Neurosarcoidosis: Stranger Than Fiction

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Introduction

Sarcoidosis, a multi-system granulomatous disease of uncertain etiology has weathered the probe of modern medicine and remains to be an enigmatic entity. It most commonly affects nonsmoking black women of ages 20-40 years. Neurosarcoidosis occurs in only 5-15% of patients with sarcoidosis.[1] It continues to pose a formidable diagnostic challenge especially in patients without a prior diagnosis of sarcoidosis. An extensive differential diagnosis list can easily delay the treatment of this potentially devastating condition. Due to the rarity of the condition and lack of precise diagnostic and therapeutic guidelines, most clinicians are not confident in its management. We present a case of neurosarcoidosis with its complicated presentation and attendant diagnostic chaos.

Case

A 26-year-old African American male was admitted for unexplained generalized seizures. Two years ago he had developed acute meningitis of unclear etiology after which he started experiencing seizures, headaches, amnesia, and progressive loss of vision in the left eye which was diagnosed as pan-uveitis. He denied fever, chills, cough, chest pains, skin lesions, or focal deficits. No other family member was reported to be sick. He had no recent travel history, denied smoking/alcohol/illicit drugs and was not taking any medicine or herbals on regular basis. At admission he was afebrile, his blood pressure was 110/66, heart rate was 78, and respiratory rate was 18. His examination as well as initial laboratory workup was essentially unremarkable. A computed tomography (CT) scan of head (without contrast), done in emergency room revealed hypodense lesions in the deep white matter of lateral aspect of right basal ganglia and subcortical white matter of left temporal lobe.

Magnetic resonance imaging (MRI) of the brain revealed nodular leptomeningeal, ependymal and pial enhancement (Figure 1). Lumbar puncture (LP) studies were remarkable only for presence of oligoclonal bands. Extensive laboratory workup including serum and cerebro-spinal fluid (CSF) angiotensin converting enzyme (ACE), rapid plasma reagent (RPR), toxoplasma antibodies, CSF herpes simplex virus (HSV) as well as tuberculosis (TB) polymerase chain reaction (PCR), prion studies, west nile virus stains, 4-vessel angiogram, purified protein derivative (PPD) skin test and brain biopsy were all negative. Neurosarcoidosis, tuberculosis (TB), fungal infections and malignancy topped the list of our differentials at this time. While a retinal biopsy was being considered, a CT chest revealed bilateral hilar lymphadenopathy (Figure 2) leading to broncho-alveolar lavage (BAL) with biopsy. Although the biopsy yet again

