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CLINICAL STUDY

Tumour-lysis-related elevation of intraocular pressure following high-dose rate brachytherapy for choroidal melanoma

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Abstract

Purpose **To describe the clinical course and management of acute tumour lysis-related intraocular pressure (IOP) elevation, which is a rare late complication of brachytherapy for choroidal melanoma.**

Methods **Seven patients out of 36 treated with Iodine-125 brachytherapy were identified who had in common: an uneventful latent period with continuing tumour regression, ended by a sudden massive release of pigmented debris in association with elevated IOP without iris neovascularization. Medications that reduce aqueous production (timolol, dorzolamide, betaxolol, and acetozolamide) were used in combinations to lower IOP.**

Results **Tumour lysis developed after a mean period of 17.4 months. IOPs ranged between 28 and 35 mmHg, which normalized in a mean period of 10.7 months under topical medications. The seven patients were inadvertently prescribed apical dose rates ranging between 118.3 to 289.16 cGy/h that were significantly higher than the rest of the group ($P = 0.000$). This complication did not develop in patients whose apical dose rates did not exceed 109 cGy/h.**

Conclusions **Acute tumour lysis associated with an elevated IOP after brachytherapy appears to be related to large tumour size and high dose rates. IOP can be lowered by topical medications but visual prognosis is poor. There is no evidence of any effect on overall prognosis of tumour lysis, elevation of IOP, or its treatment.**

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Introduction

Secondary intraocular pressure (IOP) elevation has been observed in 2% of patients with choroidal melanoma.[1] Several mechanisms may act alone or in combination to produce tumour-related glaucoma, and these include mechanical involvement of the angle or obstruction of the trabecular meshwork, angle neovascularization, peripheral synechia formation, and pushing the lens–iris diaphragm forward.[1,2] Usually, tumours involving the posterior segment cause glaucoma by iris neovascularization whereas iris or ciliary body tumours directly invade or shed pigment or tumour cells into the angle.[1] Melanomalytic glaucoma is a rare type of secondary open angle glaucoma in which the angle is infiltrated by pigment laden macrophages and phagocytosing trabecular meshwork endothelial cells as a result of pigment liberation caused by spontaneous necrosis of uveal melanomas.[2–4] We report our experience with a similar phenomenon following plaque brachytherapy characterized by a sudden massive release of pigmented material from a regressing choroidal melanoma after a latent period of time.

Patients and methods

The use of Iodine-125 plaques in the management of uveal melanomas started in January 1996 at our institution. The recommendations of the Declaration of Helsinki

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were followed. The medical records of 36 consecutive patients managed with Iodine-125 plaque brachytherapy for posterior uveal melanoma from 1996 to 1998 at a referral-based national centre were retrospectively reviewed. Those patients having tumour lysis associated IOP elevation were further studied. The age, sex, largest basal diameter, ultrasonographic thickness, apical and basal radiation dose rates, the latent period until the IOP rose, tumour thickness at the time of acute IOP elevation, implemented treatments, and outcomes were recorded (Table 1). Tumour lysis related IOP elevation was defined as follows: normal preoperative IOP, documented tumour regression after brachytherapy, sudden rise of IOP after a latent period of around 18 months accompanied by acute decrease in visual acuity, mild pain, significant amount of pigmented debris in the anterior chamber and vitreous, and no evidence of angle closure and angle neovascularization.

To treat the intraocular tumours, standard plaques were used, made of circular cutouts from 1-mm thick gold spheres with inner diameters of 10–20 mm. Iodine-125 sources at 5 mCi strengths (Model 6711, Amersham, Buckinghamshire, England) were inserted into the concave surface of the plaque using cyanoacrylate. The target dose was 100 Gy to the prescription point (tumour apex) and 300–500 Gy to the tumour base; 1 mm was allowed from the sclera in all dose calculations, which were performed on University of Southern California 1.50 plaque simulator software.[5] To test the significance of the difference between apical dose rates of patients with and without acute tumour lysis, the Mann–Whitney *U* test was used. All patients were followed every 2 months during the first postoperative year and quarterly thereafter. Patients with tumour lysis were followed on a monthly basis. At each visit, visual acuity assessment, IOP measurements (Goldmann), gonioscopy, indirect ophthalmoscopy, and A- and B-mode ocular ultrasonography were performed.

