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Scleral Changes Induced by Instillation of Mitomycin C

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To prevent recurrence of pterygium after surgical repair, topical application of mitomycin C has been prescribed in Japan since 1962. Various reports of severe scleral changes following this treatment began to appear in 1965. We now report 9 such cases, 3 men and 6 women within the age range from 48 to 73 years.

In these patients, the pterygium was excised using the bare scleral technique and mitomycin C was instilled postoperatively. The duration of topical application and the number of instillations varied. The period from operation to onset of scleral lesion was between one month and 10 years. Although the mechnisms of toxicity remain to be determined, the ophthalmologist should be aware that when mitomycin C is being instilled, scleral lesion may appear even after a long postoperative course.

INTRODUCTION

The major problem in the treatment of pterygium is to prevent recurrences after surgical excision. Even in cases of total excision of diseased tissues, there are recurrences, for example, when the corneal epithelium fails to cover the bare limbus, before the conjunctival tissues with granulation and neovascularization reach the limbal area. Consequently, the radiation therapy prescribed shortly after the surgery is often most effective. As cataracts sometimes develop or the sclera is damages after radiation therapy, the anti-neoplastic drugs, thiotepa and mitomycin C are clinically prescribed.

In 1962, KUNITOMO and MORI[14] reported that the pterygium could be treated with topical application of mitomycin C solution, however, reports of severe scleral damages induces by this treatment began to appear since 1965[7)9)10)19)21)22)24)25)27)28)29)31)–35)].

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As there is little documentation of such complications in the English literature, the findings of toxicity in 9 patients are described herein.

PATIENTS AND METHODS

The nine patients with scleral lesion after previous pterygium treatment were all referred to the Ophthalmology Clinic of Nagasaki University School of Medicine. These 3 men and 6 women, within the age range from 48 to 73 years had undergone pterygium removal by the bare scleral technique and mitomycin C was instilled postoperatively. The duration and number of instillations varied with each patient. The period from operation to onset of scleral lesion was between one month and 10 years.

Mitomycin C is an anti-tumor antibiotic complex of blue violet crystals produced by a strain of streptomyces caespitosis from clay in Tokyo, by HATA and associates[8)26)] in 1956.

Originally 0.4 mg/ml mitomycin C solution dissolved in 5 % glucose was prepared[14)], but 1 mg/ml solution (Case 7), 0.8 mg/ml solution (Case 6) and 0.2 mg/ml solution (Case 9) were also applied.

RESULTS

As shown in Table 1, the scleral lesion due to mitomycin C instillation included 2 cases of scleral thinning (Case 3, 5. Fig. 1), 2 cases of scleral ulcer (Case 7, 9. Fig. 2) and 5 cases of scleral calcification (Case 1, 2, 4, 6, 8. Fig. 3). In all these cases, medication was started immediately or within a couple of days after surgery. The number of instillations varied, that is, every 2 hours (Case 2), once a day (Case 5) 3 times a day (Case 3, 6, 8, 9) and 4 times a day (Case 1, 4, 7). The period from operation to onset of scleral lesion was between one month and 10 years.

Cases of early onset (Case 5, 7, 9.) were observed within one month, and in each, the scleral ulcer was of moderate size. Cases 5 and 7 were patients who had previous surgery for pterygium and the Case 9 patient was prescribed mitomycin C instillations for one month. Especially in Case 7, symptoms occurred 2 weeks postoperatively and regressed after 4 months but severe symptoms were observed again after 20 months. Here, scleral homograft and covering of conjunctiva had to be done. The prognosis was good in those with an early onset.

Cases of later onset (Cases 1, 2, 3, 6, 8) occurred after one year or longer. The symptoms were severe and scleral homograft and covering of conjunctiva had to be done. The relationship between the number and duration of instillations and development of scleral lesion could not be clearly defined because the eye lotions had been administrated by the patients themselves.

Calcification of the sclera occurred in 5 out of these 9 patients and a histopathological study[33)] was done on tissues from the Case 2 patient.

