Noncaseating granulomatous disease involving the meninges: a case report

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Rationale
Multiple cranial nerve palsies can be a feature of infective, inflammatory and neoplastic processes. It is very important to differentiate between these conditions as the treatment is completely different. In the case that we are reporting, meningeal biopsy helped in revealing the diagnosis.
Case Summary
A 64 year old man presented with headache for 6 weeks, facial weakness for 3 weeks and swelling of the right eye with inability to move the right eye for 1 week. Our initial impression was cavernous sinus thrombosis, but the MRI brain did not show thrombosis of the cavernous sinus. Moreover there was thickening of the meninges on the MRI. As the patient had a history of myositis and pulmonary fibrosis and he had remained on steroids, we considered a septic or an autoimmune process. We empirically started steroids and antibiotics and the patient started to improve. However, to establish a diagnosis, we decided to go for a meningeal biopsy. It showed granulomatous inflammation and staining for infections and malignancies was negative. Considering his history of autoimmune disease and pulmonary fibrosis, we diagnosed him as a case of neurosarcoidosis and gave him high dose steroids and the patient improved.
Conclusion
Meningeal biopsy is helpful in establishing the diagnosis and to differential between infectious, inflammatory and neoplastic processes.

Keywords:
granulomatous disease, meningeal biopsy, neurosarcoidosis

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Introduction

Sarcoidosis is a granulomatous disorder of unknown etiology that is characterized pathologically by the presence of noncaseating granulomas. The prevalence (estimated at 10–20 per 100 000 population) and annual incidence of sarcoidosis are not known with certainty. The disease appears to vary in incidence among geographical regions and can also aggregate in families and specific races, being three to four times more common in blacks [1].

Sarcoidosis is a multiorgan disease. Lungs are the most commonly involved organs (95%), and skin, lymph nodes, eyes, and liver each are involved in 11–16% of cases. Neurologic involvement is comparatively rare (4.6%) [2].

The neurologic manifestations of sarcoidosis can be varied and include cranial nerve palsies, aseptic meningitis, hydrocephalus, headache, seizure, neurops ychiatric symptoms, neuroendocrine dysfunction, myelopathy, and peripheral neuropathy [3]. Facial nerve is the most commonly involved cranial nerve; however, vestibulocochlear and optic nerves can also be involved [4]. Myopathy is a relatively rare feature of sarcoidosis [5], and may also develop as a complication of the treatment with steroids and immunosuppressants.

We report a case of neurosarcoidosis with a past history of muscle weakness and dyspnea, which could be part of the current illness.

Case report

A 64-year-old Asian Pakistani male presented with complaints of headache for 6 weeks, deviation of mouth toward the left for 3 weeks, and swelling of the right eye with inability to move the right eye for 1 week. He was well 6 weeks back when he developed headache, which was mild initially and gradually increased. It was more in the frontal and retro-orbital regions.

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Three weeks ago, he developed deviation of angle of mouth toward the left. He also developed hoarseness of voice. One week before presenting to the hospital, he developed pain and redness in his right eye. It was associated with periorbital swelling, proptosis, and ptosis of the right eye. He was unable to move the right eye in any direction. The vision in both eyes was normal.

He complained of low-grade fever and malaise for the past 3 weeks. His appetite was reduced and sleep was disturbed due to the eye pain. There were no complaints of shortness of breath, nausea, vomiting, or chest pain. His urinary and bowel functions were normal.

In 1991 (23 years back), he was diagnosed as a case of dermatomyositis when he developed progressive muscular weakness, dysphagia, weight loss, heliotrope skin rash, and 'shawl' sign on the neck. Autoimmune workup at that time was negative. Electromyography suggested myopathy and biopsy reported myositis. Creatinine phosphate and serum aldolase were significantly raised. He was put on steroids and azathioprine, after which his symptoms improved. His treatment was tapered and stopped over the next few years.

In December 2013 (about 6 months before his current presentation), he was labeled as a case of idiopathic pulmonary fibrosis when he complained of dyspnea, productive cough, weight loss, and fever. He also had clubbing, and chest auscultation at that time revealed scattered fine crepitations. Chest X Ray (CXR) and High Resolution Computed Tomography (HRCT) showed pulmonary fibrosis, costocardiac adhesions, and no lymphadenopathy. He was given steroids and a short course of antibiotics that improved his symptoms.

He was a retired teacher. He had never smoked or used illicit drugs. He was married and belonged to a middle socioeconomic class family.

On examination, he was an obese man with a BMI of 30 kg/m^2, lying in bed with no obvious respiratory distress. His pulse was 90/min, regular, blood pressure was 125/80 mmHg, respiratory rate was 18/min, and temperature was 37°C. He was alert, oriented, and cooperative but talked in a hoarse voice. He had marked proptosis and ptosis of the right eye with congestion and redness. External ophthalmoplegia of the right eye was observed. The right pupil was 4 mm and reactive. Fundoscopy was normal. Facial sensations were intact, with right lower motor neuron type facial weakness. The uvula was deviated to the left, and there were decreased palatal movements and absent gag reflex on the right side. Tongue movements were normal. Motor system examination revealed normal bulk and tone in all four limbs. Power was 5/5 all over, reflexes were normal, and plantars were downgoing. His sensory examination, including facial sensations, was normal. Cerebellar signs were absent and his gait was normal. Chest, cardiovascular, and abdominal examinations were normal. There was no lymphadenopathy. ENT consultation was sought and right vocal cord paralysis was found on fiber optic laryngoscopy.

