

SHORT REPORT

Diffusion weighted imaging in radiation necrosis

V Biousse, N J Newman, S B Hunter, P A Hudgins

J Neurol Neurosurg Psychiatry 2003;**74**:382–384

This case report suggests that magnetic resonance imaging with diffusion weighted imaging may help distinguish between tumour recurrence and radiation induced necrosis in patients previously treated for a brain tumour.

Although non-invasive imaging techniques such as positron emission tomography (PET), single photon emission computed tomography (SPECT), magnetic resonance imaging (MRI), spectroscopy MRI, and dynamic susceptibility contrast MRI have improved our ability to diagnose radiation necrosis, the definite diagnosis of this condition may be difficult and brain biopsy is often required.^{1,2} We report a case supporting the use of diffusion weighted MRI to differentiate radiation necrosis from tumour recurrence.

CASE REPORT

A 30 year old woman presented with a one week history of progressive right hemiparesis, ataxia, and diplopia. Her past medical history was notable for a low grade cerebellar pilocytic astrocytoma in the region of the vermis, which was surgically resected when she was 15 years old. Eight years later, she developed bilateral fourth nerve palsies. Repeat MRI revealed abnormal tissue at the superior aspect of the vermis. Suboccipital craniectomy and tumour debulking were repeated, and pathology confirmed recurrence of a pilocytic astrocytoma. The patient subsequently underwent external radiation therapy (total dose of 5400 R to the whole brain, the tumour bed, and the spinal axis) and recovered well. Yearly follow up MRI showed stable clinical and neuroimaging findings, consisting of postoperative changes in the posterior fossa from the previous midline craniotomy, and mild encephalomalacia in the medial cerebellar hemispheres.

At age 30 years old (seven years after the last recurrence), she developed a right hemiparesis over one week, associated with binocular horizontal diplopia. On examination, she had a right hemiparesis sparing the face, without sensory abnormality. It was associated with a bilateral cerebellar syndrome, worse on the right, and with left sixth and seventh cranial nerve palsies.

Repeat MRI showed a small amount of nodular soft tissue within the fourth ventricle, which was unchanged compared with her previous MRI examinations, consistent with postoperative changes. There was also a new oval area of signal abnormality (11 × 9 mm) in the left upper pons which was hypointense on T1 weighted imaging and hyperintense on T2 weighted imaging. This lesion did not enhance (fig 1).

A round lesion (12 × 12 mm) in the medial right temporal lobe and a smaller lesion in the lateral aspect of the right cerebral peduncle were hyperintense on both T1 and T2 weighted images. Neither of these lesions enhanced. On the T2 weighted gradient echo, these two lesions were mildly hypointense, suggesting small areas of haemorrhage consistent with occult vascular malformations. The periventricular white matter

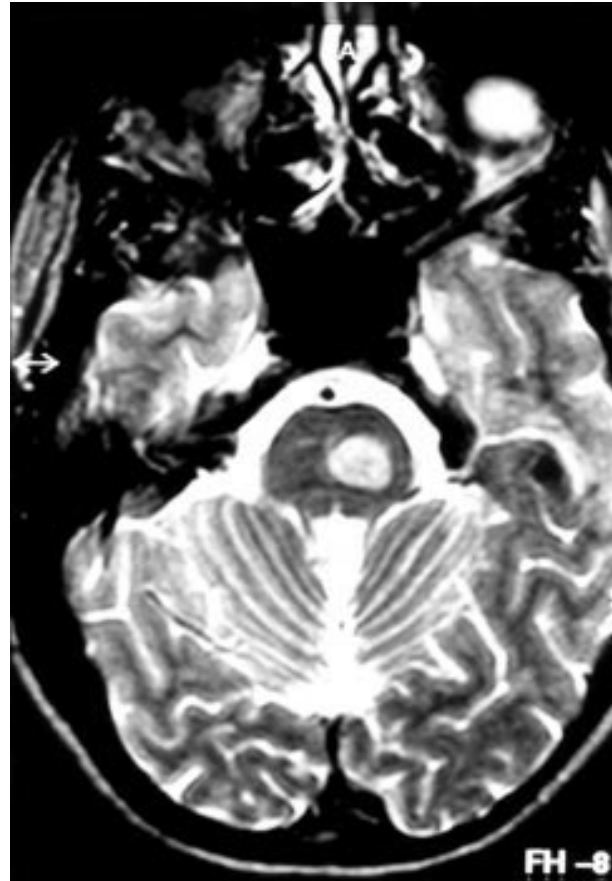


Figure 1 Axial T2 weighted image showing a round hypersignal in the pons.

appeared hyperintense on the T2 weighted image, consistent with the radiation therapy. PET with fluorodeoxyglucose (FDG) failed to show any area of increased tracer activity. The MRI was repeated with diffusion weighted images. The lesion in the left upper pons and the lesion in the medial right temporal lobe appeared hyperintense. On the apparent diffusion coefficient (ADC) map, the medial right temporal lobe lesion was slightly hyperintense, suggesting a T2 shine-through effect. The upper pons lesion was hypointense, suggesting restricted diffusion (fig 2). Magnetic resonance angiography of the cervical and intracranial vessels was normal. A coagulation work up and echocardiography were obtained and were normal.

