Neurosarcoidosis Without Systemic Sarcoidosis

—Case Report—

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Abstract

A 20-year-old male presented with symptoms of isolated neurosarcoidosis including epilepsy. Magnetic resonance imaging disclosed multiple enhanced right temporal and frontal lesions. Cerebrospinal fluid examination identified mild lymphocytic pleocytosis, and histological examination of a stereotactic brain biopsy specimen demonstrated noncaseating granulomas, so fungal or other inflammatory or granulomatous diseases were excluded. The diagnosis was cerebral sarcoidosis, despite the absence of systemic manifestations. Corticosteroid therapy improved his neurological state and radiological findings. Neurosarcoidosis is a well-recognized occurrence in systemic sarcoidosis, but diagnosis may be difficult in the absence of extracerebral manifestations.

Key words: sarcoidosis, magnetic resonance imaging, stereotactic biopsy, steroid therapy, neurosarcoidosis

Introduction

Sarcoidosis is a multisystem granulomatous disorder of unknown etiology which usually presents with varying combinations of pulmonary or cutaneous lesions, lymphadenopathy, ocular lesions, and weight loss. The prevalence of central nervous system (CNS) involvement in sarcoidosis is 3% to 5%.^{5,20,24)} Neurosarcoidosis with no systemic involvement is uncommon and difficult to identify, as this disease can mimic various conditions ranging from tumor to multiple sclerosis. We describe an unusual case of isolated neurosarcoidosis identified by biopsy and illustrate the appearance by magnetic resonance (MR) imaging.

Case Report

A 20-year-old male was admitted to Toho University Hospital with convulsions. He had suffered from paraparesis since undergoing a spinal operation 1 year previously under a diagnosis of spinal tumor at another university hospital. However, histological examination found no evidence of a neoplasm.

Subacute viral encephalomyelitis involving the conus medullaris had been initially mistaken as an intramedullary malignancy. The patient had no history of exposure to tuberculosis, parasitic disease, birds, or beryllium.

On admission, the patient was drowsy but he soon became fully alert and oriented. Language and affect were normal. The cranial nerves were intact. He had full strength, normal sensation, and co-ordination in the arms, but could not stand because both legs were so weak. MR imaging of the brain demonstrated foci of abnormal signal intensity in the white matter of the right temporal and frontal lobes as well as the left frontal lobe. These areas appeared as hypointense on the T₁-weighted images, and hyperintense on the T₂-weighted images (Fig. 1A, B). Edema surrounding the lesions had resulted in a midline shift to the left. T₁-weighted MR imaging after intravenous injection of gadolinium-diethylenetriaminepenta-acetic acid (Gd-DTPA) revealed multiple superficial contrast-enhanced nodules along the left and right sylvian and interhemispheric fissures (Fig. 1C, D). Bilateral carotid angiography found no abnormalities.

Results of routine blood tests were normal, including erythrocyte sedimentation rate, serum angiotensin-converting enzyme (ACE) activity, anti-human immunodeficiency virus antibody, and serum cryp-

Fig. 1 A: Axial T₁-weighted magnetic resonance (MR) image showing abnormal hypointense areas in the right temporal and frontal lobes. B: Axial T₂-weighted MR image showing abnormal hyperintense areas in the right temporal and frontal lobes, as well as midline shift. C, D: Axial (C) and coronal (D) T₁-weighted MR images with gadolinium-diethylenetriaminepenta-acetic acid showing multiple enhanced leptomeningeal lesions and intraparenchymal infiltrates.

tococcal antigen. Further serologic testing disclosed no evidence of viral, bacterial, fungal, or parasitic infection. A tuberculin test showed no reaction. Suboccipital puncture yielded clear cerebrospinal fluid (CSF) with 72 white blood cells/mm³, 70 lymphocytes and 2 polymorphonuclear cells. CSF analysis showed an elevated protein level (96 mg/dl), normal glucose concentration (53 mg/dl), and normal total gamma globulin concentration (27 mg/dl). Cytologic examination of CSF identified no malignant cells.

Bronchoscopy revealed no evidence of pulmonary disease, and cytologic examination of bronchial washings was negative. Total body gallium scintigraphy showed no areas of increased uptake in the lungs or elsewhere. Radiography and computed

Fig. 2 Photomicrograph of the stereotactic brain biopsy specimen. HE stain, original magnification $\times 40$.

tomography (CT) of the chest and abdomen found no evidence of extracerebral involvement by sarcoidosis. Stereotactic biopsy was performed, because elevated CSF protein and lymphocytosis, in the presence of negative cytology and negative cultures for bacteria, acid-fast bacilli and fungi, indicate the presence of a chronic infectious process. A biopsy specimen from the right cerebral cortex revealed multiple, minute noncaseating granulomas consisting of epithelioid cells and infrequent multinucleated giant cells, consistent with a diagnosis of sarcoidosis (Fig. 2).

