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Review article

Severe adverse radiation effects complicating radiosurgical treatment of brain arteriovenous malformations and the potential benefit of early surgical treatment

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ABSTRACT

Treatment of brain arteriovenous malformations (AVM) with stereotactic radiosurgery is rarely complicated by severe adverse radiation effects (ARE). The treatment of these sequelae is varied and often ineffectual. We present three cases of brain AVMs treated with SRS, all complicated by severe AREs. All three cases failed to respond to what is currently considered the standard treatment – corticosteroids – and indeed one patient died as a result of the side effects of their extended use. Two cases were successfully treated with surgical excision of the necrotic lesion resulting in immediate clinical improvement. Having considered the experience described in this paper and reviewed the published literature to date we suggest that surgical treatment of AREs should be considered early in the management of this condition should steroid therapy not result in early improvement.

1. Introduction

Stereotactic radiosurgery (SRS) is an effective and safe treatment for selected arteriovenous malformations (AVM) of the brain. The SRS obliteration rates range between 64 and 94% in the literature [1–6]. Severe adverse radiation effects (AREs) are an uncommon and late complication of SRS. AREs are characterized by oedema and cyst formation and can represent a source of significant neurological morbidity and may even be fatal. We outline three cases complicated by AREs, the current and proposed management options and discuss the role of surgical treatment.

Abbreviations: ARE, adverse radiation effects; BAVM, brain arteriovenous malformation; CT, computed tomography; DMSO, dimethyl-sulfoxide; EVOH, ethylene-vinyl alcohol copolymer; GK, Gamma Knife; HPA, hypothalomo-pituitary axis; MRI, magnetic resonance imaging; PEA, pulseless electrical activity; RIC, radiation induced changes; SRS, stereotactic radiosurgery; VEGF, vascular endothelial growth factor.

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2. Case series

2.1. Case 1

A sixteen-year-old girl presented with haemorrhage from a left-sided, posterior thalamic AVM (Spetzler-Martin grade 3). She was treated with (Leksell Gamma Knife System) and received two fields of radiation (14 mm collimator system) with a total of 25 Gy to the periphery. Control angiography in 1999 demonstrated a residual arteriovenous shunt. The residual malformation was retreated with the Leksell Gamma Knife System utilizing six fields of radiation (8 mm and 4 mm collimator systems) such that the periphery received 22.5 Gy. Control angiography in 2002 demonstrated the obliteration of the AVM. The patient re-presented in July 2010, eleven years after her second treatment to the neurology team with two episodes of speech arrest and visual obscuration. She suffered one generalized tonic-clonic seizure. She was started on a second anti-epileptic agent. Both CT and MRI imaging demonstrated a 1.5 cm area of haemorrhage within the white matter near the trigone. There was marked surrounding oedema and a 1.7 cm cystic lesion. A catheter angiogram did not demonstrate any residual nidus. Investigations were completed to rule out causes of haemorrhage, including vasculitis and thrombophilia. She was found to be

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mildly hypertensive although no underlying cause was identified. Corticosteroid therapy was initiated.

Over several weeks, she re-presented with a series of small volume haemorrhages in the area of the previously treated nidus. Each was associated with transient speech arrest and recovery to a progressively worsening baseline of expressive dysphasia. The oedema was confined to white matter around the haemorrhage and with each clinical episode was noted to increase in severity.

The abnormal area demonstrated on imaging correlated with the location of the previously treated AVM, however its morphology was significantly different (Fig. 1A and B). As such the case was discussed in a neuro-oncology setting and the decision made that the abnormality should be biopsied for further characterization.

The area was explored via an image guided craniotomy and through a lateral temporoparietal, transsulcal approach. Upon opening into the ventricular atrium, a yellow exophytic mass was identified arising from the pulvinar. It was avascular, soft and slightly granular. The lesion was debulked without intruding into the normal thalamus. Pathological examination of the material revealed radiation induced vascular changes including vessel fibrosis, dystrophic calcification, fibrinoid necrosis and cytologic atypia Fig. 2.

The post-operative outcome was good, and she made a good recovery with rapid involution of the hemispheric oedema (Fig. 1C and D). Seizure control improved significantly and there were no further haemorrhages or episodes of speech arrest.

In 2015 she was re-admitted to hospital following a small volume haemorrhage in the left temporal lobe but remote from the location of her original AVM. She had recently been diagnosed with hypertension and was non-compliant with medication at the time. On this occasion, there was no significant white matter oedema. Antihypertensive therapy was recommenced and there have been no further neurological episodes.