We made a working diagnosis of cerebral venous sinus thrombosis with differential diagnoses, including infective, inflammatory, and neoplastic diseases. We ordered MRI of the brain with magnetic resonance venogram (MRV). MRI of the brain showed

Table 1 CSF analysis

CSF analysis (August 8)	Results
Volume	5 ml
Color	Colorless
Appearance	Clear
Coagulum	Present
Xanthochromia	Not present
WBCs	35/cm^2
Neutrophils	10%
Lymphocytes	90%
RBCs	Nil
Glucose	89 mg/dl
Protein	46.3 mg/dl
LDH	<30 U/l
CSF Gram stain	Negative
CSF ZN stain	Negative
CSF cytology	Mixed inflammatory cells, negative for malignancy
CSF C/S	Negative
CSF AFB C/S	Negative

CSF, cerebrospinal fluid; LDH, lactate dehydrogenase; RBC, red blood cell; WBC, white blood cell.

Table 2 Inflammatory markers

	August 5	August 12	August 21
ESR (mm/first hour)	126	58	9
CRP (high sensitivity, mg/l)	148.16	9.5	0.72

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

Table 3 Complete blood count

Complete blood count	August 7
WBC (total)	11 100/cm^2
Hemoglobin	13 g/dl
HCT	37.9%
MCV	85.6 fl
Platelet count	293 000/cm^2

HCT, hematocrit; MCV, mean corpuscular volume.

infiltrative disease process involving the right side of the skull base, including the mastoid and the petrous apex extending anteriorly involving the right cavernous sinus. There was no evidence of dural sinus thrombosis on MRV (Tables 1–5).

Chest radiograph revealed interstitial thickening and fibrosis at both lung bases with pleural thickening. Findings suggest interstitial lung disease or pulmonary fibrosis. Two-dimensional Echo with Doppler showed grade 1 diastolic dysfunction.

We started the patient on antibiotics and steroids. To look for the cause, we planned a meningeal biopsy.

An excisional brain dural biopsy was performed and the sample was sent for histopathology. It showed fibrocollagenous tissue involved by multiple granulomas comprising epithelioid histiocytes, multinucleated giant cells, and mature lymphocytes. Rare foci of necrosis were also appreciable. Background showed mild lymphoplasmacytic infiltrate in a hyalinized stroma. No atypical cells were seen. Special stains AFB and GMS were negative for acid fast bacilli and fungus, respectively. On immunoprofile, mature B and T lymphocytes were highlighted by CD20 and CD3, respectively. Rare cells were positive for CD10. BCL-2 was positive in reactive T lymphocytes. There was no evidence of a lymphoproliferative process. Findings were in favor of a chronic granulomatous inflammation; however, the special stains were negative for microorganisms. There was no evidence

Table 4 Chemistry

LFTs, urea, and electrolytes	August 5	August 8
AST	22 U/l	
ALT	29 U/l	
Alkaline phosphatase	87 U/l	
Total bilirubin	0.4 mg/dl	
Direct bilirubin	0.2 mg/dl	
CPK	40 U/l	
LDH	281 U/l	
Sodium serum		140 mEq/l
Potassium serum		4.1 mEq/l
Chloride serum		105 mEq/l
Bicarbonate serum		24 mEq/l
Glucose		119 mg/dl
BUN		19 mg/dl
Urea		40.7 mg/dl
Creatinine	1.49 mg/dl	0.94 mg/dl
S. calcium	8.5 mg/dl	

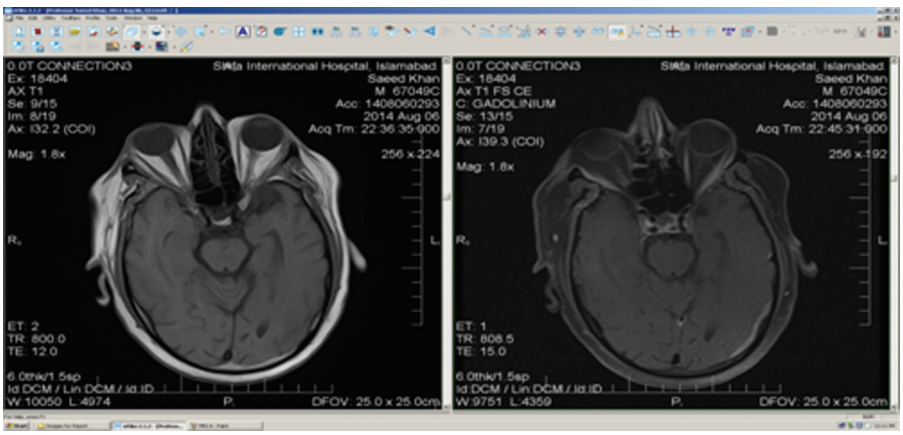
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CPK, creatinine phosphokinase; LDH, lactate dehydrogenase; LFT, liver function tests.

