CASE REPORT

Bevacizumab in vitreous haemorrhage secondary to radiation retinopathy

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SUMMARY

Radiation retinopathy is a delayed-onset side effect of radiation exposure caused by retinal ischaemia that may induce proliferative retinopathy with neovascularisation, vitreous haemorrhage and macular oedema. An otherwise healthy, 51-year-old male patient who had been diagnosed with olfactory neuroblastoma and undergone complete surgical removal of the lesion followed by cranial irradiation developed bilateral cataracts and radiation retinopathy. The patient was treated by panretinal photocoagulation (PRP), followed by three-port pars-plana vitrectomy. Recurrent episodes of vitreous haemorrhages occurred following surgery and the patient was successfully treated by one intravitreal injection of bevacizumab with resolution of vitreous blood. Vitreous haemorrhage recurred 6 months later and a scheduled treatment with intravitreal bevacizumab every 4 months was established, preventing further haemorrhagic episodes. Six months after the last injection, a new episode of vitreous haemorrhage occurred.

Scheduled intravitreal bevacizumab injections may help prevent recurrent vitreous haemorrhages in vitrectomised patients with radiation retinopathy.

BACKGROUND

Radiation retinopathy (RR) is a delayed-onset side effect of radiation exposure, with characteristic appearance of a proliferative retinopathy with microaneurysms, neovascularisation, vitreous haemorrhage (VH), hard exudates, cotton wool spots and macular oedema.¹

Giuliani *et al*² have recently revised the therapeutic options for RR. Most of the current approaches have been adapted from other ischaemic retinopathies. A panretinal laser has been used as prophylaxis against retinal proliferation and macular oedema.³ Even though retinal photocoagulation is the gold standard in most forms of ischaemic retinopathies, it may not be completely justified as a prophylactic approach in RR.² Intravitreal⁴ and periocular⁵ triamcinolone have been used to treat macular oedema secondary to radiotherapy in ocular tumours.

CASE PRESENTATION

An otherwise healthy, 51-year-old patient diagnosed with olfactory neuroblastoma underwent a complete surgical excision of the lesion followed by external beam cranial irradiation (5040 cGy during 26 weeks). During this period, the patient reported ocular discomfort in his left eye.

INVESTIGATIONS

Best-corrected visual acuity (BCVA) determined at 4 m using standard Early Treatment Diabetic Retinopathy Study (ETDRS) charts (Lighthouse, New York, USA) was 20/32 in his right eye (RE) and 20/40 in his left eye (LE). Anterior segment examination including Schirmer test was unremarkable and fundus examination revealed bilateral multiple peripapillary cotton wool spots and small preretinal haemorrhages (figure 1A). Optical coherence tomography (OCT) showed intraretinal oedema in the peripapillary area. Fluorescein angiography disclosed haemorrhages and cotton wool spots.

TREATMENT

Topical treatment with dexamethasone, diclofenac and levobunolol was started. Oral acetazolamide was started that was interrupted due to renal colic.

Fifteen months later posterior subcapsular cataract was diagnosed in his LE and uneventful phacemulsification with intraocular lens implantation was performed. Five months after cataract surgery, retinal neovascularisation and angiographic retinal ischaemia with optic disc (NVD) and retinal neovascularisation (NVE) were observed. The patient was treated by Nd-YAG capsulotomy, panretinal laser and subTenon triamcinolone injection, with resolution of NVD and NVE. During the subsequent months, several episodes of VH occurred and no bleeding source was identified. Therapeutic options were discussed and three-port pars plana vitrectomy was performed with detachment of posterior hyaloid, removal of vitreoretinal adhesions and completion of panretinal laser.

After two months, a new episode of VH grade 4⁶ occurred, resulting in BCVA hand movements. An ultrasound B-scan ruled out retinal detachment and vitreoretinal adhesions. The patient was informed about the off-label use of intravitreal bevacizumab (IVB) and a 1.25 mg injection was administered.

OUTCOME AND FOLLOW-UP

One month later BCVA was 4/10 and three further monthly injections were administered. Six months later a new haemorrhagic episode occurred in the LE and the patient was treated by scheduled IVB every 4 months for 12 months; during this period, the patient maintained BCVA and no new episodes of VH occurred. Considering that the haemorrhagic condition might have spontaneously burnt up, the patient was not re-treated during the following revision and a new haemorrhagic episode

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Figure 1 (A) Cotton-wool exudates and retinal haemorrhages associated with radiation retinopathy. (B) Optic disc and retinal neovascularisation. (C and D) Fluorescein angiography showing retinal ischaemia and neovascularisation. (E and F) Colour fundus photograph and fluorescein angiography after panretinal laser show regression of neovascularisation and oedema. (G) Baseline optical coherence tomography with mild retinal oedema. (H) Final optical coherence tomography with reduced macular oedema.

occurred 6 months after the last injection, so a new IVB was performed. No changes in intraocular pressure, inflammatory reaction or other adverse events were observed during the follow-up. The time-line of this period is summarised in [table 1](#).

