Extra-Pulmonary Sarcoidosis: Neurosarcoidosis - Case Presentation and Literature Review

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Abstract

More than a century after the description of sarcoidosis, the disease remains not well understood. Sarcoidosis is an inflammatory disease of unknown etiology characterized by noncaseating granulomas with multiple organs affected. The epidemiology reveals lung involvement in 90-95% of the patients and just 5-13% incidence of neurological involvement. We present an unusual case of a patient with medulla oblongata and retroperitoneal sarcoidosis with no other organ involvement. In addition to the case presentation and extensive up-to-date literature review on extrapulmonary sarcoidosis, we describe the difficulties in making the diagnosis and the challenge in differentiating sarcoidosis from other illnesses such as tuberculosis.

Key words: Sarcoidosis, neurosarcoidosis, medulla oblongata, retroperitoneal sarcoidosis, granuloma.

Introduction

Granulomatous diseases remain a common cause of consultation for respiratory clinicians. Of them, sarcoidosis is the most common. This disease entity was first described in 1877 by the English physician Jonathan Hutchinson [1]. In 1976 the Seventh International Conference on Sarcoidosis defined it as a multisystem granulomatous disorder of unknown etiology, most commonly affecting young adults and presenting most frequently with bilateral hilar lymphadenopathy, pulmonary infiltration and skin or eye lesions [2]. After 130 years the pathophysiology is still not well understood, but the characteristics of the lesions caused by sarcoidosis, as well as its the incidence, prevalence and organ predilection have been thoroughly described. We recently were confronted with a patient with extrapulmonary sarcoidosis that was a diagnostic challenge.

Case Presentation

A 73-year-old African-American woman with a past medical history of congestive heart failure, hypertension, gastroesophagic reflux disease, recurrent pneumonias and a 30 pack/year history of tobacco use presented to the neurology clinic complaining of vertigo which had progressively worsened over the preceding 5 months. She had no relevant concomitant symptoms. Physical exam revealed mild dysarthria, lateral gaze direction-changing nystagmus and suggested the presence of a brainstem lesion. Head magnetic resonance imaging (MRI) with and without intravenous gadolinium showed a ring-enhancing lesion in the middle of the medulla oblongata (**Figures 1-3**). A comprehensive work up for possible malignancy, sarcoidosis, tuberculosis, rheumatologic disorders and other infections was done (**Table 1**). A computed tomography (CT) of the abdomen showed multiple para-aortic lymph nodes. Purified protein

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derivative (PPD) standard was 10 mm; one month before it had been <5 mm. Because of its location a biopsy of the lesion in the medulla oblongata was not feasible. The abdominal lymph nodes were biopsed pathologically suggesting sarcoidosis. There was no evidence of infection or malignancy in the additional evaluation (**Table 2**). The patient was treated with high dose methylprednisolone, which was subsequently switched to prednisone. She was also treated with triple drug antituberculosis treatment until cultures of the biopsy material for *Mycobacterium tuberculosis* were negative. She continued isoniazide and vitamin B6 supplementation for her new positive PPD. A diagnosis of sarcoidosis with retroperitoneal and medulla oblongata involvement was made. The patient continued to improve clinically.

Discussion

The first reported case of neurosarcoidosis manifested in the medulla oblongata was presented by Mahadewa and collaborators in 2004 [3]. In that case a 59 year-old man without evidence of systemic sarcoidosis presented with a history of progressive numbness and deep sensation disturbance in the lower extremities bilaterally [3]. The lesion was able to be biopsed because it was in the dorsal side of the medulla. Also relevant from that report is that erythrocyte sedimentation rate, serum calcium and serum angiotensin converting enzyme levels were within normal limits as they where in our case [3]. In our case, because the lesion was centrally located within the substance of the medulla, (**Figures 1-3**) we were not able to obtain a biopsy. The diagnosis neurosarcoidosis was made by exclusion.

