

## **Abstract**

We present the case of a 57-year-old man with protein S deficiency and left leg deep vein thrombosis (DVT) five years prior, who developed stepwise progressive bilateral lower limb weakness, numbness/paresthesia, gait imbalance, hesitancy of micturition, and constipation in the setting of recurrent left common femoral DVT treated with apixaban. Symptoms amplified with Valsalva, corticosteroids, and post-lumbar puncture, with longitudinally extensive mid-thoracic T2-hyperintense lesion extending to the conus associated with hazy holocord enhancement on magnetic resonance imaging (MRI), raising suspicion for spinal dural arteriovenous fistula (sDAVF). Initial digital subtraction angiography (DSA) was negative for sDAVF. However, cerebral spinal fluid (CSF) was herpes simplex virus (HSV)-2 positive, and he was treated with antiviral therapy. Unfortunately, he continued to worsen despite treatment. Repeat neuroimaging twelve months after initial presentation demonstrated persistent lower thoracic/conus lesion in addition to cauda equina enhancement and subtle dorsal T2-hypointense flow voids. We raised red flags (eg, lack of clinical prodrome, no herpetic rash, no CSF pleocytosis, and rostral extent of the lesion) that suggested the HSV2 nucleic acid detection was perhaps unrelated to the neurological syndrome. Given the high index of suspicion for sDAVF, we repeated spinal vascular imaging. Spinal MRA demonstrated dilated right dorsal perimedullary veins from T10 to T11. Repeat DSA revealed a right T10 sDAVF. Microsurgical treatment rather than embolization of the fistula was successful without complication, with significant improvement in motor, sphincter, and to a lesser extent sensory function, with residual gait imbalance after inpatient rehabilitation three weeks postoperatively.

## Section 1

A 57-year-old man with protein S deficiency and left leg DVT five years prior presented with progressive bilateral lower limb weakness, numbness/paresthesia, gait imbalance, urinary hesitancy, and constipation, starting three weeks after recurrence of left common femoral DVT treated with apixaban. Two weeks later, he had a low-speed motor vehicle accident (rear-ended). Over the next two months, these symptoms worsened in a stepwise manner prompting hospitalization.

Neurological exam revealed 4+/5 hip flexion bilaterally, 4+/5 left knee flexion, spasticity, brisk patellar reflexes, bilateral Babinski sign, diminished pinprick, temperature, and vibratory sensation below the waist, and gait instability requiring a cane. MRI spine revealed a longitudinally extensive mid-thoracic T2-hyperintense lesion extending to the conus associated with hazy holocord enhancement (Figure 1 A–B A–D). MRI brain showed nonspecific T2-hyperintensities. Given concern for an idiopathic inflammatory condition and functional decline, he received intravenous methylprednisolone 1 g/day for three days, worsening after infusions.

### Questions for consideration:

1. What is the anatomic localization?
2. What is the differential diagnosis?

## Section 2

Lower limb motor function disturbance with upper motor neuron (UMN) signs implies bilateral corticospinal tract involvement below T1 level.<sup>1</sup> The sensory level below the waist (L1) suggests a lesion at around T10, as spinothalamic fibers ascend Lissauer's tract by

about three segments before they decussate. Disruption of all sensory modalities suggests a relatively large central cord lesion, involving spinothalamic and dorsal column tracts.<sup>1</sup> Gait imbalance may be due to impaired conduction of lower limb proprioceptive information along spinocerebellar and gracile fasciculus tracts.<sup>2, 3</sup> Sphincter dysfunction of bladder and bowel results from interruption of afferent feedback of distension from these organs that normally triggers voiding,<sup>2</sup> most commonly manifesting in hesitancy of micturition and constipation.<sup>3</sup> Funicular (central) pain is common with intramedullary (but not extradural) spinal cord lesions, related to spinothalamic and dorsal column tract dysfunction.<sup>3</sup>

Time from onset to nadir and imaging features help narrow the differential diagnosis for spinal cord disorders. Despite his inherited thrombophilia, spinal cord infarct was unlikely given time to nadir greater than 12 hours and lack of T2-hyperintense 'owl eyes' pattern on axial view or adjacent vertebral body infarct.<sup>4</sup> Likewise, the absence of flat 'pancakelike' disc of enhancement or spondylotic stenosis, tumor, or hematoma on imaging ruled out a compressive myelopathy. Multiple sclerosis (MS), aquaporin-4 (AQP4)-IgG-seropositive neuromyelitis optica spectrum disorder (NMOSD), and MOG antibody disease (MOGAD) associated myelitis often reaches nadir between 1 to 21 days.<sup>5</sup> Although our patient had periventricular and spinal cord lesions (dissemination in space), the periventricular lesions were not Dawson's finger in appearance, and the spinal cord lesion was longitudinally extensive and central rather than short and subpial, atypical for MS.<sup>6</sup> AQP4-IgG NMOSD and MOGAD can both present with longitudinally extensive myelitis. However, AQP4-IgG seropositive myelitis is associated with severe deficits (eg, paraplegia), tonic spasms, and patchy or ring enhancement, whereas MOGAD typically

