Radiation-induced optic neuropathy: a magnetic resonance imaging study

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Optic neuropathy induced by radiation is an infrequent cause of delayed visual loss that may at times be
difficult to differentiate from compression of the visual pathways by recurrent neoplasm. The authors describe
six patients with this disorder who experienced loss of vision 6 to 36 months after neurological surgery and
radiation therapy. Of the six patients in the series, two had a pituitary adenoma and one each had a metastatic
melanoma, multiple myeloma, cranial pharyngiomata, and lymphoepithelioma. Visual acuity in the affected eyes
ranged from 20/25 to no light perception. Magnetic resonance (MR) imaging showed sellar and parasellar
recurrence of both pituitary adenomas, but the intrinsic lesions of the optic nerves and optic chiasm induced
by radiation were enhanced after gadolinium-diethylenetriaminepenta-acetic acid (DTPA) administration and
were clearly distinguishable from the suprasellar compression of tumor. Repeated MR imaging showed
spontaneous resolution of gadolinium-DTPA enhancement of the optic nerve in a patient who was initially
suspected of harboring recurrence of a metastatic malignant melanoma as the cause of visual loss. The authors
found the presumptive diagnosis of radiation-induced optic neuropathy facilitated by MR imaging with
gadolinium-DTPA. This neuro-imaging procedure may help avert exploratory surgery in some patients with
recurrent neoplasm in whom the etiology of visual loss is uncertain.

KEY WORDS • radiation necrosis • neuropathy • gadolinium-DTPA • optic nerve •
magnetic resonance imaging

The cause of delayed visual loss after radiation therapy may be elusive since recurrence of a
malignancy involving the anterior visual pathways is usually suspected. Radiation-induced optic
neuropathy is an infrequent disorder of ischemia affecting the optic nerve and optic chiasm. Visual loss may
occur months or even years after radiation therapy and its course may be sudden in onset and rapidly progressive.
Unlike the pallid swelling of the optic nerve head that is virtually diagnostic of acute anterior ischemic optic neuropathy, the ophthalmoscopic appearance
of the optic nerve head in acute radiation-induced optic neuropathy is usually normal, although optic disc
swelling may occur with ocular irradiation. Optic atrophy develops soon afterward.

Diagnosis of radiation-induced optic neuropathy is based upon a clinical suspicion. In the face of recurrent neoplasm, surgical exploration of the anterior visual pathways may be necessary in order to ascertain the precise etiology of the optic neuropathy. We describe six patients with delayed visual loss after surgery and radiation therapy for intracranial neoplasms in whom magnetic resonance (MR) imaging with gadolinium-diethylenetriaminepenta-acetic acid (DTPA) aided in the diagnosis of radiation-induced optic neuropathy.

Clinical Material and Methods

Magnetic resonance imaging was performed with a 1.5-tesla superconducting Signa unit.* Two basic pulse
sequences were utilized. First, T1-weighted images were obtained with the following parameters: TR = 600

* Signa unit manufactured by General Electric, Milwaukee, Wisconsin.
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msec, TE = 20 msec, 4-mm thick sections, a 16-cm field of view, and two excitations (Cases 1 to 6). Second, T2-weighted images were obtained with the following parameters: TR = 2000 msec, TE = 80 msec, 5-mm thick sections, an 18-cm field of view, and one excitation (Cases 1 to 5). Axial and coronal T1-weighted images and axial T2-weighted images were obtained. Magnetic resonance imaging was performed before (T1- and T2-weighted images) and after (T1-weighted image) slow intravenous injection of gadolinium-DTPA† at a dose of 0.1 mmol/kg body weight (Cases 1 to 6). The T2-weighted pulse sequences in Case 6 were performed with a TE of 30 msec and 80 msec, and a TR of 2800 msec; the T1-weighted images had the same parameters as those described for Cases 1 to 5.

Case Reports

Case 1

This 54-year-old man complained of loss of vision in the right eye 1 year after resection of a metastatic melanoma to the right parietal cortex. Postoperatively, he received radiation therapy at a cumulative dose of 6000 rad. A conjunctival melanoma had been resected from the right eye 8 years earlier.

Visual acuity was light perception in the right eye and 20/20 in the left eye. There was a right afferent pupillary defect. Goldman visual fields were unobtainable in the right eye, but a superior temporal defect was present in the left eye (Fig. 1 upper). Ophthalmoscopv of the optic discs was normal.

