PHOTO ESSAY

Bilateral Radiation Optic Neuropathy Following Concurrent Chemotherapy and Radiation in Glioblastoma

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ABSTRACT

Radiation optic neuropathy (RON) is an iatrogenic complication that causes severe, irreversible vision loss within months to years following radiation to lesions close to the visual pathway. The authors describe a case of RON in glioblastoma after radio-sensitisation with temozolomide with sequential involvement of both optic nerves. This case provides a timeline for clinical and imaging findings with RON and specifically resolution of nerve enhancement. The authors also highlight the potential of an increase in incidence of RON in glioblastoma with advances in survival seen with greater use of second-line chemotherapy and even re-radiation.

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Introduction

Radiation optic neuropathy (RON) is an iatrogenic complication that causes severe, usually irreversible vision loss within months to years following radiation to lesions close to the visual pathway.^{1,2} It has been reported following radiation to the orbit, paranasal sinuses, skull base tumours, frontal lobe tumours, and stereotactic radiosurgery. The onset of RON on an average occurs 18 months after treatment.¹ Vision loss is usually acute and painless. It may initially occur in one eye, with the fellow eye affected weeks to months later in bilateral cases.^{3,4} Visual acuity is severely reduced in the vast majority of affected eyes. Afferent pupillary defect is an objective sign in unilateral or asymmetric cases. The optic disc may appear normal and eventually become pale in 4–6 weeks. Disc swelling may be seen if the anterior optic nerve is involved.⁵ Besides optic nerve, chiasmal injury may occur. A variety of nerve fibre bundle defects have been reported.

The pathogenesis is delayed radionecrosis where there is vascular damage, followed by subsequent neuronal injury. There is ischaemic demyelination, reactive astrocytosis, endothelial hyperplasia, obliterative endarteritis, and fibrinoid necrosis.⁶

Magnetic resonance imaging (MRI) is the study of choice in cases of suspected RON, yielding a normal pre-contrast appearance and post-contrast study showing segmental marked enhancement along the optic nerve.^{3,7}

A variety of therapeutic options have been focused on addressing the proposed inflammatory and vascular toxic mechanisms. These include corticosteroids, anticoagulation, hyperbaric oxygen, and anti-vascular endothelial growth factor agents.^{8,9} Hyperbaric oxygen has been reported to reverse vision loss at a minimum pressure of 2.4 atmospheres.¹⁰

Case report

Our patient is a 64-year-old woman who underwent complete resection of a right temporal mass that was confirmed pathologically to be a glioblastoma (Figure 1) (5.5 × 4.5 cm; World Health Organization [WHO] grade IV). She then underwent concurrent chemotherapy with temozolomide and radiation to her resection bed, receiving 46 gray (Gy) of photon radiation to the T2 abnormality and 14 Gy to the T1 abnormality for a total dose of 60 Gy in 30 fractions.

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Figure 1. Gadolinium-enhanced coronal (A) and axial (B) pre-surgical T1-weighted images demonstrating an irregular nodular and cystic mass in the right temporal lobe with associated shift to the left. Optic nerves (red arrowheads in A) are not displaced by the mass effect and do not enhance.

The right optic nerve received a maximum dose of 53.9 Gy, average 49.2 Gy over the whole nerve. The left optic nerve received a maximum of 52.2 Gy, average 33.4 Gy for the whole nerve (Figure 2D). After 1 month, she received 12 cycles of monthly maintenance chemotherapy with temozolomide and was enrolled in a clinical trial of scalp-applied grids to deliver alternating electric field current to the tumour field.

After 9 cycles of maintenance chemotherapy (about 36 weeks following radiation), she experienced gradually worsening bilateral vision loss. Examination showed visual acuity of 20/30 right eye and 20/25 left eye with early cataract in both eyes, no afferent pupillary defect and normal appearing optic discs. Humphrey visual fields showed superior arcuate scotoma in both eyes more pronounced on the left with mean deviation (MD) of -4.50 db and -6.74 db in right. Subsequently, her visual loss continued to progress in both eyes. Five months later, her examination demonstrated visual acuity of 20/50 right eye and 20/25 left eye. Visual fields showed dense superior altitudinal defect in the right eye with MD of -15.58 db and dense superior arcuate defect in the left eye with MD of -10.73 db. Repeat visual fields a month later showed similar pattern of visual field defects in both eyes.