Table 1 Scleral Lesion Following Administration of Mitomycin C after Surgery for Pterygium

Case	Age	Sex	Laterality	Operation to Onset (months)	Subjective Complaints	Mitomycin C Solution -Density-	Instillation	Complications	Clinical Management	Prognosis
1 (Ref. 32)	73	F	L	16	headache ocular pain	0.4mg/ml	4/day 2 WK or more	scleral calcification iridocyclitis	resection of calcification	good
2 (Ref. 32)	57	F	R	12	foreign body sensation ocular pain	0.4mg/ml	3/day 11 days	scleral calcification iridocyclitis sec. glaucoma	iridencleisis	enucleation
3 (Ref. 32)	51	M	R L	16	L) red eye ocular pain reduced vision	0.4mg/ml	3/day 11 days	R) thinning of sclera L) Descemetocele. iritis	topical antibiotics	L) perforation
4 (Ref. 34)	65	F	L	3	foreign body sensation red eye	0.4mg/ml	4/day 5 days	iridocyclitis scleral calcification	scleral homograft covering of conjunctiva	cataract
5 (Ref. 34)	* 60	M	R	1	red eye ocular pain	0.4mg/ml	1/day 2 days	iritis syn. post scleral thinning	covering of conjunctiva	good
6 (Ref. 34)	56	F	R	120	red eye ocular pain	0.8mg/ml 0.4mg/ml	3/day 8 days 3/day 4 days	iridocyclitis scleral calcification	scleral homograft covering of conjunctiva	good
7 (Ref. 34)	* 67	F	R	1	photophobia foreign body sensation	1mg/ml	4-5/day 3 days	iritis corneoscleral-ulcer	scleral homograft covering of conjunctiva	good
8 (Ref. 34)	56	F	L	54	headache ocular pain	0.4mg/ml	1/day 3 days	iridocyclitis scleral calcification	covering of conjunctiva scleral homograft	necrotizing scleritis
9 (Ref. 34)	48	M	R	1	epiphora	0.2mg/ml	3/day 1 Mo	scleral ulcer	scleral homograft covering of conjunctiva	good

* : Recurrent pterygium

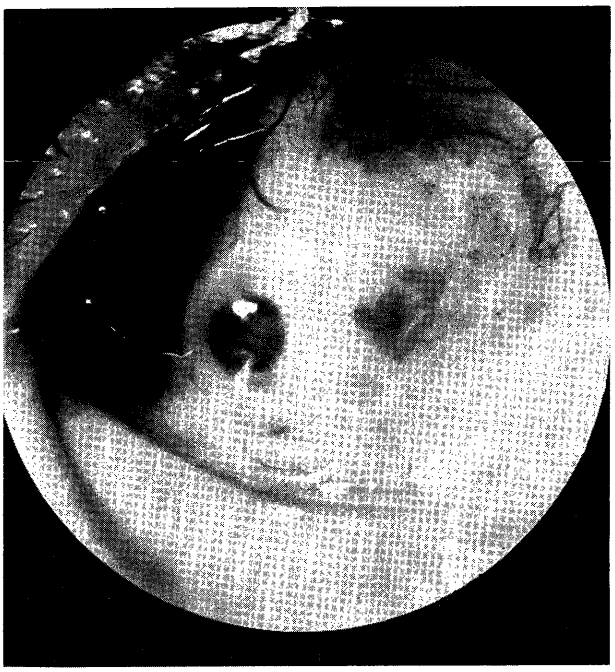

Figure 1. Scleral thinning and perforation. Case 3. (From Yamanouchi and Mishima [32])

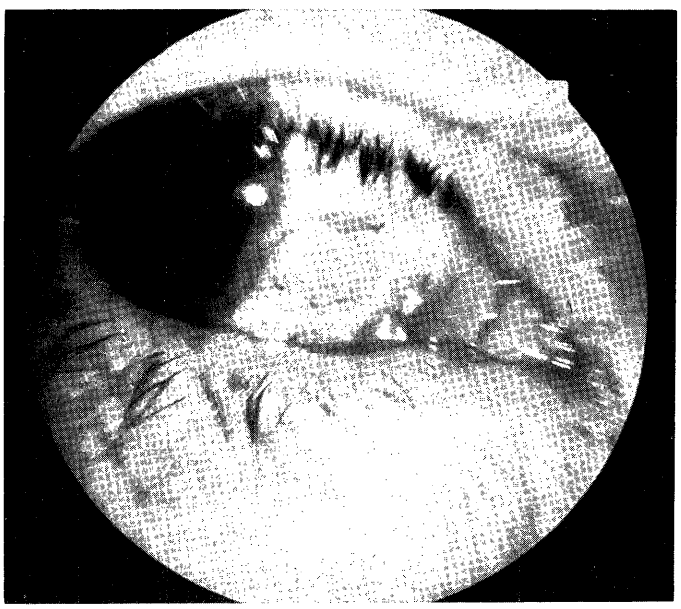

Figure 2. Scleral ulcer. Rose bengale stain. Case 9. (From Yamanouchi et al. [34])

