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Case Report

Diagnostic Challenges in Neurosarcoidosis: A Complex Case of an Elderly Patient with a History of B-cell Lymphoma

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INTRODUCTION

Sarcoidosis is a multisystem inflammatory disease of unclear etiology. It presents with non-caseating granulomatous lesions, primarily in the mediastinal lymph nodes as bilateral lymphadenopathy, but it can affect any organ system.[1] The disease has a genetic association, with a higher incidence in African Americans than in Whites (34 vs. 11 cases per 100,000). The pulmonary system is involved in 60-65% of cases, while extrapulmonary sarcoidosis occurs in 25-30% of cases.[2]

Neurosarcoidosis (NS) is a form of sarcoidosis that affects the cranial and peripheral nerves, brain, spinal cord, leptomeninges, and muscles. It can present with facial nerve palsy, optic neuritis, aseptic meningitis, and lesions in the brain or spinal cord. Severe complications occur in 5-10% of patients, including focal neurological deficits, hydrocephalus, encephalopathy, psychosis, peripheral neuropathy, and myopathy.[3] Diagnosing NS is challenging due to its nonspecific and varied presentation. Between 30% and 70% of patients exhibit neurological symptoms at initial diagnosis, and about half of them also have systemic sarcoidosis.[4] NS can present either in isolation or alongside systemic sarcoidosis.[5,6] Given its significant morbidity and an overall mortality rate of 5-20%,[3,7,8] NS should be considered in the differential diagnosis of patients with unexplained neurological symptoms.

There is no specific diagnostic marker for NS, but the following criteria aid diagnosis:

a. Radiological evidence of non-caseating granulomatous inflammation with compatible clinical presentation.
b. Pathological confirmation of systemic sarcoidosis via biopsy.
c. Nervous system biopsy consistent with NS, with or without systemic involvement.[9]

Diagnostic tests, including ophthalmologic exams, chest X-rays, angiotensin-converting enzyme (ACE) levels, and contrast-enhanced magnetic resonance imaging (MRI), provide supportive evidence. Extensive blood work is necessary to rule out alternative diagnoses such as infections or malignancies, including tests for vitamin deficiencies, toxins, serum tumor markers, and relevant serologic or blood cultures. Despite newer therapeutic options, corticosteroids remain the first-line of treatment.[8]

We present a case of NS in an elderly patient with a history of B-cell lymphoma but no systemic involvement.

CASE REPORT

A 72-year-old female with history of diffuse large B-cell lymphoma (DLBCL), mitral valve prolapse, Addison's disease, and hypothyroidism was admitted to the hospital with delirium, confusion, lower extremity weakness, and urinary incontinence. She had been diagnosed with stage 4B DLBCL five years prior and had undergone six cycles of R-CHOP chemotherapy (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone). She had been in remission for the past two years and was receiving routine follow-up care from her primary care physician and oncologist. The patient also had residual bilateral leg numbness, attributed to chemotherapy-induced peripheral neuropathy.[10]

Three months before this admission, she had been hospitalized for similar symptoms, including bilateral lower extremity weakness and urinary incontinence. Given her medical and oncologic history, an extensive workup was performed, including a complete blood count (CBC) with differential, peripheral blood smear, comprehensive metabolic panel (CMP), thyroid panel, urinalysis with reflex culture, and cerebrospinal fluid (CSF) analysis. Laboratory results were within her baseline values, and CSF cytology was inconclusive. Flow cytometry was negative for malignant cells. Extensive antibody screening for inflammatory, paraneoplastic, and autoimmune diseases also was negative. However, an elevated ACE level was noted, while serum calcium, vitamin D, and parathyroid hormone (PTH) levels were unremarkable. Urinalysis was positive for leukocyte esterase and nitrites, and urine cultures grew *Escherichia coli* (*E. coli*), confirming a urinary tract infection.