The new symptomatic lesion in the left upper pons was believed inconsistent with a recurrence of the primary tumour or a radiation induced tumour. The DWI findings were suggestive of pontine infarction, but radiation necrosis could not be ruled out. Biopsy of the lesion showed no evidence of

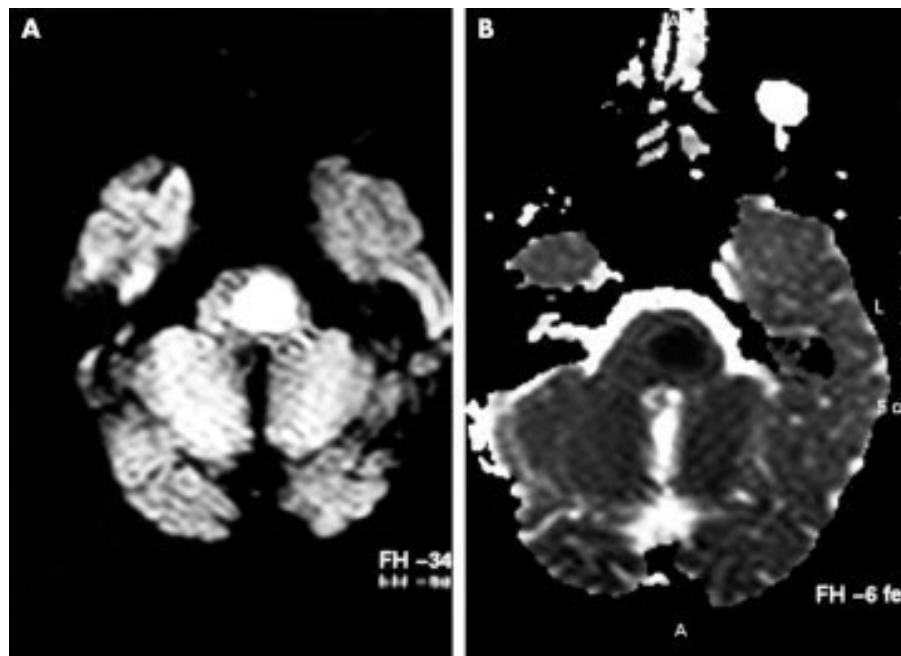


Figure 2 (A) Diffusion weighted image showing the pontine lesion as a hypersignal. (B) The same lesion is hypointense on the ADC map, suggesting restricted diffusion.

tumour; there were areas of necrosis and hyalinisation associated with thick wall blood vessels, consistent with the diagnosis of radiation necrosis.

DISCUSSION

The appearance of a new lesion seven years after radiation treatment for a primary brain tumour may represent recurrence of the tumour, radiation induced demyelination, radiation necrosis of the brain, ischaemic stroke secondary to radiation induced vasculopathy, or rarely a secondary tumour or occult vascular malformation. It can be difficult to distinguish accurately among these possibilities, especially as the clinical features of these pathological conditions and their CT and MRI appearances can be quite similar.¹⁻³ Our patient's neuroimaging showed many of these late complications from radiation treatment.

Chronic radiation injury leads to a diffuse leucodystrophy with confluent regions of subcortical gliosis and demyelination. It also damages cerebral capillaries, rendering the blood-brain barrier abnormally permeable, which explains the enhancement sometimes seen on cerebral MRI in regions of radiation necrosis. This makes the distinction between radiation necrosis and tumour recurrence very difficult in some patients.¹⁻³ Tumour recurrence was unlikely in our patient. Indeed, the pontine lesion was remote from the tumour's primary site, it appeared very bright on the T2 weighted image, it did not enhance on the MRI, there was no mass effect, and our patient's FDG-PET did not show increased uptake of the FDG in the pons. SPECT and PET studies (especially FDG-PET) are now widely used to evaluate the metabolic activities of brain tumours and are usually helpful in differentiating tumour recurrence from radiation necrosis. However, these techniques are costly and require the use of a radioactive tracer.¹ Recently developed MRI techniques such as dynamic contrast enhanced MRI and proton magnetic resonance spectroscopy have also been used in patients with brain tumours. However, because of low spatial resolution, discrepant results have been reported.²

