Med. J. Malaysia Vol. XXXI No. 1 September, 1976

The Pterygium and Mitomycin-C Therapy

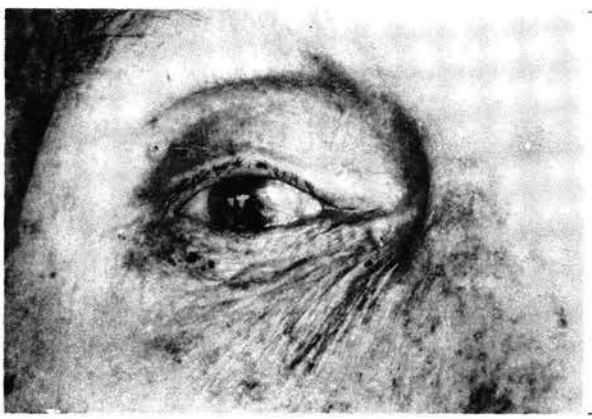
Dr. Leong Kah Choon
M.B., B.S.(Singapore), D.O.(London), A.M.(Malaysia).

and Dr. Chong Yuen Fong
M.B.(Hokkaido).

Eye Department,
General Hospital,
Ipoh.

Introduction

THE PTERYGIUM (see photograph) is essentially a triangular tongue of conjunctiva overgrowing on to the surface of the cornea of the eye. It appears as a fleshy mass, its apex extending on to the cornea with its body drawn out from its base, which merges with the bulbar conjunctiva. When active it is vascular, the vessels running along its length. Though not malignant histologically, it possesses almost malignant characteristics as it spreads inexorably across the cornea which it may cover so extensively as to occlude vision.



Histologically, the pterygium is covered by a conjunctival type of epithelium, the cells being flattened on the surface and more cylindrical in the folds, with many goblet cells. The stroma is like that of the substantia propria of the conjunctiva, with many elastic fibres, some cellular infiltration, and areas of hyaline, amyloid or cystic degeneration. As the pterygium extends across the cornea, Bowman's membrane is destroyed and fibrous granulation tissue spreads across the superficial corneal stroma, lifting the epithelium into folds.

Symptoms are variable. There may be some discomfort, with recurrent redness, and occasional gritty sensation. The pterygium grows in "fits and starts", periods of congestion and turgescence alternating with periods of quiescence and whiteness of the eye. The vision becomes increasingly affected as the pupillary zone of the cornea is invaded; this occurs even before the pterygium itself has reached the area because of the irregular astigmatism produced by the corneal folds.

Its aetiology is still not fully understood. The pterygium is one of the oldest recorded eye conditions, being already studied and described by Susruta many years before Christ (Bidyadhar, 1941). Duke-Elder states that it is a degenerative and hyperplasic process. Ultraviolet rays in solar radiation appear to be the most significant aetiological factor (Duke-Elder, 1965). Hence it is more common in tropical than temperate climes. While it may be regarded as a minor ophthalmic disorder, it is a major ophthalmic problem, because of its growth across the cornea threatening vision and its tendency to recurrence after surgery. Trevor-Roper has aptly remarked of the pterygium: "At different times, this modest growth has been incised, removed, split, transplanted, cauterized, grafted, inverted, galvanized, heated, dissected, rotated, coagulated,

repositioned and irradiated. Pterygia continue to grow, and man's ingenuity is far from exhausted." (Trevor-Roper, 1974).

In the conservative treatment of the pterygium, topical corticosteroids have been used, with equivocal results. If the condition is quiescent, no treatment is necessary. If active, surgery is indicated. At present, surgical treatment is the only satisfactory approach to the problem, supplemented in case of recurrence by:-

(1) Radiational treatment, or

(2) Instillation of anti-mitotics.

No surgical technique is universally accepted as being perfect, as shown by a recurrence rate often as high as 30 to 50%. The recurrences are distressing, for the pterygium grows again at a rapid pace and many soon become as large or larger than the original growth. Although surgical treatment of the pterygium is a simple procedure, the high recurrence rate has stimulated the introduction of a multitude of operative techniques, such as: excision leaving an area of bare sclera, excision with plastic repair, transplantation into the lower fornix, cauterization, mucous membrane graft, lamellar corneal graft, and irradiation; while many ophthalmologists have been content to toe the line of "masterly inactivity" if the pterygium is early and not encroaching too far across the cornea to obstruct vision.

