Biopsy-proven isolated sarcoid meningitis

Case report

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Neurological involvement occurs in 5% of patients with sarcoidosis. When neurological symptoms are the presenting feature of the disease, as occurs in one-half of patients with sarcoidosis, diagnosis is usually based on the clinical or histopathological demonstration of systemic involvement. In rare cases, sarcoidosis "isolated" to the central nervous system (CNS) may develop. These patients often pose a challenging diagnostic dilemma.

We recently treated a young man with meningeval sarcoidosis who demonstrated no other features of the disease. Our patient illustrates that lack of systemic involvement does not rule out neurosarcoidosis, and demonstrates the role of open brain biopsy in establishing the diagnosis.

Case Report

This 27-year-old previously healthy black man presented to The Neurological Institute with headache, mental status changes, and polyradiculopathy of 4 weeks' duration. His illness began with daily morning headaches accompanied by nausea and vomiting. After 4 days the headaches became unremitting and he noticed brief episodes of diplopia, which resolved after a few days, and decreased jumping ability on the basketball court. After 1 week of experiencing these symptoms, the patient was admitted to another hospital where his examination was considered to be normal except for the presence of meninginal signs. Lumbar puncture revealed a lymphocytic pleocytosis with elevated protein and normal glucose levels (Table 1. Days 12 and 19 of illness), and a computerized tomography (CT) scan of the head showed diffuse meningeal contrast enhancement. Antituberculous medications and prednisone were prescribed, and he experienced moderate relief of his headache. The prednisone was discontinued after 1 week, at which point he experienced worsening of his headache and new arthralgias. On Day 26 of his illness, he left the hospital against medical advice and without medication.

Two days later, the patient presented to The Neurological Institute with continued symptoms of headache, nausea, arthralgias, and generalized weakness. He denied fever, cough, weight loss, genital lesions, rashes, or tick bites, but admitted to feeling unsteady on his feet. He used alcohol and tobacco on a daily basis, but denied any human immunodeficiency virus (HIV) risk factors.

Examination. On admission, the patient was afebrile, with no evidence of stiff neck, uveitis, rashes, swelling of the joints, scrotal mass, organomegaly, or adenopathy. His neurological examination was notable for the presence of impaired concentration and short-term memory; papilledema; fine postural and head tremor; absent knee and ankle jerks; diminished sensation to pinprick, vibration, and joint position in the distal lower extremities; and inability to fully elevate on heel and toe walking with an unsteady tandem gait. The remainder of the neurological examination was normal.
Isolated sarcoid meningitis

**TABLE 1**
*Cerebrospinal fluid findings in a patient with isolated sarcoid meningitis*

<table>
<thead>
<tr>
<th>Day of Illness</th>
<th>WBC Count (no./cu mm)</th>
<th>Differential (L/M/P)</th>
<th>RBC Count (no./cu mm)</th>
<th>Protein Level (mg/dl)</th>
<th>Glucose Level (mg/dl)</th>
<th>Opening Pressure (mm H2O)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>198</td>
<td>—</td>
<td>18</td>
<td>240</td>
<td>54</td>
<td>—</td>
</tr>
<tr>
<td>19</td>
<td>101</td>
<td>—</td>
<td>105</td>
<td>336</td>
<td>69</td>
<td>—</td>
</tr>
<tr>
<td>29</td>
<td>100</td>
<td>88/6/6</td>
<td>10</td>
<td>576</td>
<td>41</td>
<td>230</td>
</tr>
<tr>
<td>40</td>
<td>161</td>
<td>94/3/6</td>
<td>9</td>
<td>609</td>
<td>42</td>
<td>300</td>
</tr>
<tr>
<td>47†</td>
<td>130</td>
<td>93/1/3</td>
<td>0</td>
<td>444</td>
<td>51</td>
<td>200</td>
</tr>
<tr>
<td>54†</td>
<td>140</td>
<td>80/1/19</td>
<td>0</td>
<td>444</td>
<td>68</td>
<td>360</td>
</tr>
</tbody>
</table>

* Abbreviations: WBC = white blood cells; L = lymphocyte; M = monocyte; P = polymorphonuclear cell; RBC = red blood cell; — = data not available.
† Subsequent to initiation of steroid administration.

Lumbar puncture on admission (Table 1. Day 29 of illness) and thereafter revealed elevated opening pressures; cerebrospinal fluid (CSF) analysis showed continued lymphocytic pleocytosis, progressively increasing protein levels, new hypoglycorrhachia, and an elevated immunoglobulin G:protein ratio (16%, normal ≤ 12%) without oligoclonal bands. Head CT and magnetic resonance imaging studies demonstrated diffuse leptomeningeal contrast enhancement with no evidence of hydrocephalus or parenchymal lesions. Electroencephalography showed poorly organized background activity (5 to 6 Hz), with random and diffuse delta frequencies. Motor and sensory nerve conduction studies were normal, with prolonged or absent F-wave responses consistent with an early polyradiculopathy. The patient refused electromyography.

Abnormal laboratory findings included: Na+ 131 mEq/liter (with inappropriate elevation of urine osmolality); erythrocyte sedimentation rate 25 mm/hr (normal 0 to 15 mm/hr); gamma-gluanosine triphosphate 167 IU/liter (normal 15 to 85 IU/liter); and total testosterone level 29 ng/dl (normal 270 to 1070 ng/dl). Borderline elevation of alkaline phosphatase, lactate dehydrogenase, serum glutamate-pyruvate transaminase, and creatine phosphokinase levels was also present on admission.

