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

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Abstract

Candida spp. myelopathies are very rare. We report a case of subacute longitudinally extensive transverse myelitis in an apparently immunocompetent 55-year-old man. 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 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, meningoencephalitis, and cerebral vasculitis developed. Fungal spinal cord infections can mimic inflammatory myelitis, and beta-D-glucan testing of both 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 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 variation 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 the patients with CNS candidiasis, the first direct CSF fungal examination and culture are 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.

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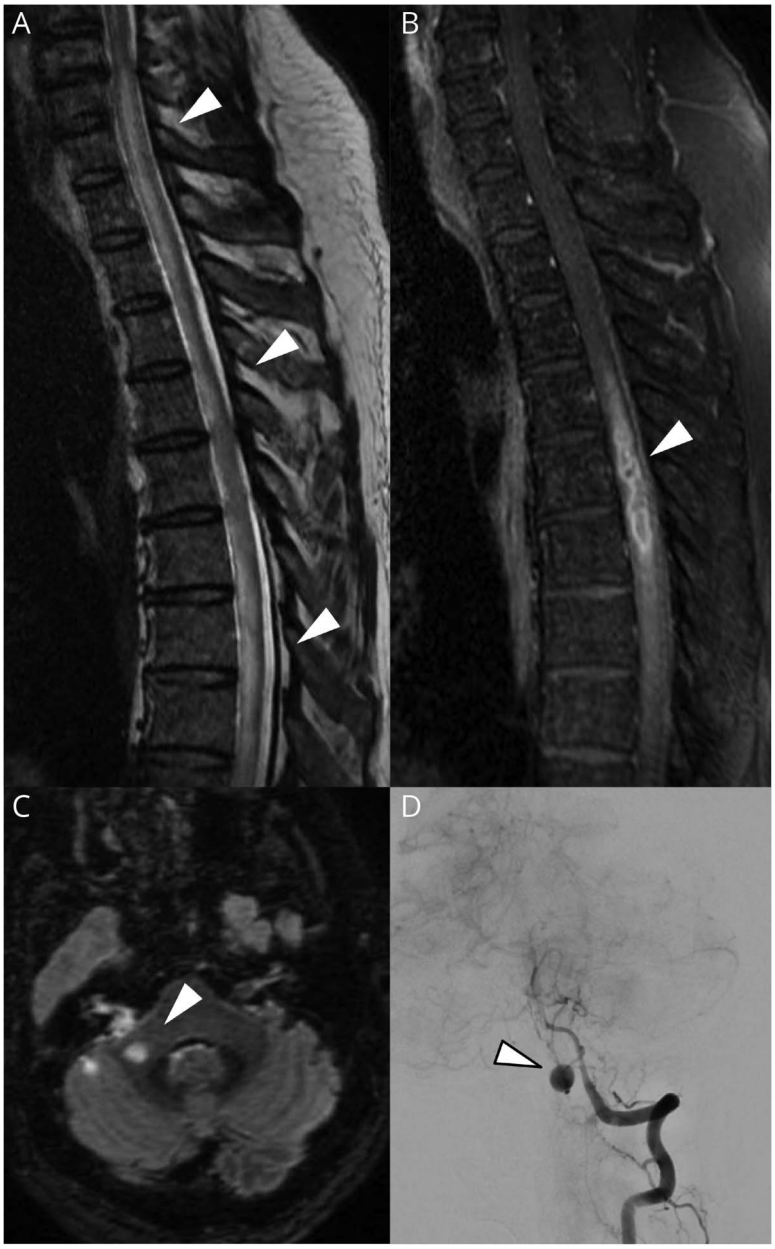
Case Report

