SOMATO PUBLICATIONS

Archives of Clinical Case Reports

Case Report

A Diagnostic Dilemma in a Rare Presentation of Neurosarcoidosis: A Case Report

Tatvam T Choksi[1]* and Pankti Reid[2]

[1]Department of Hospital Medicine , The University of Chicago Medical Center, USA

[2]Department of Rheumatology, The University of Chicago Medical Center, USA

***Address for Correspondence:** Tatvam T Choksi, Department of Hospital Medicine,The University of Chicago Medical Center, 5841 S Maryland Avenue, Chicago, IL 60637, USA, Email- tchoksi1@medicine.bsd.uchicago.edu

Received: 24 February 2018; **Accepted:** 26 March 2018; **Published:** 29 March 2018

Citation of this article: Choksi, TT., Reid, P. (2018). A Diagnostic Dilemma in a Rare Presentation of Neurosarcoidosis: A Case Report. Arch Clin Case Rep, 1(1): 001-004.

ABSTRACT

Sarcoidosis can have predominant extrapulmonary clinical presentation in about one-third of cases. Because extrapulmonary sarcoid can present with myriad of clinical manifestations, it can pose a diagnostic dilemma especially when presenting with a rare organ involvement. Herewith, we present a unique case of neurosarcoidosis, where the patient initially presented with gait abnormalities. Due to rare and non-specific clinical presentation, the diagnosis was delayed and ultimately, at the time of diagnosis, the disease had already progressed to involve multiple organ systems. The disease pattern had striking similarities with that of certain lymphomas which further complicated initial evaluation. Aggressive treatment with high dose steroids and immunotherapy was initiated but unfortunately, the patient suffered from septic shock due to severe *Clostridium difficile* infection and eventually, passed away.

Keywords: Extrapulmonary; Diagnostic dilemma; Neurosarcoidosis; Lymphoma; Multiorgan

INTRODUCTION

Sarcoidosis is a multisystem granulomatous disease of unknown etiology which has a tendency for involvement of lungs. But in around 30-35% of cases, patients can present with extrathoracic manifestations of the disease [1-3]. Diagnosis of extrapulmonary sarcoidosis presents a challenge to health care providers and is often delayed in as many as 50% of cases, especially when there is an isolated extrapulmonary organ involvement [2]. Also, certain extrapulmonary sarcoid features are more common than others. Of the patients that present with extrathoracic manifestations of sarcoidosis, only around 5-10% have clinical involvement of the nervous system [4-6]. Furthermore, these neurologic symptoms vary in presentation in different patients, further obscuring the diagnosis.

Of the neurologic presentations in sarcoidosis, the most common is that of cranial nerve neuropathy followed by peripheral nerve involvement [2]. But rarely, sarcoidosis can also affect the brain parenchyma, spinal cord and meninges. While neurologic symptoms can be further evaluated with assistance of imaging and spinal fluid analysis, these findings are non-specific. For example, magnetic resonance imaging (MRI) with contrast of the brain can show enhancement in periventricular and leptomeningeal areas [5-7,12,13] and the cerebral spinal fluid can show lymphocytic pleocytosis or protein elevation [4,5,7,13,14]. However, all these findings can often be seen in certain infections, malignancies or inflammatory processes as well [7]. Finally, the gold standard for diagnosis of neurosarcoidosis is through obtaining tissue from the nervous system which is usually a complicated procedure.

Here we present a unique case of extrapulmonary sarcoidosis where the patient had progressive neurological features as the initial symptoms; because of her rare clinical presentation, the diagnosis was delayed and later, it was challenged secondary to its aggressive nature with striking similarities to lymphoma.

Case

A 44-year old African-American female with history of end-

stage renal disease (ESRD) secondary to eclampsia, hypertension and diabetes mellitus type 2, was transferred to our institute from an outside hospital for higher level of care. Patient had initially presented to an outside hospital four months prior for ataxia and was given diagnosis of sciatica due to non-specific imaging findings. Later, the patient developed progressive diffuse abdominal pain associated with abdominal distention and pruritus; she had a decline in her mental status and ended up back in the hospital. Work up showed hepatic dysfunction with intra-abdominal lymphadenopathy and she was transferred to our facility for further evaluation and management.

