Widespread central nervous system cavernous malformations associated with café-au-lait skin lesions

Case report

KIRAN MUSUNURU, PH.D., VIRANY HUYNH HILLARD, M.D., AND RAJ MURALI, M.D.

Department of Neurosurgery, New York Medical College, Valhalla and New York; and Saint Vincent’s Hospital, Manhattan, New York, New York

The simultaneous presence of cavernous malformations in the brain and spinal cord is a very rare finding and is typically associated with familial cavernous malformations. Although they are uncommon, various skin lesions can manifest in patients with familial cavernous malformations. The authors report on a 60-year-old man in whom more than 100 lesions consistent in appearance with cavernous malformations, including several intramedullary spinal cord lesions, were found throughout the neuraxis. This patient also displayed prominent café-au-lait skin lesions, but had no additional signs of neurofibromatosis or other neurocutaneous disorders. Analysis of his DNA revealed a novel mutation in the KRIT1/CCM1 gene, thereby confirming the diagnosis of familial cavernous malformation. The presence of these lesions in every major compartment of this patient’s central nervous system underscores their indiscernible nature and the need to screen throughout the neuraxis in patients in whom familial cavernous malformations are suspected. The findings in this case add to the growing list of skin lesions associated with genetically confirmed familial cavernous malformations. In patients presenting with seizures, focal neurological deficits, or hemorrhagic stroke, the presence of unusual skin lesions should prompt consideration of familial cavernous malformations, and appropriate screening should be performed.

Key Words • familial cavernous malformation • café-au-lait skin lesion • intramedullary spinal cord lesion • gene sequencing

Cavernous malformations are well-defined lesions composed of closely packed, sinusoidal vascular channels with structurally incomplete vessel walls and no intervening neuronal parenchyma. They represent approximately 10% of all cerebrovascular abnormalities. Cavernous malformations occur as either solitary or multiple lesions and most commonly cause seizures, focal neurological deficits, and hemorrhagic stroke. Intramedullary spinal cord cavernous malformations giving rise to neurological deficits are unusual, and even more rare are cases in which multiple lesions are discovered in both the brain and spinal cord. The simultaneous presence of cavernous malformations in the brain and spinal cord is a very rare finding and is typically associated with familial cavernous malformations. Although they are uncommon, various skin lesions can manifest in patients with familial cavernous malformations. The authors report on a 60-year-old man in whom more than 100 lesions consistent in appearance with cavernous malformations, including several intramedullary spinal cord lesions, were found throughout the neuraxis. This patient also displayed prominent café-au-lait skin lesions, but had no additional signs of neurofibromatosis or other neurocutaneous disorders. Analysis of his DNA revealed a novel mutation in the KRIT1/CCM1 gene, thereby confirming the diagnosis of familial cavernous malformation. The presence of these lesions in every major compartment of this patient’s central nervous system underscores their indiscernible nature and the need to screen throughout the neuraxis in patients in whom familial cavernous malformations are suspected. The findings in this case add to the growing list of skin lesions associated with genetically confirmed familial cavernous malformations. In patients presenting with seizures, focal neurological deficits, or hemorrhagic stroke, the presence of unusual skin lesions should prompt consideration of familial cavernous malformations, and appropriate screening should be performed.

We report on a patient with a large number of cavernous malformations throughout the CNS who also had prominent café-au-lait skin lesions. Although various skin lesions have been reported in association with familial cavernous malformations, café-au-lait lesions are a novel finding. We therefore explored the possibility that the patient’s presentation may have derived from an alteration in the KRIT1/CCM1 gene.