Imaging studies, including a computed tomography (CT) scan of the chest, abdomen, and pelvis, showed no lymphadenopathy or other masses. A non-contrast MRI of the spine revealed an extensive abnormal signal from T5/6 to the conus medullaris of the central spinal cord, raising concerns for syringomyelia, acute myelitis, or a neoplastic process. A contrast-enhanced MRI of the cervical, thoracic, and lumbar spine demonstrated intramedullary enhancement at T9-T10, consistent with acute myelitis, along with degenerative disc disease and spinal stenosis at C5/6. MRI of the brain showed mild T2/FLAIR hyperintensities in the supratentorial white matter, predominantly periventricular. The differential diagnosis included chronic microangiopathy, transverse myelitis, demyelinating disease, and migraine vasculitis. The patient was treated with intravenous glucocorticoids and ceftriaxone for five days. Given her improvement and preference, a spinal cord biopsy was deferred. The urinary tract infection resolved with antibiotics, and she was discharged to a rehabilitation facility for lower extremity strengthening.

One month later, she was readmitted with recurrent urinary incontinence and lower extremity weakness. MRI of the lumbar and thoracic spine showed an interval increase in enhancement within the thoracic spinal cord from T9-T11, with an associated syrinx from T4-T5, raising suspicion for an intramedullary mass. CSF cytology and flow cytometry remained negative. Given the possibility of central nervous system (CNS) relapse of DLBCL, a bone marrow biopsy was performed. A spinal cord biopsy was again recommended but deferred. A

multidisciplinary team discussion was held, and the patient opted for a therapeutic trial of radiotherapy. She received 10 cycles of external beam radiation (total dose: 3,000 cGy) to the thoracic spine. Due to her history of Addison's disease and prior responsiveness to systemic steroids, she also was treated with dexamethasone in addition to hydrocortisone. By the sixth cycle of radiation, her lower extremity weakness showed partial improvement, but urinary incontinence persisted. Repeat urinalysis was negative for infection. After completing radiation, she was transferred to inpatient rehabilitation on a three-week dexamethasone taper.

During rehabilitation, she developed dysuria, and urine cultures were positive for *E. coli* and *Proteus vulgaris*. She was treated with a seven-day course of cefdinir. Shortly thereafter, she was transferred back to acute care due to fever, worsening leg weakness, and thrombocytopenia. Brain MRI showed scattered diffusion abnormalities in the right posterior frontal and occipital lobes, along with microvascular infarcts and patchy leptomeningeal enhancement restricted to the right occipital lobe. Repeat thoracic spine MRI showed persistent T2 signal changes but decreased craniocaudal enhancement compared to prior imaging. Urine cultures revealed multi-drug-resistant *E. coli*, and meropenem was initiated based on culture sensitivities.

A repeat bone marrow biopsy was performed, which showed no evidence of lymphoma but revealed non-necrotizing granulomatous inflammation. This prompted a broader differential diagnosis, including infectious, rheumatologic, and neoplastic causes. Further workup included bronchoscopy with bronchoalveolar lavage (BAL), urine and blood cultures, CSF studies, and serologic testing. BAL was negative for malignancy, organisms, acid-fast bacilli, *Histoplasma* antigen, and *Pneumocystis jirovecii*, showing only a reactive lymphoid infiltrate. QuantiFERON® Gold testing for tuberculosis was negative. CSF studies ruled out viral, fungal, and bacterial infections. Antibody panels for paraneoplastic syndromes, vasculitis, and autoimmune diseases were negative. A CT angiogram of the chest ruled out pulmonary embolism but showed findings consistent with severe acute lung injury, including ground-glass opacities, septal line thickening, and varicoid bronchial dilation, suggesting diffuse alveolar damage.

After ruling out CNS lymphoma, infections, and autoimmune conditions, a diagnosis of NS was made. This was based on the presence of chronic granulomatous inflammation in the bone marrow, pancytopenia, persistent T2 signal changes in the thoracic spinal cord (T9-T11), and abnormal brain MRI findings. The patient was transferred to the intensive care unit due to worsening respiratory distress and hypoxia. She was intubated, mechanically ventilated, and started on intravenous methylprednisolone (1,000 mg for three days), followed by prednisone (60 mg daily). Despite aggressive treatment, she developed septic shock requiring vasopressors. On day five, she succumbed to refractory shock and cardiopulmonary arrest.