At the time of our initial encounter, her vital signs were stable. She was sluggish to respond to questions and had mild asterixis. Though the patient was alert and oriented to person, place and time, she was not able to provide detailed information about her condition. Per family, her cognitive function had a gradual decline over the past 2 months. Her abdominal exam revealed mild ascites and palpable hepatomegaly 3 cm below the right costal margin.

Initial laboratory data are noted in Table 1.

Chest radiograph did not show any gross pathological changes. Computed tomography (CT) scan of the head without contrast demonstrated diffuse prominence of the cerebral ventricles out of proportion to cortical atrophy suggesting possibility of normal pressure hydrocephalus and non-specific patchy white matter changes. Contrast-enhanced CT scan of the abdomen and pelvis showed hepatosplenomegaly & interval development of significant adenopathy in retroperitoneum, peripancreatic or mesenteric root and porta-hepatis.

Extensive work up for lymphadenopathy was therefore undertaken to look for potential etiologies (Table 2 and Table 3).

MRI of the brain without contrast revealed hyperintense lesions in periventricular white matter which were deemed non-specific and again showed disproportionate enlargement of the ventricles for the degree of volume loss suggesting communicating hydrocephalus or normal pressure hydrocephalus. MRI of the spine without contrast was obtained which was negative for any abnormality. CSF pathology showed atypical lymphocyte population suspicious for lymphoma, but flow cytometry revealed only a predominance of CD5 positive T cells with rare polyclonal B cells which was not consistent with lymphoma. PET/CT was then pursued and showed diffuse hypermetabolic lymphadenopathy with maximum SUV of 15.6 within liver and spleen concerning for lymphoma. She had multiple abnormal lymph nodes in the celiac, peri-pancreatic and porta hepatis regions with the largest one being 2X2 cm in diameter as well as evidence of a hypoechoic lesion in the left lobe of liver. So, an endoscopic ultrasound (EUS) guided biopsy was planned and appropriate fine needle aspiration cytology (FNAC) of the liver lesion was performed to obtain the

Table 1: Initial laboratory data.

Laboratory test	Result	Normal range
WBC	10.7 10*3/uL	3.5-11 10*3/uL
Hgb	9.2 g/dL	11.5-15.5 g/dL
Platelets	206 10*3/uL	150-450 10*3/uL
MCV	70 fL	81-99 fL
Ferritin	848 ng/mL	10-220 ng/mL
Vitamin B12	1601 pg/mL	240-900 pg/mL
Alkaline Phosphatase	177 U/L	30-120 U/L
AST	13 U/L	8-37 U/L
ALT	5 U/L	8-35 U/L
Total bilirubin	3.8 mg/dL	0.1-1 mg/dL
Serum albumin	3.1 g/dL	3.5-5 gm/dL
Ammonia	72ug/dL	20-70 ug/dL
Calcium	9.4mg/dL	8.4-10.2 mg/dL
Phosphorus	5.6mg/dL	2.5-4.4 mg/dL

Table 2: Work up for potential differential diagnoses.

Test	Result	Normal range
TB Skin test PPD	Negative	
Quantiferon gold	Negative	
Cultures, blood	Negative	
Hepatitis B and hepatitis C serology	Negative	
Mycobacterial cultures, sputum	Negative	
-Serum RPR/ Syphilis diagnosis IgG Ab; -EBV by PCR, blood; -CMV by PCR, blood; -Cryptococcal Ag, blood; -Blastomyces Ab, serum; -HIV Ag Ab by reflex; -Toxoplasma gondii IgG Ab; -Coccidioides Ab, serum; -Histoplasma Ab, serum	All Negative	
Histoplasma Ag, urine	Negative	
Angiotensin-converting Enzyme	54.5u/L	8-48 U/L
Antinuclear IFA level	1:320 titer	0-80 titer
Rheumatoid factor	<8 iu/mL	<14 iu/mL
Vascular ANCA IFA	<20 titer	<20 titer
Anti-DNA double stranded	<10 titer	<10 titer
Cryoglobulin	<0.5%	0-0.5%
C3 complement	108 mg/dL	83-188 mg/dL
C4 complement	32 mg/dL	18-45 mg/dL

Table 3: Lumbar puncture with cerebrospinal fluid (CSF) analysis for possible etiologies.

