

Short report

Early-delayed radiation rhombencephalopathy

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SUMMARY A 37-year-old woman developed an early-delayed rhombencephalopathy 7 weeks after completing a course of radiotherapy to a glomus jugulare tumour. The clinical features, comprising nystagmus, skew strabismus, unilateral facial weakness, dysarthria and ataxia, are compared with four previously reported patients with this syndrome.

The adverse effects of radiation on the brain have been customarily classified into acute, late-delayed and early-delayed reactions. Acute reactions occur during the course of the radiotherapy or immediately afterwards and most commonly consist of mild transient symptoms of nausea, vomiting, headache and fever.¹ Other examples of acute reaction are the transient deterioration which may follow irradiation of a brain tumour¹ and the severe, often fatal acute encephalopathy developing after combined chemotherapy and radiotherapy for meningeal leukaemia.²

Late-delayed encephalopathy³ is the most common reaction to brain irradiation, occurring months to years after treatment. It results in focal necrosis of the irradiated brain and often presents as a space occupying lesion; the course is usually progressive and the treatment is excision of the necrotic tissue.

Early-delayed encephalopathy occurs six to 12 weeks following cessation of radiotherapy and may take several forms. A syndrome comprising somnolence, fever, anorexia and occasionally EEG changes is not infrequently seen transiently after prophylactic cranial irradiation for leukaemia.^{4,5} Irradiation of brain tumours may be associated with a transient neurological deterioration in the early-delayed period in as many as half of the patients.⁶ An unusual syndrome of early-delayed brain stem dysfunction with characteristic clinical and neuropathological features was first described in 1963 by

Rider⁷ in three patients who received incidental irradiation of their posterior fossa during treatment for neoplasms in or around the middle ear. The necropsy of one of these three patients has been reported⁸ and a further case with similar clinical and pathological features was described by Lampert and Davis in 1964.⁹ Although reference is made to this early-delayed rhombencephalopathy in reviews of radiation-induced brain damage,^{3,10} no further examples of this syndrome have been reported. We report here a case of early-delayed radiation reaction, clinically identical to the four cases of Rider⁷ and Lampert and Davis,⁹ but associated with a cerebrospinal fluid pleocytosis and a clinical improvement during steroid therapy.

Case report

A 37-year-old right-handed woman presented with a seven year history of left sided tinnitus and deafness. A left glomus jugulare tumour was diagnosed by biopsy of material in the left middle ear. She underwent a left radical mastoidectomy and sub-total excision of the tumour. Post operative angiograms showed some residual tumour in the jugular bulb, but neither a CT scan nor the angiogram showed any intracranial extension of the tumour. She received radiation to the tumour as shown in the figure. The modal tumour dose was 4940 rads in 20 fractions over 26 days. The maximum tumour dose was 5200 rads and the mean dose for the brain stem was 1950. The posterior oblique field (field 1) was 6 × 6.5 cm, 120% weighted with a 50° wedge; the anterior oblique field (field 2) was 6 × 7 cm, 100% weighted with a 50° wedge.

Seven weeks after cessation of radiotherapy she woke with diplopia and later that day developed mild ataxia of gait. Three days later the diplopia and ataxia became

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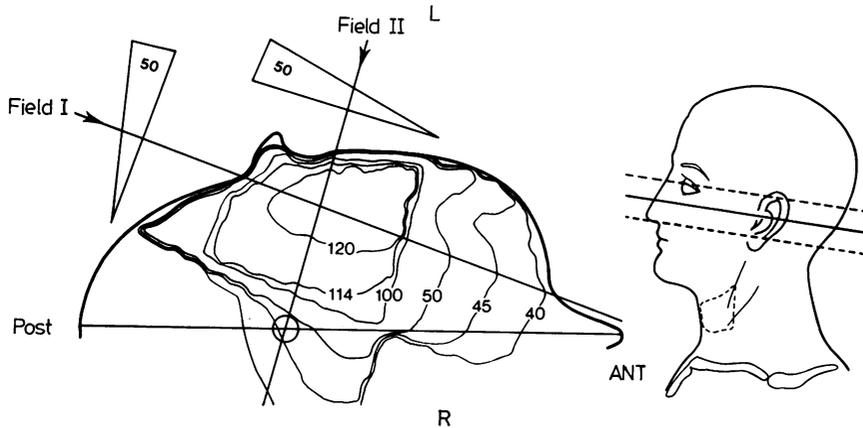


Figure Axial section of the head in the plane of irradiation.