Case Report

History. This 60-year-old, right-handed African-American man presented with numbness, paresthesia, and weakness throughout his right hand. His symptoms had worsened progressively after a sudden onset 2 months previously. Four years before presentation, he had first felt tingling in the tips of several fingers of his right hand. Carpal tunnel syndrome was diagnosed 8 months before presentation, and he had undergone an endoscopic carpal tunnel release; this procedure provided only a temporary abatement of symptoms. He initially denied any other neurological problems, but after repeated questioning he remembered having suffered a few seizures in the past. He also reported that his deceased sister had had an extended history of seizures beginning in early adulthood. He had no children, and his parents were deceased; he did not know of any neurological symptoms experienced by his parents or...
Cavernous malformations associated with café-au-lait skin lesions

other relatives. He had a history of hypertension, hypercho-
lesterolemia, and atherosclerotic disease.

Examination. Neurological examination revealed de-
creased vibratory, pain, and temperature sensations; de-
creased motor strength; and no reflexes in the right upper
extremity. The left hand and arm were unaffected. He had
pain when turning his neck to the left and looking down, but
he was otherwise asymptomatic. Results of the patient’s
electrodiagnostic studies were unremarkable. Admission
MR images of the cervical spine revealed a large intra-
medullary, heterogeneous-appearing, hemorrhagic lesion at
the C4–5 level consistent in appearance with a cavernous
malformation (Fig. 1). Two smaller lesions are seen at the C6–7 and T1–2 levels.

Genetic Analysis. Genomic DNA was prepared from the
patient’s blood with a sequencing kit (QIAGEN Blood
Maxi Kit; QIAGEN, Inc., Valencia, CA). All 16 coding exons of the KRIT1/CCM1 gene and their associated splice acceptor/donor sites were screened for mutations. Polymerase chain reaction primers to amplify products spanning the first four coding exons and part of the fifth exon were designed using the MacVector software suite (Accelrys, Cambridge, UK). The remainder of the fifth and the last 12 exons were amplified with previously reported polymerase chain reaction primers, and all exons were assayed for mutations as described elsewhere. 20 A point mutation was found in exon 7 corresponding to nucleotide 409 of the coding sequence, with a guanine changed to a cytosine (Fig. 3). The predicted effect of this novel missense mutation is to alter amino acid 137 from aspartate to histidine (D137H).

Discussion

Cavernous malformations are not an uncommon phenomenon, occurring in an estimated 0.4 to 0.8% of the general population, but few come to clinical attention. 17 Familial cavernous malformations may account for up to 50% of cases. 19 Although most documented examples have been seen in supratentorial locations, that is, the cerebrum and basal ganglia, these lesions have also been observed in the brainstem, the cerebellum, and, most infrequently, the spinal cord. The case described here is remarkable for the presence of more than 100 cavernous malformations distributed across every one of the aforementioned compartments, a finding that to our knowledge has not been previously reported. It has been emphasized that cavernous malformations found in different parts of the neuraxis should be viewed as related pathological entities and that patients presenting with these lesions in the spine should be screened for the same ones in the brain. 10, 25 Our case dramatically reinforces this thinking: the initial detection of three spinal cord lesions in our patient led us to suspect familial cavernous malformations, one of which resp ected no boundaries in the CNS, presenting a highly unusual pattern of angiogenesis and/or vasculogenesis.

The fact that our patient’s deceased sister had a history of seizures, which are the most common clinical finding linked to cavernous malformations, indicates that his disorder resulted from familial disease rather than a spontaneous germline mutation. Linkage analysis of a number of familial cases with cavernous malformations has identified three possible associated genes, CCM1, CCM2, and CCM3. The first gene, CCM1, was recently cloned, 13, 20 and CCM2 and CCM3 have been mapped to chromosomal loci 7p13-15 and 3q25.2-27, respectively. 9 The CCM1 gene was found to encode the previously characterized KRIT1 protein, which is thought to interact with the Krev-1/rap1a member of the Ras family of guanosine triphosphatases. 21 More than 40 distinct mutations in the KRIT1/CCM1 gene have been identified so far in patients with familial cavernous malformations, confirming the encoded protein’s relevance to the development of these lesions. 23 The function of the KRIT1 protein remains unclear, although its involvement in familial cavernous malformations implicates it in the processes of angiogenesis and/or vasculogenesis.