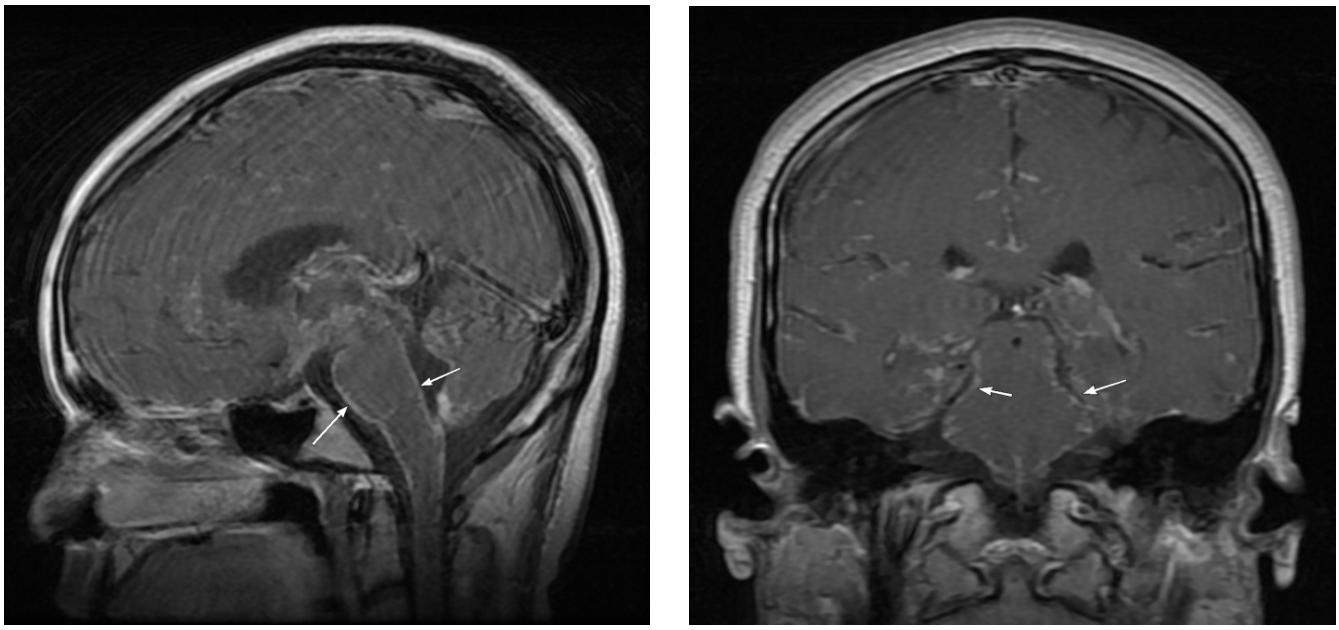

Fig. 1: *MRI brain with contrast showing lepto-meningeal thickening and nodularity (arrows).*

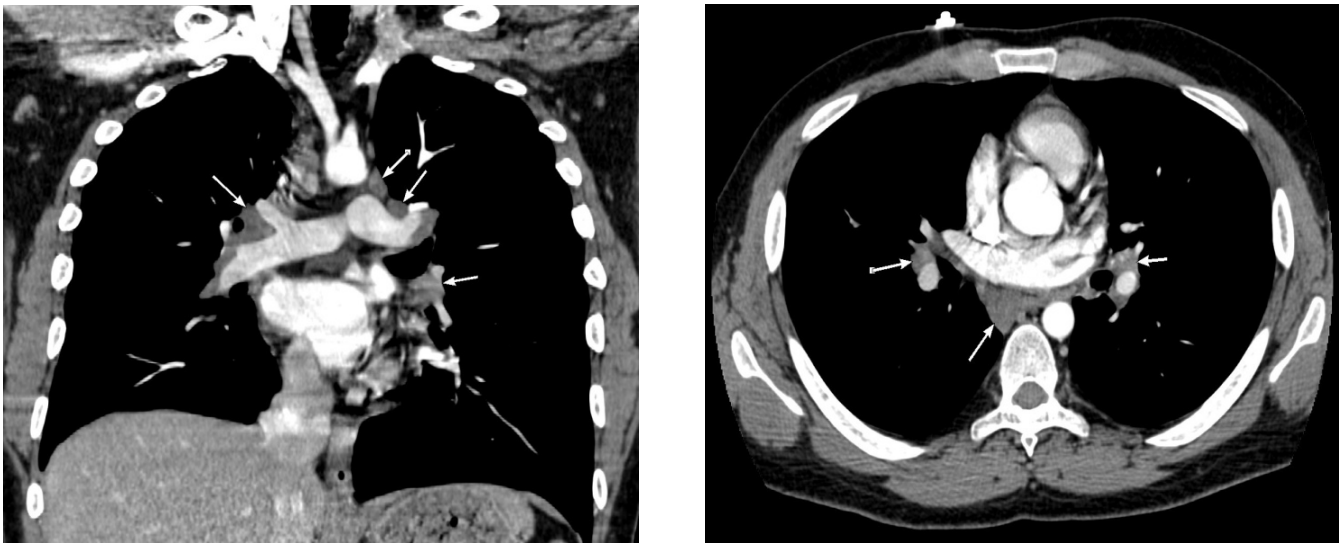

Fig. 2: *CT chest with contrast showing bilateral hilar lymphadenopathy (arrows).*

was negative, the BAL studies were significant for lymphocytosis of 26% and a CD4/CD8 ratio of 5.8 which was highly consistent with sarcoidosis. A repeat LP also showed a CSF CD4/CD8 ratio of 4.4. Noncaseating granulomas were not detected in any biopsy. However, based on clinical presentation, exclusion of other diagnoses, and highly suggestive laboratory tests a diagnosis of sarcoidosis was established and steroids were initiated at a dose of 70mg/day. The patient showed a very good response with resolution of symptoms and has remained asymptomatic in 12 months of follow up.