worse over a period of 36 hours and in addition she developed mild slurring dysarthria and incoordination of the left arm. At this time she showed no abnormality on examination of the cardiovascular, respiratory or abdominal systems and she was normotensive. The positive findings on neurological examination were bilateral conjugate phasic horizontal nystagmus on lateral gaze, most marked on gaze left, failure of full abduction of the left eye producing diplopia, mild weakness of the left side of the mouth, deafness of the left ear, moderate slurring dysarthria, ataxia of the left arm, and trunkal ataxia. In other respects examination of her higher cerebral functions, cranial nerves, limbs and gait revealed no other abnormality. Her reflexes were brisk and symmetrical and the plantars flexor. The following investigations were normal; full blood count, erythrocyte sedimentation rate, anti-nuclear factor, auto-antibody screen, serology, urea, electrolytes, glucose, liver function tests, calcium, phosphate, ECG, CT scan, EEG. A lumbar puncture gave CSF at a pressure of 80 mm of water, with 14 lymphocytes/ μ l, protein 0.31 g/l, IgG 7%.

She received a course of dexamethasone reducing over seven weeks and a three day course of an intravenous high dose multivitamin preparation. During the first month the clinical features remained unchanged except that she developed a skew strabismus on gaze left due to failure of depression of the right eye and of elevation of the left. Since then there has been a gradual progressive improvement and 6 months after the onset of the brain stem disturbance she had a mild slurring dysarthria, mild trunkal ataxia and a slight asymptomatic skew strabismus. There has been no clinical evidence of recurrence of her glomus jugulare tumour.

Discussion

The four cases described by Rider⁷ and by Lampert and Davis⁹ and the case that we report show a striking uniformity in the radiation parameters, interval between radiation and presentation and the clinical features. The necropsy findings of the two

patients who died soon after the onset of the syndrome are also very similar.^{8,9} Of the three patients described by Rider,⁷ one had a recurrent basal cell carcinoma in the middle ear, another a squamous cell carcinoma of the middle ear and a third had a glomus tumour of the jugular bulb as did the patient whom we report. All three patients received a maximal tissue dose of about 5500 rads of cobalt-60 radiation, over approximately one month. The number of fractions varied from 27 to 16. Although the fields were different in each case, all were in the same axial plane as our patient and a similar dose of radiation was delivered to the brain stem and adjacent tissues. The patient reported by Lampert and Davis⁹ received a tumour dose of 5702 rads by a multiple field technique for a carcinoma of the left tonsil, but they did not provide information about the duration and fractionation of the radiation, orientation of the fields or estimated radiation dose to the brain stem.

In each of these four cases a similar clinical syndrome developed two to three months after finishing the course of radiation. Rider's patients suffered nausea and vomiting, soon followed by ataxia, dysarthria and dysphasia; examination showed gross cerebellar ataxia, horizontal nystagmus and Romberg's sign. One patient has a sixth nerve palsy and extensor plantar response. The patient reported by Lampert and Davis⁹ developed ataxia, left hemiparesis, right 12th cranial nerve paresis and nystagmus over a period of two days. In all four patients investigation was normal including CSF examination. These clinical features are similar to those of our patient, who developed ataxia, dysarthria and an ophthalmoplegia over a few days, seven weeks after finishing radiotherapy; the CT scan was normal but unlike the previously described cases, the CSF contained an excess of lymphocytes.

The outcome in this syndrome is variable. Two of Rider's⁷ patients began to recover within four weeks and were well within 6 to 8 weeks, but the patient with the recurrent basal cell carcinoma and the patient of Lampert and Davis⁹ died four weeks and one week respectively after the onset of the brainstem disturbance. Our patient showed a gradual improvement while taking steroids and six months after the onset of the rhombencephalopathy her slight neurological deficits were not troublesome. The patients of Rider⁷ and of Lampert and Davis⁹ received no specific treatment: it is not known whether the steroids influenced the clinical course of our patient. Necropsy^{8,9} of the two patients who died revealed a similar picture of disseminated patchy demyelination that was restricted to the volume of tissue irradiated and that was maximal in those parts which received the highest dose. Microscopic examination demonstrated a marked astrocytic, microglial and lymphocytic response associated with the focal demyelination. The vascular and necrotic changes that are observed in the late-delayed radiation reaction were absent.