Magnetic resonance imaging revealed mild encephalomalacia at the site of previous resection of the metastatic melanoma to the right parietal cortex. Prior to the administration of contrast agent, the optic nerves and optic chiasm were normal in appearance on T1- and T2-weighted imaging. Following gadolinium-DTPA administration, enhancement of the right intracranial optic nerve and a subtle lesion of the left optic nerve were seen (Fig. 1 lower left). While metastasis to the right optic nerve was initially suspected, repeat imaging 3 months later using gadolinium-DTPA enhancement showed that both lesions had spontaneously resolved (Fig. 1 lower right). However, visual acuity remained at light perception only in the right eye; the temporal hemianopsia persisted in the left eye and optic atrophy developed.

Case 2

This 65-year-old acromegalic woman complained of sudden loss of vision in both eyes 9 months prior to our examination. She had undergone transphenoidal resection of a pituitary adenoma 3 years earlier and had received a total dose of 4500 rad of radiation therapy delivered in 25 fractions of 150 rad/day postoperatively. At the time of admission for surgery, neuro-ophthalmic examination showed 20/20 visual acuity in each eye and normal Goldmann visual fields.

Our examination revealed that visual acuity had dropped to 20/70 in the right eye and 20/30 in the left eye. A right afferent pupillary defect was elicited. Goldman visual fields showed a superior temporal defect in the right eye and a superior altitudinal defect in the left eye (Fig. 2 upper). Eye movements were normal. Bilateral optic atrophy was seen on ophthalmoscopic examination.

Magnetic resonance imaging revealed recurrence of a pituitary adenoma with parasellar extension toward the left cavernous sinus; suprasellar extension of the tumor was not seen (Fig. 2 lower pair). Prior to the administration of contrast material, the optic nerves and optic chiasm appeared normal on T1- and T2-weighted imaging. After gadolinium-DTPA administration, MR imaging revealed enhancement of the left optic nerve. Due to the absence of suprasellar extension of the adenoma, surgical intervention was not advocated. Radiation-induced optic neuropathy was believed to be the cause of blood-brain barrier disruption and accumulation of gadolinium-DTPA in the left optic nerve.

Case 3

This 51-year-old man lost peripheral vision in the left eye 2 1/2 years after transphenoidal resection of a

†Gadolinium-DTPA supplied by Berlex Laboratories, Wayne, New Jersey.
pituitary adenoma and postoperative radiation therapy. He had received a cumulative dose of 5340 rad delivered in 27 fractions. While computerized tomography (CT) during evaluation of his headaches had revealed the tumor, visual symptomatology was absent. At the time of admission for surgery, visual acuity in the right eye was limited to counting fingers at a distance of 1 foot due to traumatic injury to the globe sustained 30 years earlier, and in the left eye it was 20/20. An automated visual field was unobtainable with the right eye but normal for the left eye.

Our examination showed visual acuity was limited to counting fingers at 1 foot in the right eye and 20/25 in the left eye. The patient had a right afferent pupillary defect. Visual field testing showed a central scotoma in the right eye and a temporal hemianoptic scotoma in the left eye (Fig. 3 upper). The left optic disc was atrophic, but the right disc was not visualized with the ophthalmoscope due to opacity of media. Magnetic resonance imaging showed a recurrent pituitary adenoma within the sella and profuse gadolinium-DTPA enhancement of the optic chiasm and adjacent optic nerves, believed to be radiation induced (Fig. 3 lower pair). Both T1- and T2-weighted MR images without contrast enhancement failed to demonstrate an abnormality visualized at the sites of intrinsic gadolinium-DTPA enhancement of the optic nerves and optic chiasm. Two months later the patient's visual examination remained unchanged.

Case 4
This 64-year-old man complained of progressive visual loss in the left eye for 5 days and complete loss of vision in the right eye 3 months before. He had received radiation therapy and chemotherapy 1 year earlier for a lytic lesion of the clivus after diagnosis of multiple myeloma. A total dose of 4450 rad was delivered to the base of the skull in 17 fractions.

Visual acuity was no light perception in the right eye and 20/50 in the left eye. There was a left amaurotic pupillary defect. Goldmann visual fields were unobtainable in the right eye, but showed a superior altitudinal defect in the left eye (Fig. 4 upper). Right optic atrophy was seen on ophthalmoscopic examination, but the left optic nerve head was normal.