The diagnosis of central nervous system sarcoidosis is challenging when there is not the possibility for brain biopsy because of the topography and possible damage. Confirmation of the diagnosis by biopsy of other involved organs has been described as an alternative [4]. Differentiating between sarcoidosis and tuberculosis has been a challenge for clinicians. Several studies demonstrate the close relation between sarcoidosis and tuberculosis. Some researchers were not able to demonstrate mycobacterial DNA in sarcoid lesions and others have amplified mycobacterial DNA of different species. These studies were not correlated with PPD [5-9]. PPD at a standard dose that is equivalent to 5 Units, which is the dose that we used in our patient, has a sensitivity for active disease that varies from 65%-94% [10]. A sensitivity of 85% has been described in patients with tuberculoma. PPD can have false positives for M. tuberculosis because of the antigens shared with other mycobacteria including many non tuberculosis mycobacteria and M. bovis BCG [11,12]. Cultures of mycobacteria require just 10 to 100 organism to detect M. tuberculosis. As a result, the sensitivity of culture range from 80% to 93% [10,13,14]. There is one case of sarcoidosis, supported by repeated biopsies confirming non caseating granuloma, negative mycobacterium cultures, negative PPD and complete response to corticosteroids, that was later complicated with mycobacterium tuberculosis septic arthritis. In this paper's conclusion, the author stated that mycobacterium tuberculosis most probably occurred after the patient was immunocompromised with the steroids [15].

Sarcoidosis has a prevalence of 1 to 20 per 100,000 population worldwide including the U.S. Its prevalence is as high as 102 per 100,000 population in Sweden [16,17]. The incidence of sarcoidosis in the United States is 3.8 fold higher in African Americans than Caucasians [18]. The exact cause of sarcoidosis is unknown. Familial clustering is occasionally noted but the absolute risk of coincident disease is less than 1% and therefore screening of asymptomatic family members is not generally necessary [17]. Genetic studies of sarcoidosis have demonstrated that specific gene polymorphisms are involved in both susceptibility to and phenotypic determination of the disease [19]; these include human leukocyte antigen genes for the major histocompatibility complex, cytokines such as tumor necrosis factor alpha and several chemochines [20]. HLA class II alleles may be markers for the phenotypic pattern of sarcoidosis [21].

The characteristic sarcoid pathology is the noncaseating granuloma, also described as the non-necrotizing granuloma. Noncaseating granuloma is an aggregate of tightly clustered epithelioid cells, often with Langerhans or foreign body-type giant cells.

Central necrosis is unusual. In chronic disease, the granulomas may become enclosed within fibrous rims or scars. Two other microscopic features are often present in the granulomas: laminated concretions composed of calcium and proteins known as Schaumann bodies and stellate inclusions known as asteroid bodies enclosed within giant cells. These asteroid bodies are found in approximately 60% of the granulomas [2].

Sarcoidosis has predilection for the lungs; for unknown reasons, the lungs are affected in 90-95% of patients. Intrathoracic and peripheral lymphadenopathy occurs in 40-90% of cases. Skin is involved in 25%, ophthalmologic involvement occurs in 20-25%, cardiac involvement is seen in 5-76%, nervous system 5-13%, kidneys 20%. There are few cases reported of retroperitoneal lymph node involvement [22-25].

The central nervous system (CNS) location, presentation and manifestations of sarcoidosis are varied. Meningeal granulomatosis is the most common form of central nervous system disease; with its predilection for the base of the brain, cranial nerve palsy occurs in about half of patients with neurosarcoidosis [26]. Cranial nerves VII and II are most frequently involved [17,27]. Other manifestations are less common and include focal lesions in central nervous system or spinal cord, peripheral neuropathy, carpal tunnel syndrome and muscle involvement [28-33].

The diagnosis of sarcoidosis is one of exclusion. Neurosarcoidosis becomes even more difficult to diagnose because of the risk of complications when trying to obtain adequate samples of the affected tissue. Intracranial neurosarcoidosis remains a very difficult diagnosis, particularly in the absence of systemic signs of the disease [34].