Prednisone therapy was initiated at a dose of 20 mg daily. Radiography showed dramatic improvement. MR imaging after 12 weeks of steroid therapy demonstrated nearly complete resolution of the abnormal regions. After the patient was discharged home, treatment with prednisone (5 mg/day) and an anticonvulsant was continued. The patient has been followed up to the present time and has had two additional seizures. Follow-up MR imaging 3 years after initiation of treatment demonstrated no recrudescence of granulomatous disease (Fig. 3).

Discussion

Neurosarcoidosis may involve virtually any portion of the nervous system, and clinical features are protean. Cranial neuropathy is the most common manifestation of neurosarcoidosis, and peripheral seventh cranial nerve paresis is the most frequent. Other manifestations include aseptic meningitis, hydrocephalus, peripheral neuropathy, myopathy, and CNS parenchymal disease such as encephalopathy, vasculopathy, seizures, and focal or mass lesions. The diagnosis of neurosarcoidosis usually

Fig. 3 Magnetic resonance (MR) images taken 3 years after initiation of steroid therapy. **left:** T₁-weighted MR image with gadolinium-diethylenetriaminepenta-acetic acid showing no abnormal enhancement. **right:** T₂-weighted MR image revealing clear reduction in the hyperintense areas in the white matter and periventricular region.

depends upon demonstration of systemic sarcoidosis as well as exclusion of other possible causes of the patient's neurological disorder. Neither neurosarcoidosis nor systemic sarcoidosis can be ruled out on the basis of normal serum ACE activity, and no serum or CSF study is specific for the diagnosis of sarcoidosis. The vast majority of patients presenting with neurosarcoidosis will show evidence of thoracic disease upon investigation. If no evidence of systemic sarcoidosis is present when the neurological complaints are investigated, the diagnosis of neurosarcoidosis becomes more difficult.

Isolated neurosarcoidosis is extremely rare, with only 29 cases including the present one described since CT was introduced.^{1-4,7-14,16-19,21,23,25,26)} The patients were 17 males and 12 females, aged from 15 to 58 years (mean 37.1 years). Seizures were the most common manifestation, as six patients had generalized convulsions. Other major clinical signs included cognitive dysfunction (5 patients), headache (4 patients), visual disturbance (4 patients), motor weakness (3 patients), anosmia (2 patients), and diplopia (2 patients). CT and MR imaging detected mass lesions in 18 patients and leptomeningeal involvement in 11 patients. The diagnosis was established histologically in all except two cases. MR imaging is the best method for detecting changes due to neurosarcoidosis, and shows a wide range of findings including abnormal enhancement of the CNS parenchyma and meninges, ventriculomegaly, and periventricular and white matter lesions.¹⁵⁾ Typically, the periventricular and multifocal white matter

lesions are most apparent on T₂-weighted imaging. MR imaging with Gd-DTPA most frequently demonstrates thickening and abnormal enhancement of the leptomeninges, especially in the basal cistern and hypothalamic regions. This distribution is highly suggestive of sarcoidosis, although such findings are not specific. MR imaging cannot generally differentiate neurosarcoidosis from other inflammatory, infectious, or idiopathic etiologies, or from neoplasm. The differential diagnosis of CNS sarcoidosis is quite broad. Tuberculosis, and fungal and bacterial infections can cause diffuse leptomeningitis that is enhanced by gadolinium. The MR imaging appearances of meningeal carcinomatosis, leukemia, and lymphoma can also be indistinguishable from those of neurosarcoidosis.²²⁾

Histological demonstration of noncaseating granulomas limits the differential diagnosis to granulomatous conditions as sarcoidosis, brucellosis, syphilis, tuberculosis, leprosy, cat-scratch fever, glanders, and mycotic infections including histoplasmosis. Dramatic and complete response to steroid therapy is particularly typical of neurosarcoidosis.¹⁹⁾ Histological diagnosis is very important to avoid the damages of treatment based on only clinical and neuroradiological data. In this case, a stereotactic biopsy guided the choice of treatment and avoided the risks of "blind" treatment as well as craniotomy. Stereotactic biopsy is minimally invasive but highly effective to obtain histological information.⁶⁾ Biopsy may be the best diagnostic method if the radiological findings and laboratory data suggest different etiologies for the lesions.

Large controlled studies of the treatment of neurosarcoidosis have not been performed and current therapy is partly based on experience with pulmonary sarcoidosis. A trial of steroid therapy is almost always indicated once the diagnosis is established. Most patients respond to treatment, but one third eventually suffer recurrence at the initial site of involvement.²⁰⁾ Failure to respond to steroids alone warrants the implementation of adjuvant therapy such as administration of immunosuppressive agents or radiotherapy.²⁶⁾

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