2.2. Case 2

In 2002 a sixteen-year-old male was diagnosed with a seizure disorder. Imaging demonstrated a right frontal AVM (Spetzler-Martin grade 3). He underwent radiosurgery using the Leksell Gamma Knife System with eleven fields of radiation (8 mm and 4 mm collimator systems) such that the periphery received 20 Gy. A residual AVM was embolized with Ethylene-vinyl alcohol copolymer (EVOH) soluted in Dimethyl-Sulfoxide (DMSO) (Onyx; ev3, Irvine acquired by Covidien) in 2007.

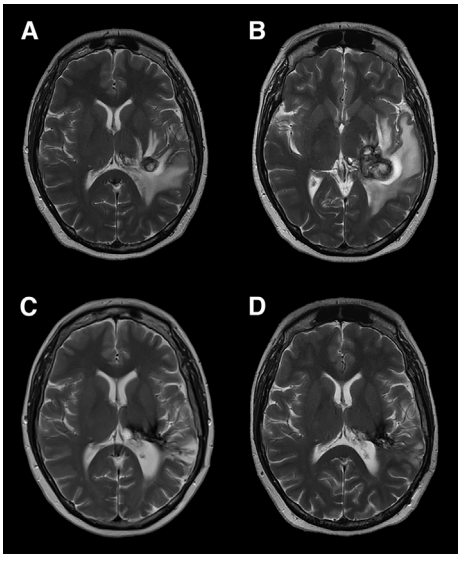

Fig. 1. T2 weighted axial MRI images at various stages, (A) At the time of re-presentation (B) immediately pre-op (C) three months post-op (D) one-year post-op.

Following the embolization his seizures were well-controlled with carbamazepine and lamotrigine. He was only troubled by auras, but no complex-partial or generalized seizures. Control angiography demonstrated that the AVM had been obliterated.

Seven years after his endovascular treatment and fourteen years after radiosurgical treatment he developed increasingly frequent partial seizures. These primarily affected his left arm, with spontaneous resolution after two minutes. Over three months, secondary generalization became common and he was admitted to hospital for treatment of status epilepticus. The subsequent imaging demonstrated haemorrhage in the region of the previously treated AVM with surrounding vasogenic oedema. A second antiepileptic drug was introduced at this point. Catheter angiography demonstrated no residual arteriovenous shunt.

Headaches developed which became progressively more disabling and a mild right hemiparesis evolved in the months following this episode. Seizure control continued to deteriorate, and it was not possible to reduce or withdraw steroid therapy. In fact, despite this ongoing steroid treatment sequential MR imaging showed progressively worsening right hemispheric oedema (Fig. 3A and B). Surgical cytoreduction of the residual necrotic nidus was recommended.

There was a dramatic clinical improvement within weeks of surgery. Post-operative imaging demonstrated improvement in the degree of the perilesional oedema (Fig. 3C–F). The steroid therapy was weaned to stop over a period of one month. The seizures decreased to an aura every other day but a generalized tonic-clonic seizure only when the patient was late taking his antiepileptic medications. It was deemed safe to discontinue one of his antiepileptic medications with good seizure control on two instead of three drugs.

2.3. Case 3

This patient presented at the age of 45 following a WFNS grade I subarachnoid haemorrhage. Imaging demonstrated that this was secondary to a ruptured flow aneurysm associated with a large AVM (Spetzler-Martin grade 6). The aneurysm was treated by coil embolization emergently to manage the time sensitive aspect of the lesion. The AVM was subsequently treated at another centre in 2010 using a Leksell Gamma Knife System with volumetrically fractionated SRS with an 18 Gy (marginal dose) given to a 10.9 cc volume and a further 18 Gy was administered to an 8.8 cc volume. Severe perilesional oedema developed following her treatment and she was commenced on corticosteroid therapy. She continued receiving steroids for two years but was intermittently compliant.

She presented to a peripheral emergency room in 2012 with acute confusion and fever. Imaging performed did not demonstrate any haemorrhage. She was treated empirically with antibiotics and antiviral therapy. She was not known to be on steroid treatment by the admitting team and no collateral history of same was established. MRI scan demonstrated the by-now usual appearance of perilesional cytotoxic oedema without recent haemorrhage. During this admission, she suffered a PEA cardiac arrest with a return of circulation after approximately 18 min but with absent brainstem reflexes. There was evidence of hypoxic ischemic brain injury secondary to her cardiac arrest (high signal in the hippocampi and corticospinal tracts). A lumbar puncture had demonstrated 1450 red cells and a protein count over 1 g. Her febrile illness was thought likely contributed to by the adrenal suppression caused by the long-term steroid therapy and its subsequent acute withdrawal.

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