The current neurosarcoidosis diagnostic classification system requires biopsy positive evidence of typical granulomas in nervous tissue, or systemic sarcoidosis accompanied by typical symptoms combined with evidence for central nervous system inflammation [4,27,35]. The role of angiotensin converting enzyme in the cerebrospinal fluid remains unclear. Angiotensin converting enzyme (ACE) levels in cerebrospinal fluid (CSF) had a sensitivity of 24% and a specificity of 95% in one study; but that study had no detailed description of the assay [27,36]. Other researchers found that serum angiotensin converting enzyme (ACE) levels were always normal [35]. Cranial magnetic resonance imaging (MRI) has become of great importance for the diagnosis of neurosarcoidosis; MRI has a high sensitivity but poor specificity. Sensitivity has been reported as 64-90% [27,37]. Using Chest X ray (CXR) looking for lymphadenopathy to support the diagnosis of neurosarcoidosis was found to be not sensitive in one study; the current recommendation is to perform a computed tomography of the chest if negative CXR and suspicion [27,35].

The treatment of choice for patients with sarcoidosis involving the CNS is glucocorticoids for at least 6 months [38]. The majority of the patients have a good response [1,27,39-43]; 55% to 66% reported to show complete recovery [27,44]. The second line therapy is cytotoxic drugs like methotrexate, cladribine, azathioprine, chlorambucil, cyclophosphamide and cyclosporin; and immunomodulators like chloroquine, hydroxychloroquine and infliximab. Some promising results have been achieved but no definitive data for the safety and effectiveness of these therapeutic regimens have been reported [27,37,39-41,44]. The fundamental pathophysiology of sarcoidosis remains unknown and, therefore, definitive treatments are difficult to describe with certainty. In some cases radiation has been found to be an effective treatment. Two different mechanisms for radiation effects on granulomatous have been suggested: radiation induced direct cytotoxicity in the macrophages, lymphocytes and plasma cells that make up the granulomatous lesions and radiation induced phenotypic alterations within the cellular matrix that inhibit the autocrine and paracrine signals [44,45]. The current recommendation for radiotheraphy in neurosarcoidosis is failure of the primary medical treatment to induce remission. Radiotherapy has been shown to have minimal adverse sequelae [1,38,44].

Conclusions

Extrapulmonary sarcoidosis has multiple possible presentations. Neurosarcoidosis can be elusive and require a high level of suspicion to make this diagnosis. A trial of glucocorticoids is warranted in patients with documented or suspected neurosarcoidosis.

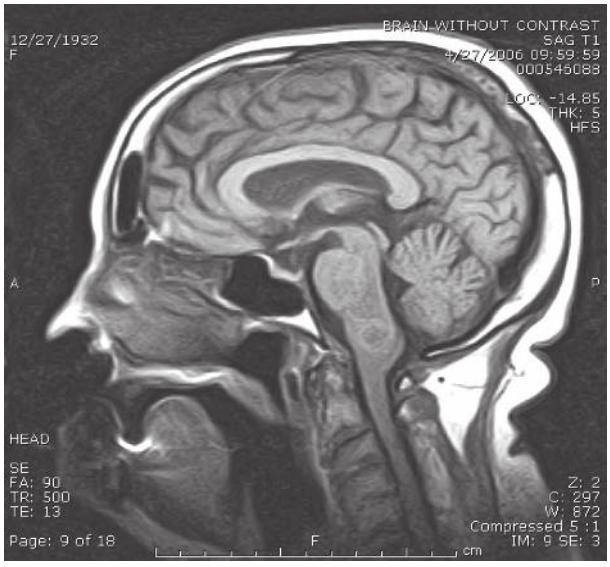
Table 1. RELEVANT LABORATORY VALUES

	Values	Reference
Serum calcium	8.9 mg/dl	9.0-10.5 mg/dl
Serum albumin	3.3 g/dl	3.5 – 5.5 g/dl
Serum corrected calcium	9.46 mg/dl	8.7-10.3 mg/dl
Serum antinuclear antibody	Negative	Negative
Serum rheumatoid factor	Negative	Negative
Serum erythrocyte sedimentation rate	25 mm/hour	0-25 mm/hour
Serum angiotensin converting enzyme	12 Units/L	<40 Units/L
Serum human immunodeficiency virus 1/2 antibody	Nonreactive	Nonreactive
Serum cryptococcal antigen	Negative	Negative
Rapid plasma reagin	Nonreactive	Nonreactive

