Clinical Case Report

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Case report: middle-aged woman from Ghana with unsteady gait and enlarging cerebellar mass

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Abstract

Rationale: Neurosarcoidosis (NS) is an uncommon manifestation of systemic sarcoidosis, with a propensity for middle-agedwomen. Often discovered only at autopsy, rates of neurologic involvement (5%–10%) reported in the literature underscore a lack of sensitivity and specificity in current diagnostic methods.

Patient concerns: Herein, we describe a 53-year-old woman who presented with gait imbalance and distal extremity muscular weakness. She was known to harbor a brain mass (4 years in duration) that was monitored and recently seemed to enlarge.

Diagnosis: A subsequent brain biopsy showed necrotizing granulomatous inflammation suggestive of NS. However, no clinical or radiologic evidence of activity was found in other organs.

Interventions and outcomes: Ultimately, endo and transbronchial biopsies were performed, providing histologic confirmation of systemic sarcoidosis.

Lessons: This approach is advised in all instances of suspected NS where systemic involvement is in question.

Abbreviations: ACE = angiotensin-converting enzyme, BAL = bronchoalveolar lavage, CSF = cerebrospinal fluid, CT = computed tomography, EBBx = endobronchial biopsy, MRI = magnetic resonance imaging, NS = neurosarcoidosis, TBBx = transbronchial biopsy.

Keywords: cerebellar mass, neurosarcoidosis, sarcoidosis, transbronchial biopsy

1. Introduction

Sarcoidosis (also known as Besnier–Boeck disease) is a well-known inflammatory disorder of the lung and other organ systems, with a clear predilection for young or middle-aged adults.[1–3] Neurosarcoidosis (NS) is an uncommon manifestation of systemic sarcoidosis that occurs more often in middle-aged women.[3–7] Often undetected until autopsy, the 5% to 10% rate of neurologic involvement reported in the literature indicates that current diagnostic methods lack sensitivity and specificity.[7–14] It is also of note that NS is more likely to develop within 2 years of systemic disease onset.

The etiology of sarcoidosis is still speculative at present, with very little evidentiary support. Thus, it remains a diagnosis of exclusion, having ruled out other granulomatous processes. Treatments may differ dramatically and be harmful if an improper diagnosis is made.[1,4,11,13,15,16] Isolated NS, devoid of other organ involvement, is a rare but often significant cause of morbidity and mortality.[2,5,11,15,17–23] Necrotizing NS is prone to vasculitic patterns.[13] A subset of patients (10%–30%) with systemic sarcoidosis display signs/symptoms of NS at presentation, with peripheral and central forms equally distributed.[5,23,24] Systemic sarcoidosis is eventually diagnosed in most of such patients (80%–95%) through further investigations.[2,4,5,22–24]

2. Case presentation

Bronx Lebanon Hospital Center Institutional Review Board approved the publication of this manuscript. This 53-year-old woman was hospitalized for progressive worsening of unsteady gait, diffuse headache, and distal extremity weakness. The patient was born in Ghana and had lived in Belgium for several years, 2 years earlier relocating to the United States. Clinically, she was hypertensive and complained of migraine headaches, but she denied any deleterious habits. Computed tomography (CT) of the brain performed 1 and 2 years prior revealed a cerebellar mass, unchanged in size. On admission, vital signs were normal, with exception of blood pressure (150/90 mm Hg). Her chest was clear to auscultation, bilaterally; her cardiac rate and rhythm were regular, with no murmurs or added sounds; and no organomegaly was palpable. No skin lesions or lymphadenopathy were apparent. During neurologic examination, positive Romberg sign, and finger-to-nose test were elicited. Pertinent laboratory results were as follows: hemoglobin, 13.3 g/dL; white blood cell count, 6.4 k/μL; and serum calcium, 9.3 mg/dL. Other tests, including HIV and