Negative or normal studies specifically directed at detecting systemic manifestations of sarcoidosis included chest x-ray films, chest CT scans, gallium isotope images, pulmonary function tests including diffusing capacity, serum calcium analysis, 24-hour urinary calcium excretion levels, anergy skin tests, serum and CSF angiotensin-converting enzyme levels, CSF T-cell subset analysis, and slit-lamp examination. Studies performed to identify an infectious cause of meningitis were negative. These studies included: bacterial, fungal, viral, and mycobacterial cultures of blood and CSF; HIV and T-cell subset analysis; purified protein derivative skin testing; rapid plasma reagent and serum Lyme disease antibody titers; and CSF tests for syphilis, cryptococcal antigen, and Lyme disease titers. Additional normal studies included: complete blood counts, a coagulation profile, electrocardiography, urinalysis, and all other serum chemistries; tests for antinuclear antibodies and latex fixation; serum protein electrophoresis; abdominal ultrasound imaging; CSF cytology; thyroid function tests; and serum cortisol, luteinizing hormone, follicle-stimulating hormone, and prolactin analysis.

**Treatment.** The patient was treated briefly with antituberculous medications until purified protein derivative and chest CT scans were negative; thereafter, he was observed off medications. The serum sodium level corrected with fluid restriction. He experienced continued intermittent headache, nausea, and vomiting, and his gait worsened slightly. On Day 41 of his illness, the patient underwent open right temporal brain biopsy. Four days later, he experienced severe headache, followed by a 1-hour episode of acute confusion and agitation. A CT scan of the head was unchanged, and he was started empirically on dexamethasone (10 mg every 6 hours). The diagnosis of neurosarcoidosis was confirmed pathologically the following day; microscopic examination revealed a moderate lymphocytic infiltrate in the leptomeninges with occasional perivascular lymphocytes and several noncaseating granulomas adjacent to small vessels in the subpial cerebral cortex (Fig. 1). No necrotizing vascular lesions were identified. Acid fast and Gomori methenamine-silver stains were negative for the presence of mycobacterial and fungal organisms, respectively, as were all cultures.

After receiving dexamethasone for 3 days, the patient was switched to prednisone at a dose of 60 mg/day. His headaches resolved, rapid improvement of his mental status and gait was noted, and repeat CSF examinations demonstrated reduction in the white blood cell count and protein (Table 1). He was discharged on Day 56 of his illness.

**Discussion**

Sarcoidosis is a granulomatous inflammatory disease of unknown etiology. In the majority of patients, multiple organ systems are affected, most frequently the lungs (87%), lymph nodes (28%), skin (18%), and eyes.
The diagnosis is most secure when noncaseating granulomas are demonstrated histologically in patients with the characteristic clinical features, and when other causes of granulomatous inflammation have been excluded.

Biopsy-proven isolated neurosarcoidosis is rare. Combining four large series, sarcoïdosis of the CNS occurred in the absence of systemic manifestations in 11 (9%) of 119 patients. In only three instances was the diagnosis supported by CNS tissue biopsy; in the remainder, sarcoïdosis was confirmed either at post-mortem examination or on the basis of a positive Kveim skin test (the antigen for which is no longer widely available). Among three recently reported cases of isolated neurosarcoidosis, biopsy was positive in one, negative in another (possibly reflecting the advanced state of disease in this case), and not performed in a third patient with only nonspecific CSF and neuroimaging findings to support the diagnosis.

Our patient presented with a syndrome best characterized as chronic meningitis, with persistent and progressive neurological symptoms in the setting of abnormal CSF of 6 weeks' duration. Besides sarcoïdosis, the differential diagnosis of chronic meningitis includes carcinomatous meningitis, immunological diseases such as vasculitis, and infection with mycobacteria, fungi, parasites, spirochetes, or viral organisms. The potential harm of immunosuppression in infectious chronic meningitis demands that a positive diagnosis be obtained, if possible, before treating empirically for suspected CNS sarcoïdosis. Although the clinical features of our patient were considered compatible with sarcoïdosis, particularly the demonstration of hypotesteronism which is suggestive of hypothalamic-pituitary involvement, the unusual aspect of his presentation was the absence of demonstrable systemic disease.

Meningeal and brain biopsy established the presence of noncaseating granulomatous inflammation in our patient, consistent with sarcoïdosis. Although the pathological distinction between sarcoïdosis and primary granulomatous angiitis is controversial, the absence of mural vascular lesions argues against the latter. Muscle and nerve biopsy may also provide histopathological confirmation of sarcoïdosis in some patients; however, the majority have evidence of intrinsic neuromuscular disease. Because electrophysiological testing revealed a polyradiculopathy without distal nerve involvement (perhaps an early form of previously described peripheral neuropathy syndromes), we believed that muscle and nerve biopsy would be of low yield in our patient.

The role of a diagnostic biopsy in patients with isolated neurosarcoidosis is not fully defined. Most authors have focused on the utility of brain biopsy in patients with space-occupying lesions. However, our experience demonstrates that this procedure can also be of value in patients with diffuse meningeal involvement, and indicates that biopsy may be necessary to rule out isolated meningeal neurosarcoidosis in patients with undiagnosed chronic meningitis.

References

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