Contrast-enhanced MRI head did not reveal tumour progression, and her Karnofsky performance score (KPS) continued to be 90%. Gadolinium-enhanced coronal T1-weighted images did not show optic nerve abnormalities prior to concurrent chemotherapy and radiation.

However, 36 weeks after beginning of concurrent radiation and temozolomide, there was enhancement of the left optic nerve before optic nerve after exiting the optic canal; the optic tracts and intracanalicular and orbital regions of the nerve were unaffected (not shown) (Figure 2A). This enhancement increased at 45 weeks and was accompanied by enhancement of the right optic nerve. Subtle enhancement of the left side optic chiasm was present (Figure 2B). After a further 9 weeks, enhancement diminished, more so on the left (Figure 2C).

Discussion

Factors associated with RON development include patients age, dose of radiation, time-dose fractionation parameters, and proximity of radiation to the optic nerve.^{11,12} Bilateral RON has been described in glioblastoma patients receiving bevacizumab as well as after radio-sensitisation by temozolomide.^{13,14} Development of RON in our patient could be due to radiation alone; however, there is a possibility of radio-sensitisation with temozolomide.

There is no consensus on the dose of radiation below which RON does not develop. Optic nerve and chiasm are the dose-limiting structures during radiation planning for regional tumours. The risk of RON for doses in the 55–60 Gy range is 3–7% when fractions of 1.8–2.0 Gy are used.¹⁵ A total cumulative dose of fractionated radiation above 50 Gy is associated with an increasing risk of RON.¹ The risk becomes less with a total dose of 50 Gy

Figure 2. Enhanced coronal post-surgical T1-weighted images showing optic nerve abnormalities following radiation and temozolomide treatment. The optic nerves are indicated by red arrows; white asterisks denote abnormal enhancement. (A) At 36 weeks after beginning of therapy, there is enhancement of the left optic nerve after exiting the optic canal. The optic tracts and intracanalicular and orbital regions of the nerve were unaffected (not shown). (B) Approximately 9 weeks after the scan shown in A, both optic nerves now enhance. Subtle enhancement of the left optic chiasm was present, but not in other regions of the nerve (not shown). (C) After a further 9 weeks, persistent but decreased enhancement is seen in the right optic nerve. (D) Isodose curves for delivered radiation to the tumour. Orange asterisks indicate optic nerve locations. Dose estimates on labeled curves: 1–30 Gy; 2–48 Gy; 3–54 Gy; 4–57 Gy.

and with fractional doses of <1.9 Gy.¹⁵ However, in our case, there was sequential involvement of both optic nerves with injury initially present on the left, which was the side having less radiation exposure (Figure 2A–D). We cannot explain this sequential development of imaging findings, although on clinical examination she had worse vision loss in the right eye.

Optic nerve enhancement on MRI can be seen in various infections, inflammatory disorders, as well as infiltration of the nerve with tumour, arachnoidal adhesions around the chiasm, or leptomeningeal spread.¹⁶ New neurologic deficits are always a concern for recurrence of tumour. Delayed vision loss with optic nerve enhancement following radiation could be due to radiation neuropathy, but tumour recurrence remains a concern.¹⁶ However, there is limited literature to support the role of MRI

to aid the diagnosis of RON and differentiate it from tumour progression. In RON, there is usually resolution of enhancement, which might not be the case with tumour infiltration. This was reported in a previous case where resolution of enhancement was seen after 3 months.¹⁶

In various reported cases in the literature, there is subsequent involvement of both optic nerves.^{16,17} Enhancements can precede clinical symptoms.¹⁷ It has been suggested that the vision loss to the fellow eye can be prevented by early treatment with hyperbaric oxygen. Diagnosis of early involvement of the fellow optic nerve can be made by investigating for enhancement on serial imaging.¹⁷ Our case helps support the timeline of optic nerve enhancement after radiation and involvement of the fellow optic nerve. More evidence of a similar finding may help design studies to investigate involvement of fellow

eye and timely administer preventative therapies. We anticipate a potential increase in incidence of RON with improved survival in glioblastoma. This improved survival includes US Food and Drug Administration (FDA) approval of new agents along with greater understanding of the genetic biology of the disease. With increasing survival, further therapies including re-radiation are likely to be received; we anticipate an increased incidence of RON in primary brain tumors.¹⁸

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

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