques of free conjunctival autograft and rotational conjunctival flap showed comparable results in terms of reducing the recurrence rate. These researchers stated that these two methods are safe and effective methods for pterygium surgery and have few complications.[68] The flap technique can be safely performed when conjunctival characteristics do not allow conjunctival autograft, with similar recurrence rates and significantly shorter operative time. In addition, conjunctival autograft may require peribulbar anesthesia and traction sutures, while they are almost unnecessary for the flap technique. Also, there is no risk of loss and inversion of the graft in the flap technique, and the structure of the vessels is preserved with a better healing process and a reduction in the risk of graft necrosis. However, the flap cannot be considered in the case of large pterygium where a wider graft is needed.[49]

LIMBAL CONJUNCTIVAL AUTOGRAFT TECHNIQUE

Another method related to the conjunctival autograft is the method of LCAG, in which the limbal tissue is placed in the source of the transplant and then transferred to the desired site.[44] This treatment technique was presented by Kenyon et al.[69] The limbal area of the edge of the cornea is approximately 0.5 mm wide, which is in front of the sclera. In order to understand ocular surface disorders, Noel Rice emphasized the importance of LSCs, which are vital for normal corneal epithelial regeneration. LSCs have been found to play an important role in the pathogenesis of pterygium.[70] In this technique, the grafts prevent the proliferation of the remaining tissue, and the addition of LSCs may cause faster healing and anatomical reconstruction of the area.[44] The added limbal epithelium acts as a barrier between the conjunctiva and the cornea, and since the lack of LSCs plays an important role in the pathogenesis of pterygium, transplantation of these stem cells may restore the barrier and prevent pterygium recurrence.[71] In the long term, the recurrence rate of pterygium after LCAG shows a statistically significant advantage compared to AM grafts and bare sclera.[44] The recurrence rate in this treatment method has been reported to be less than 7%.[69] Also, in this treatment technique, fibrin glue is used to maintain the limbal conjunctival graft, and this creates a statistically significant reduction in recurrence and operation time. Possible complications of this technique include hematoma, Tenon's granuloma, pannus formation, and pseudopterygium.[44] In a meta-analysis performed to compare the rate of pterygium recurrence after LCAG and other techniques, the results showed that the rate of recurrence after LCAG was lower compared to the bare sclera technique, conjunctival autograft, or intraoperative mitomycin C. There was no statistically significant difference in the recurrence rate after LCAG and AM transplantation.[71] Fayez conducted a study to compare the safety and effectiveness of limbal conjunctival transplantation versus conjunctival autograft for the treatment of pterygium and reported that with an average follow-up of 62 (with a range of 36–96) months, 10 patients (10%) of the conjunctival autograft group and 1 patient (1%) of the limbal conjunctival group experienced the recurrence of pterygium. No signs of LSC deficiency were observed during follow-up. Based on their findings, the limbal conjunctival technique is safer and more effective than the conjunctival autograft technique in preventing recurrence after pterygium removal.[60]

AMNIOTIC MEMBRANE GRAFT TECHNIQUE

AM grafts were first described by Davis et al. for use as a surgical material in skin grafts and, since 1995, have been increasingly used for the treatment of a variety of ocular surface conditions including persistent corneal epithelial defects, acute chemical burns, and cicatricial conditions such as Stevens-Johnson syndrome and ocular cicatricial pemphigoid.[72] The AM is the innermost layer of the placenta (consisting of a thick base membrane and

an avascular stromal matrix) that can be used as a graft with anti-inflammatory and anti-fibrotic properties, and it is also able to provide multiple growth factors and differentiation of epithelial cells without the risk of immune reactions.[42,49] Due to these features, the human AM has been considered useful in several ocular surgeries including pterygium and other conjunctival diseases. Typically, it should be placed on the bare sclera, with the basement membrane facing up and the stroma facing down. Fibrin glue may also be used to stabilize the graft of the AM to the underlying sclera.[49] An AM graft is usually used to cover the bare sclera. These grafts may help prevent recurrence through anti-inflammatory properties, promotion of epithelial growth, suppression of TGF-β signaling, and suppression of fibroblasts, as well as direct contact with fibroblasts associated with Tenon's fascia.[44,73] AM grafting is also useful for patients with scarred conjunctival donor sites, cases that need large grafts, or patients that need to preserve the conjunctiva for possible future glaucoma surgery.[44] This technique can be useful during the surgical reconstruction of the cutting the pterygium area through a number of mechanisms. The stromal component and the basal layer covering AM are similar to the structure of the natural human conjunctiva, and they can provide a platform for the growth of the conjunctival epithelial layer and the cornea. The coating property of AM reduces postoperative pain by protecting the scleral nerve endings. Probably, the presence of AM may create an obstacle to the abnormal growth of conjunctival stem cells in the lower limbus and facilitate the proliferation of normal LSCs.[6] It is also potentially a simpler and shorter method than alternative methods because this method eliminates the need to prepare a conjunctival graft with the proper thickness and quality for optimal grafting after removing the Tenon's layer.[74] Both conjunctival autograft and AM techniques can be effective in preventing recurrence.[73] The recurrence rate of pterygium following amniotic membrane graft (AMG) has been reported to be between 14.5 and 27.3%. While grafts have greatly improved the recurrence rate after pterygium surgery, they are not without complications. Reported complications include wound dehiscence, Tenon's granuloma, conjunctival cyst, necrotizing scleritis, and donor-site subconjunctival fibrosis.[72]

