Pearls & Oy-Sters: Spinal Cord Candidiasis Linked to CARD9 Deficiency Masquerading as a Longitudinally Extensive Transverse Myelitis

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SUMMARY:
Candida spp. myelopathies are very rare. We report a case of subacute longitudinally extensive transverse myelitis in an apparently immunocompetent 55-year-old male. After a negative infectious workup, corticosteroids and plasma exchange were initiated. Although there was a transient initial improvement, symptoms then worsened, and the lumbar puncture was repeated. Candida albicans was isolated in the cerebrospinal fluid (CSF) and a diagnosis of spinal cord candidiasis was made. Gene panel sequencing for inborn immune deficiencies identified a homozygous disease-causing CARD9 variant. Despite antifungal treatment, necrotic myelitis, meningo-encephalitis, and cerebral vasculitis developed. Fungal spinal cord infections can mimic inflammatory myelitis, and beta-D-glucan testing of both the serum and CSF may help narrow down the diagnosis. In cases of severe or unexpected invasive Candida spp. infection, even adults and apparently immunocompetent patients should be screened for inborn immune deficiencies and CARD9 deficiency in particular.
PEARLS:

- Longitudinally extensive transverse myelitis (LETM) is a diagnostic emergency with principally autoimmune, inflammatory, and infectious etiologies. Spinal cord candidiasis is an exceptional cause of LETM.

- *Candida* spp. infection of the central nervous system (CNS) commonly involves meningitis and cerebral abscesses but, rarely, mimics inflammatory myelitis. A search for underlying immunocompromised condition should be pursued.

- First described in 2009, autosomal, recessive mutation in the caspase-associated recruitment domain-9 (CARD9) gene is responsible for the lack of recruitment of neutrophils to the site of fungal infections, especially in the CNS.¹

OY-STERS:

- In CNS candidiasis, usual signs indicative of an ongoing infection can be absent initially, with only mild pleiocytosis in the CSF and no fever.

- In about half of CNS candidiasis patients, the first direct CSF fungal exam and culture is negative. However, CSF beta-D-glucan testing has high sensitivity and specificity for fungal infections.

- The adult onset observed in several CARD9-deficient patients is very uncommon for inborn errors of immunity. Even adults and apparently immunocompetent patients should be tested for CARD9 deficiency if they have a severe or unexpected *Candida* spp. infection.

REPORT:

