Disseminated Cavernous Malformations Due to *KRIT1* Gene Mutation Causing Seizure and Spastic Paraparesis

Dear Editor,

Disseminated cerebral cavernous malformations (CCMs) are rare developmental vascular anomalies of the nervous system with varied presentation. Most of the complications are due to microhaemorrhages inside CCMs or compression caused by them. Familial cases caused by CCM1 mutations in genes like *KRIT1* (CCM1), *MGC4607* (CCM2), and *PDCD10* (CCM3) have disseminated CCMs.[1] There are only four described cases in literature with concomitant spinal and brain CCMs due to *KRIT1* gene mutation. We describe the fifth case in which the diagnosis was missed for at least 9 years after the initial characteristic presentation of seizures.

A 19-year-old boy, born out of a nonconsanguineous parentage with normal birth and developmental milestones, presented with a 2-year history of progressive stiffness of both lower limbs. The stiffness was associated with difficulty in getting up from sitting position and occasional crossing of legs while walking. There was no history of radicular pain, slippage of footwear, wasting of limbs, fasciculations, clonus, sensory complaints, or bowel and bladder disturbances. Family history was significant in the form of upper limb tremors in one of the maternal cousins. Past history was significant for intermittent episodes of diffuse dull-aching holocranial headache since the age of 5 years. These headaches occurred at a frequency of one or two per month, were not preceded by aura, used to occur at any time of the day, were mild to moderate in intensity, not associated with photo/phonophobia, and used to subside on taking analgesics. He also had a history of one episode of unknown onset bilateral tonic–clonic seizure at 10 years of age, for which he received antiepileptics for 6 months. He underwent a brain noncontrast computed tomography (NCCT) scan at 14 years of age, and it revealed multiple calcifications in bilateral cerebral hemispheres [Figure 1]. He was diagnosed to have multiple calcified neurocysticercosis.

General examination was unremarkable. His mini mental state examination (MMSE) score was 30/30. Cranial nerve examination was within normal limits; fundus examination did not show papilledema. Motor system examination revealed normal bulk of all four limbs, grade 2 spasticity of bilateral lower limbs, and normal power of all four limbs. Deep tendon reflexes were brisk in all four limbs with absent abdominal reflexes and bilateral extensor plantar response. Sensory examination, cerebellar examination, and extrapyramidal system examination were within normal limits. He was noted to have spastic gait with occasional scissoring of his legs while walking.

Investigations revealed a normal hemogram and renal, liver, and thyroid function tests. Serum vitamin B12

level was within normal limits. Serum venereal disease research laboratory (VDRL) and viral markers (hepatitis B, hepatitis C, and human immunodeficiency virus) were negative. He subsequently underwent a contrast-enhanced magnetic resonance imaging (CEMRI) of the spine, which revealed a cavernoma at the C6 level compressing the spinal cord [Figure 2]. Magnetic resonance imaging (MRI) brain revealed multiple intracranial cavernomas [Figure 3]. His clinical exome sequencing revealed a pathogenic frameshift heterozygous mutation (c. 1356_1357delTC; p.Gln455fs*24) in exon 11 of chromosome 7 (*KRIT1* gene). He was referred to the department of neurosurgery for further management.

CCMs are developmental vascular anomalies characterized by abnormal dilatation of capillaries, without brain parenchymal involvement.[1] Fifty percent of patients with CCMs may be asymptomatic and are diagnosed on neuroimaging for unrelated conditions.[2] Clinical presentations like intermittent headaches, seizures, intracranial bleeds, and other focal neurologic deficits are described. Usually, the onset of symptoms is in the second to fourth decade, but can also begin in infancy or in old age. Familial cases comprise 20%, are transmitted in an autosomal dominant fashion, and are associated with multiple CCMs.[1] Mutations in three genes have been implicated in familial cases of CCMs, namely, *KRIT1*, *MGC4607*, and *PDCD10*. KRIT1 loss-of-function mutations are responsible for 53%–65% cases. The gene is mapped to chromosome 7q21–22. *KRIT1* is the largest of the three genes and encodes a protein comprising 736 amino acids, which is important for stabilizing endothelial cell–cell junctions.[3] Mutations in *KRIT1* lead to the absence of tight junctions in the blood–brain barrier. These blood vessels become more fragile and lead to deposition of hemosiderin due to chronic microhemorrhages. These patients usually present with seizures and may have cutaneous vascular malformations as well.[4]

There are only few reports in literature describing coexisting intracranial and spinal cavernous malformations due to *KRIT1* mutation [Table 1].[5-8]

Our patient was initially misdiagnosed as multiple calcified intracranial neurocysticercosis in view of multiple calcified lesions; cavernomas were diagnosed when he presented with spastic paraparesis and an MRI spine with brain was done. There was a long delay in his diagnosis due to the nonspecific complaints of headache from 5 years of age and also because calcifications on NCCT were passed on as calcified neurocysticercosis. The intermittent episodes of headache since childhood and one episode of seizure at a later age may be attributed to intermittent intracranial bleeds into the cavernomas.