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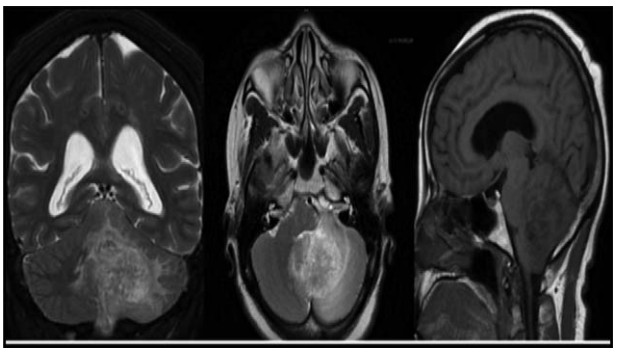

Figure 1. MRI Brain: Heterogeneous hyperintense mass (coronal T2- and axial T2-weighted images) and iso-hypointense mass (sagittal T1-weighted image), with peripheral edema and narrowed, displaced fourth ventricle (dilated ventricles visible in sagittal T1-weighted image).

drug screen, were unremarkable. Magnetic resonance imaging (MRI) of the brain showed enlargement of the cerebellar mass, 4th ventricle effacement, and vasogenic edema (Fig. 1).

The patient underwent suboccipital craniotomy, with resection of the left cerebellar mass. Pathology findings are shown in Fig. 2. CT images of the chest revealed mediastinal and subhilar lymphadenopathy, with normal parenchymal tissue. Cerebrospinal fluid (CSF) cell count, cultures, serum *Histoplasma* antigen, and collagen vascular work-up were negative. Serum angiotensin-converting enzyme (ACE) level was 7 U/L. Bronchoscopy was performed, obtaining the following: bronchoalveolar lavage (BAL), endobronchial biopsy (EBBx) of carina, and transbronchial biopsies (TBBxs) of upper lobe. The lavage fluid (white blood cell count, 160 cells/mm^3) contained 83% lymphocytes, with a CD4:CD8 ratio of 5.8. Pathology findings are shown in Fig. 3.

3. Discussion

Sarcoidosis is a multisystemic granulomatous disease of uncertain etiology that occurs in all ethnic groups worldwide, although a higher prevalence is found among African Americans. The pathogenesis is subject to debate, but genetic predisposition, environmental exposure, overexpression of a specific T-lymphocyte receptor, *Mycobacteria*, and *Proprionibacteria* have been implicated.[4,17,25,26] NS is reported in 5% to 10% of patients with sarcoidosis and is frequently associated with systemic disease; however, 10% to 17% of patients with NS have no apparent systemic involvement.[7,16,17,21,22] The leptomeninges are primarily affected, but parenchymal spread occurs through Virchow–Robin spaces (at base of brain), making cranial nerves most susceptible.[8,21,22,25,27,28]

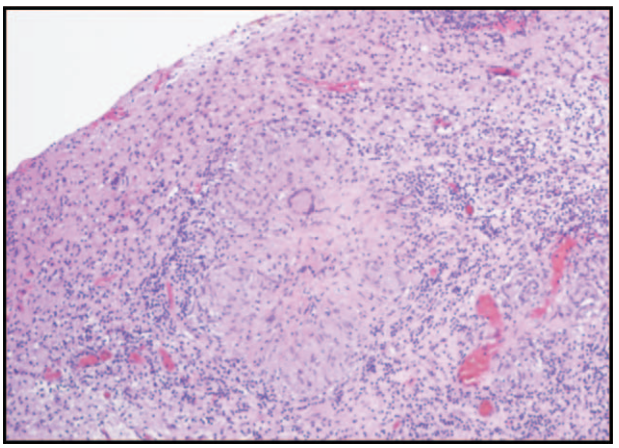

Figure 2. Brain Biopsy: Large non-necrotizing epithelioid granuloma and few giant cells in cerebellar tissue, consistent with sarcoidosis (H&E x 100).

