Aggressive course of multiple de novo cavernous malformations

Case report

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The risk of hemorrhage from an intracerebral cavernous malformation has been estimated at 2%–4% per year. In patients with multiple cavernous malformations, typically there are 1 or 2 dominant lesions that result in symptoms. This report highlights an unusual case of recurrent hemorrhage from de novo cavernous malformations.

This 35-year-old man had a generalized seizure in 2007. Magnetic resonance imaging performed at the time showed multiple hemorrhagic lesions suggestive of cavernous malformations. Two years later, the patient had clinical symptoms referable to a midbrain hemorrhage. This lesion was not present on 2007 standard and gradient echo images. One year later, the patient had another clinical hemorrhage at the cervical medullary junction. This lesion was also not present on earlier imaging. Genetic testing was negative for the known familial types of cavernous malformation. A lesion was biopsied to ensure correct diagnosis, and the results were pathologically consistent with a cavernous malformation. The patient had a fourth clinical hemorrhage in 2011 from a separate lesion. All hemorrhage symptoms were mild, and he returned to normal functioning and work after each hemorrhage.

This case highlights several unusual features of the known natural history of intracerebral cavernous malformations. In this case, resection of the hemorrhagic lesion would not have altered future hemorrhage risk since each new hemorrhage was from a de novo lesion. (DOI: 10.3171/2011.8.JNS11751)

Key Words • cavernous malformation • aggressive hemorrhage • vascular disorders

The risk of hemorrhage from an intracerebral cavernous malformation has been estimated at 2%–4% per year. In patients with multiple cavernous malformations, there typically are 1 or 2 dominant lesions that result in symptoms. This case highlights an unusual case of recurrent hemorrhage from de novo cavernous malformations.

Case Report

This 35-year-old right-handed man had no known family history of cavernous malformation, seizure, or intracerebral hemorrhage, and is not of Hispanic heritage. He had no prior history of radiation therapy or brain surgery. He first underwent MR imaging of the brain in 2004 because of the perception of reduced concentration at work. The imaging findings were completely normal, although no gradient echo sequences were performed (Fig. 1). In 2007, the patient experienced a generalized tonic-clonic seizure and was hospitalized. Brain MR imaging showed numerous lesions including an acute hemorrhage in the right cerebellum and a hemorrhagic lesion in the inferior right temporal lobe (Fig. 2). Additional imaging over time showed that the lesions were stable and unlikely to be neoplastic. These lesions were believed to most likely represent cavernous malformations.

In January 2009, the patient had sudden onset of diplopia and decreased taste. Brain MR imaging showed an acute hemorrhage in the midbrain (Fig. 3). There was no evidence of a cavernous malformation at this site in 2007 on gradient echo imaging. The patient returned to normal within 6 weeks.

In February 2010, the patient had a sudden loss of feeling in the left arm and leg along with uncontrolled
hiccups. Brain MR imaging showed an acute hemorrhage at the cervical medullary junction (Figs. 4 and 5). There had been no cavernous malformation present at this site on prior MR images. Conventional angiography was performed and did not show any pathological entities. The patient also underwent transesophageal echocardiography to rule out myxoma as a cause of multiple intracranial hemorrhages, which did not show any findings. The patient improved to normal and returned to work.

In March 2010, the patient returned because of the concern of whether his lesions were truly due to cavernous malformations or another cause. Genetic testing was recommended and performed by Prevention Genetics in Marshfield, Wisconsin. Using genomic DNA extracted from the patient’s cells, DNA amplification and sequencing of the full coding regions of the indicated exons were performed (16 coding exons of KRIT1/CCM1; 10 coding sequences of CCM2/MGC4607; and 7 coding exons of PDCD10/CCM3). In this patient, for the KRIT1/CCM1, CCM2, and PDCD10/CCM3 genes, no sequence variants were found that would have been likely to cause cerebral cavernous malformations.

Eventually, the patient underwent biopsy of a lesion in June 2010, which was pathologically consistent with...
Aggressive cavernous malformation

A cavernous malformation. The patient was started on a low-dose statin empirically due to theoretical benefit in a mouse model.1

In February 2011, the patient had acute onset of left facial numbness and incoordination of the left upper extremity. He was still able to work despite these mild symptoms. However, additional MR imaging showed 4 new small areas of hemorrhage, including one in the lateral cerebellar hemisphere and another near the left trigeminal nucleus. The patient was last seen in June 2011. He is doing well and is back to normal neurologically.

Discussion

This case highlights several unusual and aggressive features of a patient with cavernous malformation, which are different from the typical natural history. For one, the patient had a very aggressive course of multiple hemor-

![Brain MR imaging study. Selected T2 sequences showing the old hemorrhagic lesion in the right cerebellum and right inferior temporal lobe (small arrows). A new acute hemorrhage is seen in the right midbrain (large arrow). Note that there was no right midbrain lesion present in Fig. 2.](image1)

![Brain MR imaging sequences (T2 sequences [upper] and susceptibility-weighted sequences [lower]) demonstrating an acute hemorrhage at the cervicomedullary junction (arrow). There was no lesion at the cervicomedullary junction on previous images. Also noted are multiple old hemorrhagic lesions.](image2)
rhages within a 3-year period. In prospective studies, the average risk of hemorrhage from a cavernous malformation is 2%–3% per year. In patients with prior hemorrhage, the risk of repeat or recurrent hemorrhage ranges from 4% to 60% per year.2 In general, however, studies on recurrent hemorrhage risk from cavernous malformations have been referable to the initial lesion. Second, each hemorrhage tends to be from a new de novo lesion. Therefore, removing the lesion that has bled would not seem to alter the risk of future bleeding. De novo lesions have been described in the familial form of cavernous malformations at a rate of about 0.4 per patient-year.3 The third unique feature of this case is the repetitive number of hemorrhages without significant morbidity. The patient continues to work at the management level with a gradu-