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Subconjunctival ocular argyrosis Following Treatment with Ruthenium 106 Brachytherapy for Choroidal Melanoma

Aya Khasati[a], Caroline Thaung[b], Hardeep S. Mudhar[c], Bart Wagner[d], Patricia Goggin[e], Ian Stoker[f], Mandeep S. Sagoo[g,h], Bertil Damato[g], Hibba Quhill[g,i]

[a] Imperial College London, London, UK

[b] Department of Eye Pathology, UCL Institute of Ophthalmology, London, UK

[c] Department of Histopathology, Royal Hallamshire Hospital, Sheffield, UK

[d] Electron Microscopy Unit, Department of Histopathology, Royal Hallamshire Hospital, Sheffield, UK

[e] Biomedical Imaging Unit, University Hospital, Southampton NHS Foundation Trust, Southampton, UK

[f] Department of Radiotherapy, St Bartholomew's Hospital, London, UK

[g] Department of Ocular Oncology, Moorfields Eye Hospital, London, UK

[h] NIHR Biomedical Research Centre for Ophthalmology at Moorfields Eye Hospital and University College London Institute of Ophthalmology, London, UK.

[i] Sheffield Ocular Oncology Service, Department of Ophthalmology, Royal Hallamshire Hospital, Sheffield, UK

Short Title: Ocular Argyrosis Following Ruthenium Eye Brachytherapy

Corresponding Author: Ms. Hibba Quhill

Department of Ophthalmology, Royal Hallamshire Hospital, Glossop Road, Sheffield, UK, S10 2JF

Tel: 0114 2711900

E-mail: hibba.quhill@nhs.net

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Abstract (272 words)

Introduction

Ruthenium-106 (Ru-106) brachytherapy is one of the commonest eye-sparing treatments for choroidal melanoma. These patients require long-term surveillance of the treated tumour remnant to ensure there is no local recurrence. New or progressive pigmented lesions in treated eyes are often regarded as suspicious – especially if there are concerns of extra-scleral extension.

Case Presentations

We present two cases of posterior choroidal melanoma treated five and ten years previously with Ru-106. Both cases developed subconjunctival dark/black lesions on the anterior surface of the eye in the quadrant of the conjunctival peritomy during Ru-106 treatment. Both had similar findings on histopathology: black, non-organic, particulate foreign material of varying confluence, deposited on elastin and collagen fibres. Energy dispersive X-ray microanalysis confirmed the material contained silver.

Discussion

The Ru-106 applicator consists of a radioactive core of Ru-106, encapsulated within pure silver as a radiation shield. During surgical insertion, stainless steel suture needles and forceps can occasionally scratch the applicator's silver eyelets and scatter microscopic particles of elemental silver into the operative field. These particles were likely deposited within the subconjunctival tissues of these patients during brachytherapy administration, leading to localised ocular argyrosis. Iatrogenic ocular argyrosis should be considered in the differential diagnosis of new pigmented lesions in patients treated with Ru-106 brachytherapy. This study is the first to unequivocally identify the cause of some post-brachytherapy ocular surface pigmentation as caused by silver.

Introduction

Ruthenium-106 (Ru-106) brachytherapy is commonly utilised for suitable small to medium-sized uveal melanomas [1]. The radioactive core of the Ru-106 plaque (Eckert & Ziegler BEBIG, Germany) is encased within pure silver sheets which act as a radiation shield (Figure 1A). Ru-106 has a half-life of 373.6 days which allows for multiple uses over a one-year period [2]. With good patient selection and fine surgical technique, Ru-106 brachytherapy is associated with high rates of local tumour control [3,4]. However, a recent literature review of twenty-one retrospective studies reports variable local tumour control rates ranging between 59-98%, with an overall weighted mean of 84% efficacy [5].

Ru-106 treated patients are monitored closely by ophthalmologists to detect local tumour recurrence and other complications. New pigmented lesions are of concern as they may indicate recurrence or extrascleral extension [6]. However, not all pigmented ocular lesions in uveal melanoma patients are melanocytic in origin, as we report.