CCMs on NCCT head can appear as amorphous calcifications similar to calcified Neurocysticercosis (NCC) and tend to get misdiagnosed, as happened in this case. MRI clinches the diagnosis; the cavernomas have a "popcorn-like" appearance on T1 and T2W images.[9] Gradient-recalled Echo (GRE) MRI can detect hemosiderin-filled brain tissue and can be employed for precise delineation of the cavernomatous lesions. Susceptibility-weighted (SW) imaging can detect CCMs more accurately and also identify unbled CCMs. Microsurgical

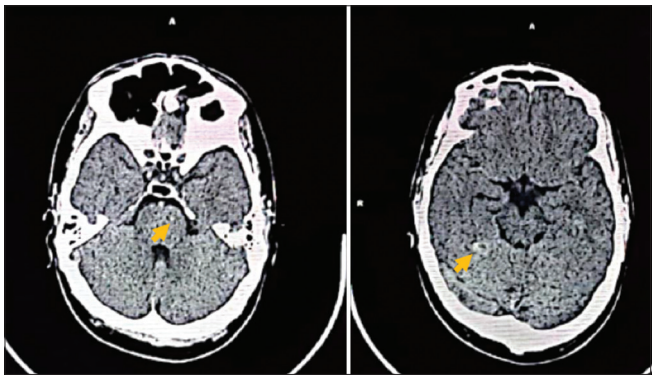

Figure 1: NCCT brain showing multiple calcified lesions. NCCT = noncontrast computed tomography

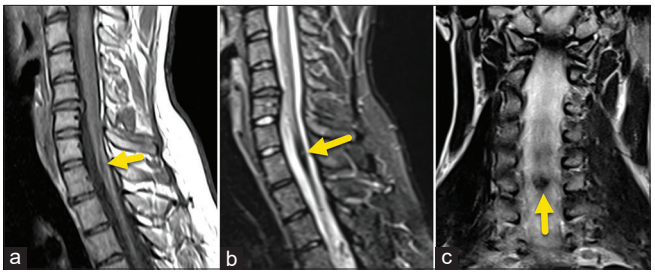

Figure 2: Sagittal T1-WI (a), sagittal (b), and coronal T2-WI (c) show a focal T2-hyperintense lesion (arrows) that is isointense on T1-WI and hyperintense on T2-WI, with surrounding hypointensity that suggests a cavernoma with hemosiderosis T1-WI = T1-weighted image, T2-WI = T2-weighted image

Table 1: Previously described cases of spinal CCMs due to *KRIT1* mutation

Author, year	Age of the patient/gender	Clinical features	Cavernoma location
Lee *et al*., 2010[5]	65 years/M	Gait disturbance and left foot paresthesia	Temporal lobe, right thalamus, cervical, thoracic, and lumbar spinal cord
Russo *et al*., 2017[6]	26 years/M	Intracranial germ cell tumor postradiotherapy	Pons, cerebellum, C7 segment of the spinal cord
Yang *et al*., 2016[7]	10 months/M	Seizures	Left perisylvian, right parietal areas, thoracic cord
Chang *et al*., 2019[8]	Age- not mentioned/F	Weakness of lower limbs	Multiple brain lesions, thoracic cord

CCMs=Cerebral cavernous malformations

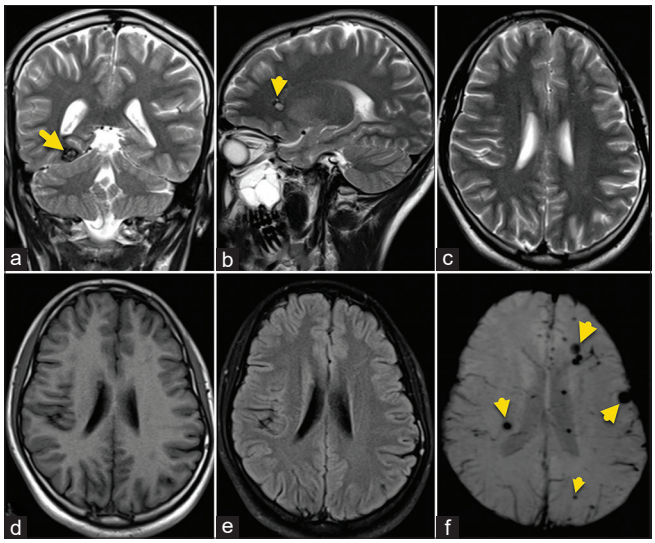

Figure 3: T2-weighted coronal (a) and sagittal (b) images reveal right occipital (arrow) and left frontal (arrow) hyperintense lesions with hypointense margins, consistent with cavernomas. At the level of corona radiata, axial T2-weighted imaging (c), T1-weighted imaging (d), and FLAIR (e) all appear normal, but susceptibility-weighted imaging (f) reveals multiple foci of hypointensities (arrows in f), suggesting cavernomas, which are not visible on conventional T1-weighted, T2-weighted, and Fluid attenuated inversion recovery (FLAIR) images

resection and stereotactic radiosurgery can be employed for symptomatic CCMs, and conservative management is used for incidental lesions.[10] Our patient was referred to neurosurgery for excision of his spinal cord cavernoma. However, surgery is awaited till date because of financial constraints.

As many as 40% of patients with a spinal CCM may harbor a similar intracranial lesion.[11] So, it is prudent to screen patients with intracranial cavernous malformations to screen for spinal CCM and vice versa. Genetic testing is not recommended for single lesions without a family history. Multiple CCMs and coexisting spinal and intracranial CM merit genetic testing, as molecular diagnosis might be beneficial for early diagnosis and treatment of the family members.[12]

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Conflicts of interest
There are no conflicts of interest.

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