DISCUSSION

NS exhibits considerable variability in outcomes, influenced by several critical factors. These include the severity and extent of disease, the specific neuroanatomical sites involved, and the timeliness of presentation and diagnosis.[3]

In the presented case, the patient's symptoms of lower extremity weakness and urinary incontinence were nonspecific. NS can manifest as spinal cord lesions and peripheral nerve involvement. Approximately 5-10% of patients with sarcoidosis initially present with neurological symptoms.[7] Notably, patients with cranial nerve involvement are more likely to receive an early diagnosis and have better outcomes. This contrasts with the current case, where peripheral neuropathy was the presenting feature. A study of 54 patients with NS found that certain clinical presentations correlated with better outcomes.[11] For example, patients with cranial neuropathies (except for bilateral optic neuritis), myelopathies, seizures, and headaches had a higher likelihood of favorable responses to treatment. In particular, most patients with facial nerve palsy or hearing loss showed either complete resolution or significant improvement.[11]

Serologic tests commonly used in diagnosing sarcoidosis include ACE, adenosine deaminase, serum amyloid A, and soluble interleukin-2 receptor. In this case, the patient had an elevated ACE level, while all other tests were negative. However, the diagnostic utility of ACE remains controversial. A meta-analysis reported a sensitivity of 76% and specificity of 80%, suggesting that while serum ACE levels may assist in diagnosing and assessing disease activity in sarcoidosis, isolated ACE measurements should be interpreted with caution.[12]

The differential diagnosis of noncaseating granulomas is broad and includes infectious, malignant, autoimmune, and toxic etiologies, as well as sarcoidosis. Diagnostic tests such as blood cultures, BAL, viral screening, flow cytometry, neoplastic and paraneoplastic antibody panels, and inflammatory markers can help narrow the differential.[13] In this case, an extensive workup was largely unremarkable. The presence of noncaseating granulomas, elevated ACE levels, and radiological findings ultimately supported the diagnosis of NS.

Primary central nervous system lymphomas (PCNSL) are aggressive malignancies, almost always due to DLBCL.[14] While 40% of DLBCL patients experience relapse or refractory disease, only 2-5% have CNS involvement, making such relapses rare but often devastating.[15,16] Moreover, the variable radiological features in immunocompetent versus immunocompromised patients further complicate diagnosis.[17] Although tissue biopsy remains the gold standard, radiological findings and CSF studies can be useful in cases where biopsy is not feasible.[18] Given the patient's spinal cord involvement, a trial of radiation therapy was considered.

A 2020 study examined the time to diagnosis in patients with sarcoid-associated myelopathy. Among those without a prior sarcoidosis diagnosis, the median time from symptom onset to NS diagnosis was five months. However, delays varied significantly, ranging from 1 to 50 months, depending on MRI findings.[11] Regarding disease outcomes, 52% of patients experienced moderate to severe disability. After one year, 50% showed improvement, 26% worsened, and 24% remained stable.[10] This variability in time to diagnosis highlights its potential impact on prognosis, as delayed treatment may contribute to disease progression.

CONCLUSIONS

Both NS and CNS lymphoma can present with similar neurological deficits, creating significant diagnostic challenges.[19] Additionally, both conditions can have nonspecific radiological findings, further complicating differentiation. This case underscores these challenges, particularly given the patient's history of DLBCL, which has the potential to progress to CNS lymphoma. While bone marrow biopsy, radiological findings, and clinical presentation can aid in diagnosis, prognosis remains poor despite advancements in diagnostic techniques.

