Acquired cerebellar cavernous angioma following childhood radiotherapy in a patient with Neurofibromatosis type 1

Frank Van Calenbergh, Philippe Demaerel[1], Raf Sciot[2] and Johan van Loon

Departments of Neurosurgery, [1]Radiology (neuroradiology) and [2]Neuropathology, University Hospital Gasthuisberg, Catholic University Leuven, Belgium

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Abstract

We report the unusual case of a patient with neurofibromatosis type I, who was irradiated 16 years previously for a mesencephalic glioma causing hydrocephalus, and who developed a cerebellar haemorrhage caused by a histologically confirmed cavernous angioma, that was invisible on several earlier MRI scans. The different hypotheses concerning the de novo formation of cavernous angiomas (venous obstructive disease and genetic abnormalities) are succinctly reviewed.

Key words : Cavernoma ; cavernous angioma ; radiotherapy ; secondary tumour ; neurofibromatosis type 1.

Introduction

Cavernous angiomas or cavernomas have traditionally been considered to be congenital malformations, but recently a *de novo* appearance has been illustrated in some cases, both in the familial form of the disorder (19), and also in the sporadic form (2, 5). Prior radiotherapy to the brain may play a role in the pathogenesis of these lesions. We recently treated a patient with neurofibromatosis type 1 (NF-1), who developed a cavernous angioma.

Case report

In 1982, when she was four years old, this patient with neurofibromatosis type I (multiple small and large café-au-lait spots, cutaneous neurofibromas in the face and the neck and two plexiform neurofibromas in the hypochondric region and the lumbar region, which were resected) developed obstructive hydrocephalus due to a lesion of the mesencephalon. At that time the lesion was considered to be a low grade astrocytoma. A ventriculoperitoneal shunt was inserted. There was no family history of cavernoma or arteriovenous malformation, and no family members are known with NF-1.

In 1985, the lesion had slightly increased in volume, and was irradiated (local field, 56 Gy, fractionated) without prior histological diagnosis. In 1988, a biopsy was performed at an other hospital, proving the lesion to be a pilocytic astrocytoma, and stereotactic implantation of radioactive seeds (I-125 for approx. 4 weeks) was done. Details about this procedure are lacking. The patient developed minor mental retardation and partial pituitary insufficiency, necessitating substitution with thyroid hormone. She was otherwise well until 1997 when a second tumour was diagnosed after complaints of dizziness and unsteadiness. This tumour, located in the frontal interhemispheric region anterior to the corpus callosum, was also considered to be a low grade glioma. Because of the paucity of symptoms and the absence of a neurological deficit, it was decided to perform regular surveillance scanning and only operate when the lesion would prove to be progressing.

Approximately two weeks before admission at the age of 19 years, the patient fell, with persisting complaints of vertigo, unsteadiness of gait, nausea and vomiting. At first, it was thought that a vestibular dysfunction caused the symptoms. An otolaryngology consultant found normal vestibular function, and considered a more central origin. Because of an increase in the symptoms, the patient was finally admitted for observation. Neurological examination showed the stigmata of neurofibromatosis and the known signs of the mesencephalic tumour (oculomotor palsy, nystagmus, bilateral Babinski signs, and slight dysmetria).

CT scan and MRI showed a subacute hematoma in the cerebellar vermis, with a peripheral small mixed intensity lesion suggesting a cavernous angioma. In retrospect, this lesion was not seen on the different MRI scans done in the previous year for follow up of the frontal glioma (Fig. 1a & b). Additionally, the frontal and mesencephalic gliomas remained unchanged, and periventricular signal changes were seen, presumably caused by post-irradiation leuco-encephalopathy. Vertebral artery

FIG. 1a. — MRI of the posterior fossa (T2-weighted image), one year before the cerebellar haemorrhage, demonstrating the absence of a vascular malformation.
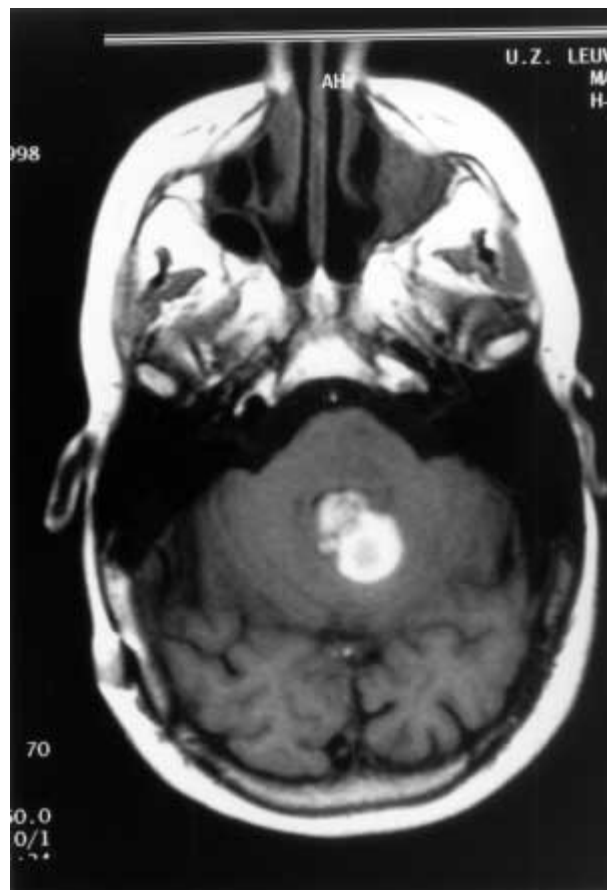

FIG. 1b. — MRI of the posterior fossa (T1-weighted image), showing a vermian haematoma with a peripheral lesion suggestive of a cavernoma.

angiography did not demonstrate abnormal vessels or tumour blush.