OTHER ADJUVANT TECHNIQUES AND TREATMENTS

Despite advances in surgical instruments, microscopes, suture materials, and drugs, as well as techniques developed, studied, and tested in clinical research worldwide, recurrence of pterygium is still considered a serious problem.[41] Since the rate of recurrence of pterygium after surgery is high, several adjuvant treatments have been proposed to reduce the recurrence rate. Among them, mitomycin-C (MMC) and 5-fluorouracil (5-FU) are commonly used. 5-FU was first synthesized by Dushinski et al. in 1957. This compound is a fluorinated pyrimidine antimetabolite that, when exposed to the cornea, inhibits the proliferation of conjunctival fibroblasts and Tenon's capsule, and also inhibits the proliferation of corneal epithelial cells. This preventive action is thought to reduce the rate of recurrence, but the related recurrence rates have been reported to be between 11.4 and 60%.[42] Mitomycin (MMC) is an alkylating agent with cytotoxic effects that inhibits DNA synthesis and is widely used in ophthalmology. MMC leads to the death of cells caused by the inability to repair the genotoxic damage caused by alkylation. It acts against all cells regardless of the cell cycle and even in cells that do not synthesize DNA.[34] Mitomycin C has direct secondary effects on tissues and is associated with persistent epithelial defects and ischemic necrosis of the sclera.[75] Bevacizumab (Avastin) is a human monoclonal antibody to VEGF that is used intravenously and is mainly approved for the treatment of colorectal cancer. Various clinical studies worldwide have used bevacizumab for intravitreal injection and have confirmed its safety and efficacy in macular degeneration and macular edema.[34,38] Alsmman et al. reported

that preoperative combined injection of Avastin and MMC is safe and effective in reducing postoperative recurrence of pterygium. Histological and immunohistological changes were observed in the form of decreased fibrovascular activity and degeneration of extracellular matrix and nerve axons.[34] Teng et al. also reported the effectiveness of Bevacizumab in the treatment of primary pterygium with a short-term reduction of irritation.[76] There are also reports of the effect of local use of IFN-α-2b in the treatment of pterygium.[75,77,78] Interferons (IFNs) are cytokinins that are secreted by cells in response to a variety of stressful factors, including infection and tumors.[77] They are glycoproteins that have anti-proliferative and antiviral effects.[75] While the exact mechanism of action of interferons is unknown, research has shown that interferon alpha-2b (IFN alpha-2b) has a local application for external eye disorders, including viral keratoconjunctivitis and squamous neoplasia of the eye surface, small cancers, squamous cells and the basal cells of the skin, and recurrent pterygium management.[77,79–81] The recombinant form of (IFN-α-2b) has been used with good results in conjunctival intraepithelial neoplasia and conjunctival papilloma.[75] Calcineurin inhibitors, such as cyclosporine A (CsA), are anti-inflammatory agents that suppress T-helper cells selectively, control interleukin synthesis, and inhibit vascular endothelial growth factor.[82] CsA can also suppress the change from fibroblast to myofibroblast via the inhibition of myofibroblast markers induced by TGF-beta2.[83] A meta-analysis comparing recurrence rate after different surgical techniques showed conjunctival autograft and CsA 0.05% eye drop as the most efficient methods.[84] However, the results of studies are controversial in this regard, and some have suggested no significant effect for CsA on recurrence rate.[85,86]

CONCLUSION

Pterygium is one of the eye lesions that, in some cases, can cause damage to an individual's vision. Among the various risk factors, the most important factor for the development and progression of this disorder is exposure to UV rays. In many cases, this disease is treated through surgery and removal of the lesion. One of the important issues related to the surgical methods is the recurrence of pterygium after surgery. Newer treatment and surgical methods, such as conjunctival autograft and AM techniques, have a lower recurrence rate. On the other hand, the use of adjuvant treatments such as mitomycin C, 5-FU, local use of interferons alpha-2b, and Avastin are also effective in reducing the recurrence rate.

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