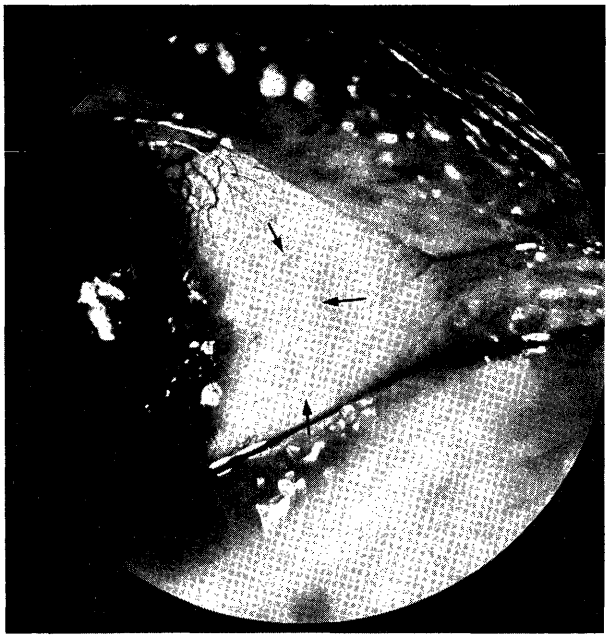

Figure 3. Scleral calcification (arrows). Case 2. (From Yamanouchi [33])

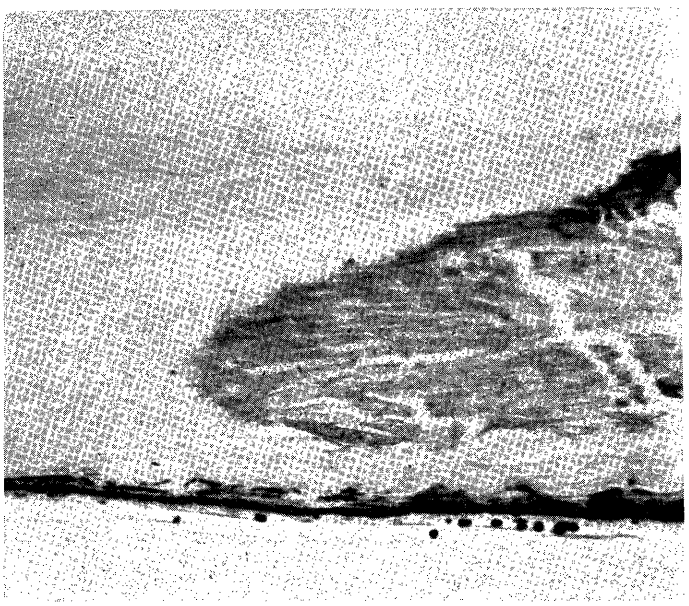

Figure 4. Sharp demarcated calcification of Case 2. H-E stain. (From Yamanouchi [33])

Case 2. The patient was a healthy 57-year-old Japanese woman who underwent surgery for pterygium of the right eye on January 27, 1965, and was treated with mitomycin C instillation 3 times daily for 11 days. On January 27, 1966, she complained of a foreign body sensation and pain in the right eye. Her condition was diagnosed as secondary glaucoma and she was referred to our clinic. On admission, scleral calcification of the medial limbal sclera was evident (Fig. 3). Iridencleisis was performed but ocular tension remained elevated and finally the eyeball had to be enucleated. Microscopic examination showed a sharp demarcated calcification area. There was no evidence of inflammation (Fig. 4).

Therapy: It is difficult to determine the onset because scleral lesion due to mitomycin C progresses insidiously and sometimes appears a long time after the surgery. If the scleral lesion is superficial, instillation therapy of antibiotics and antiinflammatory agents may be effective. If the focus is deep, the full thickness of the sclera should be resected with a portion of the surrounding healthy sclera and the defect restored with supplemental materials. These materials can be preserved human sclera, fascia lata, periosteum, conjunctiva and TENON capsule, buccal mucous membrane, auricular cartilage, and so on. We used preserved human scleral homograft in 6 cases and favorable results were obtained in 5. In Case 8, the scleral necrosis had extended all round the sclera and corneal ulcer developed.

DISCUSSION

To prevent regrowth of the pterygium, radiotherapy (X-ray, radon, radium and strontium 90) have been prescribed[3)4)6)17)23)30)]. The use of anti-neoplastic drugs gradually was favored as radiotherapy sometimes leads to formation of cataracts. Both irradiation and anti-neoplastic drugs are effective against rapidly growing neoplastic tissue, particularly the endothelium of newly formed blood vessels.

With regard to the pathological aspect of recurrence after pterygium excision, the first factor is neovascularization into the cornea from the limbus and the second is early junction formation between the corneal and conjunctival epithelia. This junction forms granulation tissue near the limbus area.

