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Cervical Cord Hemorrhage in Cerebral Cavernous Malformations

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Dear Editor,

Cavernous malformations are vascular malformations of the central nervous system, with the lesions comprising clusters of abnormal small blood vessels that are mostly detected intracranially. Mutations in *KRIT1*, *CCM2*, and *PDCD10* have been found to cause cerebral cavernous malformations (CCMs). CCM proteins can bind different molecules such as scaffolding proteins and kinases, and form a CCM signaling complex (CSC). Mutant CCM proteins impair the function of the CSC and cause endothelial barrier dysfunction and hyperpermeable blood vessels.[1] Twenty percent of CCMs are familial cases with an autosomal dominant pattern, with incomplete penetrance and variable expressivity. Mutations in *KRIT1*, *CCM2*, and *PDCD10* account for 50%, 20%, and 10% of familial cases, respectively.[1] Most cases with widespread lesions are hereditary, and cases with isolated lesions may exhibit mosaicism.[2] The clinical presentation varies with the location, number, and size of the lesions. Recurrent hemorrhage in the lesions causes neurological deficits in CCMs patients.

Intramedullary spinal cavernous malformations (ISCMs) are rare, accounting for 5−12% of all intraspinal vascular malformations.[3] However, the prevalence of ISCMs is high (about 70%) in cases of familial CCMs and is positively correlated with the age at onset and number of lesions.[4] Here we report on a case of ISCMs presenting with hemiplegia, including providing imaging, pathological, and genetic data.

A 62-year-old female complained of numbness and a paroxysmal sense of discharge, weakness in the upper left limb for 8 months, and progressive weakness in the lower left limb for 4 months. Pain in the waist had resulted in schwannoma of the left lumbar nerve root being diagnosed 4 years previously. Resection of the schwannoma produced the sequela of numbness in her left lower limb. At the current presentation, a neurological examination revealed that the strength of the left upper limb was Medical Research Council scale (MRC) grade 3/4, with distal muscles more severely affected than proximal muscles. The strength of the left lower limb was MRC grade 4. The strength of the right extremities was normal, and ataxia was not found. Analgesia was revealed in the upper left limb. Hypesthesia was found below the left knee, which was presumed to be a remnant sign from the schwannoma resection in the lumbar nerve root 4 years previously. Her proprioception was normal. Tendon reflexes were active except for Achilles reflexes. Hoffman and Babinski signs were positive bilaterally, and more prominent in the left. Brain susceptibility-weighted MRI showed diffused lesions consistent with CCMs in the cerebral hemispheres, cerebellum, and brain stem (Fig. 1A-C). A physical examination indicated the damage of the cervical spinal cord, and so we performed the cervical MRI, which revealed oval intramedullary mixed signals (about 0.9 cm × 0.7 cm × 1.9 cm), predominantly on the left side at the fifth cervical vertebra level (Fig. 1D-F). Whole-exome sequencing identified that the patient carried a mutation in *KRIT1*, which was confirmed by Sanger sequencing. No mutation was detected in either *CCM2* or *PDCD10*. Combined with the genetic analysis, CCMs caused by a known *KRIT1* mutation