Computerized tomography and MR imaging showed a lytic lesion of the clivus and dorsum sellae. While the optic nerves appeared normal on T1- and T2-weighted MR imaging prior to the use of the contrast agent, enhancement of both intracranial optic nerves was seen.
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Fig. 4. Case 4. *Upper:* Goldmann visual field was unobtainable in the right eye, but showed a superior altitudinal defect in the left eye. *Lower:* Magnetic resonance image revealing profuse gadolinium-DTPA enhancement of both intracranial optic nerves (arrows).

Fig. 5. Case 5. *Upper:* Tangent-screen visual fields showing an inferior altitudinal defect in the right eye (O.D.) 3 years after transsphenoidal surgery. O.S. = left eye. *Lower Left:* Magnetic resonance (MR) image showing encephalomalacia of the left frontal cortex. Prior to contrast administration, the right optic nerve (arrow) appeared normal. *Lower Right:* An MR image following gadolinium-DTPA administration revealing enhancement of the right optic nerve.

After intravenous gadolinium-DTPA administration (Fig. 4 lower). Lumbar puncture revealed acellular cerebrospinal fluid (CSF) and the absence of malignant cells and oligoclonal bands, but an elevated protein level of 63 mg/dl. The patient declined surgical exploration and a planned biopsy of the right optic nerve ipsilateral to the blind eye, although a pathological diagnosis of a plasmacytoma involving the optic nerves could have been treated with additional chemotherapy.

Two months later visual acuity in the left eye had dropped to no light perception and optic atrophy had developed. Visual loss was believed to be radiation induced.

Case 5

This 63-year-old man complained of visual loss in the right eye 3 years after transsphenoidal resection of a craniopharyngioma. Postoperatively, he had received 6400 rad of radiation therapy delivered in 32 fractions. Visual acuity during the admission for surgery was 20/20 in the right eye and 20/40 in the left eye. Automated visual fields showed a bitemporal hemianopsia that was denser in the left eye. Three weeks after surgery, visual acuity was 20/20 in each eye and the visual field deficits had completely resolved.

Eighteen months later the patient complained of headaches, confusion, nausea, and vomiting. Magnetic resonance and CT studies showed a lesion in the left frontal cortex; a left frontal craniotomy was performed. Pathological examination of a biopsy specimen taken from the left frontal lobe revealed a grade 2 astrocytoma. Postoperatively, the patient received additional therapy with radiolabeled monoclonal antibodies.

Eighteen months subsequent to immunoradiotherapy, the patient complained of visual loss in the right eye. Our examination showed visual acuity was 20/40 in the right eye and 20/25 in the left eye. There was a right afferent pupillary defect. Tangent-screen visual fields showed an inferior altitudinal defect in the right eye, although the left eye was normal (Fig. 5 upper). Ophthalmoscopy was normal.

Magnetic resonance imaging showed encephalomalacia of the left frontal cortex and gadolinium-DTPA enhancement of the right optic nerve (Fig. 5 lower pair). No abnormality of the optic nerves or optic chiasm was seen on precontrast T1- and T2-weighted MR imaging. Two weeks later, visual acuity dropped to counting fingers at 2 feet, and optic atrophy developed in the right eye. Visual loss in the right eye was believed to be radiation induced.

Case 6

This 66-year-old woman had a 3-week history of blurred vision involving both eyes, although it was worse in the left eye. She had received 5228 rad delivered to the base of the skull in 28 fractions for a
lymphoepithelioma at this site 8 months earlier. A neuro-ophthalmic examination during admission for biopsy of this tumor showed that visual acuity was 20/25 in each eye and confrontation visual fields were normal. There was a left sixth cranial nerve palsy and decreased sensation in the distribution of the maxillary and mandibular divisions of the fifth cranial nerve. Computerized tomography showed a large nasopharyngeal mass with bone erosion at the base of the skull, widening of the left foramen ovale, and invasion of the middle cranial fossa. Six months after radiation therapy, shrinkage of the tumor was seen on MR imaging, which also revealed a small extra-axial high parietal enhancing mass consistent with a meningioma.

Our examination 8 months after radiation therapy showed that visual acuity was 20/25 in the right eye and light perception in the left eye. A left afferent pupillary defect was elicited. Automated visual fields showed a superior altitudinal defect in the right eye and a dense central scotoma in the left eye (Fig. 6 upper). Ophthalmoscopy showed that the optic discs were normal.