We present two patients who developed progressive subconjunctival pigmentation after Ru-106 brachytherapy for posterior choroidal melanoma, caused by silver deposition originating from the Ru-106 plaque.

Case Reports

Case 1

A 56-year-old Caucasian woman presented with a two-week history of new pigmented lesions on the nasal bulbar surface of the right eye. Her past ocular history included right nasal juxtapapillary choroidal melanoma (base 8.8 mm x 6.9 mm, 1.1mm thickness pre-treatment), which was treated 5 years prior with Ru-106 brachytherapy (prescribed dose of 80 Gray (Gy) to the apex, applied using a 20 mm notched (manufacturer's model 'COB') plaque) [2]. At the time of this presentation, the treated choroidal tumour-remnant in the right eye appeared inert and stable with no evidence of re-growth. Systemic metastatic screening was also negative.

On examination, corrected Snellen visual acuities were 20/30 bilaterally. Conjunctival and subconjunctival pigmented greyish lesions were noted on the nasal bulbar surface of the right eye, mainly centred in the inferonasal quadrant (Figure 2c and 2d). These had not been present previously (Figure 2a and 2b). The pigmentation was monitored closely with serial photography: the patient and clinicians noticed subtle progression over time (Figure 2e and 2f).

After two months of close observation, the patient became increasingly concerned that the pigmentation represented extra-scleral deposits of viable melanoma, especially given the pigmented lesion was localised to the area of the Ru-106 applicator location. There was no evidence of primary tumour re-growth or extra-ocular extension on serial B-scan ultrasound and imaging. However, the patient requested enucleation for possible extra-ocular tumour growth.

An initial incisional biopsy of the pigmented sub-conjunctival and conjunctival tissue was performed under local anaesthetic with sedation. Histopathology showed deposits of black non-organic material within the lamina propria deposited as clumps and in a curlicue pattern (Figure 3a and 3b). Foreign-body type multinucleate giant cells were present around the clump deposits (Figure 3a). The material deposited in a curlicue configuration, reflecting its predominant deposition on elastin fibres, in preference to collagen fibres (Figure 3b). Perl's stain, used to detect iron, and Fontana-Masson stain, used to detect melanin, were negative (not shown). Melan A immunohistochemistry, which highlights melanocytic cells, was negative (not shown).

The pigmentation was restricted to the tissues which had been manipulated during the previous Ru-106 treatment. This supported the suspicion that silver deposited at the time of surgery likely caused localised argyrosis. Medical records confirmed that the Ru-106 plaque applicator used in this patient had been deployed 30 times prior to this use. As there was no evidence of melanoma recurrence, enucleation was avoided.

Case 2

A 74-year-old Caucasian male presented for annual ophthalmic monitoring. He had a past ocular history of right choroidal melanoma (superiorly located, base 8.5mm x 7.3mm, 2.7mm thick pre-treatment) treated 10 years previously with Ru-106 brachytherapy (20mm circular plaque - manufacturer's model 'CCB') delivering 100 Gy to the apex). This particular Ru-106 plaque applicator had been used 32 times previously. Following brachytherapy, the patient developed radiation retinopathy and was treated with intravitreal bevacizumab.

On examination the visual acuity was 20/200. Fundal examination was precluded due to posterior synechiae and significant cataract. B-scan ultrasound showed a collar-stud choroidal mass lesion with a maximum elevation of 5.6 mm and a base of 8.8 mm. Intraocular tumour regrowth was judged likely due to the increase in size of the mass. Multifocal subconjunctival pigmented lesions were also noted in the superior and superior-temporal bulbar ocular surface (Figure 4).

The patient underwent uneventful secondary enucleation. Histopathology of the enucleation specimen confirmed intraocular regrowth of malignant melanoma but showed no extra-scleral extension. Examination of the pigmented subconjunctival lesions revealed non-organic black material deposited as clumps and in a curlicue pattern, identical to that seen in the previous case (Figure 3c). The patient recovered well and remains under systemic metastatic surveillance.