Thiotepa which was used before the development of mitomycin C is a anti-neoplastic alkylating agent of the nitrogen mustard family. It has an active antimitotic effect on rapidly growing cells and few side effects. The conception of the topical application of anti-neoplastic drugs was based on LANGHAM's report[15)] that thiotepa inhibited the corneal vascularization in alloxanized rabbit eyes. Thiotepa has been used in low concentrations such as 1:2000 dilution and has produced clinical effectiveness for the postoperative treatment of pterygium. This solution is applied several times a day for 6 to 9 weeks postoperatively. Usually these are no signs of irritation or recurrence during 1 to 3 years follow-up.

MEACHAM[18)] was the first to report the use of thiotepa in the prevention of re-

current pterygium in 1962 and many cases were reported[1)5)11)13)14)16)18)]. The recurrent rates in these reports are summarized on the Table 2.

KUNITOMO and MORI[14)] was the first to prescribe mitomycin C to inhibit the recurrence after pterygium removal, in 1962. They found mitomycin C to be a non-irritating agent and more effective than thiotepa in inhibiting granulation formation. Thereafter mitomycin C has been widely used in Japan and to date there are no reports of scleral lesion. But lesions due to mitomycin C have been reported[7)9)10)12)19)21)22)24)25)28)29)31)32)-34)36)] by inches.

Pterygium recurs in over 30 % of various types of excisions. With the use of beta irradiation and topical application of anti-neoplastic drugs, the recurrence rates were considerably reduced.

According to MORI *et al.*[20)], the recurrence rate was 13 %, using mitomycin C solution. YAMASHITA and ADACHI[35)] reported that the recurrence rate was 39 %, using mitomycin C, as compared with 43 % in control eyes. However, there are only a few summarized data on mitomycin C treatment after pterygium surgery, as shown on Table 2, and the problem of late complications remained.

In beta irradiation after pterygium surgery, the occurrence of scleral necrosis or scleral deep ulceration, albeit rare, has been reported: CAMERON 1972[3)], CAPPIN 1973[5)], TARR and CONSTABLE 1980[30)], MATSUDA 1981[17)] and NOSHIRO 1981[23)]. As for mitomycin C instillation, KUNITOMO and MORI[14)] reported no incidence of serious eye lesions in their patients. Later MORI[21)] described patients with scleromalacia perforans or necrotizing scleritis due to mitomycin C instillation and he proposed that systemic disease such as rheumatism may be the cause. However, scleral changes have been documented in Japanese literature, as summarized in Table 3: TAKANO 1966[27)], YAMANOUCHI and MISHIMA 1967[32)], TANAKA 1970[29)], OOTSUKI *et al.* 1971[25)], HIBINO and MIZUSAWA 1976[9)], MINODA 1978[19)], ODASHIMA and NIITSU 1978[24)], YAMANOUCHI 1978[33)], YAMANOUCHI *et al.* 1979[34)], KITANO *et al.* 1981[12)], and FUKAMACHI and HIKI-

Table 2 Recurrence Rate due to Administration of Anti-neoplastic Drugs

	No. of eyes	Recurrence rate		
		thiotepa %	mitomycin C %	control %
Cassady	17	0		
Meacham	30	1		
Joselson & Muller	46	2.1		27.2
Liddy & Morgan	26	4		
Asregadoo	102	6.8		
Kleis & Pico	48	8.3		31.3
Kunitomo & Mori	31	16.1		
Mori et al.	89		13	
Nanba & Hisashige	40		7.4	
Yamashita & Adachi	28	35.7		
	23		39	
	23			43

Table 3 Scleral Lesion Due to Mitomycin C Instillation Pterygium Operation Summary of Literature

Author	Age	Sex	Laterality	Operation to Onset (month)	Subjective Complaints	Mitomycin C Solution -Density-	Instillation	Complications	Clinical Management
[27] Takano 1966	*			12		0.4mg/ml	2/day 20 days	scleral ulcer	beta irradiation
[10] Horita 1968	51	M	R	24	ocular pain	0.4mg/ml	4/day 1WK 1/day 1WK	scleral ulcer	covering of conjunctiva
[29] Tanaka 1970	* 60	M	R	12	thinning of sclera	0.4mg/ml	3/day 2 WK	thinning of sclera	scleral homo-graft covering of conjunctiva
[25] Ootsuki et al. 1971	46	F	L		foreign body sensation red eye	0.2mg/ml	4/day 35 days	scleral ulcer	scleral homo-graft covering of conjunctiva
[9] Hibino et al. 1976	53	F	R L	36				R, L, scleral calcification thinning	scleral homo-graft covering of conjunctiva
[28] Takatsuki 1978	52	M		7		0.4mg/ml	4/day 1 WK	scleral ulcer corneal ulcer iritis sec. glaucoma	
[20] Minoda 1978				10			3/day 1 WK	scleral per-foration endophthal-mitis	
[24] Odashima & Niitsu 1978	64	F	R	21	ocular pain	0.4mg/ml	4/day 1 WK	scleral thin-ning calcification iritis	covering of conjunctiva
[12] Kitano et al. 1981	52	F	L	12	ocular pain red eye		1/day 1 WK	scleral ulcer iritis hypopyon	fascia late transplant
[7] Fukamachi & Hikita 1981	53	M	R	2	ocular pain red eyer	0.4mg/ml	3/day 11 day	scleral necroze iritis	
	* 44	M	L	3	reduced vision	0.4mg/ml	3/day 1 WK	scleral perfo-ration uveitis	