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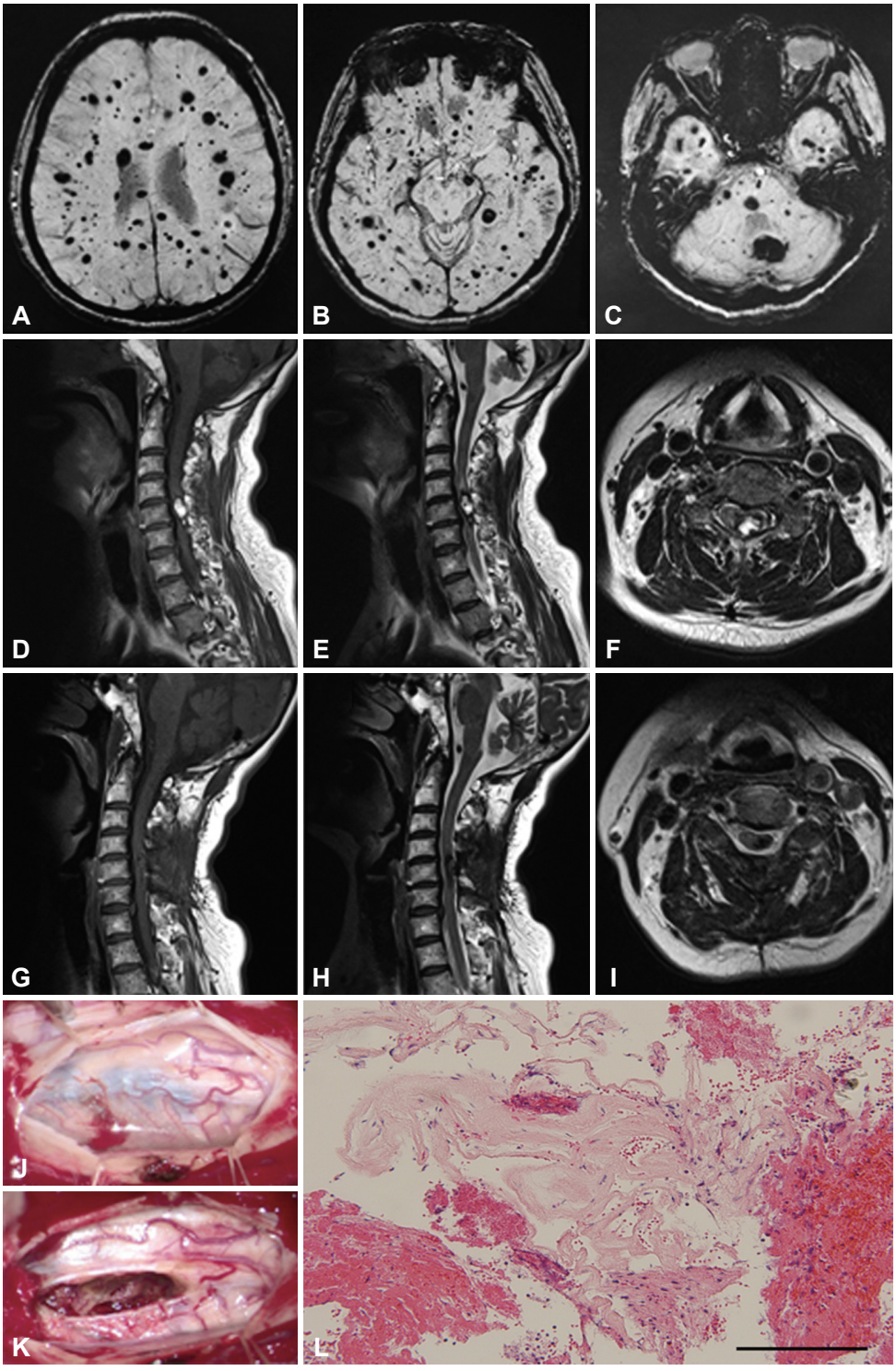

Fig. 1. MRI of the brain and the cervical spinal cord, as well as the pathological findings. A-C: Susceptibility-weighted images revealed numerous lesions of different sizes consistent with cerebral cavernous malformations in the cerebral hemispheres, cerebellum, and brain stem. D: Sagittal T1-weighted images of the cervical spinal cord revealed a hyperintense lesion at the fifth cervical vertebra level. E: Sagittal T2-weighted images revealed a heterogeneous hyperintense lesion with a hypointense rim. F: Axial T2-weighted images of the cervical spinal cord contained intramedullary mixed signals of an oval shape surrounded by circular hypointense signals, predominantly on the left side. G–I: Sagittal T1-weighted images (G), sagittal T2-weighted images (H), and axial T2-weighted images (I) of the cervical spinal cord revealed postoperative changes at the 6-month follow-up. J: A blue-purple intramedullary mass under the pia mater was exposed during the operation. K: The intramedullary mass was totally resected. L: A histopathological examination showed hyperplasia of vessels, which had thin vascular walls and thrombosis, accompanied with gliosis and fresh and old hemorrhages (hematoxylin-eosin; scale bar=200 μm).

(c.1362_1363delTC; p.Gln455ArgfsTer24) was diagnosed.[5]

Some CCMs patients are asymptomatic, whereas our patient exhibited hemicervical spinal cord syndrome and progressive hemiplegia, supporting the diagnosis of ISCMs. Due to the recurrent hemorrhage signals in cervical MRI being larger than 1 cm and the presence of progressive hemiplegic symptoms, the ISCMs were resected. An intramedullary blue-purple vascular mass (Fig. 1J) was resected in its entirety (Fig. 1K). Its pathology suggested that it was hyperplastic vascular tissue from the thin vascular wall, and a local thrombosis with fresh and stale bleeding accompanied with glial cell proliferation were observed (Fig. 1L). Six weeks after the operation, the grip strength of her left hand was improved, and the weakness of her left lower limb was not aggravated.

Cervical MRI performed at a 6-month follow-up visit showed postoperative changes of ISCMs (Fig. 1G-I), and the left limb weakness remained. The brain MRI findings were normal for her two daughters, who were negative for the *KRIT1* mutation.

This case presented with progressive numbness and weakness of the left limbs, and cerebrovascular disease or cervical spondylopathy was suspected initially. However, cervical MRI revealed a mixed lesion of fresh and old intramedullary hemorrhage. The mutation identified in *KRIT1* further supported the diagnosis of ISCMs. In view of the large cervical lesion and progressive neurological deficit in the patient and the low risk of subsequent hemorrhage after ISCMs resection,[6] ISCMs resection was performed. This case provides a precision medicine demonstration of ISCMs.

Ethics Statement

This study has been approved by the Ethics Committee of the Xuanwu Hospital of Capital Medical University (No. 2021[034]). Informed consent for genetic testing and publication of photo graphs has been obtained from the patient.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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