Specimens from both cases were submitted for further analysis to formally identify the non-organic material. Transmission electron microscopy (TEM) showed electron-dense bodies, with an irregular outline that were 10 to 200 nm in size (Figure 3d). Unfortunately, this did not help to identify the material.

Energy dispersive X-ray (EDX) microanalysis was performed using an EDAX Genesis system, to determine the elemental composition of the black material. EDX microanalysis is a technique carried out in an electron microscope. During TEM, characteristic X-rays are emitted from samples. A detector located on the side of the microscope column is used to collect the X-rays and analysis of these allows qualitative and quantitative results on elemental composition to be obtained.

It must be noted that this technique cannot reliably detect elements with atomic number < 5 nor elements present at concentrations below 100 parts per million. It cannot determine the molecular composition of the materials. Error can be introduced to EDX analysis if traditional TEM heavy metal staining is employed; heavy metals are characterised by several EDX peaks that may mask other elements present in the sample. The samples in these cases were prepared without staining, avoiding this. Ninety nanometre sections were taken from the unstained histopathology blocks and placed onto formvar-coated grids, then imaged on a Tecnai 12 TEM at 80kV.

EDX microanalysis revealed that the black material in both cases contained silver (predominant component) and sulphur (lesser component) (Figure 3e). Copper was detected from the grid bars used for mounting the specimen. The EDX microanalysis therefore confirmed the presence of silver within the black material deposited in both cases.

Discussion

It has been well established that chronic exposure to silver-containing material can increase the risk of developing ocular argyrosis [7]; previous reports document cases as a consequence of silver ingestion [8], exposure from longstanding eyelash tint use [9,10], and occupational exposure to silver such as in metal foundry workers and jewellers [11–13]. Isolated iatrogenic causes have also been recorded secondary to use of silver sutures in previous strabismus surgery [14] and use of silver-containing eye drops (Argyrol) [15].

Review of the literature identified two reports of pigmented episcleral lesions in patients treated for intraocular tumours [16,17]. The first report dates to 1971 and documents the presence of episcleral pigmented lesions following cryotherapy of an intraocular astrocytoma [18]. Histopathological findings of these lesions were consistent with 'focal collections of melanin surrounded by epithelioid giant cells'. The second report, published in 2006, was a case series of 211 patients who developed pigmented episcleral lesions following iodine brachytherapy for uveal melanoma [19]. Histopathological examination was carried out on one eye with pigmented deposits, which showed trans-sclerally

migrating macrophages and was negative for melanoma cell markers. Although this study showed a high incidence of pigmented deposits following brachytherapy for uveal melanoma, an association with silver was not identified. The pigmented lesions in our two cases appear to present similarly to these previous reports. However, to our knowledge, this is the first report to describe a link between Ru-106 brachytherapy and ocular argyrosis.

Ru-106 plaque applicators are made of silver with a core of radioisotope [2]. Manipulation and handling of the plaque is performed using the eyelets, to avoid damaging the delicate concave surface leading to radioisotope leakage. Sutures are passed through the eyelets to secure the plaque to the scleral surface to administer treatment. Suture needles and micro-forceps used are made from surgical steel (plastic forceps are advised by the manufacturer but are impractical as they are too large for the small spaces involved and bend when pressure is applied). Given surgical steel is much harder than silver [20], the medical instruments and needles occasionally scratch the eyelets intraoperatively, at times scattering fine particles of silver onto the ocular surface (Figure 1B). A well-used plaque will often display multiple scratches and irregularities of the eyelets because of this. The authors suggest that in the cases presented, minute silver particles were deposited in the subconjunctival space during administration of Ru-106 brachytherapy. The location of the pigmentation in both cases was not localised to the position of the plaque eyelets per-operatively; however, all were within the area of conjunctival peritomy. We speculate that metallic particles of silver and silver compounds (produced by the breakdown of metallic silver bathed in biological fluids of the ocular tissues) were transported by macrophages and within the extracellular fluid to the positions seen in our cases on the anterior bulbar ocular surface.