A 55-year-old male, with no medical history apart from recurrent cutaneous *Pityriasis versicolor* infections, presented to the emergency room with afebrile violent abdominal pain after a four-day subacute course of dysuria and paraparesis. Routine biology tests and a
lumbar CT-scan were unremarkable. He was admitted to the neurology department three days later with paraplegia and intense lumbar pain. A spinal cord MRI with gadolinium enhancement showed a longitudinally extensive transverse myelitis from T4 to T6 (Figure 1A, 1B) with swelling extending to the cervical segment. A brain MRI showed a small lateral-ventricular nonspecific, non-enhancing white-matter hyperintensity, without a central vein sign. The first lumbar puncture retrieved moderate lymphocytic pleocytosis (28/µL), proteins at 1.48 g/L, and normal glycorrhachia. An extensive infectious workup including next-generation sequencing of infectious pathogens in the CSF was negative. There was no evidence of tuberculosis or auto-immune systemic disease, anti-myeline oligodendrocyte glycoprotein (MOG) and anti-aquaporin 4 (AQP4) antibodies were negative. Inflammatory myelitis was suspected and a cycle of ten steroid pulses and four plasmaphereses was started with initial neurological improvement. Three weeks after the disease onset, the symptoms worsened with ascension of the sensory level at C4. A spinal MRI showed an extension of the myelitis to the medulla oblongata (figure not shown). The main hypothesis was a premature relapse at the end of the steroid therapy, and methylprednisolone was reintroduced at 240 mg. At week four, the patient developed fever with repeated sterile blood cultures: a second lumbar puncture retrieved 8000 neutrophils/µL with proteins at 6.73 g/L. Beta-D-glucan was positive in the serum at 496 pg/ml but was not tested in the CSF. CSF culture was positive for *Candida albicans*, voriconazole was introduced at 6 then 4 mg/kg/12h, along with cefotaxime and amoxicillin. Because of suspected immunodeficiency, an antituberculous quadritherapy regimen (rifampicin, isoniazid, ethambutol and pyrazinamide) was added, as co-infections are frequent in immunocompromised patients, and we searched for inborn errors of immunity. Gene panel sequencing (Inne Panel, Twist, see eAppendix for more information) identified a homozygous CARD9 variant c.865C>T (p.Gln289*), which is a known disease-causing variant. At this time, secondary infectious vasculitis was suspected when a brain MRI
revealed arterial irregularities and an infarct on the cerebellar peduncle (Figure 1C). Voriconazole was replaced by liposomal amphotericin B after one week because interaction with rifampicin led to undetectable levels of residual voriconazole; Candida albicans remained detectable in the CSF until then. At week 6 from the onset of symptoms, altered consciousness and brain imaging revealed intraventricular bleeding. The patient was transferred to the intensive care unit where the monitored intracranial pressure increased daily. Cerebral arteriography found a voluminous aneurism of the posterior inferior cerebellar artery (Figure 1D), which was embolized during the same procedure. Symptoms worsened and backflow on the transcranial doppler was followed by cerebral death. The autopsy did not find evidence for disseminated extra-neurological candidiasis. Histopathological analysis of the medulla showed large necrotic lesions (Figure 2A, 2B, hematoxylin and eosin staining) with numerous septate pseudohyphae and fungal spores on the border (Figure 2C, Grocott staining). There were intense inflammatory infiltrates around the arterial wall, indicating arteritis. The patient’s relatives received workups for CARD9 deficiency, and genetic counseling is ongoing. To date, only heterozygous mutations have been diagnosed in the family, and no family history of fungal infections has been reported.

DISCUSSION:
Longitudinally extensive transverse myelitis (LETM) is a neurological emergency that requires prompt etiological diagnosis for adequate management. Fungal myelopathies are rare, especially in apparently immunocompetent patients.

Reports of invasive Candida infections of the CNS with defined clinical and microbiological criteria are scarce, with most involving the brain and meninges: there are very few reports of Candida myelitis. Patients with severe Candida infections usually have an underlying
immunodeficiency. 4 CARD9 deficiency, first reported in 2009, 1 is an autosomal recessive primary immunodeficiency caused by loss-of-function mutations in the CARD9 gene, which encodes a signaling protein essential for recruitment of neutrophils to the site of fungal infections. 5 This phenotype includes recurrent fungal infections by dermatophytes, 6 Candida spp, or Phaeohyphomycetes involving various organs, especially lymph nodes, skin and nails, and CNS. Secondary Candida localization in the CNS during fungemia is extremely rare. CARD9 plays a crucial role in recruiting neutrophils to the CNS via the production of IL-1β and CXCL1 chemokines by the microglia. 7 A recent case series identified four patients with a CARD9 homozygous mutation and Candida meningo-encephalitis, of whom one seven-year-old girl presented with several medullary enhancing lesions associated with meningitis and cerebral abscesses. 8 A larger cohort of 24 patients with CNS candidiasis found two CARD9 deficiencies but no description of intramedullary lesions: most cases involved micro- or macro-abscesses and meningitis. 9 As in our case, half of the patients had a negative CSF fungal culture on the first lumbar puncture, underscoring the importance of repeat testing. Beta-D-glucan levels in the CSF may be a sensitive diagnostic tool for fungal CNS infections: it has been suggested that beta-D-glucan testing has a sensitivity of 96% and specificity of 95% for Candida meningitis. 10 Testing for beta-D-glucan in the CSF may be judicious in cases of severe myelitis of undetermined etiology, before moving on to immunosuppressive therapies. CSF metagenomic next-generation sequencing can purportedly detect all potential pathogens (viruses, bacteria, fungi, and parasites) in a single assay. It is an emerging tool for the diagnosis of CNS infections but remained negative in our case. As fungi are common contaminants, positive results require interpretive caution. On the other hand, fungi are usually present in low loads and share large parts of their genome with humans, which may alter sensitivity (because part of the fungal DNA is filtered during the analysis process).
The physiopathology of CNS candidiasis remains unclear: although the primary lesion may have been a fungal abscess, histopathological findings suggest an initial vasculitic mechanism, with fungal filaments found within vascular walls. A case of intradural but extramedullary *Candida* infection in a patient with parenteral nutrition has been described, with end-arteritis obliterans causing medullary infarction, and Grocott staining showing yeasts and hyphae. Vasculitis lesions may be a route by which *Candida* can invade the CNS. In our case, histopathological analysis shows intense inflammatory infiltrates of arterial walls. Moreover, the patient initially improved with immunotherapy which suggests that part of the disease was mediated by an inflammatory process: a transient response to immunotherapy could be explained by a non-specific anti-edema effect.