Discussion

Although neurosarcoidosis occurs in only 5-15% of patients with sarcoidosis,[1] its symptoms can be devastating and life threatening. Unfortunately, it can present with any neurologic symptom making its diagnosis a daunting challenge. 50-75% of neurosarcoid patients present with cranial neuropathies predominantly facial nerve palsy.[2] Other presentations include: meningeal disease including aseptic meningitis and mass lesions, hydrocephalus, seizures, psychiatric manifestations, endocrinopathies, spinal cord involvement and peripheral neuropathies.[3,4]

Table 1: *Differential diagnosis of neurosarcoidosis based on presentation.*

Presentation		**Differential Diagnosis**
Cranial neuropathy		• Multiple sclerosis • Lyme's disease • Bell's palsy
Meningeal disease	Aseptic meningitis	• Viral meningitis including HIV • Tuberculous meningitis • Syphilitic meningitis
	Granulomatous mass	• Meningioma
Encephalopathy		• Syphilis • CNS vasculitis
Parenchymal mass lesions		• Primary CNS neoplasm • Metastasis • Chronic infections like toxoplasmosis, TB and fungal infections

The diagnosis of neurosarcoidosis can be established by compatible clinical, radiologic and histological picture. There is no 'gold standard' test, only suggestive features are present and it remains a diagnosis of exclusion. Neurosarcoidosis can be an overwhelming diagnostic challenge particularly in patients who do not have an established diagnosis of sarcoidosis. The list of differential diagnosis is long; however a more practical approach is shown in table 1.

Based on presentation, patients can be classified into possible, probable or definitive neurosarcoidosis cases as suggested by Zajicek et al[5] in table 2.

MRI with gadolinium contrast enhancement is the preferred imaging modality for neurosarcoidosis. Basal leptomeningeal involve-

Table 2: *Criteria for neurosarcoidosis.*

Zajicek et al [5]	
Definite	Clinical presentation suggestive of neurosarcoidosis with exclusion of other possible diagnoses and the presence of positive nervous system histology
Probable	Clinical syndrome suggestive of neurosarcoidosis with laboratory support for CNS inflammation (elevated levels of CSF protein or cells, the presence of oligoclonal bands or MR imaging evidence compatible with neurosarcoidosis) and exclusion of alternative diagnoses together with evidence for systemic sarcoidosis (through positive histology, including Kveim test, or at least two indirect indicators from Gallium scan, chest imaging, and serum angiotensin-converting enzyme)
Possible	Clinical presentation suggestive of neurosarcoidosis with exclusion of alternative diagnoses where the above criteria are not met

ment is seen in majority of patients.[3] CSF findings are nonspecific and usually include predominantly mononuclear cell pleocytosis and high protein content. Rarely, increases in the concentration of ACE,[6] IgG-index,[7] oligoclonal bands,[7] and CD4/CD8 lymphocyte ratios[8] have been reported. Brain biopsy if positive for non-caseating granulomas can be invaluable.

It is of utmost importance to search for systemic sarcoidosis early in the course of disease. After a thorough physical examination pertinent tests should be obtained. Serum ACE concentration has poor predictive value while serum interleukin-2-receptor is better for monitoring disease activity.[9] Lungs are involved in 90% of sarcoid cases and should be imaged first. BAL is proving to be a useful diagnostic modality. The triad of a CD4 to CD8 ratio > 4:1, a lymphocyte percentage greater than or equal to 16%, and a trans-bronchial biopsy demonstrating non-caseating granulomas has been reported to have 100% positive predictive value (PPV) for distinguishing sarcoidosis from other interstitial lung diseases, and an 81% PPV for distinguishing sarcoidosis from all other diseases. Biopsy of different organs should be considered early in uncertain cases.

Our case posed an extremely difficult diagnostic challenge as we could not get positive tissue diagnosis despite repeated attempts. However, ocular presentation in conjunction with seizures and psychiatric symptoms, MRI brain findings, high CSF CD4/CD8 ratio, bilateral hilar lymphadenopathy, classic BAL findings, and exclusion of other causes, all pointed to neurosarcoidosis. The diagnosis was further augmented by favorable response to steroids.

Conclusion

Diagnosing neurosarcoidosis in hitherto sarcoid naïve patients can be extremely challenging. Protean neurological manifestations, lack of a definitive diagnostic test, and a wide range of differential diagnosis all significantly add to the challenge. Search for extra-neural disease (skin, lungs, eyes, lymph nodes) should be done early in the course. Corticosteroids are the mainstay of treatment. However, they can eliminate the evidence of systemic inflammation and hence should preferably be withheld until the diagnosis is established. The importance of prompt treatment with steroids in this possibly fatal condition calls for expeditious workup and diagnosis.

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