Extraocular extension of uveal melanoma can present similarly to the cases presented above; patients may present with scleral discolouration or subconjunctival pigmentated lesions [7,19]. Distinguishing features of ocular argyrosis include that the deposits tend to be grey-black, not brown, and may be more granular or 'dust-like' rather than nodular extraocular tumours. It is important to distinguish the two conditions: extra-scleral uveal melanoma has great metastatic propensity, poor prognosis and high mortality rates [20]. In contrast, localised ocular argyrosis is of limited clinical consequence having been described as predominantly a cosmetic issue that does not result in vision loss [7,21].

There have been some reports of argyrosis causing adverse effects. Stafeeva et al describe a case with an association between ocular argyrosis and reduced visual acuity bilaterally and nyctalopia [22]. This finding is echoed by Sarnat-Kucharczyk et al. who suggest the nyctalopia could be linked to photoreceptor damage [11]. In both cases, the patients were exposed to larger amounts of silver for a prolonged period. No functional consequences of ocular argyrosis were identified in our cases.

Conclusion

This report presents the association of ocular argyrosis and Ru-106 brachytherapy used to treat choroidal melanoma. In our experience, this is an uncommon occurrence. In the context of a patient presenting with subconjunctival dark or black deposits, with a history of Ru-106 brachytherapy, one should consider ocular argyrosis in the differential diagnosis. Biopsy of the affected tissue can prevent unnecessary secondary enucleation for presumed extra-ocular extension.

Statement of Ethics

Written informed consent was obtained from the patients for publication of this case series and all accompanying images. All procedures contributing to this research were conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Specific ethical approval was not required in line with national guidelines, as this was a retrospective descriptive study.

Disclosure Statement

There are no conflicts of interest to declare.

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Author Contributions

Aya Khasati wrote the manuscript. Caroline Thaung and Hardeep Singh Mudhar provided histopathological commentary and edited the manuscript. Bart Wagner and Patricia Goggin provided specialist analyses and commentary and edited the manuscript. Ian Stoker, Mandeep S. Sagoo and Bertil Damato edited the manuscript. Hibba Quhill designed the study, co-wrote and edited the manuscript.

Data Availability Statement

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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Figure Legends

Figure 1. (a) Ru-106 plaque applicator, consisting of a coating of Ru-106 encapsulated within pure-silver sheets. The applicator is handled and sutured to the sclera using the eyelets (arrow) which are also made of silver. Reprinted with permission from Eckert & Ziegler BEBIG. (b) Intraoperative photograph through the operating microscope during a Ru-106 plaque insertion procedure on a different patient from the cases described in this report, showing 'scratched' eyelets and tiny particles of silver (arrows) released onto the ocular surface during handling.

Figure 2. Clinical imaging for Case 1: External photographs of the anterior segment: (a-b) 1 year after Ru-106 treatment (c-d) 5 years after Ru-106 treatment at presentation with ocular surface pigmentation, and (e-f) 2 months after ocular surface pigmentation detected.

Figure 3. (a) Haematoxylin and Eosin (H&E) stained section from Case 1 showing a black solid deposit (broad black arrow) surrounded by multinucleate giant cells (thin black arrow). The black arrow to the left points to a similar giant cell but the deposit is not in the plane of the section or has fallen out during processing (magnification x200). (b) H&E showing that the predominant deposition pattern of the black material was curlicue indicating its deposition on elastin fibres, in preference to collagen (magnification x400). (c) H&E from Case 2 showing solid and curlicue deposits of an identical nature to that seen in Case 1 (magnification x200). Deposition is also seen in blood vessel walls, likely related to the presence of elastin. (d) Transmission electron micrograph of the black deposits (Case 2) showing electron dense bodies with an irregular outline (magnification: x 20 000). E: Energy dispersive X-ray (EDX) spectrum from Case 2, showing a peak at silver (Ag Ka - black arrow). Other elements identified include oxygen (O Ka), sulphur (S Ka) and copper (Cu Ka). The copper is from the mounting grid used for the specimen.

Figure 4. External photographs of the anterior segment of the right eye of Case 2 showing multiple subconjunctival pigmented spots, taken weeks before enucleation of the eye for intraocular recurrence.