Elevated IOP as a rule was managed with medications that reduce aqueous production, such as acetozolamide 250 mg q.i.d., timolol maleate 0.5% b.i.d., dorzolamide hydrochloride 2% t.i.d., and betaxolol hydrochloride 0.5% b.i.d. Atropine sulphate 2% t.i.d. and dexamethasone phosphate %0.1 t.i.d. were prescribed to all patients. The IOP was deemed controlled whenever the measurements were at or below 22 mmHg for 2 consecutive months after discontinuation of the drops. Metastatic surveys were performed on all patients.

Results

Seven patients were identified who had tumour lysis related elevation of IOP. These consecutive patients were the first to be treated with this modality. All eyes initially showed continuous tumour regression and had IOPs below 18 mmHg. At the last examination before the acute attack, visual acuities ranged between counting fingers and 20/200, and no eye had radiation retinopathy. All seven patients were examined on emergency basis a day or two after the appearance of their symptoms. The major complaints were acute blurring of vision accompanied by pain that was typically not severe. IOPs at this stage ranged from 28 to 35 mmHg. The most characteristic feature common to all seven patients was the massive presence of golden-brown or rust coloured material or cellular debris in the anterior chamber and vitreous, which impeded the visualization of fundus details. A portion of the pigmented material was small and uniform in size while the rest formed coarse aggregates. No patient had corneal oedema, angle closure, and vitreous haemorrhage. Gonioscopy failed to reveal angle and iris neovascularization. None of the seven patients were aphakic or pseudophakic.

The median time for the development of this complication was 19 months and the Kaplan–Meier estimates showed that the probability of developing

Table 1 Patients with lysis of choroidal melanoma after brachytherapy

Patient	*Age/ gender*	*Largest tumour diameter (mm)*	*Thickness (mm)*	*Basal dose rate (cGy/h)*	*Apical dose rate (cGy/h)*	*Latency[a] (months)*	*IOP when tumor lysis first detected (mmHg)*	*Tumour height when lysis first detected (mm)*	*Duration of medical treatment (months)*	*Final IOP (mmHg)*
1	70/M	13.5	8	424.02	120.12	13	35	7.0	11	19
2	52/F	15	11	620.57	202.51	19	32	1.5	12	12
3	70/M	16	10.7	572.65	196.96	25	30	6.3	8	20
4	35/F	15	8.7	510.83	161.24	27	28	4.4	14	21
5	55/M	15	12	680.08	240.61	7	30	9.0	12	22
6	65/M	13	12.5	724.03	289.16	10	28	7.3	6	18
7	35/M	12	8	367.43	118.30	21	32	5.7	12	12

M: male, F: female; IOP: intraocular pressure.
[a]Latency denotes the time interval between plaque removal and the first detection of tumour lysis associated with intraocular pressure elevation.

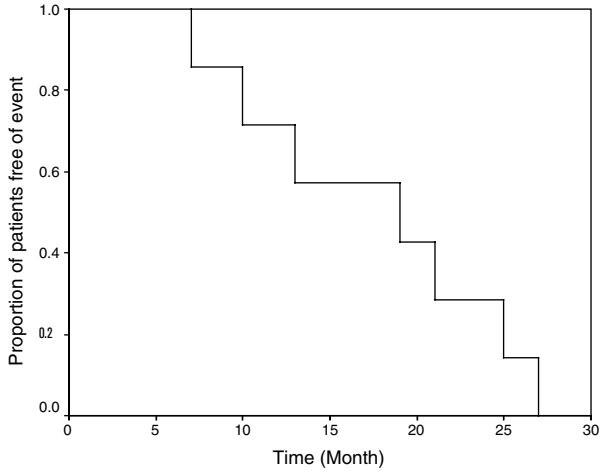

Figure 1 High dose-rate brachytherapy in seven cases: Kaplan–Meier estimates of patients free of tumour lysis related acute intraocular pressure elevation.

