Cerebral radiation necrosis complicating stereotactic radiosurgery for arteriovenous malformation

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Abstract
A patient presented with symptoms and signs of raised intracranial pressure and increasing focal deficit 13 months after stereotactic radiosurgical treatment of an arteriovenous malformation (AVM). Computed Tomography (CT) showed a mass lesion at the site of the previous abnormality typical of radiation necrosis, but with features identical to those of a malignant neoplasm. Biopsy confirmed cerebral radiation necrosis. The radiation dose was 25 Gray to the periphery of two overlapping 14 mm collimator fields, delivered in a single dose. Treatment with steroids led to improvement in the symptoms and signs of raised intracranial pressure, but not the focal deficit. Radiation necrosis is a consequence of the large doses required to obliterate AVMs and is a limiting factor in their treatment. It is important for clinicians referring patients for stereotactic radiosurgery to be aware of this complication, and to be able to recognise and treat it.

Late radiation necrosis that occurs after cranial irradiation was first described in 1930 by Fischer,1 and has been extensively reported since.2-17 There is only one report of radiation necrosis after stereotactic radiosurgery for AVMs, affecting three of 135 patients treated in Sweden,18 and this is the first report of radiation necrosis following AVM radiosurgery in the United Kingdom, documented with both radiology and histology.

Case report
An eighteen year old girl presented in 1965 with sudden severe headache and drowsiness, while she was 36 weeks pregnant. She had a dense left hemiparesis and a temporal visual field deficit. Cerebral angiography showed an AVM in the region of the right basal ganglia, supplied by both anterior and middle cerebral arteries, with a small contribution from the posterior cerebral artery. She was not offered operation, and improved, but was left with a mild hemiparesis. Twenty two years later she developed sudden headache and worsening of the left hemiparesis. Computed tomography (CT) showed calcification in the region of the right basal ganglia, and haematoma extending into the lateral ventricle. Angiography showed a 14 mm by 22 mm by 30 mm AVM (fig 1a). Operation was declined, and she was referred for stereotactic radiosurgery which was performed at the national centre in Sheffield. Two overlapping 14 mm collimator fields were used to deliver 25 Gray to the periphery of the lesion in a single dose.

Figure 1  Right Carotid Angiogram, (a) AVM fed by anterior and middle cerebral arteries. (b) 13 months after treatment, demonstrating almost complete obliteration of the AVM, and an avascular mass between the anterior and middle cerebral vessels.
Figure 2  CT. (a) 3 months after treatment; calcification in the right basal ganglia region and surrounding region of low attenuation. (b) 13 months after treatment; peripherally contrast enhancing mass, with surrounding low attenuation region and mass effect. (c) 18 months after treatment; resolution in mass effect and reduction in low attenuation region size.

Thirteen months after receiving radiosurgery she developed headache, vomiting, reduced short term memory, increased left hemiparesis and bilateral papilloedema. At the site of the previous AVM the CT showed an irregular peripherally contrast enhancing mass with extensive white matter oedema and midline shift (fig 2b). Angiography showed complete obliteration of the AVM (fig 1b), except for a small residuum fed by the posterior cerebral artery. As the CT appearances were compatible with either radiation necrosis or a malignant tumour, stereotactic biopsy was performed. Histology showed the typical features of cerebral radiation necrosis; endothelial proliferation, intramural thrombus, perivascular lymphocyte cuffing and fibrinoid necrosis (fig 3).

She was treated with dexamethasone for three months. The symptoms and signs of raised intracranial pressure disappeared, but the hemiparesis became worse. After stopping steroids her condition remained static. CT 18 months after treatment showed resolution of the surrounding oedema, and considerable reduction in the size of the mass lesion (fig 2c).

Of the first 93 patients with an arteriovenous malformation who have been treated in Sheffield, this patient is the first to develop radiation necrosis. All have been treated using 8 mm, 14 mm or 18 mm collimator systems, 61 with single fields, 26 with two adjacent fields and six with three more fields. The treatment volume (the volume receiving at least 50% of maximum dose) was 5278 mls. Seventeen other patients have had a similar volume treated, and three have had a larger volume irradiated, the maximum being 10366 mls.