REFERENCES

[1] Drent M, Crouser ED, Grunewald J. Challenges of sarcoidosis and its management. N Engl J Med 2021; 385(11):1018-1032. PMID: 34496176.
[2] Wills AB, Adjemian J, Fontana JR, et al. Sarcoidosis-associated hospitalizations in the United States, 2002 to 2012. Ann Am Thorac Soc 2018; 15(12):1490-1493. PMID: 30199648.
[3] Fritz D, van de Beek D, Brouwer MC. Clinical features, treatment and outcome in neurosarcoidosis: Systematic review and meta-analysis. BMC Neurol 2016; 16(1):220. PMID: 27846819.
[4] Arkema EV, Grunewald J, Kullberg S, Eklund A, Askling J. Sarcoidosis incidence and prevalence: A nationwide register-based assessment in Sweden. Eur Respir J 2016; 48(6):1690-1699. PMID: 27471207.
[5] Nozaki K, Scott TF, Sohn M, Judson MA. Isolated neurosarcoidosis: Case series in 2 sarcoidosis centers. Neurologist 2012; 18(6):373-377. PMID: 23114669.
[6] Carlson ML, White JR, Espahbodi M, et al. Cranial base manifestations of neurosarcoidosis: A review of 305 patients. Otol Neurotol 2015; 36(1):156-166. PMID: 25029595.
[7] Bradshaw MJ, Pawate S, Koth LL, Cho TA, Gelfand JM. Neurosarcoidosis: Pathophysiology, diagnosis, and treatment. Neurol Neuroimmunol Neuroinflamm 2021; 8(6):e1084. PMID: 34607912.
[8] Sambon P, Sellimi A, Kozyreff A, et al. Epidemiology, clinical presentation, treatment, and outcome of neurosarcoidosis: A mono-centric retrospective study and literature review. Front Neurol 2022; 13:970168. PMID: 36388212.
[9] Stern BJ, Royal W, Gelfand JM, et al. Definition and consensus diagnostic criteria for neurosarcoidosis: From the Neurosarcoidosis Consortium Consensus Group. JAMA Neurol 2018; 75(12):1546-1553. PMID: 30167654.
[10] Okada N, Hanafusa T, Sakurada T, et al. Risk factors for early-onset peripheral neuropathy caused by vincristine in patients with a first administration of R-CHOP or R-CHOP-like chemotherapy. J Clin Med Res 2014; 6(4):252. PMID: 24883150.
[11] Murphy OC, Salazar-Camelo A, Jimenez JA, et al. Clinical and MRI phenotypes of sarcoidosis-associated myelopathy. Neurol Neuroimmunol Neuroinflamm 2020; 7(4):e722. PMID: 32269072.
[12] Hu X, Zou L, Wang S, Zeng T, Li P, Shen Y, Chen L. Performance of serum angiotensin-converting enzyme in diagnosing sarcoidosis and predicting the active status of sarcoidosis: A meta-analysis. Biomolecules 2022; 12(10):1400. PMID: 36291609.
[13] Eid A, Carion W, Nystrom JS. Differential diagnoses of bone marrow granuloma. West J Med 1996; 164(6):510-515. PMID: 8764626.
[14] Villano JL, Koshy M, Shaikh H, Dolecek TA, McCarthy BJ. Age, gender, and racial differences in incidence and survival in primary CNS lymphoma. Br J Cancer 2011; 105(9):1414-1418. PMID: 21915121.
[15] Eyre TA, Kirkwood AA, Wolf J, et al. Stand-alone intrathecal central nervous system (CNS) prophylaxis provide unclear benefit in reducing CNS relapse risk in elderly DLBCL patients treated with R-CHOP and is associated increased infection-related toxicity. Br J Haematol 2019; 187(2):185-194. PMID: 31215036.
[16] Ferreri AJM. Risk of CNS dissemination in extranodal lymphomas. Lancet Oncol 2014; 15(4):e159-169. PMID: 24694639.
[17] Lin X, Khan IRA, Seet YHC, Lee HY, Yu WY. Atypical radiological findings of primary central nervous system lymphoma. Neuroradiology 2020; 62(6):669-676. PMID: 32077984.
[18] Schaff L. Central nervous system lymphoma. Continuum (Minneap Minn) 2023; 29(6):1710-1726. PMID: 38085895.
[19] Baehring JM, Damek D, Martin EC, Betensky RA, Hochberg FH. Neurolymphomatosis. Neuro Oncol 2003; 5(2):104-115. PMID: 12672282.

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