Disseminated Aspergillosis in a Patient With Neurosarcoidosis: Persistent Contrast Enhancement in CNS Despite Prolonged Antifungal Treatment: A Case Report

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ABSTRACT

A 56-year-old Caucasian man was diagnosed with definite neurosarcoidosis after he presented with progressive bilateral lower extremity weakness and dysesthesia. He was started on a combination immunosuppressant regimen of dexamethasone, methotrexate and infliximab. Two months into treatment with immunosuppressants, he developed devastating disseminated aspergillosis which clinically stabilized with aggressive antifungal treatment however had a protracted radiological course despite prolonged anti-fungal treatment for over two years. Interestingly, he remained in remission from neurosarcoidosis off immunosuppression during the same period.

This case emphasizes need for vigilance for fungal infections in patients treated with combination immunosuppressive therapy particularly TNF-α inhibitors such as infliximab.

KEYWORDS: neurosarcoidosis, tumor necrosis factor-α inhibitors, central nervous system aspergillosis, voriconazole, case report

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Introduction

Sarcoidosis, a disease with protean manifestations, involves the central and peripheral nervous system in 5-15% of patients.[1] Characterized by a granulomatous immune response in the nervous system,[2] neurosarcoidosis causes substantial morbidity. Consensus treatment guidelines for neurosarcoidosis are lacking. While corticosteroids remain the mainstay treatment in neurosarcoidosis, tumor necrosis factor–α (TNF-α) inhibitors such as infliximab has emerged as a treatment option for refractory and steroid-dependent patients.

Infliximab is a chimeric mouse–human monoclonal antibody against tumor necrosis factor-α (TNF-α), a cytokine involved in granuloma formation and maintenance.[3] A common strategy in long-term management of severe neurosarcoidosis is to use oral immunosuppressants such as mycophenolate, methotrexate, or azathioprine in combination with infliximab to minimize the risk of neutralizing anti-infliximab antibodies. This combination, however, further increases the risk of serious infections. In a large multi-institutional retrospective study of patients with neurosarcoidosis treated with infliximab, infection rate was close to 10%.[4]

We report a case of neurosarcoidosis treated with combination immunosuppressive therapy including infliximab who developed disseminated aspergillosis.

Case Report

A 56-year-old Caucasian man presented to clinic with a 6-week history of progressive dysesthesia in bilateral arms and legs up to the buttocks and gait difficulties.

He was found to have a multi-focal enhancing and longitudinally extensive lesion with dorsal subpial enhancement on MRI of the cervical and thoracic spine extending from C2 to mid T4 level (Figure 1). Brain MRI was unremarkable. Biopsy of a pulmonary mass showed a granuloma that was not definitive for sarcoidosis. CSF analysis twice revealed persistent pleocytosis (18-61 cells/mm3) and elevated protein but no hypoglycorrhachia. CSF lymphoma markers and ACE levels were unremarkable. Neuromyelitis optica and myelin oligodendrocyte glycoprotein antibodies were also negative. Given the lack of tissue diagnosis and an inconclusive prior lung biopsy, a spinal cord biopsy was done and showed noncaseating granulomas consistent with definite neurosarcoidosis. He was discharged on an oral taper of dexamethasone starting at 15 mg