In recent times, anti-neoplastic drugs in the form of eye-drops had been advocated in the treatment of pterygium after surgery; these drugs had been claimed to reduce the recurrence rate of the pterygium after operation. In 1960, Langham reported on the use of topical triethylene thiophosphoramide (thio-tepa) to prevent alloxan-induced vascularization of rabbit cornea. In 1962, Meacham was the first to report on the use of a thio-tepa solution on the eye to prevent recurrence of pterygium after surgery. He used the drug on 19 cases of pterygium for eight weeks after surgery and found no recurrence, the follow-up in some being one year. In Japan, Mori (1962) used it on 31 cases after pterygium surgery for two weeks and had a 16% recurrence rate. In the United States of America, Liddy and Morgan (1966) used thio-tepa on 26 eyes after pterygium surgery for six weeks and found a 4% recurrence. Kleis and Pico (1973) of Puerto Rico used the drug on 48 cases of pterygium for six weeks post-operatively, and found a recurrence rate of 8%. On the local scene, one of us (Leong, 1969) used topical thio-tepa on 9 out of 18 cases of pterygium for a period of eight weeks post-operatively, and noted a recurrence rate of 11% compared to 44% in those not on thio-tepa. In Japan, Kunitomo and Mori (1963) announced the use of the anti-neoplastic antibiotic Mitomycin-C (MMC) as an eyedrop solution for the prevention of pterygium after surgery. They used it for two weeks post-operatively, and found no recurrence in the 17 cases operated on. They had also used topical thio-tepa on 31 cases and noted a 16% recurrence rate. Hence, they concluded that topical MMC was superior to thio-tepa in the prevention of pterygium recurrence after surgery.

The purpose of this paper is to report on a clinical trial of the drug Mitomycin-C used topically on the eye to test its degree of efficacy in the prevention of pterygium recurrence after surgery. Previously, one of us (Leong, 1969) had reported on the successful use of topical thio-tepa as a simple therapeutic procedure for both primary and recurrent pterygia, and had advocated its use as especially suitable for places where the pterygium was common but where elaborate and expensive facilities were not readily available. Mitomycin-C is a much cheaper preparation than thio-tepa and its comparative effectiveness would recommend its use in developing countries like Malaysia where the pterygium is a common occurrence.

Materials and Methods

Mitomycin-C is an anti-neoplastic antibiotic isolated from *streptomyces caespitosus*. Its crystal is a deep bluish-violet colour. It has a molecular weight of 1,120. Its molecular form is C54H69-N13019. It acts by inhibiting the synthesis of deoxyribonucleic acid (DNA), although the exact point of attachment to D.N.A. remains unknown. Used systemically, the drug is potentially toxic to the haemopoietic tissues. Used topically on the eye in its therapeutic dosage, it is not appreciably absorbed systematically, and is not apparently harmful to the eye. 2 mg. of Mitomycin-C is dissolved in 5 ml. of 5% glucose solution, forming a solution of 1:2,500 dilution, which had been found to be relatively stable when kept in the refrigerator for ten days (Kunitomo and Mori, 1963).

In this clinical trial, altogether 32 eyes with pterygium were operated on over a period from mid-June, 1974, to mid-October, 1974. The eyes belonged to 30 patients, 18 of whom were females and 12 males. Among these, there were 20 Chinese, 6 Malays and 4 Indians. All the pterygia were primary ones, except for 3 which were recurrent pterygia which had been operated upon previously. Most of the pterygia were advanced cases encroaching across much of the cornea.

All the patients were admitted into hospital one day before operation, when total white cell counts and differential white cell counts were done, and a 5-day course of prophylactic oral tetracycline was started. The method of pterygium operation was the same in all cases, and was performed by one of us (C.Y.F.) for uniformity. This was a combination of the bare sclera and transplantation techniques. Under local anaesthesia, the head of the pterygium was carefully dissected off from the cornea with a Bard-Parker blade. Two straight incisions were made in the conjunctiva radially upwards and downwards to the periphery. The subconjunctival tissues in the isolated body of the pterygium were excised up to the episclera, taking care not to involve the horizontal rectus muscle as well. The pterygial head was then transfixed by a needle and suture which transplanted it into the lower fornix, underlying the fornix conjunctiva to which it was tied. The suture was removed after four days. The sclera was left bare to be epithelialized later on. Atropine drops and antibiotic-corticosteroid ointment, with pad and bandage, were applied to the operated eye for 24 hours.

At the first dressing the next day, the pad and bandage were removed. Two drops of the special Mitomycin-C eyedrops were applied three-hourly to the operated eye, as well as antibiotic-corticosteroid eyedrops four times daily, for two weeks. Weekly total white cell counts and differential white cell counts were done for two successive weeks. The patients were discharged from hospital at the end of this two weeks' course of treatment, to continue antibiotic-corticosteroid eyedrops till the eye was white. They were instructed to return for regular outpatient checks for any signs of recurrence of the pterygium. Recurrence of the pterygium was judged on the appearance of revascularization of cornea previously covered by the pterygium.