Magnetic resonance imaging showed marked enhancement of the left optic nerve and perhaps subtle enhancement of the right nerve (Fig. 6 lower). The T₂ weighted and spin-density images failed to show any abnormality at the sites of gadolinium-DTPA enhancement in the optic nerves.

Discussion

Neuro-Ophthalmological Evaluation

The diagnosis of visual loss after neurological surgery and radiation therapy may be unclear, even after a thorough neuro-ophthalmic examination. Optic nerve ischemia induced by radiation was suggested by the altitudinal visual field deficits in Case 2 (left eye), and Cases 4, 5, and 6. However, Cases 1, 2 (right eye), and 3 had temporal hemianopsias that appeared more consistent with chiasmal compression by a mass lesion.

Role of Surgery

The role of surgery in radiation-induced injury to the brain appears to be diagnostic, since the lesions of brain necrosis revealed by MR or CT studies are often difficult to distinguish from recurrent tumor.11,21,23 Exploratory surgery may play a dual role by the procurement of diagnostic tissue specimens and by allowing decompression of the visual pathways through resection of the culprit tumor, if present. While such intervention was not indicated in Cases 2 and 3, in whom MR imaging clearly showed the absence of suprasellar extension of the tumors, it could have provided pathological support of our clinical diagnosis of radiation-induced visual loss. Diagnostic surgery was not performed at the onset of visual loss in Case 1 due in part to the lack of benefit of additional treatment for recurrent melanoma. In Case 4, surgical intervention was declined although a pathological diagnosis of a plasma-cytoma involving the optic nerves could have been treated with additional chemotherapy. However, the absence of malignancy in the CSF and a normal serum immunoglobulin level suggested that this malignancy was in remission. Surgical exploration and pathological examination of the biopsy specimen obtained from the left frontal cortex in Case 5 revealed a secondary malignancy. At the time of recurrent visual loss, MR imaging showed that the mass lesion had resolved and encephalomalacia of the left frontal cortex was then present. In this patient, the enhancement of the right optic nerve with gadolinium-DTPA was believed to be radiation induced. Due to the lack of surgical tissue specimens in our series the diagnosis of radiation-induced visual loss was not absolute.

Radiation Therapy

While 80% of our patients received "safe" doses of radiation therapy, Case 4 received daily fractions of radiation therapy exceeding 250 rad. Such fractions have been associated with a substantially higher incidence of radiation-induced optic neuropathy, despite the fact that the cumulative dosage fell within an acceptable range.14,26,28

Utilization of radiation therapy in acromegaly is associated with a greater risk of radiation-induced optic neuropathy in comparison to other varieties of pituitary adenomas.2,4,25,29 Peck and McGovern25 described radiation necrosis of the brain in three acromegalic patients treated with 9775 rad in three fractions.
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rad in four fractions, and 8150 rad in two fractions, respectively. Schatz and coworkers' described radiation-induced visual loss in two acromegalic patients, each treated with 5000 rad in 25 fractions. Atkinson and associates' described radiation-induced visual loss in four of 23 acromegalic patients treated with 4240 rad in 15 fractions (two patients), 4380 rad in 14 fractions (one patient), and 4520 rad in 15 fractions (one patient). In a series of 87 patients with pituitary adenomas treated with 4250 rad, Hammer reported radiation-induced visual loss in three acromegalic patients, but this complication was only seen in one other patient who had a chromophobe adenoma. Two of Hammer's patients received 280 rad/day, and a third was treated with 210 rad/day. The etiology for the increased susceptibility to radiation-induced injury in acromegaly is unclear. We believe the greater susceptibility of the optic nerves to radiation-induced injury in acromegaly is illustrated by the loss of vision in our Case 2 and occurred despite her having received the lowest fractionation of radiation therapy (150 rad/day) in our series and in a review of the medical literature.

MR Imaging

The etiology of lesions in the optic nerves as visualized by MR imaging may initially be confusing. Due to the gadolinium-DTPA-enhancing lesion seen on MR imaging, our Case 1 was initially suspected of harboring metastatic melanoma to the right optic nerve. However, repeated MR imaging showing spontaneous resolution of this lesion was inconsistent with a malignant neoplasm such as melanoma, and helped us to exclude a possible recurrence of malignancy in this patient in whom visual acuity remained poor.