Although Le Bihan *et al* suggested more than eight years ago that tumour recurrence and radiation damage might be distinguished using diffusion weighted imaging,⁴ we have

been able to find only two anecdotal cases of radiation necrosis in which diffusion weighted imaging was done.^{5,6} Le Bihan *et al* hypothesised that high perfusion would be shown in tumour recurrence, while radiation damage would cause low perfusion and apparently decreased diffusion; these were the findings in our patient and in the two previously reported cases.^{5,6}

Pontine infarction was suggested by the radiological findings in our patient, and she underwent a workup looking for causes of cerebral infarction. Radiation induced vasculopathy may affect both the large arteries (such as the basilar artery) and the small perforating vessels, and may cause infarction of any size. Pathology showed evidence of necrosis at the level of the pons, which is non-specific and could result from either infarction or radiation necrosis. However, the presence of thickened blood vessels in addition to necrosis made the diagnosis of radiation induced necrosis more likely.

The appearance of radiation induced necrosis on diffusion weighted imaging is of great interest as this may represent a non-invasive inexpensive way to distinguish between tumour recurrence and radiation necrosis in patients previously treated for a primary brain tumour, and result in a reduced number of brain biopsies. The fact that radiation necrosis presents as restricted diffusion on diffusion weighted imaging is not surprising given the potential role of ischaemia in the occurrence of radiation necrosis.

Authors' affiliations

V Biousse, N J Newman, Departments of Neurology, Neurological Surgery, and Ophthalmology, Emory University School of Medicine, Atlanta, Georgia, USA

S B Hunter, Department of Pathology, Emory University School of Medicine

P A Hudgins, Department of Radiology, Emory University School of Medicine

Competing interests: none declared

Correspondence to: Dr Valérie Biousse, Neuro-Ophthalmology Unit, Emory Eye Center, 1365-B Clifton Rd, Atlanta, Georgia 30322, USA; vbiousse@emory.edu

Received 6 June 2002

In revised form 15 August 2002
Accepted 11 November 2002

REFERENCES

- 1 **Amirjamshidi A**, Abbassioum K. Radiation-induced tumors of the central nervous system occurring in childhood and adolescence. *Childs Nerv Syst* 2000;**16**:390–7.
- 2 **Kumar AJ**, Leeds NE, Fuller GN, et al. Malignant gliomas: MR imaging spectrum of radiation therapy- and chemotherapy-induced necrosis of the brain after treatment. *Radiology* 2000;**217**:377–84.
- 3 **Sugahara T**, Korogi Y, Tomiguchi S, et al. Posttherapeutic intraaxial brain tumor: the value of perfusion-sensitive contrast-enhanced MR imaging for differentiating tumor recurrence from nonneoplastic contrast-enhancing tissue. *Am J Neuroradiol* 2000;**21**:901–9.
- 4 **Le Bihan D**, Turner R, Douek P, et al. Diffusion MR Imaging: clinical applications. *Am J Roentgenol* 1992;**159**:591–9.
- 5 **Park SH**, Chang KH, Song IC, et al. Diffusion-weighted MRI in cystic or necrotic intracranial lesions. *Neuroradiology* 2000;**42**:716–21.
- 6 **Tung GA**, Evangelista P, Rogg JM, et al. Diffusion-weighted MR imaging of rim-enhancing brain masses: is markedly decreased water diffusion specific for brain abscess? *Am J Radiol* 2001;**177**:709–12.

HISTORICAL NOTE

Neurofibromatosis

Friedrich Daniel von Recklinghausen (1833–1910) was born in Gütersloh, Westphalia, and graduated in Berlin in 1855. In 1881, as a tribute to Rudolf Virchow's 25th year Jubilee, he wrote his classical article on neurofibromatosis.¹ The first patient, a 55 year old woman who was admitted because of lung haemorrhages, died a few hours after admission to the hospital and was autopsied. Skin tumours had been present since the age of 3. At autopsy the following findings were noted:

"Innumerable nodules, almost over the entire outer skin layer (Plate 1), for the most part on stalks, while others sat on broad bases and were mostly simple spheres in all possible sizes. The larger ones, however, were especially polypous, up to 5 cm long and 4 cm thick, all covered with completely intact, almost smooth skin; although on the sacrum there was a flatly pressed, mushroom-shaped nodule, lightly ulcerated on its surface, while another small ulcerated nodule appeared on the left side of the trunk . . .