			Normal range
Lumbar puncture	Opening pressure	32 mm Hg	8-15 mm Hg
	CSF WBC Lymphocyte predominance	15 83%	0-5 40-80%
	CSF Protein	35 mg/dL	15-45 mg/dL
	CSF Glucose	32 mg/dL	50-70 mg/dL
	CSF ACE	<10 U/L	<10 U/L
	VDRL CSF; Culture and stain CSF; Cryptococcus antigen, CSF; Culture, fungal CSF; Culture, AFB CSF; Mycobacterium tuberculosis DNA by CSF PCR	All negative	

histopathological diagnosis and, a separate right inguinal lymph node biopsy was also performed. Final biopsy results came back positive for necrotizing granulomatous inflammation which, in the absence of any fungal/ mycobacterial infection, were consistent with sarcoidosis and not lymphoma.

For the extensive extrapulmonary sarcoidosis with neurological involvement and overall disease burden, aggressive immunosuppressive therapy was initiated. She was started on the pulse dose of intravenous methylprednisolone 1000 mg for 3 days and then was transitioned to prednisone 60mg daily. After seven days, prednisone dose was decreased to 40 mg daily and along with it, infliximab infusions were initiated. Given stability, the patient was subsequently discharged to a long-term care facility with close follow up for her disease.

Unfortunately, after only two infliximab infusions in addition to prednisone 40 mg daily, she developed severe *Clostridium difficile* infection and was hospitalized to the intensive care unit for septic shock. She did not recover and eventually, passed away.

Discussion

Extrapulmonary sarcoidosis can involve variety of organs and the manifestations can be vast [2-4]. A case control etiologic study of sarcoidosis (ACCESS) demonstrated more extrathoracic involvement in African American population as compared to Caucasians and higher frequency in females compared to males [3,9,10] . Also, it was noted that involvement of eyes, cranial nerves and neurosarcoid are more common in females [3,10]; and African American patients are more likely to suffer debilitating illness [4,10,11].

The diagnosis of neurological sarcoidosis represents a challenge for health care providers especially when neurological features are the presenting symptoms and when neurosarcoidosis occurs in isolation [11]. It has been difficult to develop definitive criteria for the diagnosis of neurosarcoidosis in the absence of positive nervous system histology, largely because considerable variations have existed between presentations among different patients [5]. Neurological involvement can be an acutely severe presentation or can run a very indolent course [3,21]. When presenting as an indolent illness, the disease can gradually progress and the diagnosis is brought to attention when the patient develops a different organ involvement. Also, as aforementioned, investigative tests including MRI and lumbar puncture lack specificity of findings [5,6,12,13]. Therefore, in the absence of positive histological diagnosis of nervous system in the suspected patient population, the diagnosis of neurosarcoid remains dependent on the presence of systemic involvement with positive tissue biopsy of the involved extraneural organ and along with this, elevated angiotensin converting enzyme (ACE) level, abnormal chest radiograph and/or abnormal gallium scan further contributing to the diagnosis [5]. Performing blind biopsy on an extraneural organ, in the absence of symptoms, signs or laboratory markers suggestive of that organ involvement, remains of uncertain importance in the diagnosis of neurosarcoidosis [5].

Zajicek et al. [5] described that around 21% of neurological sarcoidosis cases had involvement of brainstem/ cerebellum while only 5-7% patients developed hydrocephalus. Around 10% demonstrated some form of cognitive decline [5]. Additionally, the study of 54 cases by Pawate et al. [13] showed that only 4% of cases had ataxia. Our patient, thus, had a rare neurological presentation with ataxia as the initial symptom. Due to the initial non-specific image findings, a systemic etiology for gait problem was not investigated. It was only later, with progressive clinical and cognitive decline, that the patient's underlying systemic disease was explored.