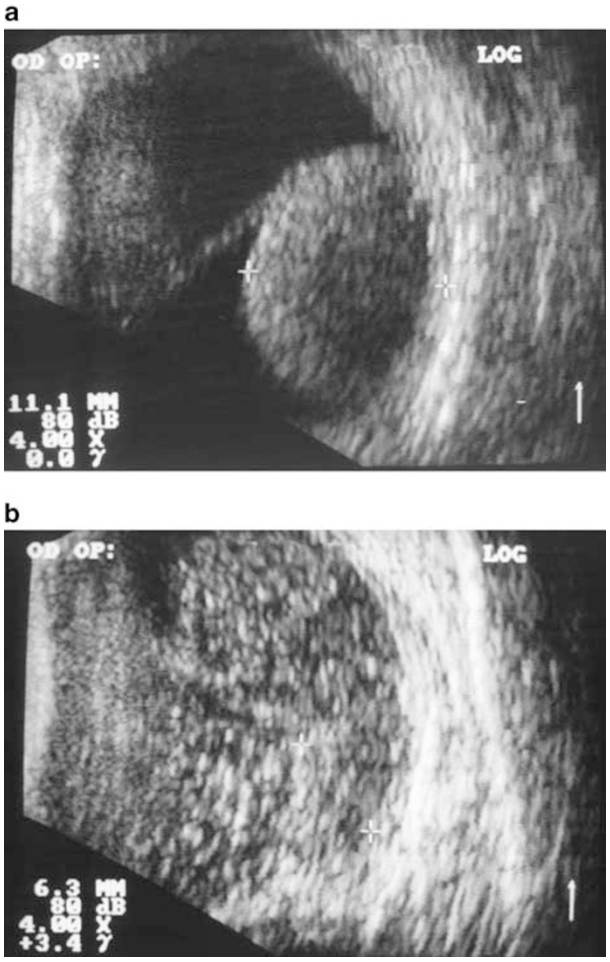

Figure 2 Patient 3. (a) B-mode ultrosonographic view of the tumour before plaque brachytherapy. (b) B-mode ultrasonography of the same eye a few days after the start of patient's complaints showing massive amount of debris dispersed into the vitreous.

tumour lysis related IOP elevation was 30% at 10 months and 83% at 25 months postoperatively if the apical dose rate was over 118.3 cGy/h (Figure 1). The mean preoperative tumour thickness in patients suffering tumour lysis was 10.1 mm, whereas it was 6.9 mm in patients who did not develop this complication. Ultrasonographic tumour thickness ranged between 1.5 and 9 mm at the time of tumour lysis (Figure 2). In patients with tumour lysis, the prescription point (tumour apex) dose rates varied between 118.3 to 289.16 cGy/h and tumour base dose rates ranged from 376.43 to 724.03 cGy/h. In the remaining patients, the dose rates at the prescription points were between 64.08 and 109 cGy/h and the scleral dose rates varied between 367.2 and 517.52 cGy/h (Figure 3). Apical dose rates of the first seven patients were significantly higher than the rest of the treated cases ($P = 0.000$).

Follow-up was available to the end of December 2001. With the exception of acetozolamide, which was discontinued after 2 weeks, the drops were used for a mean period of 10. 7 months (range: 6–14 months). None of the patients failed to respond to medical treatment ($P = 0$; 95% CI = 0–0.41). However, two patients (nos. 2 and 5) developed neovascular glaucoma 16 and 23 months after the cessation of the drops and 47 and 42 months after plaque removal, respectively. These two patients were managed by diode laser transscleral cyclophotocoagulation. One eye (patient no. 4) became phthisical 10 months after the discontinuation of the drugs. An acceleration of progression of nuclear sclerosis was also observed in these seven patients compared to those who did not have a similar episode. Intraocular or orbital recurrence was not found in any of the patients during a mean follow-up of 61.3 months (range: 54–67 months). One patient (no. 6) died from presumed liver metastasis.

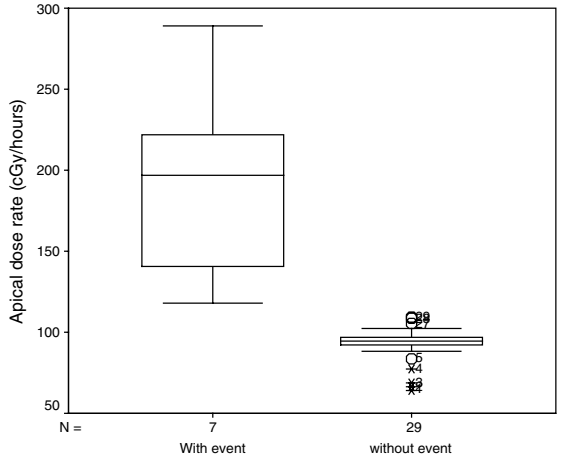

Figure 3 Box-plot graph showing apical dose rates of patients with and without acute tumour lysis.