In general, the skin of the entire body had a dirty brown colour; closer examination revealed the existence in many places, particularly on the trunk and throat, of innumerable brown pigmentation spots . . .

On the left side, on the femoral nerve, in the middle of the thigh below the origin of the saphenous nerve, there was a spindle-shaped tumour 32 mm long, 7 mm thick, running along the posterior side of the nerve. At the knee was another small tumour on the saphenous nerve. There were small tumours on the muscle rami of the femoral nerve. The lateral cutaneous (femorocutaneous) nerve exhibited two tumours, one below the branching point on the upper ramus, the other a hand-width above it . . .

The spinal cord and brain were unremarkable, even under microscopic examination. Death resulted from pulmonary haemorrhage from a pulmonary artery aneurysm."

The autopsy report was followed by a histological description: there were no signs of nerve fibre neoplasia or "fatty degeneration". Even in larger neurinomas, the nerve fibres could be distinguished. Although still myelinated, some fibres showed an increase of connective tissue.

The second case history was a 47 year old man with unaffected relatives; he had observed the number of skin tumours had increased since he was 15. Von Recklinghausen found enlargement of the peripheral nerves he could distinguish from skin fibromas. With his colleague, Friedrich Jolly, he noted normal sensibility for pain as well as the irritability of the muscle by electric stimulus of the median nerve. Four small nodules examined microscopically disclosed the same findings as in the first case. He decided that "fibromas formed in the greater trunks in layers, but at first started in primitive nerve fibres."

An earlier account of generalised neurofibromatosis is contained in a monograph by RW Smith (1849),² who refers to

www.jnnp.com

many prior examples, but Von Recklinghausen first provided the necessary histological detail and demonstrated a hereditary disease characterised by *café au lait* spots combined with multiple peripheral nerve tumours and other dysplastic abnormalities of the skin, nervous system, bones, endocrine organs, and blood vessels.³

We now know that the neurofibroma is the hallmark lesion of NF1, whereas the schwannoma is the typical peripheral nerve tumour of NF2. The NF1 gene product is neurofibromin, a negative regulator of signal transduction; this suggests possible approaches for treatment. Von Recklinghausen is remembered for three distinct discoveries:

- (a) multiple neurofibromatosis;
- (b) osteitis fibrosa cystica (hyperparathyroidism);
- (c) Haemochromatosis.

He was assistant to Virchow for 6 years, then became Professor of Pathology, first at Königsberg, next Würzburg, and in 1872 at Strasburg, where he remained an active teacher and researcher until his death. Trousseau gave the 'first description' of haemochromatosis, in 1865,⁴ but von Recklinghausen in 1889 provided the name with a full description.⁵ In 1862, while still Virchow's assistant, he published two important papers, one showing that connective tissue contained spaces, which were drained by lymphatics⁶ and in which cells were present: 'von Recklinghausen's canals'. He showed these cells had amoeboid movements and identified them as leukocytes. He identified granular cells in the mesentery of the frog, later named mast cells by Ehrlich (1879).

He established the method of using silver to stain the lines cell junctions and his work led to Cohnheim's studies on leukocyte migration and inflammation. Cohnheim was an assistant in the laboratory at that time.

He was a typical histopathologist of his time but even though he had made vital contributions to the early understanding of inflammation he was resistant to certain changes such as the introduction of the microtome. He trained many leaders in German pathology, including Friedlander Zahn and Aschoff. A colourful personality, he was an industrious enthusiast, but strangely opposed Koch's concept that the tubercle bacillus was the cause of tuberculosis. He was considered second only to Virchow in an era of great German pathologists.

J M S Pearce

304 Beverley Road, Anlaby, Hull HU10 7BG, UK; jmspearce@freenet.co.uk

References

- 1 **Crump T**. Translation of case reports in Ueber die multiplen Fibrome der Haut und ihre Beziehung zu den multiplen Neuromen by F. v. Recklinghausen. *Adv Neurol* 1981;**29**:259–75.
- 2 **Wilson SAK**. *Neurology*. London: Edward Arnold, 1940:1526.
- 3 **Pearce JMS**. The central nervous system pathology in multiple neurofibromatosis. *Neurology* 1967;**17**:691–7.
- 4 **Trousseau A**. Glycosuria saccharine diabetes. In: *Lectures on clinical medicine*, vol 3. London: New Sydenham society 1870:491–527.
- 5 **Von Recklinghausen FD**. Über haemachromatose. *Berlin klin wscrh* 1889;**26**:295–6
- 6 **Von Recklinghausen FD**. *Die lymphgefasse und ihre beziehung zum bindegewebe*. Berlin: A. Hirschwald 1862.