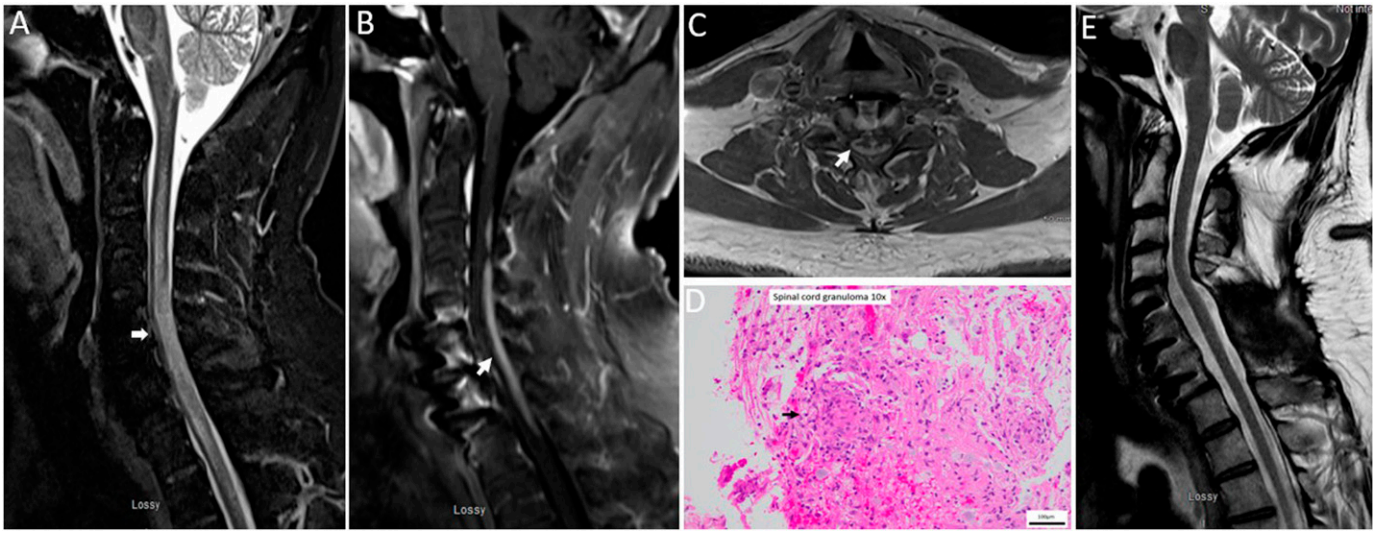

Figure 1. Sagittal T2-weighted MRI of the cervical spinal cord (A) demonstrates longitudinally extensive transverse myelitis (LETM) involving most of the cervical and upper thoracic cord from C2-T4 (arrow). Dorsal subpial enhancement associated with neurosarcoidosis-related LETM as shown on sagittal T1-weighted and axial T1-weighted MRI with gadolinium (B, C respectively; arrows). Spinal cord biopsy showed non-caseating granulomas (D; black arrow) on hematoxylin and eosin staining in a background of a mixed inflammatory infiltrate composed of lymphocytes, macrophages, and occasional plasma cells. Sagittal T2-weighted MRI of the cervical spinal cord two months after combination therapy with infliximab and methotrexate showed resolution of the spinal cord signal abnormality (E). Scale and magnification (D) 100 μm, 10×.

daily along with combination of methotrexate 15 mg weekly and infliximab 5 mg/kg.

Two months later while on this combination regimen of dexamethasone taper, methotrexate 15 mg weekly and infliximab (received 2 infusions), he developed dyspnea and was found to have new pulmonary nodules and cavitary lesions. Simultaneously, he developed right eye blindness. Repeat brain and orbital MRI showed innumerable ring-enhancing lesions in the brain, right endophthalmitis, episcleritis and orbital cellulitis extending from adjacent frontal lesions with surrounding edema concerning for infection (Figure 2). Previous sarcoidosis-related spinal cord abnormalities had resolved completely and immunosuppressants were discontinued. Fungitell test came back positive with a value greater than 500 pg/mL (reference range: <80 pg/mL) and liposomal amphotericin B was initiated. A biopsy of his largest cavitary lung nodule and the vitreous culture of the right eye confirmed *Aspergillus fumigatus*. Specifically, tuberculosis and malignancy were absent. With a diagnosis of disseminated aspergillosis, amphotericin was transitioned to voriconazole for continued maintenance therapy of disseminated aspergillosis. Unfortunately, he lost all vision in the right eye and underwent enucleation, which substantiated the diagnosis of aspergillosis on histological analysis (Figure 3).

Further surveillance MRIs demonstrated regression of the newly developed lesions, yet persistent contrast enhancement in the brain, despite two years of voriconazole treatment with clinical improvement. Voriconazole was ultimately discontinued due to exfoliative dermatitis, and given his clinical status, no other antifungals were initiated. The patient remains in clinical and radiological remission without immunosuppressive therapy as of 30 months later.

Written informed consent was acquired from the patient for clinical information and medical images to be published.

Discussion

TNF-α inhibitors increase the susceptibility to invasive fungal infections by inhibition of interferon-γ production, decreased expression of pattern-recognition receptors, and leukocyte apoptosis.[5] Inhibition of granulomas by TNF-α blockade results in a failure to compartmentalize these intracellular fungi and leads to disseminated disease.[5] The antecedent granuloma could have been a nidus for quiescent aspergillosis in an immunocompetent individual that reactivated in the setting of infliximab treatment. When assessing the risk of aspergillosis, various factors including the underlying disease being treated, pre-existing lung disease, neutropenia and use of concurrent immunosuppression must be considered.[6]

A fumigatus is the most common cause of invasive pulmonary aspergillosis and hematogenous spread to the CNS is common.[7] *Aspergillus* sp. are angio-invasive resulting in a wide range of complications including brain abscesses, infarcts, mycotic aneurysms, and hemorrhage. Invasive aspergillosis carries a high mortality rate despite treatment.[7,8]