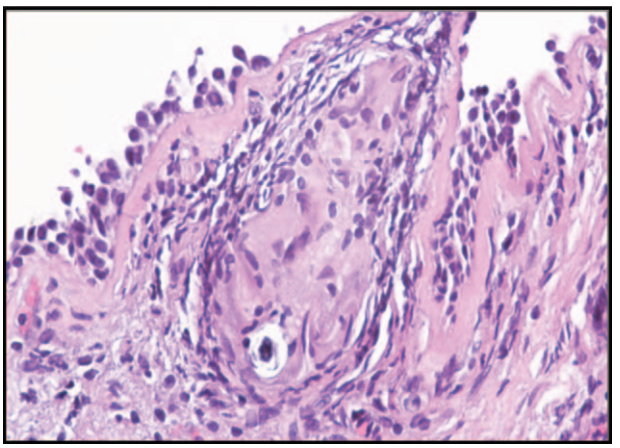

Figure 3. FOB TBBX: Subepithelial bronchial tissue displaying well-formed granuloma of sarcoidosis; note giant cell inclusions (Schaumann bodies) and epithelioid cells (H&E x 400).

Manifestations of NS are highly unpredictable, because all areas of the brain are vulnerable.[5,7,13,18,21,23,24,26] Clinical signs include cranial and peripheral neuropathies; myopathies; meningeal and parenchymal involvement; and spinal cord syndromes.[8,9,12,14,16,18,28,29] Chorea, cerebral vasospasm, progressive multifocal leukoencephalopathy, and vasculitis are rare.[1,2,4,16,18,20,22,25,30–33] The cranial neuropathies are not restricted, but nerves VII, II, and VIII are most commonly involved. Although generally unilateral, palsy of cranial nerve VII may be bilateral in up to one-third of patients.[8,9,12,14,16,18,28,29] Neurologic features of sarcoidosis are summarized in Table 1.

3.1. Radiologic manifestations

Hydrocephalus, intracranial calcification, and enhancing nodules may be found on brain CT; however, MRI with gadolinium is more sensitive and is thus the modality of choice.[4,8,16–18,29,34,35] Central nervous system sarcoidosis has been classified by Dumas according to MRI findings as follows: type I, parenchymal lesions on T1-weighted images; type II, periventricular and deep white matter lesions with plaques of high T2 signal intensity resembling multiple sclerosis; or type III, multifocal patchy lesions of increased signal intensity in subcortical white matter (similar to small-vessel atherosclerosis).[15,27,31,36] Leptomeningeal involvement is the most common manifestation of NS.[15,27,31,35,36]

3.2. Diagnosis

Diagnosis of NS is considered definitive (histologic confirmation of affected neural tissue, excluding all other granulomatous disorders), probable (clinical features and neuroimaging suggestive of NS [excluding alternative diagnoses], with histologic evidence of systemic sarcoidosis), or possible (presentation

Table 1

Manifestations of neurosarcoidosis.

Affected area	Clinical Findings	Imaging Findings
Cranial nerves	I: anosmia	Thickening and enhancement of meninges
	II: visual symptoms	
	III, IV, VI: ocular movement disorders	
	VIII: dizziness, dysphagia, dysarthria	
Meninges	Headache, nausea, ataxia, cranial neuropathies	Communicating hydrocephalus; obstructive and nonobstructive hydrocephalus
Parenchymal	Seizures, encephalopathy, endocrine, and hypothalamic dysfunction	Intracranial space-occupying lesions
	Focal motor or sensory deficits, visual changes	White matter lesions, subcortical or periventricular
Spinal cord	Weakness, paresthesias	Multifocal, focal, or diffuse enhancement of cord or meninges
	Myelopathy	
Peripheral nervous system	Chronic sensorimotor axonal polyneuropathies	
	Acute or chronic inflammatory demyelinating polyneuropathies	
	Autonomic neuropathy	
	Ulnar and peroneal nerves	
Myopathies	Muscle weakness	