A posterior fossa midline craniotomy was performed to evacuate the haematoma and remove the cavernous angioma. This had the typical raspberry appearance, and histological examination confirmed the diagnosis by demonstrating the typical endothelium-lined large thrombosed avascular spaces (Fig. 2). The postoperative course was uneventful, and the complaints of nausea and vertigo gradually subsided.

Discussion

The possible role of radiotherapy in the genesis of cavernous angiomas was first suggested by Wilson (18). Since then, several other published cases have demonstrated that the association of previous central nervous system radiotherapy with cavernomas and other occult vascular malformations, although rare, is not extremely exceptional (4, 8, 10, 13, 15). From these articles, some special features of the cavernous angiomas after irradiation have appeared. Histologically, the endothelium-lined vascular spaces have only minimal stroma in between, and calcifications and organised thrombi are not seen. Cavernomas are seen more frequently
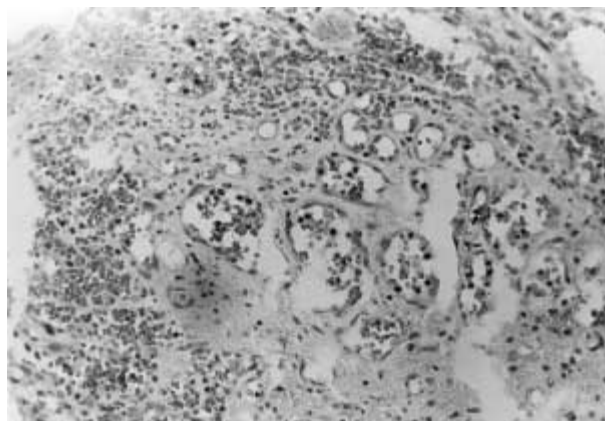

FIG. 2. — Histological examination of the cavernoma, showing the typical irregular thin-walled vascular structures.

after childhood radiotherapy, and they possibly have a higher tendency for clinically overt bleeding (4, 14), as was also the case in our patient.

Radiation therapy of the central nervous system is known to cause late changes, including radionecrosis, pituitary disturbances, mental and intellectual changes, and probably also secondary tumours. These tumours are thought to be the result of genetic changes induced by the radiation

(activation of proto-oncogenes or loss of tumour suppressor genes). Because of the difficulties in ascribing a given second tumour either to these changes or to the genetic abnormalities inherent to the syndrome, the absence of syndromes known to develop multiple tumours, e.g. neurofibromatosis, is generally requested before considering a given tumour as radiation-induced (17).

The gene responsible for neurofibromatosis type 1 (NF-1, von Recklinghausen disease), has been identified and localized to chromosome 17q (9). It is well known that NF-1 can be associated with vascular lesions, usually occlusive disease with a Moyamoya-like appearance, or aneurysms (21). Cavernous angiomas however are not included in the spectrum of NF-1, and in an extensive Medline and literature search we did not find a single example of this association.

Although most cases of cavernous malformation are sporadic, some large families are known, e.g. some Hispanic-American families in whom a mutation in the KRIT1 gene on chromosome 7q was identified (20).

The pathogenesis of acquired cavernous malformations is still a matter of debate, but some mechanisms can be proposed. It is well known that cavernomas often co-exist with venous malformations. Some authors (1) have therefore suggested that the cavernoma develops secondary to venous occlusion. Radiation therapy is known to cause vascular occlusion, and stereotactic radiosurgery for inoperable arteriovenous malformations is using this as a therapeutic effect. It may be hypothesised that radiotherapy can also occlude some normal veins, thereby inducing the formation of a cavernous angioma. Some growth factors can possibly also play a role, and have been found to be elevated after radiation (16). Angiogenetic factors are also known to be expressed in the capillary bed (3). At the present time, it is impossible to prove that the occurence of the cavernous angioma in our patient was induced by a combination of two factors : radiotherapy can induce vascular occlusion and NF-1 is associated with occlusive vascular disease, but also with an upregulation of growth factors in brain endothelial cells (12).

In our patient, because of the associated NF-1 tumours, frequent surveillance scanning with MRI (however not with gradient echo images) had been done, and the region of the vermis did not show any lesions one year before the subacute haemorrhage that was the presenting sign of the cavernous angioma. The radiation dose to the vermis had been 56 Gy 13 years previously, and probably a small additional but unknown dose at the moment of interstitial brachytherapy, 10 years before the haemorrhage. This confirms the suspicion (2, 14) that radiation induced and other *de novo* cavernomas are of a more aggressive nature than the classical type. This concern may have implications for the radiosurgical treatment of cavernous angiomas : indeed, some series have found a high incidence of bleeding following radiosurgery (7), and other authors have demonstrated that radiosurgery does not cause histologic vascular obliteration of the cavernoma (6). A possible explanation for this apparent contradiction may be that the large dilated caverns do not thrombose, but the smaller draining veins do. Surgical resection of accessible cavernomas found after radiotherapy has to be taken into consideration before clinically important haemorrhage occurs.

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F. VAN CALENBERGH,
Department of Neurosurgery,
University Hospital Gasthuisberg,
Herestraat 49,
B-3000 Leuven (Belgium).
E-mail : Frank.Vancalenbergh@uz.kuleuven.ac.be.