Table 5 Antibody profile

Test	Result
ACE level	29 U/l (normal<52 U/l)
ANA	Negative
Nucleosome antibodies	Negative
dsDNA antibodies	Negative
Histones antibodies	Negative
Anti-Sm/RNP	Negative
Anti-RO (SS-A)	Negative
Anti-LA (SS-B)	Negative
Antismooth muscle antibody	Negative
Anti-Scl-70	Negative
c-ANCA antibody	Negative
p-ANCA antibody	Negative
HBsAg	Negative
Hepatitis C virus Ab	Negative
HIV Ag/Ab combo	Negative
Brucella abortus antibody	Negative
Brucella melitensis antibody	Negative
RPR	Negative
TPHA	Negative

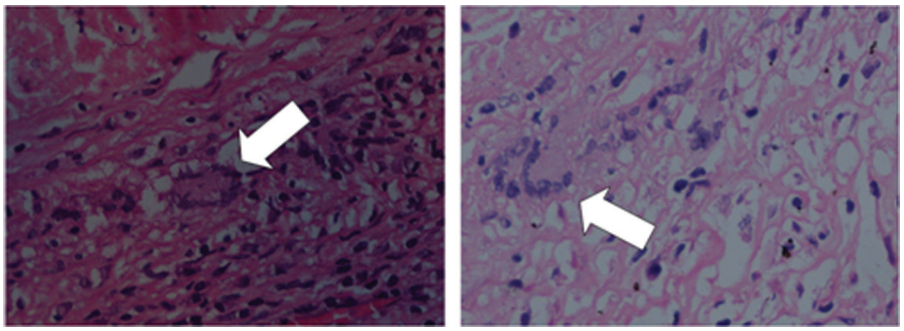
ACE, angiotensin converting enzyme; ANA, antinuclear antibodies; RPR, rapid plasma regain, TPHA, treponema pallidum hemagglutination assay.

Figure 1



MRI brain axial T1 and T1 post-gadolinium images showing infiltrative disease process involving the right side of the skull base, including the mastoid and the petrous apex extending anteriorly involving the right cavernous sinus.

Figure 2



Histological sections of the meninges showing fibrocollagenous tissue involved by multiple granulomas (white arrows) comprising epitheloid histiocytes, multinucleated giant cells, and mature lymphocytes.

of a necrotizing granulomatous disease like Wegener's granulomatous and they were consistent with sarcoidosis.

Because of a suspicion of neurosarcoidosis, we stopped the antibiotics and gave him high-dose intravenous dexamethasone 8 mg 6 hourly for 5 days. The patient started to improve. The patient's headache settled, facial weakness and eye movements improved, and periorbital swelling resolved. His erythrocyte sedimentation rate dropped from 126 to 58 to 9 mm/h after initiation of steroid therapy, and high-sensitivity C-reactive protein dropped from 148 to 9.5 to 0.72 mg/l. He was discharged on oral prednisolone 1 mg/kg/day. Azathioprine 100 mg/day was started at the time of discharge. On follow-up after 2 weeks, he was asymptomatic and back to his normal baseline status.

Considering his history of autoimmune diseases, MRI findings, and biopsy report, we made a diagnosis of neurosarcoidosis (Figs 1 and 2).

Discussion

Meningeal biopsy is an effective and relatively noninvasive procedure that can help in establishing the diagnosis of multiple cranial nerve palsies wherein infective, inflammatory, or neoplastic causes are suspected.

Neurosarcoidosis is a rare disease that usually occurs in patients who have already been diagnosed as having sarcoidosis, but it can also be the first manifestation of sarcoidosis. This patient had not been diagnosed as a case of sarcoidosis, but he did have a history of myositis and pulmonary fibrosis. His MRV was negative for cavernous sinus thrombosis, and hence we considered neurosarcoidosis bearing in mind his history.

The main differentials of neurosarcoidosis are infections and malignancies. It is important to differentiate neurosarcoidosis from these diseases because the steroid and immunosuppressants used for neurosarcoidosis can potentially flare up the infections such as cryptococcus and tuberculosis. Moreover, leaving malignant conditions like carcinomatous meningitis and lymphoma without treatment can be extremely dangerous for the patient.

Histologic confirmation of the diagnosis of sarcoidosis should always be considered. If there is no appropriate extraneurologic organ for biopsy, the involved neural tissue should be biopsied. Biopsy of the dura mater and leptomeninges is less invasive compared with biopsy of the brain or spinal cord parenchyma, and hence it is a better option for tissue diagnosis [3]. After discussing the case with neuroradiologist and neurosurgeon, we went ahead with meningeal biopsy, as the meninges appeared to be thickened on the MRI. Histopathology showed chronic noncaseating granulomatous inflammation and was negative for markers of infections and malignancies. Hence, we diagnosed him as a case of neurosarcoidosis and started steroids and immunosuppressants and he responded very well.

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Conflicts of interest

There are no conflicts of interest.

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