suggestive of NS but no neurohistologic confirmation or evidence of systemic sarcoidosis).[37–40] Unfortunately, there are no guidelines for diagnostic work-up, given the rarity of this condition. It is imperative to demonstrate sarcoidosis in other bodily organs. Normal chest imaging is found in one-third of patients.[13,21] Serum ACE levels are elevated in 60% of patients, but this finding has limited sensitivity (60%) and specificity (70%). Other tests focus on excluding causes of granulomatous disease. Abnormal CSF findings, such as elevated protein level, lymphocytic or neutrophilic pleocytosis, and low glucose, are present in >50% of patients. Various inflammatory markers (oligoclonal bands, IgG index, and soluble CSF interleukin-2 receptors) may be increased as well. The CSF ACE level corresponds with a diagnosis of NS at levels >8 nmol/mL (sensitivity, 55%; specificity, 94%).[9,14,16,41]

Thoracic and ophthalmologic involvement is often seen in patients with NS, indicating the importance of procuring tissue at other likely sites. Bronchoscopy with BAL, EBBx, and TBBX is a sensitive and specific diagnostic method.[12,14,42–45] Even without pulmonary parenchymal involvement, which otherwise increases the chance of success, the diagnostic yield is close to 40%.[46,47] A combination of bronchoscopic techniques also enhances the diagnostic yield.[43,48–54] A CD4:CD8 ratio >3.5 for BAL has a positive predictive value of 76% (sensitivity, 53%; specificity, 94%), despite negative histopathology.[22,55] Useful parameters in establishing a diagnosis of "probable NS" are chest CT, elevated BAL CD4:CD8 ratio, and CSF CD4:CD8 ratio >5.[1,12,16–18,22,25,28,56–58] Gallium-67 scans, BAL samples, and ACE levels can be used to monitor disease activity.[35,57–62]

3.3. Pathology

The histologic hallmarks of sarcoidosis and NS are noncaseating epithelioid granulomas, variably with multinucleated giant cells, flanked by lymphocytes, plasma cells, and mast cells.[7,16,22,23,25,32,63]

3.4. Treatment

Steroids remain the mainstay of treatment, although they have proven less effective for NS than for multisystem sarcoid. Oral prednisone (20–40 mg daily) is the standard treatment, delivering intravenous pulse therapy to severely affected patients. The duration of therapy is usually 6 to 12 months.[4,16,64] Antimetabolites, such as methotrexate, azathioprine, cyclophosphamide, chlorambucil, cyclosporine, hydroxycholoroquine, mycophenolate mofetil, and tacrolimus, are reserved for patients with refractory disease. Tumor necrosis factor-alpha inhibitors (ie, infliximab and etanercept) have shown promise as well, especially in treating steroid-unresponsive NS,[65–70] and radiation therapy has been used with success in instances of drug-resistance.[17] Relapses of NS generally involve the initial site. Those suffering peripheral neuropathies and bulbar manifestations may benefit from intravenous immunoglobulin administration. One-third of patients with NS develop chronic and unresolved disease, and others experience long-term steroidal side effects. Ultimately, intracranial NS carries a higher mortality risk.[4,17,39]

Surgical intervention is warranted as emergency treatment in patients with increased intracranial pressure and seizures.[4,64] Elective brain biopsy is also an accepted diagnostic technique for accessible lesions. Because of the risks involved, a therapeutic trial of steroids has been suggested instead.[16,20,71]

In our patient, neither CSF analysis nor ACE level was suggestive of NS, and other efforts to diagnose granulomatous disease were negative. Bronchoscopy performed in search of systemic sarcoidosis eventually brought diagnostic confirmation. The patient was then started on prednisone and remained asymptomatic after 3 months of follow-up surveillance. Although cranial nerve palsies are often a feature of NS (frequently Bell palsy, visual symptoms, and dizziness), this particular case demonstrates how establishing systemic involvement greatly facilitates a diagnosis of NS. Thus, bronchoscopic BAL and biopsy (EBBx, TBBx) should be considered in this setting, serving as an adjunct or alternative to brain biopsy in patients with presumptive NS.

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