* : Recurrent pterygium

TA 1981[7].

According to these reports, the scleral lesions following administration of mitomycin C after surgery for pterygium include scleral ulcer, scleral thinning, scleral calcification, corneal perforation, scleral perforation, iritis, secondary glaucoma and endophthalmitis. The duration from operation to onset of scleral lesion is between 7 months and 3 years. Most occurrences were one or more years later.

According to KUNITOMO and MORI[14], exsudate on the wound surface begins to diminish after 1 week, owing to the topical application of mitomycin C, and the wound surface becomes paler than healthy areas after 12 to 14 days. In this area there is a poor vascular zone and inflammatory signs are not apparent. The sclera takes on a porcelain-like appearance. This whitened area is considered the origin of the scleral lesion.

The early symptoms induced by mitomycin C instillation include allergic blephalitis and blephalo-conjunctivitis associated with itching. About 1 week later, the patient may complain of ocular pain, foreign body sensation, red eye, headache, epiphora, photophobia and reduced vision. On slit-lamp examination, diffuse superficial keratitis, scleral ulcer and iridocyclitis with aqueous flare, exsudate in the anterior chamber, precipitate and posterior synechiae are evident. These sysmtoms are regarded as a barometer of intraocular detriment induced by mitomycin C and its application should be immediately withdrawn.

The later symptoms are scleral thinning, ulcer, calcification and necrosis, corneal and scleral perforation, corneal ulcer, secondary glaucoma and endophthalmitis. These complications are severe and progressive.

Scleral thinning after mitomycin C instillation may be due to suppression of development of collagen fiber in the process of wound healing. Mitomycin C inhibits the development of granulation tissue and growth of the new vessel formation on the wound surface. Hence, scleral thinning indicates a decrease in fibrous connective tissue formation.

Calcification of the sclera was observed in 5 out of 9 patients we treated. The cause of this calcification was not clearly identified. Whether mitomycin C is directly related to the calcification of scleral collagen is unknown, but such cases of scleral calcification are aften reported in the literature. These scleral damages rarely develop spontaneously, therefore, mitomycin C instillation after pterygium removal may become an important factor.

BLOOMFIELD *et al.*[2] reported a case of acute corneal calcification in an uremic patient with corneal exposure and suggested that hypercalcemia, high calcium-phosphorus products, local increase in pH and local tissue damage helped to trigger rapid and dence calcification of soft tissues. They stated that the release of calcium and phosphorus from injured cells will increase the Ca-P products locally, and activation and/or release of cellular enzymes such as alkaline phosphatase, acid phosphatase and ATP-ase also may predispose to local calcification and that the corneal exposure will promote the calcification.

TARR and CONSTABLE[30] stated that factors contributing to radio-necrosis of sclera include surgical trauma, particularly cautery, scleral exposure, the influence of the damaged conjunctiva and tears, but not the dose of radiation. These factors are the same as those relating to mitomycin C instillation where the grade of operative invasion of the sclera and the action of mitomcyin C on the sclera are important factors. The difference in the onset of scleral in our patients may be related to the surgical damage as well as the number and duration of mitomycin C instillations. In our patients, scleral calcification was observed in patients 56 to 73 years of age. Therefore, aging of the sclera also may be a pertinent factor. YOKOYAMA[36] noted 4 cases of scleral lesion out of 57, due to mitomycin C instillation after pterygium excision.

MORI[21] recommended the use of 0.2 mg/ml solution of mitomycin C, as this dose did not lead to a scleral lesion and there was no difference in recurrence rates, as compared with the use of 0.4 mg/ml solution. However, scleral ulcer occurred 0.2 mg/ml solution of mitomycin C has been observed. Therefore, great care should be taken when prescribing mitomycin C solution, regardless of the dose.

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