Corrected calcium: serum calcium + 0.8 (4 – serum albumin)

Table 2. RELEVANT STUDIES OF THE RETROPERITONEAL GRANULOMA

Culture for mycobacteria	Negative
Gomori methenamine silver GMS	No fungi
Periodic acid schiff	No yeast or hifa
Truant	No organism
Kinyoun's	No acid fast bacilli
Polymerization Microscopy	No crystals
Flow Cytometry	No diagnostic abnormality
Gram stain	Negative



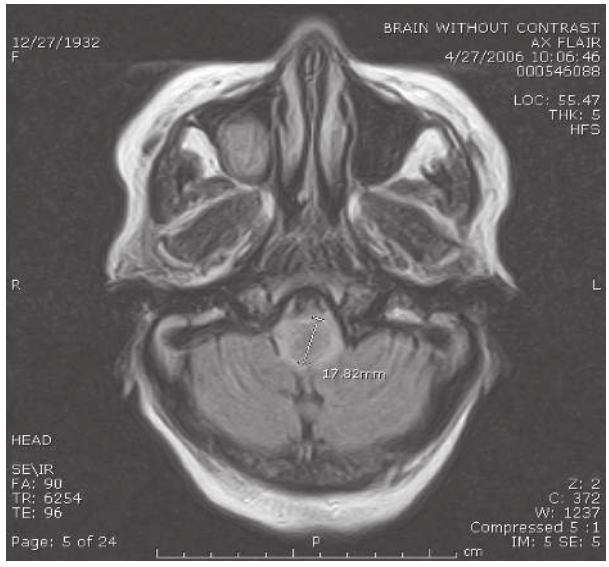


Figure 1 and 2. (SAGITAL AND TRANSVERSAL) MAGNETIC RESONANCE OF THE BRAIN WITHOUT CONTRAST REVEALS A MASS LIKE EXPANSION OF THE MEDULLA ASSOCIATED WITH A FAIRLY DENSE SOLID CORE AND MILD SURROUNDING EDEMA. APPROXIMATELY 2 CM IN DIAMETER.

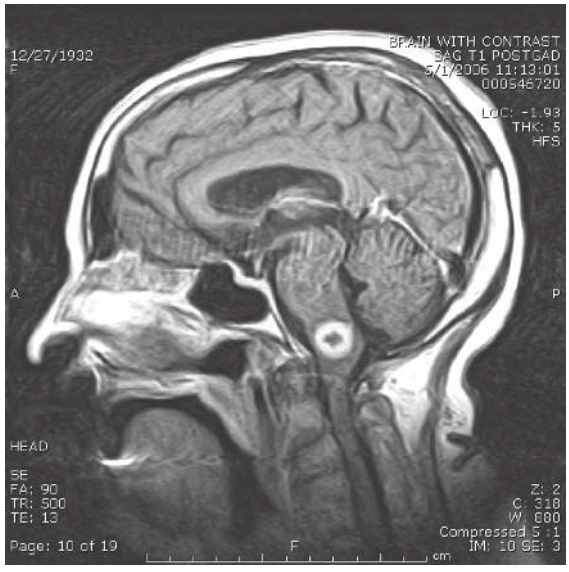


Figure 3. MAGNETIC RESONANCE OF THE BRAIN WITH CONTRAST REVEALS ABNORMAL EXPANSION OF THE MEDULLA WITH A ROUND ENHACING MASS LOCATED CENTRALLY WITHIN THE MEDULLA MEASURING APPROXIMATELY 1.6 X 1.7 X 1.9 CM. THERE IS A CENTRAL NON-ENHACING COMPONENT.

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