A case of isolated neurosarcoidosis associated with psychosis

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ABSTRACT

Sarcoidosis is a rare inflammatory disorder of undetermined etiology, and is characterized by noncaseating granulomatous lesions. Sarcoidosis may affect many organs or systems of the body, most commonly the lungs (87%) and thoracic lymph glands (28%), but the eyes, nervous system, heart, kidneys, bones, and joints may be affected. Most patients with sarcoidosis have no symptoms; the disease is often detected on routine chest radiographs with bilateral perihilar enlargement of lymph glands. Symptoms, if present, include cough, shortness of breath, and arthritis. Nervous system involvement (neurosarcoidosis) is reported in 5-15% of sarcoidosis patients.

Neurosarcoidosis is an uncommon but severe, sometimes life-threatening, manifestation of sarcoidosis. Isolated neurosarcoidosis without signs of systemic disease is a rarity. Intracranial neurosarcoidosis is very difficult to diagnose especially in the absence of systemic signs of the disease due to its non-specific clinical presentation, and its neuroradiological imaging findings. Here, we report a case of isolated neurosarcoidosis that presented with headache and paranoid psychotic syndrome. It was diagnosed by means of a stereotactic brain biopsy, after a detailed investigation, which had failed to detect any systemic involvement. Our objective in presenting this particular case is to highlight the importance of stereotactic biopsy findings in the diagnosis of isolated neurosarcoidosis in patients presenting with psychiatric symptoms and with diffuse white matter involvement.

Case Report. A 36-year-old male patient presented to our clinic. He had a pulsating headache on the left side of his forehead of 4 weeks duration. He also complained of weight loss and forgetfulness. His medical history indicated that he was diagnosed with paranoid syndrome and depression in the last 2 years, and was treated with...
several neuroleptics and anti-depressive drugs. His relatives reported some beneficial effects when he made regular use of the therapeutics; however, he did not, in fact, use the therapeutics regularly. Family history was noncontributory. His general physical and systemic examinations were unremarkable. He was agitated and sometimes confused, but neurological examination did not reveal any focal motor or sensory deficits. His Standardized Mini-Mental State Examination test score was 22.5 Psychiatric examination on admission revealed an atypical paranoid syndrome with auditory hallucinations and disorganized paranoid thoughts. Risperidone, 4 mg/d (Janssen, Istanbul, Turkey) and esitalopram 10 mg/d (Lundbeck, Istanbul, Turkey) was started.

An MRI of the brain revealed bilateral, symmetric, frontal, parietal and to a certain extent left temporal deep white matter located pathological signal increase on T2 and FLAIR sequences (Figures 1A & 1B), with a linear contrast enhancement of all perivascular areas at the deep white matter that also reaches to the subcortical area (Figure 1C). In his MR spectroscopy, a partial decrease in the N-acetyl aspartate peak was observed, and in the EEG, small quantities of diffuse theta and delta activities were observed.

His plain chest x-ray was unremarkable. Routine blood and urinary examinations, electrolyte levels including calcium, sodium, potassium, erythrocyte sedimentation rate, hepatitis markers, thyroid hormones, thyroid peroxidase and thyroglobulin antibodies, anti-human immunodeficiency virus antibodies (anti-HIV), and tumor markers (carcinoembryonic antigen alpha-fetoprotein, carbohydrate antigen 19-9, carcinoma antigen 15-3, and free prostate specific antigen were within normal limits. Fecal occult blood test was negative. Twenty-four hour urinary calcium levels were normal. The level of leukocyte arylsulphatase for the diagnosis of metachromatic leukodystrophy was found to be 196.6 nmol NC mg/protein/hour (normal range: 50-126). Anti-nuclear antibody screen was negative.

The lumbar puncture opening pressure was increased (62 cm H₂O) on sitting position. The CSF analysis showed elevated protein (83.4 mg/dl), normal glucose concentration (91 mg/dl), and mildly elevated cell count (12/mm³ leucocytes, 10 of them lymphocytes). Viral, bacterial, and fungal microscopy and cultures were negative. Cytological examination of the CSF did not show any atypical cell, and oligoclonal bands were not present. A stereotactic brain biopsy from the right frontoparietal region was performed for the definitive diagnosis. In the biopsy material, chronic granulomatous infection reaction was detected and was assessed as sarcoidosis due to the lack of caseification necrosis (Figures 2A & 2B). He was examined by an ophthalmologist, a dermatologist, and a pulmonologist with the intent of detecting any involvement of systemic sarcoidosis. The ophthalmologic evaluation was normal. The skin biopsy matched the seborrhic dermatitis and treatment was arranged. Serum angiotensin converting enzyme (ACE) (18 U/L), IgE, eosinophil cationic protein levels, and Alatop test investigated for a pulmonary

![Figure 1](image-url) - Diffuse white matter signal changes (arrows) are seen on T2 weighted A), and FLAIR sequences images B). On contrast enhanced T1 weighted image C), barely visible enhancing lines (arrows) are noted within white matter areas.
Involvement were normal. Tuberculosis skin test was negative. The diffusing capacity of the lungs for carbon monoxide, respiratory function test, and thorax CT results were all found to be normal. Gallium scanning revealed no uptake related to systemic sarcoidosis.