Our patient developed a severe *Candida* infection at the age of 55. As cases of CNS candidiasis remain scarce, looking for CARD9 deficiency in patients with no evident risk factors for invasive fungal infections (i.e., parenteral nutrition, malignant hemopathies, or other causes of immunosuppression) may be pertinent, even in adults with no notable medical history.

Our patient was treated with voriconazole, before switching to amphotericin B. The clinical guidelines of the Infectious Diseases Society of America—based on low-quality evidence due to the small number of cases of CNS candidiasis—indicate that amphotericin B with or without oral flucytosine should be used before step-down therapy to fluconazole. Adjunctive granulocyte-macrophage colony-stimulating factor (GM-CSF) therapy has been reported to produce complete clinical remission in patients with CARD9 deficiency who have relapsing spontaneous CNS candidiasis despite antifungal therapy. Unfortunately, the rapid course of the infection and transfer to the intensive care unit, and the post-mortem determination of CARD9 deficiency, meant that we could not try GM-CSF therapy with our
patient. Management of severe CNS infections remains difficult because of the rarity of these presentations.

**CONCLUSION**: CNS candidiasis should be considered in cases of severe LETM myelitis with a poor response to immunotherapy, even in apparently immunocompetent patients and in the absence of purulent meningitis. Because the initial direct examinations and fungal cultures can be negative, there is special interest in beta-D-glucan testing in the CSF. Patients should also be screened for CARD9 deficiency in cases of severe CNS fungal infection when no alternative predisposing factor is identified.

[http://links.lww.com/WNL/C176]
REFERENCES:


Figure 1: MRI findings

MRI data showing extensive myelitis from C6 to the terminal cone on T2 sequences (sagittal C5–T9 in panel A), with a centromedullary necrotic lesion from T4 to T6 on T1-weighted post-gadolinium images (sagittal C5–T9 on panel B). Brain MRI showing right cerebellar peduncle infarct caused by the arteritis (panel C). Vertebro-basilar angiography with multiples arterial stenosis and aneurysm of the left posterior inferior cerebellar artery indicating arteritis (panel D).
**Figure 2: Histopathological data**

**Panel A:** Histopathological analysis of the thoracic medulla (haematoxylin and eosin, scale bar: 2.5 mm), showing large necrotic lesions (stars) on the left side of the spinal cord.

**Panel B:** View of the anterior spinal artery of the thoracic medulla (haematoxylin and eosin, scale bar: 250 µm), showing intense inflammatory infiltrates of the arterial wall (arrow), indicating arteritis.

**Panel C:** Meningeal vessels of the thoracic medulla (Grocott staining, scale bar: 100 µm), with lymphoplasmacytic infiltrates and mycelial filaments (arrow).
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