Café-au-lait skin lesions are most commonly associated with NF1, or von Recklinghausen syndrome. 2 The presence of six or more large skin lesions that are more than 1.5 cm in diameter is considered virtually diagnostic of NF1. Our patient fulfilled this criterion with more than a dozen large café-au-lait skin lesions evident on his body, yet he displayed none of the other major findings associated with NF1: neurofibromas in the skin, iris nevi (or Lisch nodules) in the eyes, or any of a variety of other CNS tumors (although notably, he did have cavernous malformations); the absence of most of these major findings precluded a definitive clinical diagnosis of this disease. Café-au-lait skin lesions occur with variable frequency in a number of other disorders, including neurofibromatosis Type 2, Albright syndrome, tuberous sclerosis, Watson syndrome, the LEOPARD syndrome, and ataxia telangiectasia. 4 Our patient has none of the signs commonly found in these conditions. Moreover, there is no reported association of cavernous malformations with any of these conditions. Thus, we think it unlikely that the patient’s presentation is due to an alteration in one of the genes implicated in these syndromes. It is more plausible that a mutation in a CCM gene is responsible for the café-au-lait skin lesions, although we cannot exclude with certainty the possibility that there is an alteration in another gene, for example, the NF1 gene. The extremely large size of the NF1 gene (60 exons, 350 kilo bases) and the low sensitivity of the commercially available diagnostic test (protein truncation test) 14 made it prohibitive to screen for a mutation in this gene.

There have been several recent reports of various cutaneous lesions associated with familial cavernous malformations, including hyperkeratotic cutaneous capillary venous malformations, cherry angiomas, blue rubber bleb nevi, and angiookeratomas. 4, 5, 9, 12, 17, 23, 26 Indeed, specific mutations in
Cavernous malformations associated with café-au-lait skin lesions

KRIT1/CCM1 have been linked to such skin lesions manifesting in patients from families whose members have cavernous malformations. Cutaneous lesions can therefore serve as an important diagnostic marker in patients in whom familial cavernous malformations are suspected. The finding of café-au-lait skin lesions increased our suspicion that a genetic alteration was responsible for our patient’s condition. Accordingly, we screened his DNA for mutations in his KRIT1/CCM1 alleles and found a novel mutation predicted to change amino acid 137 of the KRIT1 protein (D137H). A different alteration of this same amino acid has previously been reported in a family with cerebral cavernous malformations (D137G).\(^{2,23}\) Strongly implicating our patient’s mutation as the cause of his CNS and cutaneous lesions. Patients with D137G have not been reported to harbor cutaneous lesions; the difference in the amino acids resulting from the D137H and D137G mutations (histidine compared with glycine) and the variable penetrance of the familial cavernous malformations syndrome in affected individuals may explain why our patient has café-au-lait skin lesions.

Conclusions

We have described a patient with an extraordinary number of cavernous malformations pervading his CNS, prominent café-au-lait skin lesions, and a genetic alteration in KRIT1/CCM1. Our case adds to a growing list of skin lesions associated with familial cavernous malformations and reinforces the thinking that the screening of patients in whom familial cavernous malformations are suspected (as well as their family members) should include a thorough dermatological examination. Furthermore, clinicians encountering patients with unusual skin lesions who present with seizures, focal neurological deficits, or hemorrhagic stroke should consider familial cavernous malformations in the differential diagnosis.

Acknowledgments

We are grateful to Ms. Arlene Stolper Simon and Ms. Lisa Feldman for their excellent assistance in the preparation of this manuscript.

References

25. Vishnev AG, Zabranski JM, Spetzler RF: Patients with spinal cord cavernous malformations are at an increased risk for multiple neuraxis cavernous malformations. Neurosurgery 45:30–33, 1999

Manuscript received February 6, 2003. Accepted in final form April 4, 2003. Address reprint requests to: Raj Murali, M.D., Department of Neurosurgery, New York Medical College, Munger Pavilion, Valhalla, New York 10595. email: raj_murali@nymc.edu.

J. Neurosurg. / Volume 99 / August, 2003 415