Voriconazole is the drug of choice for aspergillosis, including CNS infection, given its CNS permeability. However, there is extensive variability with voriconazole non-linear pharmacokinetics. Therapeutic drug monitoring is needed to achieve adequate blood trough levels to prevent

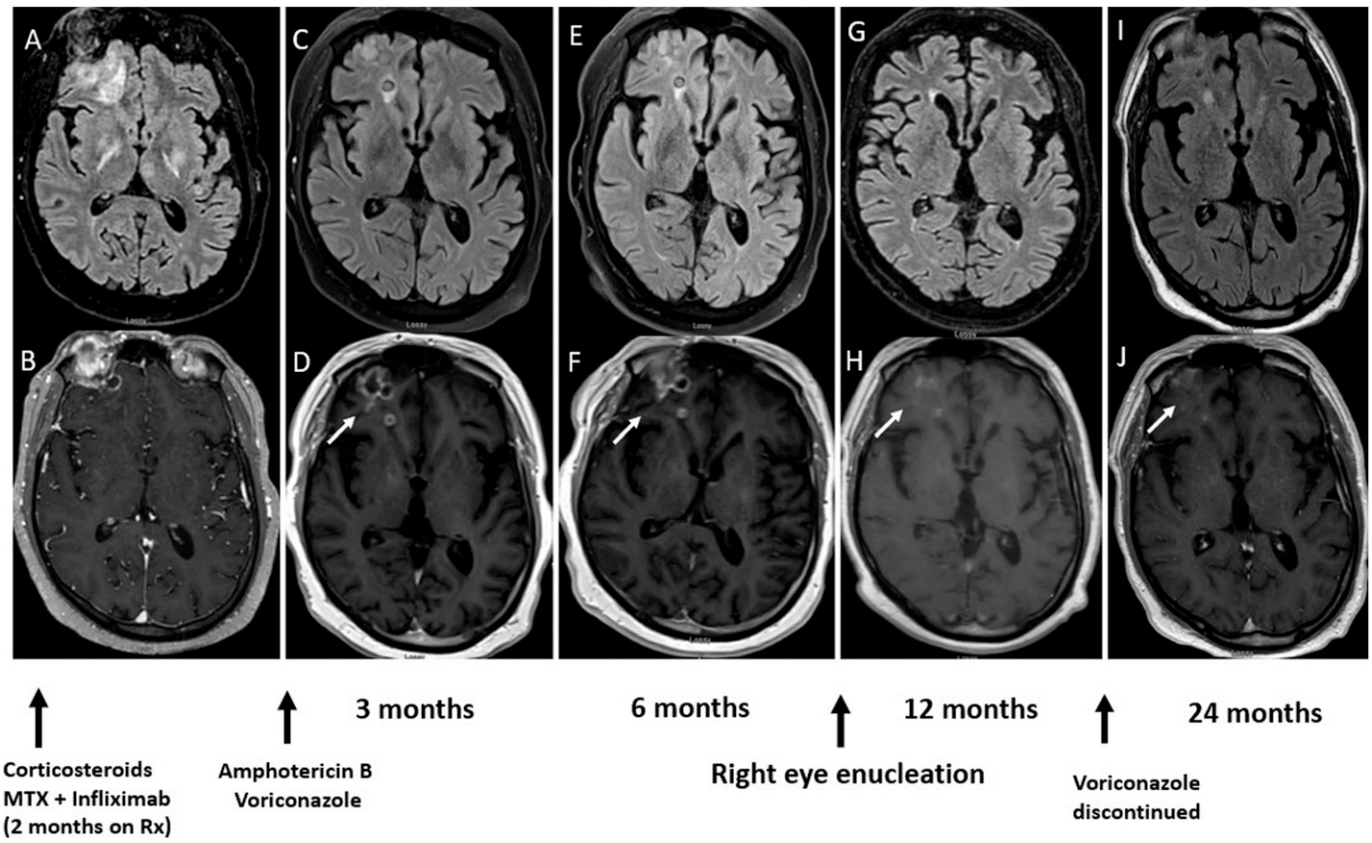

Figure 2. Axial T2/FLAIR MRI showing multiple brain parenchymal lesions most prominently in the right frontal lobe (A) and simultaneous enhancing lesions on axial T1-weighted MRI with gadolinium (B). Follow up at 3 months (C), (D), 6 months (E), (F), 12 months (G), (H) and 24 months (I), (J) showed significantly reduced but persistent enhancement despite treatment with voriconazole for two years.