DISCUSSION

RR is secondary to the effect of radiation on sensitive retinal tissues. Even though most of the reported cases are related to radiotherapy for intraocular tumours, RR may also be secondary to cephalic, nasopharyngeal, orbital and paranasal tumours.² Parsons *et al*⁷ observed that there were no cases of RR at doses below 45 Gy but that the incidence increased at doses greater than 45 Gy.

The role of vascular endothelial growth factor (VEGF) in pathological angiogenesis associated RR was proposed by Aiello.⁸ Intravitreal anti-VEGF drugs (especially bevacizumab) have been successfully used to treat RR macular oedema secondary to brachytherapy for choroidal melanoma, showing reduction of macular thickness with visual acuity improvement and amelioration of retinal haemorrhage and exudation.⁹ Intracameral bevacizumab has been used to treat neovascular glaucoma following brachytherapy for a choroidal melanoma, resulting in a decreased intraocular pressure.¹⁰ Isolated case reports on the use of pegaptanib sodium¹¹ and ranibizumab¹² to reduce macular oedema have been published with limited follow-up. However, because of the potential complications and the need for repeated injections, the role of anti-VEGF therapy

Table 1 Time-line of the reported events and management

Date	February 2008	August 2008	November 2009	April 2009	June 2010	July 2010
Event	Olfactory neuroblastoma	Radiation retinopathy	Cataract	NVD+NVE	Vitreous haemorrhage	Vitreous haemorrhage
Procedure	Surgery, starts radiotherapy	Medical management	Phaco-emulsification surgery	Panretinal laser, triamcinolone	None	None
Date	September 2010	October 2010	December 2010	February 2011	March 2011	April 2011
Event	Vitreous haemorrhage	Vitreous haemorrhage	Vitreous haemorrhage	Vitreous haemorrhage	None	None
Procedure	None	None	Vitrectomy, endolaser	Bevacizumab injection	Bevacizumab injection	Bevacizumab injection
Date	May 2011	November 2011	March 2012	July 2012	November 2012	May 2013
Event	None	Vitreous haemorrhage	None	None	None	Vitreous haemorrhage
Procedure	Bevacizumab injection	Bevacizumab injection	Bevacizumab injection	Bevacizumab injection	No treatment	Bevacizumab injection

in the long-term management has not been yet fully elucidated. To the best of our knowledge, intravitreal anti-VEGF drugs have not been previously used to manage recurrent VH in patients with RR.

Uneventful cataract surgery has been associated with an increase in the aqueous levels of VEGF,¹³ which may induce worsening of proliferative and oedematous changes in patients with RR, as it occurs with diabetic retinopathy.¹⁴ In the present case, retinal NVE and ischaemia occurred shortly after uneventful cataract surgery.

VH secondary to RR has been previously reported in 4% of the eyes during the first year and 15% during the first 5 years after plaque brachytherapy,¹⁵ and has been managed by a panretinal laser and vitrectomy.^{15 16} However, and as occurs with diabetic retinopathy, recurrences may affect the patients' quality of life, and an adequate management protocol has not been established. IVB has been previously reported in the management of recurrent VH in vitrectomised eyes with diabetic retinopathy.^{17 18}

Recurrent VH has been attributed to persistent vitreoretinal NVE.¹⁹ IVB may induce temporary regression of retinal NVE, which may allow spontaneous clearance of VH. However, due to the reported half-life of the anti-VEGF effect,²⁰ periodical reinjections may be required. IVB is a less invasive alternative to surgery in recurrent VH in vitrectomised eyes.

Randomised, controlled prospective studies, including other possible therapeutic possibilities, will probably establish the optimal treatment for these cases.

Learning points

- ▶ Vitreous haemorrhages may occur in patients with radiation retinopathy despite complete panretinal laser treatment.
- ▶ Intravitreal bevacizumab may allow clearance of vitreous haemorrhage in patients with radiation retinopathy.
- ▶ Scheduled intravitreal injections may be required to prevent further episodes of vitreous haemorrhage.

Contributors JAM was involved in design, data acquisition, patient management and writing. GY-C was involved in data acquisition. MES-M was involved in critical revision of the manuscript. JMR-M was involved in critical revision of the manuscript and patient management advice.

Competing interests None.

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