A 55-year-old man, with no medical history apart from recurrent cutaneous *Pityriasis versicolor* infections, presented to the emergency department with afebrile violent abdominal pain after a 4-day subacute course of dysuria and paraparesis. Routine biology tests and a lumbar CT scan were unremarkable. He was admitted to the neurology department 3 days later with paraplegia and intense lumbar pain. A spinal cord MRI with gadolinium enhancement showed a LETM from T4 to T6 (Figure 1, A and B) with swelling extending to the cervical segment. A brain MRI showed a small lateroventricular nonspecific, nonenhancing white-matter hyperintensity, without a central vein sign. The first lumbar puncture revealed 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 autoimmune systemic disease, and anti-myeline oligodendrocyte glycoprotein and anti-aquaporin 4 antibodies were negative. Inflammatory myelitis was suspected, and a cycle of 10 steroid pulses and 4 plasmaphereses was started with initial neurologic 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

Figure 1 MRI Findings



MRI data showing extensive myelitis (arrows) from C6 to the terminal cone on T2 sequences (sagittal C5–T9 in panel A), with a centromedullary necrotic lesion (arrow) from T4 to T6 on T1-weighted postgadolinium images (sagittal C5–T9 in panel B). Brain MRI showing a right cerebellar peduncle infarct (arrow) caused by the arteritis (panel C). Vertebrobasilar angiography with multiple arterial stenosis and aneurysm (arrow) of the left posterior inferior cerebellar artery indicating arteritis (panel D).

was a premature relapse at the end of the steroid therapy, and methylprednisolone was reintroduced at 240 mg. At week 4, the patient developed fever with repeated sterile blood cultures: A second lumbar puncture retrieved 8,000 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*, and voriconazole was introduced at 6 then 4 mg/kg/12 h, along with cefotaxime and amoxicillin. Because of suspected immunodeficiency, an antituberculous quadritherapy regimen (rifampicin, isoniazid, ethambutol, and pyrazinamide) was added because coinfections are frequent in immunocompromised patients, and we searched for inborn errors of immunity. Gene panel sequencing (Inne Panel, Twist; see eAppendix 1, links.lww.com/WNL/C176 for more information) identified a homozygous *CARD9* variant c.865C>T (p.Gln289*), which is a known disease-causing variant.[2] 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 1 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 aneurysm 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 extraneurological candidiasis. Histopathologic analysis of the medulla showed large necrotic lesions (Figure 2, A and B, 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 variations have been diagnosed in the family, and no family history of fungal infections has been reported.

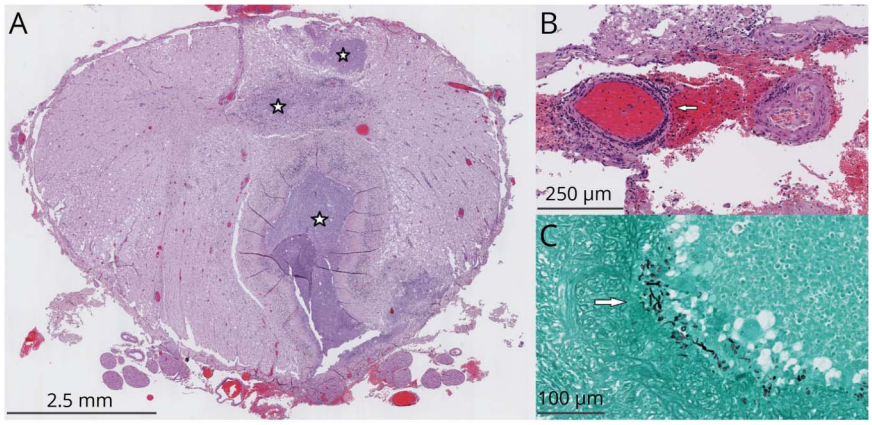
Discussion

LETM is a neurologic emergency that requires prompt etiologic 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,[3] with most involving the brain and meninges: There are a 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 variations in the *CARD9* gene, which encodes a signaling protein essential for the 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 through the production of interleukin 1β and CXCL1 chemokines by the microglia.[7]

A recent case series identified 4 patients with a *CARD9* homozygous variant and *Candida* meningoencephalitis, of whom one 7-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 2 CARD9 deficiencies, but no description of intramedullary lesions: Most cases involved microabscesses or macroabscesses and meningitis.[9] As in our case, half of the patients had a negative CSF fungal culture on the first lumbar

Figure 2 Histopathologic Data



(A) Histopathologic analysis of the thoracic medulla (hematoxylin and eosin, scale bar: 2.5 mm), showing large necrotic lesions (stars) on the left side of the spinal cord. (B) View of the anterior spinal artery of the thoracic medulla (hematoxylin and eosin, scale bar: 250 μm), showing intense inflammatory infiltrates of the arterial wall (arrow), indicating arteritis. (C) Meningeal vessels of the thoracic medulla (Grocott staining, scale bar: 100 μm) with lymphoplasmacytic infiltrates and mycelial filaments (arrow).