Magnetic resonance imaging proved most useful in excluding suprasellar compression of the optic chiasm by recurrent neoplasms of pituitary origin. Cases 2 and 3 illustrate this point best. While both patients had intrasellar and parasellar recurrence of pituitary adenomas, MR imaging with gadolinium-DTPA clearly demonstrated intrinsic lesions of the optic nerves and optic chiasm that were readily distinguishable from compression by these tumors.

Optic nerve enhancement is believed to represent radiation-induced disruption of the blood-brain barrier and accumulation of gadolinium-DTPA within the optic nerve. The damaging effects of ionizing radiation to cerebral and extracerebral vasculature are well documented. Gadolinium-DTPA enhancement of the optic nerve may indicate the persistence of endothelial cell proliferation, hyalinization and thrombosis of blood vessels that result in ischemia to the optic nerve, and the syndrome of radiation-induced optic neuropathy.

The reason for continued gadolinium-DTPA enhancement of the right optic nerve in our Case 4 at 3 months after loss of vision in the right eye is unclear. However, the persistence of this finding may indicate that pathological processes were still in an active phase and were a threat to vision in the contra-lateral eye, which was ultimately lost. On the other hand, resolution of gadolinium-DTPA enhancement of the right optic nerve in our Case 1 suggests that remission of this disorder may no longer have posed a threat to vision in his contralateral eye.

Gadolinium-DTPA enhancement of intracranial lesions on MR images is nonspecific. Disruption or absence of the blood-brain barrier in tumor vessels results in the enhancement of intracranial neoplasms that are also visualized by nonenhanced MR imaging. Displacement of the optic nerves and chiasm would have been visualized on precontrast T₁- and T₂-weighted MR images if recurrent tumor had been the cause of visual loss by compression of the anterior visual pathways. The gadolinium-DTPA enhancement of the optic nerves and optic chiasm is nonspecific and may also be associated with infectious and noninfectious inflammatory disorders, metastatic tumors, and leptomeningeal spread of tumor, among other causes. Other disorders with documented alterations in permeability of the blood-brain barrier include optic neuritis and multiple sclerosis.

No abnormalities of the optic nerves and optic chiasm were seen on T₂-weighted images in our patients despite the often florid enhancement with gadolinium-DTPA on T₁-weighted images. Brain lesions that enhance with paramagnetic contrast agents are also typically bright on T₂-weighted images. Since the optic nerves and optic chiasm are extensions of the brain, abnormalities are to be anticipated on T₂-weighted images. Several factors may have contributed to the absence of such findings. The spatial resolution of the T₂-weighted images is far less than that of the T₁-weighted images. The lower signal-to-noise ratio of T₂-weighted images does not allow the thinner sections and smaller field of view achievable on the T₁-weighted images with or without contrast medium. Consequently, for modest lesions in relatively small structures such as the optic nerve and optic chiasm, this can contribute to a failure to detect the gadolinium-DTPA-enhancing lesions visible on T₁-weighted images. Another factor probably contributing to the difficulty in discerning abnormalities of the anterior visual pathways on T₂-weighted images is that the contrast between the anticipated bright lesion of the optic chiasm, nerves, and tracts may be difficult to visually separate from the surrounding bright CSF in the suprasellar cistern. In other regions of the brain, bright lesions on T₂-weighted images stand out due to their contrast with the surrounding darker white matter. While other pulse sequences of weighting intermediate between T₁ and T₂ might have been of some benefit in showing a contrast difference, our Case 6 had a proton-density T₂-weighted dual-echo sequence that failed to show any abnormality of the optic nerves or optic chiasm. It is also possible that disruption of the blood-brain barrier resulting in gadolinium-DTPA enhancement might occur prior to the pathological changes that result in abnormalities on T₂-weighted images, such as in the early lesions associ-
ated with disorders of primary demyelination of the central nervous system (CNS). The failure of T$_1$-weighted imaging to visualize certain CNS lesions revealed by gadolinium-DTPA enhancement on T$_2$-weighted images is not unique to our study.

While pathological confirmation of radiation-induced damage was absent, our series indicates that MR imaging with gadolinium-DTPA may help to differentiate the intrinsic abnormalities of the optic nerves and chiasm associated with radiation-induced optic neuropathy from compression of suprasellar tumors. This neuro-imaging procedure may help to avert exploratory surgery in patients with recurrent neoplasm in whom the etiology of visual loss is uncertain.

References

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