Aside from varied presentations, the ability of extrapulmonary sarcoidosis to masquerade as different pathologies further contributes to its diagnostic difficulty. Our patient, later in the course of her illness, developed abdominal pain, fatigue and weight loss. CT scan of the abdomen and pelvis showed massive intra-abdominal and pelvic lymphadenopathy with compression features on surrounding structures which explained her peri-hepatic ascites and abnormal liver function tests. With the patient's extensive lymphadenopathy, significant weight loss and progressive neurological features in the absence of aforementioned infectious etiologies along with rarity of neurosarcoidosis, lymphoma with neurological involvement was initially higher on the differential. Lack of specificity of diagnostic testing further hindered our ability to easily elucidate the diagnosis. Traditionally, 18-fluorodeoxyglucose PET (FDG-PET) scans have been used to differentiate benign from malignant conditions when evaluating lymphadenopathy [8,15,16]. Sarcoid-involved tissues and lymphoma are both FDG avid [8]. To possibly help decipher, it has been suggested that maximum SUV value of more than or equal to 13 is considered suspicious for malignancy, especially aggressive lymphomas [8,15,16]. Sarcoid affected tissues are considered to have an average SUV_{max} of 3.5+/-1 [8]. Our patient had SUV_{max} of 15.4. This was highly suggestive of lymphoma, but tissue biopsies from multiple sites suggested necrotizing non-caseating granulomas and no evidence of lymphoma. This likely represents the fact that our patient suffered from a very aggressive form of sarcoidosis as evident from significant hypermetabolic activity and necrotizing nature of non-caseating granulomas. It is important to remember that an association between sarcoidosis and lymphoma is known and both conditions can be co-existent [8,17]. Therefore, it is useful to obtain biopsy from multiple involved sites to establish the appropriate diagnosis before any new intervention/ therapy is undertaken [8].

Systemic corticosteroids are considered as the first-line treatment for extrapulmonary sarcoidosis with higher doses used for neurological involvement [3,18]. In neurosarcoidosis, a short course of pulse dose of intravenous methylprednisolone followed by maintenance oral corticosteroids is usually prescribed in those with significant compromise or whom chronic course is likely [22]; other alternative immunosuppressive therapy with agents like methotrexate, azathioprine, mycophenolate mofetil, etc. may be considered [22]. Treatment with TNF-α inhibitor infliximab in CNS sarcoidosis has shown promising results including in several refractory cases [22, 23]. Though no studies comparing various neurosarcoidosis treatment options to one other are there, expert consensus recommends that alternative therapies may be considered early in the course of treatment along with high-dose corticosteroids in those with manifestations suggesting aggressive disease such as brain parenchymal inflammation, hydrocephalus or optic neuropathy [22]. For these patients, the benefits of aggressive therapy may outweigh the associated risks. For patients with elevated intracranial pressures or hydrocephalus, a ventriculoperitoneal (VP) shunt should be offered for symptomatic relief. Unfortunately, the review of literature suggests that despite maximum treatment, the disease may remain problematic and the patients may continue to deteriorate [5,19,20].

Conclusion

Acknowledging the fact that extrapulmonary sarcoidosis can have varied presentations, considering it on the differential in a timely manner in appropriate patient population is vital. Additionally, it can mimic as a different clinical pathology. In particular, clinical and radiological features of sarcoidosis and lymphoma can have significant overlap, and both can co-exist; therefore, biopsies from multiple sites should be performed when the presentation raises a dilemma. Due to rarity of cases and relatively non-specific investigative findings, neurosarcoidosis continues to pose a diagnostic and therapeutic challenge.