Despite elaborate examinations of the other organs, no other involvement was found and he was diagnosed as isolated neurosarcoidosis. For 7 days he was treated with intravenous methylprednisolone (1000 mg/day) (Mustafa Nevzat, Istanbul, Turkey). Oral prednisolone (Pfizer, Istanbul, Turkey) maintenance treatment was started at one mg/kg/day and continued with dosages that were reduced by 5 mg each week. Three months after this treatment, his headaches ceased, his dysmnesia decreased, and his weight lost stopped. Comparing the cranial MR images at admission with those at the third month of the treatment, no changes in the localization or sizes of the lesions were observed. During his 6 months follow-up, no other organ involvement or relapse was found. He has no psychological symptoms, but he is continuing take risperidone (2 mg/day).

**Discussion.** Sarcoidosis is a multisystem granulomatous disease of undetermined etiology. Sarcoidosis can be seen at all ages, but most commonly affects young adults. Neurosarcoidosis generally occurs in patients, who have known active disease with substantial systemic involvement. Clinical manifestations of neurosarcoidosis are numerous and diverse. The most common presentations of neurosarcoidosis are cranial neuropathies, aseptic meningitis, encephalopathy, vasculopathy, seizures, cognitive and psychiatric symptoms, focal parenchymatous disease of the hypothalamus, hydrocephalus, myelopathy, peripheral neuropathy, and myopathy.

The definitive diagnosis of neurosarcoidosis is reached through a combination of clinical and laboratory findings. Elevated pressure, increased total protein, decreased glucose, mononuclear pleocytosis, oligoclonal bands and increased IgG index can be identified in CSF analysis. Measuring of the ACE level in the serum and CSF is thought to be useful in the diagnosis of sarcoidosis. Increased ACE levels in the serum have been reported in 5-80% of patients with neurosarcoidosis. Although ACE levels indicate disease activities in sarcoidosis, it is not accepted to be sufficient by itself as diagnostic criteria because ACE levels are elevated in a variety of disorders such as CNS infections and malignant brain tumors.

Cranial MRI findings including non-enhancing periventricular and multifocal white matter lesions, enhancing parenchymal mass lesions, leptomeningeal involvement (especially in basal cisterns and hypothalamic regions), enlargement of the ventricles, and dural involvement are reported in neurosarcoidosis. Generally, the appearance of the lesions is nonspecific and they cannot be distinguished from other inflammatory infectious diseases or malignancies. Cranial MRI of our patient revealed white matter involvement that also reached the subcortical area. On literature review, we were unable to identify previous reports of bilateral white matter involvement sparing gray matter. We excluded the diagnosis of metachromatic leukodystrophy that shares similar white matter changes, since arylsulphatase A activity was not decreased.
Whole body gallium scan and whole body fluorodeoxyglucose positron emission tomography (F-FDG PET) have been considered as useful tools to search for systemic sarcoidosis when initial investigation is unrevealing. In systemic sarcoidosis, gallium scintigraphy may show radioactivity uptake at inflammation sites, including mediastinum, lungs, liver, spleen, salivary glands, lacrimal glands, and eye. The F-FDG PET imaging can also be used to evaluate the extension of the disease, and additionally to target an optimal biopsy site. According to results of a previous study, it has been suggested that F-FDG PET can detect pulmonary lesions to a similar degree as gallium scintigraphy, although F-FDG-PET appears to be a better evaluation tool of extrapulmonary involvement.

Neurosarcoidosis is one of the many medical illnesses that may present with psychiatric symptoms requiring a careful search for organic etiologies when medical evaluation raises clinical suspicion. Psychiatric diseases are rarely seen in neurosarcoidosis. Neurosarcoidosis develops in 5-15% of sarcoid patients, and among neurosarcoidosis patients, 20% will display psychiatric symptoms. Reports of CNS sarcoidosis have described mental status changes associated with delirium or dementia, and a diversity of psychiatric symptoms that include hallucinations, delusions, euphoria, depressive personality changes, aggressiveness, apathy, and cognitive deficits.

The definitive diagnosis of neurosarcoidosis is confirmed by biopsy findings. On histological examination, the essential lesion in sarcoidosis consists of a focal collection of epithelioid cells surrounded by a rim of lymphocytes, frequently with the giant cells, but caseation is lacking. The pathologic diagnosis of sarcoidosis is to some extent one of exclusion, as its appearance may simulate granulomatous inflammation due to other diseases. Differential diagnoses are made especially between the principal noninfective granulomatous disease, including Wegener’s disease, idiopathic hypertrophic pachymeningitis, and isolated (granulomatous) angiitis of the CNS. The stereotactically brain biopsy findings of our patient revealed non-caseating granuloma and peripheral epithelioid multinucleated histiocytes and lymphocytes. Wegener’s disease and granulomatous angiitis were excluded because of the lack of necrotizing vasculitis. The granulomas are smaller and more discrete, and the granulomatous inflammation is largely restricted to blood vessels in granulomatous angiitis of the CNS. Stereotactic biopsy findings are especially important in patients with isolated neurosarcoidosis because of the lack of evidence of systemic involvement. Most of the neurosarcoidosis symptoms positively respond to a corticosteroid treatment and, if the response is good, the treatment can then be stopped by tapering off the dosages. However, one third of the patients may have relapse, and relapse has a tendency to be in the original location of the neurosarcoidosis. Other treatment options such as immunosuppressant agents or radiotherapy may be required in cases of severe progression of the disease, frequent attacks, or the side effects of corticosteroids. During follow-up of our patient treated with corticosteroids, no relapse was been noticed.

In conclusion, isolated neurosarcoidosis is an uncommon cause of psychosis. The diagnosis of isolated neurosarcoidosis should be kept in mind for patients with neurologic or psychiatric symptoms, or both. Cranial MRI finding may be suggestive for diagnosis, and stereotactic brain biopsy is a minimally invasive tool for confirmation.

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References