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 a 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, histopathologic 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,[11] with endarteritis 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, histopathologic 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 nonspecific antiedema effect.

Our patient developed a severe *Candida* infection at the age of 55 years. 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.[12] 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.[13,14] Unfortunately, the rapid course of the infection and transfer to the intensive care unit, and the postmortem 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 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.

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Appendix *(continued)*

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References

1. Glocker EO, Hennigs A, Nabavi M, et al. A homozygous *CARD9* mutation in a family with susceptibility to fungal infections. *N Engl J Med*. 2009;361(18):1727-1735.
2. Vaezi A, Fakhim H, Abtahian Z, et al. Frequency and geographic distribution of CARD9 mutations in patients with severe fungal infections. *Front Microbiol*. 2018;9:2434.
3. De Pauw B, Walsh TJ, Donnelly JP, et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) consensus group. *Clin Infect Dis*. 2008;46(12):1813-1821.
4. The French Mycoses Study Group, Lortholary O, Renaudat C, Sitbon K, Desnos-Ollivier M, Bretagne S, Dromer F. The risk and clinical outcome of candidemia depending on underlying malignancy. *Intensive Care Med*. 2017;43(5):652-662.
5. Drummond RA, Collar AL, Swamydas M, et al. CARD9-dependent neutrophil recruitment protects against fungal invasion of the central nervous system. *PLoS Pathog*. 2015;11(12):e1005293.
6. Lanternier F, Pathan S, Vincent QB, et al. Deep dermatophytosis and inherited CARD9 deficiency. *N Engl J Med*. 2013;369(18):1704-1714.
7. Drummond RA, Swamydas M, Oikonomou V, et al. CARD9+ microglia promote antifungal immunity via IL-1β- and CXCL1-mediated neutrophil recruitment. *Nat Immunol*. 2019;20(5):559-570.
8. Lanternier F, Mahdaviani SA, Barbati E, et al. Inherited CARD9 deficiency in otherwise healthy children and adults with Candida species–induced meningoencephalitis, colitis, or both. *J Allergy Clin Immunol*. 2015;135(5):1558-1568.e2.
9. Chaussade H, Cazals X, Desoubeaux G, et al. Central nervous system candidiasis beyond neonates: lessons from a nationwide study. *Med Mycol*. 2021;59(3):266-277.
10. Malani AN, Singal B, Wheat LJ, et al. (1,3)-β-d-glucan in cerebrospinal fluid for diagnosis of fungal meningitis associated with contaminated methylprednisolone injections. *J Clin Microbiol*. 2015;53(3):799-803.
11. Merwick Á, Minhas Z, Curtis C, Thom M, Choi D, Mummery C. Intradural extramedullary spinal candida infection. *Pract Neurol*. 2015;15(5):400-404.
12. Pappas PG, Kauffman CA, Andes DR, et al. Clinical practice guideline for the management of Candidiasis: 2016 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2016;62(4):e1-e50.
13. Gavino C, Cotter A, Lichtenstein D, et al. CARD9 deficiency and spontaneous central nervous system candidiasis: complete clinical remission with GM-CSF therapy. *Clin Infect Dis*. 2014;59(1):81-84.
14. Celmeli F, Oztoprak N, Turkkahraman D, et al. Successful granulocyte colony-stimulating factor treatment of relapsing Candida albicans meningoencephalitis caused by CARD9 deficiency. *Pediatr Infect Dis J*. 2016;35(4):428-431.

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