Results

One of the operated eyes developed an allergic reaction with congestion, chemosis and swelling of eyelids three days after starting Mitomycin-C and antibiotic-corticosteroid eyedrops, and medication was stopped. With the remaining 31 eyes, no untoward reaction was noted. The operated eyes were not unduly congested, and patient tolerance was good.

Thus, excluding one allergic case, 31 eyes with pterygium were operated on between June and October, 1974; these were given a follow-up of more than one year to date to detect any recurrence. These eyes had post-operative Mitomycin-C eyedrops instilled for two weeks. Of the 31 eyes, 5 eyes showed recurrence of pterygium despite topical Mitomycin-C therapy. Of these 5 cases, 3 recurred among the 28 primary pterygium cases, and 2 recurred in the 3 recurrent pterygium cases which had re-operation in this series. This would indicate that Mitomycin-C is more effective in preventing recurrence in primary pterygium than in already recurrent pterygium. All the recurrences occurred within six months of surgery. Hence, our follow-up period of more than one year would justify a sufficient lapse of time to allow any recurrence to develop. The recurrent cases occurred in 2 Chinese females, 1 Chinese male, 1 Malay female and 1 Indian male. With 5 recurrences out of 31 cases, this works out to a recurrence rate of 16.13%.

Discussion

In the treatment of pterygium, the high recurrence rate after operation has always posed a serious problem. Not only does the pterygium recur after surgery, but the recurrent pterygium grows again at a more rapid and angrier pace, soon becoming as large or even larger than the original growth. In places where the pterygium is common, conservative treatment is generally preferred to radical excision: corticosteroid eye preparations being employed to relieve the congestion of an actively growing pterygium in the hope of slowing down its growth towards the centre of the cornea. This timidity in taking to surgery is rather paradoxical; the operation on a pterygium is a short, minor surgical procedure performed under local anaesthesia requiring only simple instruments and the patient can even be treated as an outpatient. Ultimately, conservative treatment has still to give way to surgery as soon as the pterygium has advanced far enough to threaten to involve the axial zone of the cornea and thereby obstruct vision. Out of a multitude of therapeutic devices, at present the only satisfactory procedures which ensure minimal recurrence rates are lamellae keratoplasty, surgery followed by irradiation, and surgery followed by the use of topical anti-mitotics. The latter procedure would appear to be the treatment of choice where elaborate and sophisticated equipment is not available.

Duke-Elder has stated that the recurrence rate of pterygium after surgery can often be as high as 30 to 50%. Any therapeutic procedure that could appreciably reduce this high recurrence rate would be a valuable adjunct to the surgery of pterygium. Topical thio-tepa therapy has been claimed by enthusiastic proponents to be able to reduce this high rate to one varying from zero to 16%. Now there is an equivalent therapeutic agent in the form of Mitomycin-C, which has been claimed by Kunitomo and Mori to reduce the recurrence rate to zero. However, in our clinical trial, a recurrence rate of

16% has been demonstrated. This would place topical Mitomycin-C therapy in the prevention of pterygium recurrence after surgery on a sound enough basis to recommend its use as a cheap adjunct to pterygium surgery, especially suitable for countries where the pterygium is common but where elaborate and expensive facilities are not available, as in many developing countries. Hence, topical Mitomycin-C therapy is advocated as a simple, cheap and effective means of preventing recurrence of pterygium after surgery.

Summary

The pterygium is essentially a triangular tongue of conjunctiva growing across the cornea. Though the pterygium may be regarded as a minor ophthalmic disorder, it is a major ophthalmic problem, because its growth across the cornea threatens vision, and it has a tendency to recur after surgery. A multitude of therapeutic measures has been proposed for this modest growth, with varying degrees of success. A simple but effective therapeutic procedure is a 2-weeks' course of an anti-neoplastic antibiotic drug, Mitomycin-C, in the form of eyedrops applied three-hourly to the operated eye, to reduce the high recurrence rate of pterygium after surgery. In a clinical trial of this drug involving 31 eyes, there were only 5 recurrences of the pterygium after surgery, giving a recurrence rate of 16%, which is comparable to the results of clinical trials of another antimitotic drug, Thio-tepa, used for the same purpose. Since Mitomycin-C is a much cheaper preparation, it would recommend itself as the treatment of choice in countries where the pterygium is common but where elaborate and sophisticated facilities are not readily available.

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