Discussion

The characteristic feature of radiation-related glaucoma is the latent period between treatment and elevation of IOP.[2] Rubeosis iridis obstructing the trabecular meshwork and induction of a rapidly maturing radiation cataract that displaces the lens–iris diaphragm anteriorly account for the majority of cases.[2] A recent study found neovascular glaucoma (NVG) in 21% of cases at 5 years and in 38% of cases at 15 years following brachytherapy for large tumours.[6] In that series, tumour thickness varied between 8–16 mm, and apical dose rates ranged between 9 and 182 cGy/h.[6] Another study reporting on 630 choroidal melanomas involving the macula showed that NVG developed in 3.2% of patients whose apical dose rates ranged between 13 and 229 cGy/h (median: 80 cGy/h).[7] The high apical and basal dose rates, most probably due to calculation errors, in our seven patients are comparable to the upper limits in these larger studies. Neither study, however, alludes to massive tumour lysis.[6,7] Since 1996, the Collaborative Ocular Melanoma Study started to calculate the absorbed dose at the prescription point as 85 Gy, which traditionally used to be 100 Gy.[8] Under this new formalism, the apical dose rate can be as low as 42 cGy/h but does not exceed 105 cGy/h.[9] We did not encounter acute massive tumour lysis in patients whose apical dose rates were lower than 109 cGy/h.

Damage to tumour vasculature is a hallmark of radiation injury. In all, 50% of uveal melanomas have vessel damage and necrosis within a year following irradiation.[10] Less elevated tumours tend to show early effects, whereas necrosis appears later in larger tumours.[10] It may be likely that the acute disintegration of the tumour and massive pigment shedding in our patients are related to the late effects of radiation on tumour vasculature. Not infrequently, pigmented intravitreal debris originating from the surface of a melanoma can be observed after brachytherapy.[11] However, overwhelming dissolution of posterior uveal melanoma to the point of causing acute rise in IOP is highly unusual. Recently, seven patients were reported with collar-button-shaped choroidal melanomas, which shed pigment after an average of 6 years following Iodine-125 brachytherapy.[12] In some of these patients, massive pigmented debris obscured fundus details. However, there was no indication in that report that pigment spilling into the vitreous was associated with high IOP.[12] In a patient similar to ours but without a history of brachytherapy, spontaneous necrosis of a posterior uveal melanoma with heavy pigment dispersion rose the IOP to 46 mmHg ultimately leading to enucleation of the eye.[13] Our limited experience indicates that medical treatment can successfully lower the IOP and suppress the inflammation.

Two distinct types of pigmented material in the vitreous may be observed following brachytherapy. The first type is irregularly clumped, dark gold coloured debris, which is most likely formed by necrotic tissue and macrophages with ingested pigment.[12] The second type of debris consists of clusters of brownish spherules that are suspended throughout the vitreous and that are probably formed by malignant cells.[12] We have noted a mixture of both types of debris in our cases. Currently, there is no convincing evidence for an unfavourable prognosis and hence no justification for an immediate aggressive approach in these cases.[11,12] However, it should be borne in mind that proliferating tumour cells were demonstrated in 31% of irradiated eyes enucleated for reasons other than regrowth.[14]

Our relative inexperience in brachytherapy in the beginning coupled with inappropriate prescription of overdose radiation to our early patients would probably account for the development of acute tumour lysis-related IOP elevation. On the other hand, the majority of tumours that underwent acute lysis were large sized at the outset and it is known that such tumours may have chronic ischaemia and necrotic areas, which are significantly aggravated by radiation. The retina overlying the tumour becomes thin and atrophic following irradiation.[15] All these factors combined together might also have facilitated the massive debris spillover. Another important aspect is that the topical medications that were used would probably be not sufficient in cases with ordinary primary open angle glaucoma and similar IOPs. It is likely that the gradual clearing of the debris from the trabecular meshwork might also have a significant contribution to progressive decrease of IOP.

This study shows that every possible measure should be taken to assure the prescription of appropriate radiation dose before plaque application, and that large tumours have a risk of developing glaucoma, which may take up to 1 year to control. It may then be argued that enucleation may still be offered as a reasonable option for larger tumours.

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