Since oligodendrocytes are particularly sensitive to radiation¹¹ and since the turnover time of myelin is between five weeks and two months,¹² it has been suggested^{6,7,13} that the early-delayed radiation reaction may be due to a transient abnormality in the biochemical mechanisms that maintain myelin. Early-delayed rhombencephalopathy may be related to the transient neurological symptoms such as dysaesthesia or Lhermitte's phenomenon which are not uncommon three to four months following irradiation of the spinal cord.^{13,14} The similarity of this transient radiation myelopathy both to early-delayed rhombencephalopathy and to multiple sclerosis suggests that it is also associated with demyelination. There are no histological reports of necropsies performed during or soon after the onset of this cord syndrome, though Jones¹³ reports a patient dying 10 months following a transient radiation myelopathy whose cord showed "a little myelin pallor". Mastaglia¹⁵ examined the spinal cord of rats during the early-delayed period following a single dose of 100-6000 rads and noted a breakdown of paranodal myelin and nodal widening, as well as a generalised and random degeneration throughout the white matter. Lecky *et al*¹⁶ obtained normal spinal somatosensory evoked potentials measured directly after and six months after incidental cord irradiation in six patients, including two patients who developed transient neurological symptoms.

Early-delayed rhombencephalopathy following incidental brain stem irradiation is rare. No other cases have been observed at the Regional Radiotherapy Centre in Newcastle upon Tyne among 26

patients with glomus jugulare or middle ear tumours who received similar radiation doses to the patients who developed early-delayed rhombencephalopathy. However, subclinical demyelination may have occurred and some patients may not have reported transient mild symptoms. It is not known why only a few patients should develop clinically significant early-delayed radiation rhombencephalopathy; an inherited diathesis or a concomitant acquired subclinical CNS disorder, such as multiple sclerosis, may be responsible.

References

- 1 Young DF, Posner JB, Chu F, Nisce L. Rapid-course radiation therapy of cerebral metastases: results and complications. *Cancer* 1974;**34**:1069-76.
- 2 Oliff A, Bleyer WA, Poplack DG. Acute encephalopathy after initiation of cranial irradiation for meningeal leukaemia. *Lancet* 1978;**2**:13-15.
- 3 Sheline GE, Wara WM, Smith V. Therapeutic irradiation and brain injury. *Int J Radiat Oncol Biol Phys*;1980;**6**:1215-28.
- 4 Freeman JE, Johnston PGB, Voke JM. Somnolence after prophylactic cranial irradiation in children with acute lymphoblastic leukaemia. *Br Med J* 1973;**4**:523-5.
- 5 Parker D, Malpas JS, Sandland R, Sheaff PC, Freeman JE, Paxton A. Outlook following "somnolence syndrome" after prophylactic cranial irradiation. *Br Med J* 1978;**4**:554.
- 6 Hoffman WF, Levin VA, Wilson CB. Evaluation of malignant glioma patients during the postirradiation period. *J Neurosurg* 1979;**50**:624-8.
- 7 Rider WD. Radiation damage to the brain—a new syndrome. *J Canad Assoc Radiol* 1963;**14**:67-9.
- 8 Lampert P, Tom MI, Rider WD. Disseminated demyelination of the brain following Co⁶⁰ (Gamma) radiation. *Arch Pathol* 1959;**68**:322-30.
- 9 Lampert PW, Davis RL. Delayed effects of radiation on the human nervous system. "Early" and "late" delayed reactions. *Neurology (Minneapolis)* 1964;**14**:912-7.
- 10 Cairncross JG, Posner JB. Neurological complications of malignant lymphoma. In: Vinken PJ, Bruyn GW, eds. *Handbook of Clinical Neurology, Vol 39*. Amsterdam: North Holland Publishing, 1980:27-62.
- 11 Zeman W, Samorajski T. Effects of radiation on the nervous system. In: Berdjis CC, ed. *Pathology of Irradiation*. Baltimore: Williams and Wilkins, 1971:213-7.
- 12 Norton WT. Myelin. In: Albers RW, Siegel GJ, Katzman R *et al*, eds. *Basic Neurochemistry*. Boston: Little, Brown and Company, 1972:365-84.
- 13 Jones A. Transient radiation myelopathy (with reference to Lhermitte's sign of electrical paraesthesia). *Br J Radiol* 1964;**37**:727-44.
- 14 Boldrey E, Sheline G. Delayed transitory clinical

- manifestations after radiation treatment of intracranial tumours. *Acta Radiol (Ther) (Stockh)* 1966; **5**:5-10.
- ¹⁵ Mastaglia FL, McDonald WI, Watson JV, Yogendran K. Effects of X-radiation on the spinal cord: an experimental study of the morphological changes of the central nervous fibres. *Brain* 1976;**99**:101-22.
- ¹⁶ Lecky BRF, Murray NMF, Berry RJ. Transient radiation myelopathy: spinal somatosensory evoked responses following incidental cord exposure during radiotherapy. *J Neurol Neurosurg Psychiatry* 1980; **43**:747-50.