affects the central grey matter (H sign) with faint or absent enhancement on imaging. Autoimmune connective tissue disease (eg, sarcoidosis, Behçet, lupus, Sjögren's) was less likely without systemic symptoms.<sup>5, 7</sup> Neurosarcoidosis may cause longitudinally extensive lesions but lesions tend to be avidly enhancing with dorsal subpial and central canal predilection (trident sign). Supportive nucleic acid detection and serology may rule in infectious myelitis. Paraneoplastic myelopathies are rare and tend to cause lateral or dorsal tract-specific signal changes on imaging (tractopathy).<sup>5</sup>

Symptom progression beyond 21 days suggests a metabolic myelopathy (eg, B12, copper, vitamin E deficiency) or spinal dural arteriovenous fistula (sDAVF).<sup>5</sup> The UMN pyramidal signs and sensory ataxia could suggest a subacute combined degeneration due to B12 or copper deficiency. Still, there was no dorsal inverted 'V' appearance or lateral column involvement on axial T2 imaging.<sup>8</sup> In an older patient, with progressive lower thoracic myelopathy involving the conus, with or without T2-hypointense flow voids, worsening with steroids, sDAVF must be investigated by spinal vascular imaging as early intervention to obliterate the fistula improves outcome.<sup>4</sup>

### **Question for consideration:**

What are the next steps in evaluation and management?

### **Section 3**

Initial digital subtraction angiography (DSA) was negative for sDAVF. CSF showed one white blood cell (WBC)/ $\mu$ l, four red blood cells (RBC)/ $\mu$ l, normal glucose (57 mg/dl), mildly elevated protein (55 mg/dl), no oligoclonal bands, negative cytology and flow cytometry. He noticed substantial worsening after lumbar puncture. HSV2 PCR was positive in CSF,

for which he received intravenous acyclovir for two weeks then oral valcyclovir for two weeks outpatient. Additional laboratory studies were negative for HSV1, varicella zoster virus (VZV), west nile virus (WNV), enterovirus, Borrelia burgdorferi, human immunodeficiency virus (HIV), antinuclear antibody, myeloperoxidase antibody, proteinase 3, and lupus anticoagulant. B12 (490 mg/dl), folate (11.6 mg/dl), and vitamin D (23.6 mg/dl) were normal.

Seven months later, he sought readmission for worsening paraparesis (4/5 on right and 4+/5 on left with UMN distribution), gait imbalance requiring a walker, intensified lower extremity dysesthesia and numbness, and pronounced urinary retention and constipation, amplified by exertion. Imaging redemonstrated the lower thoracic/conus lesion (Figure 1 ~~C-D~~ ~~E-H~~) in addition to cauda equina enhancement (Figure 1 ~~E~~ ~~I-J~~) and subtle flow voids (Figure 1 ~~C.b.~~ ~~F~~). Nerve conduction studies and electromyography were normal. He started tamsulosin and finasteride for urinary retention and a bowel regimen for constipation. Repeat CSF studies demonstrated xanthochromia, 3690 RBCs / $\mu$ l, no WBCs, elevated protein (70 mg/dl), normal glucose (64 mg/dl). Repeat HSV2 PCR was negative in CSF. Serum AQP4 and MOG antibody testing were negative. Paraneoplastic autoantibody (Mayo Clinic) panel was negative. He continued to worsen on outpatient follow-up (eg, 3/5 lower limb weakness with UMN distribution).

### **Questions for consideration:**

1. What are additional diagnostic considerations?
2. What further testing can help make the diagnosis?

### Section 3

Elsberg syndrome (ES) first described in the 1930s is a myeloradiculitis related to herpes infection (eg, HSV-2 and VZV).<sup>9</sup> Due to rapid viral clearance, the highest yield for nucleic acid detection is 3-14 days after onset.<sup>10</sup> HSV and VZV IgG index or IgM is preferred when CSF is obtained late.<sup>10</sup> Savoldi et al. defined diagnostic criteria for ES and established exclusion criteria (eg, myelitis rostral to T9) to distinguish ES from other mimics. Among patients with suspected ES and identified alternative diagnosis, 41 of 213 (19%) had vascular myelopathy (sDAVF and infarction).<sup>10</sup>