**Discussion**

Stereotactic radiosurgery permits a high dose of ionising radiation to be delivered to a localised volume of brain. The dose is delivered using precisely collimated narrow beams of radiation, enabling a steep dose gradient to be achieved. Sharply circumscribed lesions can be produced, with little exposure of adjacent tissue. Stereotactic radiosurgery has been used to treat intracranial tumours such as pituitary adenomas, pinealomas, acoustic schwannomas and meningiomas, as well as functional disorders such as intractable pain, trigeminal neuralgia, Parkinson’s disease and epilepsy. More recently it has been used to treat surgically inaccessible AVMs; in a series of 104 patients with AVMs, Leksell described total obliteration in 87% of patients two years after treatment.16

Three groups of brain reactions to external beam irradiation are described: acute reactions which occur during treatment; early delayed reactions which occur a few weeks to three months after completion of radiotherapy, and late delayed reactions which occur from several months to many years later.16 Acute and early
delayed reactions are usually self-limiting. Late delayed reactions are of two types; loss of volume due to cerebral atrophy, or a mass lesion, clinically and radiologically mimicking a malignant tumour. Both may be progressive or irreversible. The three cases reported by Steiner, following stereotactic radiosurgery, presented with mass lesions which responded to steroids, or were self limiting.19

There are many case reports of cerebral radiation necrosis following external beam radiotherapy, but few correlate the number of cases affected with the population treated. Risk factors for radiation necrosis include total dose, treatment time and dose fractions. Using these three parameters Ellis calculated a Nominal Standard Dose (NSD) to standardise the biological effect of different treatment regimes. This has been modified by various authors to estimate the threshold above which cerebral radiation necrosis occurs.20-23 Patient risk increases with higher dose, or the same dose given in a shorter period, or in fewer fractions. Stereotactic radiosurgery uses large doses of irradiation (up to 100 Gray) to small volumes of tissue (up to 30 mm diameter) in a single fraction. The dose per unit volume of tissue, even at the periphery of the lesion, is many times greater than that used in conventional external beam irradiation. This is likely to lead to more cases of brain necrosis, albeit confined to a small volume of tissue. The three previously reported cases received doses of more than 60 Gray to a single field, or more than 40 Gray to two overlapping fields.19

The response of blood vessels to irradiation consists of reactive proliferation of the endothelial lining and subendothelial connective tissue, which may subsequently obliterate the lumen. This is the basis of the therapeutic effect of radiation on AVMs.19 Similar vascular features are seen in delayed cerebral radiation necrosis; thickened vessel walls, endothelial proliferation, fibrinoid necrosis, hyaline and amyloid deposition, perivascular lymphocytic infiltration and intraluminal thrombosis in medium and small sized arteries. Parenchymal changes occur predominantly in white matter, and include coagulative necrosis, cystic cavitation with gliosis and patchy demyelination. The pathogenic mechanism is probably primarily vascular, with necrosis and glial loss secondary to ischaemia, but three other hypotheses have been proposed; direct injury to glial cells, particularly oligodendroglia, may produce white matter degeneration and demyelination,24 an autoimmune reaction may result from endothelial damage (vasculitis) or glial antigen release following glial injury, or intracellular free radicles induced by radiation may damage lipid membranes, producing cell membrane dysfunction and cell death.25

The development of a mass lesion at least three months after radiation treatment for an AVM is more likely to be due to radiation necrosis than a radiation induced intrinsic malignant tumour. There are only 17 case reports of post-irradiation gliomas,26-27 although fibrosarcomas and malignant meningiomas have been reported more commonly. Biopsy may be required to make the diagnosis if malignant glioma, radiation necrosis or abscess cannot reliably be distinguished by CT or magnetic resonance imaging. Steroids are the only useful medical treatment, and may partly protect against late necrosis if given at the time of irradiation.22 Resection of accessible regions of focal necrosis can be worthwhile, but is unlikely to be of use in patients with partly obliterated, surgically inaccessible AVMs.

With the increasing use of localised high dose radiotherapy, such as stereotactic radiosurgery, proton beam therapy, and interstitial brachytherapy, radiation necrosis will be seen more often. Careful follow up of all patients having treatment is important to determine the true incidence of radionecrosis; modification of treatment doses and volumes may be required. In the United Kingdom, patients with AVMs treated with radiosurgery are referred to a few specialised centres for treatment, but are followed up in peripheral units. It is important for
those clinicians involved in the long term follow up of these patients to be familiar with the presentation and management of radiation necrosis, as the prognosis is relatively good if only small volumes of brain have been irradiated.

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