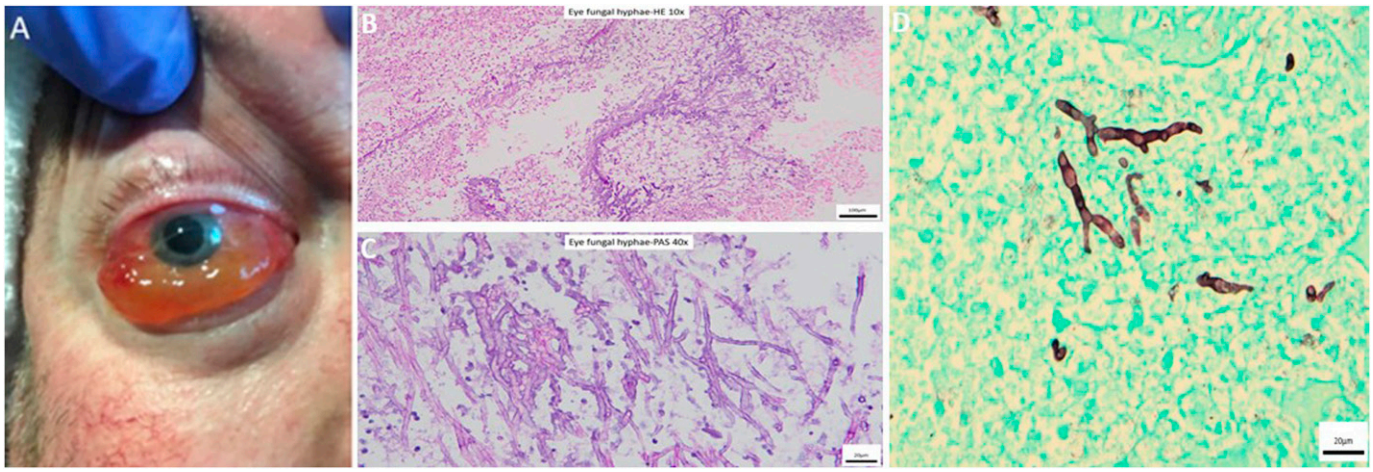

Figure 3. External examination of right eye showed severe chemosis, periorbital edema and proptosis (A). Pathological examination of the enucleated eye showed fungal hyphae on hematoxylin and eosin stain (B), (C) on a background of extensive acute and chronic inflammation, edema, necrosis, and abscess formation. Grocott-Gomori methenamine silver stain of the left lower lung biopsy specimen showed septate hyphae with acute angle branching, with a morphology consistent with Aspergillus (D). Scale and magnification (B) 100 μm, 10×; (C) 20 μm, 40×; (D) 200 μm, 40×.

breakthrough fungal disease. Furthermore, CSF levels of voriconazole range widely[9] and this may explain our patient's persistent, albeit significantly reduced, enhancement two years since the onset of the disease.

A combination of antifungal therapy and prompt surgical intervention when appropriate improves the survival rate of patients with fungal neuroinfections. Duration of anti-fungal therapy is not well defined, and current recommendations are to

continue treatment based on clinical and radiological improvement.[6] Prophylactic Antifungal prophylaxis is recommended in certain high-risk groups (e.g., transplant patients),[6] but future research is necessary to determine if pre-emptive prophylaxis has a role during immunosuppression in neurosarcoidosis.

In our patient it remains unclear whether the persistent CNS enhancement might be explained by voriconazole's erratic pharmacokinetics despite good CNS permeability or related to delayed radiological improvement in an immunosuppressed individual. There was concern of ongoing neurosarcoidosis-related inflammation, but this seems less likely given his continued clinical improvement off immunosuppressants for over 2 years.

Conclusion

In conclusion, this case demonstrates the need to remain vigilant for fungal infections in patients with neurosarcoidosis treated with TNF-α inhibitors. This case also emphasizes importance of early aggressive, and often prolonged treatment of CNS fungal infections and raises the question whether prophylactic antifungal agents may be warranted in such patients on combination immunosuppression.

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Author Contributions

Lakshman Arcot Jayagopal: Conceptualization, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing, Afsaneh Shirani: Formal analysis, Methodology, Writing – review & editing, Kelly Cawcutt: Formal analysis, Writing – review & editing, Jie Chen: Data curation, Writing – review & editing, Ana Yuil-Valdes: Data curation, Writing – review & editing, Rana Zabad: Formal analysis, Methodology, Writing – review & editing

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