We identified red flags arguing against ES in our patient. He had no history of herpetic rash, no CSF pleocytosis, inadequate antiviral treatment response, sequential rather than contemporaneous nerve root and spinal cord enhancement, and thoracic lesion rostral to T9, extending continuously rather than discontinuously to the conus. Due to these red flags and a high index of suspicion for sDAVF, we recommended repeat angiography. Spinal MRA was initially preferred due to periprocedural risks (eg, bleeding risk on apixaban) and demonstrated dilated right dorsal perimedullary veins from T10 to T11 (Figure 2 A-B). Repeat DSA revealed a right T10 sDAVF (Figure 2 C) confirmed by DynaCT (Figure 2 D). Embolization appeared an unsafe option due to fistula location and risk of ischemic complication. Microsurgical disconnection of the fistula was successful without complication (Figure 2 E-G), with significant improvement in motor/gait, sphincter, and to a lesser extent sensory function after inpatient rehabilitation three weeks postoperatively.

## Discussion

sDAVF results from an acquired arteriovenous connection between a radiculomeningeal artery and vein, causing arterialization of the vein, venous hypertension, venous stasis, and spinal cord ischemia.<sup>4</sup> Valsalva, corticosteroids, and lumbar puncture may worsen deficits by elevating venous pressure.<sup>4, 11</sup> Treatment is by endovascular embolization (80% efficacy) or microsurgical interruption of the fistula (98% efficacy). Early treatment may improve or stabilize neurological deficits. Clinical severity before treatment predicts outcome.<sup>4</sup> While DSA is the gold standard for diagnosis, it is not perfect. In one study, 53 of 80 patients (66%) received delayed diagnosis of sDAVF, of which 19% had previously normal angiogram.<sup>12</sup> Atherosclerosis of segmental arteries and thrombosis or vasospasm of veins may negatively affect angiographic sDAVF detection.<sup>4</sup>

Trauma<sup>4</sup> or local venous occlusion<sup>3, 13</sup> may contribute to fistula development. Onset preceded any trauma in our patient by several weeks suggesting an atraumatic etiology. Disrupted outflow by venous occlusion may enlarge pre-existing vascular channels leading to incompetence of any valves and persistent arteriovenous shunt, even after thrombus resolution. Venous ischemia and vascular distension may also induce the release of angiogenic factors, vascular endothelial growth factor (VEGF), and hypoxia-inducible factor-1 (HIF-1) that promote collateralization.<sup>14</sup> Whether indolent HSV2 angiopathy promotes sDAVF development is unknown. Yet, the positive predictive value of viral PCR is imperfect (~54%).<sup>15</sup> Viral nucleic acid detection in CSF may be unrelated to the neurologic disorder.

Identifying imaging patterns may improve early detection and outcome. In one study of 44 patients with sDAVF and intraparenchymal enhancement, 19 (43%) exhibited the

'missing-piece' sign, defined by at least one non-enhancing area within a long segment of holocord enhancement.<sup>12</sup> We detected a mismatch between the length of T2-hyperintensity and enhancement, rather than the 'missing piece sign'. Better contrast egress in non-enhancing portions of lesion underlies this finding. Spinal MRA can be helpful in indirectly locating the fistula by demonstrating dilated perimedullary veins with a sensitivity of 80-95%.<sup>4</sup> In our patient, spinal MRA helped localize the level and laterality of the fistula within one segment.

## References

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## Figure 1.

Title: Initial and follow up MRIs.

Legend: MRI findings approximately four months (A-B) and 12 months (C-E) after initial presentation demonstrates persistent longitudinally extensive T2-hyperintensity extending from T6-T7 to conus on sagittal STIR (A.b, C.b) throughout the central cord (A.a, C.a), with subtle flow voids (C.b). Hazy holocord gadolinium enhancement from T8-T9 to conus on sagittal (B.b, D.b) and axial (B.a, D.a) T1-weighted imaging. Cauda equina gadolinium enhancement on axial (E.a) and sagittal (E.b) view on T1-weighted post-contrast imaging. Axial images (A.a, B.a, C.a, D.a) were captured at T10-T11 and (E.a) at L4.

## Figure 2.

Title: Spinal vascular imaging and microsurgical fistula obliteration.

Legend: Spinal MRA demonstrates dilated right dorsal perimedullary veins from T10 to T11 on sagittal (A, arrows) and coronal (B, arrows) views. Digital subtraction angiography of the right T10 radicular artery showing the fistula (C, single arrow) leading to arterialized dorsal spinal veins (C, arrowhead). DynaCT during right T10 contrast injection showing similar findings (D). Intraoperative image of proximal arterialized vein exiting the fistula (E, arrow) and the engorged arterialized veins of the posterior aspect of the spinal cord. Intraoperative Indocyanine Green (ICG) infusion via intravenous route showing early arterial filling of the posterior spinal veins (F). Post successful disconnection of the fistula with ICG infusion no longer showing early arterialized veins (G).