References

1. Rizzato, G., Tinelli, C. (2005) Unusual presentation of sarcoidosis. Respiration, 72(1): 3-6.
2. Rizzato, G., Palieri, G., Maria Agrati, A., Zanussi, C. (2004) The organ-specific extrapulmonary presentation of sarcoidosis: a frequent occurrence but a challenge to an early diagnosis- A 3-year-long prospective observational study. Sarcoidosis Vasculitis And Diffuse Lung Disease, 21(2):119-126.
3. Judson, MA. (2007) Extrapulmonary Sarcoidosis. Seminars in Respiratory and Critical Care Medicine, 28(1): 83-100.
4. Rao, DA., Dellaripa, PF. (2013) Extrapulmonary Manifestations of Sarcoidosis. Rheum Dis Clin North Am, 39(2): 277-297.
5. Zajicek, JP., Scolding, NJ., Foster O., Rovaris, M., Moseley, IF., Scadding, JW., et al. (1999) Central nervous system sarcoidosis-diagnosis and management. QJM, 92(2): 103-117.
6. Shah, R., Rboerson, GH., Cure, JK. (2009) Correlation of MR imaging findings and clinical manifestations in neurosarcoidosis. Am J Neuroradiol, 30(5): 953-961.
7. Imbodden, JB., Hellmann, DB., Stone, JH. Rheumatology Current: Diagnosis and Treatment. 3rd edition. Chapter 54. Textbook. ISBN 978-0-07-163805-0
8. Goswami, T., Siddique, S., Cohen, P., Cheson, B. (2010) The sarcoid-lymphoma syndrome. Clin Lymphoma Myeloma, 10(4): 241-247.
9. ACCESS Research Group. (1999) Design of A Case Control Etiology Study of Sarcoidosis (ACCESS). J Clin Epidemiol, 52 (12): 1173-1186.
10. Baughman, RP., Teirstein, AS., Judson, MA., Rossman, MD., Yeager, HJR., Bresnitz, EA., et al. (2001) Clinical characteristics of patients in a case control study of sarcoidosis. Am J Respir Crit Care Med, 164(10): 1885-1889.
11. Rybicki, BA., Major, M., Popovich, J Jr., Maliarik, MJ.,Lannuzzi, MC. (1997) Racial differences in sarcoidosis incidence: a 5-year study in a health maintenance organization. Am J Epidemiol, 145(3): 234-241.
12. Sherman, JL., Stern, BJ. (1990) Sarcoidosis of the CNS: comparison of unenhanced and enhanced MR images. Am J Neuroradiol, 11: 915.
13. Pawate, S., Moses, H., Sriram S. (2009) Presentations and outcomes of neurosarcoidosis: a study of 54 cases. QJM, 102(7): 449.
14. Joseph, FG., Scolding, NJ. (2009) Neurosarcoidosis: a study of 30 new cases. J Neurol Neurosurg Psychicatry, 80(3): 297.
15. Juweid, ME., Cheson, BD. (2006) Positron-emission tomography and assessment of cancer therapy. N Eng J Med, 354(5): 496-507.
16. Juweid, ME., Cheson, BD. (2005) Role of positron emission tomography in lymphoma. J Clin Oncol, 23(21): 4577-4580.
17. Brincker, H. (1989) Coexistence of sarcoidosis and malignant disease: casuality or coincidence? Sarcoidosis, 6(1): 31-43.
18. American Thoracic Society/ European Respiratory Society. Statement on sarcoidosis. Joint statement of the American Thoracic Society (ATS)., the European Respiratory Society (RS) and the World Asociation of Sarcoidosis and Other Granulomatous Diseases (WASOG) adopted by the ATS Board of Directors and the ERS Executive Committee.(1999), Am J Resp Crit Care Med, 160: 736-755.
19. Delaney, P. (1977) Neurologic manifestations in sarcoidosis: review of the literature, with a report of 23 cases. Ann. Intern. Med, 87(3): 336-345.
20. Oksanen, V. (1986) Neurosarcoidosis: clinical presentations and course in 50 patients. Acta Neurol. Scand, 73(3): 283-290.
21. Hoitsma, E., Sharma, OP. (2005) Neuosarcoidosis. European Respiratory Journal Monograph, 10: 164-187.
22. Stern BJ. Neurologic sarcoidosis. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. (Accessed on March 29, 2018)
23. Gelfand JM, Bradshaw MJ, Stern BJ, Clifford DB, Wang Y, et al. (2017). Infliximab for the treatment of CNS sarcoidosis. Neurology, 89 (20): 2092-2100; DOI: 10.1212/WNL.0000000000004644.