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Isolated Neurosarcoidosis—A Diagnostic Enigma

Case Report and Discussion

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Neurosarcoidosis is a rare, but well-recognized cause of hypopituitarism with a predilection for the hypothalamus. We describe a case of panhypopituitarism in a 57-yr-old Asian lady, associated with an infiltrating hypothalamo-hypophyseal lesion, and other intracranial deposits, initially diagnosed as cerebral tuberculomata. Despite antituberculous therapy, the intracranial lesions progressed with significant clinical deterioration. Repeated lumbar puncture, magnetic resonance imaging scans, liver biopsy and Gallium scan were noncontributory, and the diagnosis of isolated neurosarcoidosis was established only following biopsy of an intracranial lesion. The lesion regressed on steroid and azathioprine therapy. Isolated neurosarcoidosis poses a considerable management problem. We review recent advances in the investigation, diagnosis, and treatment of this condition.

Key Words: Neurosarcoidosis; hypopituitarism; ACE; CSF; biopsy.

Introduction

Sarcoidosis is a multisystem disorder of unknown etiology characterized by the development of noncaseating epitheliod granulomata. The clinical manifestations can be widespread and the lesions metachronous. About 5% of patients with sarcoidosis have clinical involvement of the nervous system *(1)*; however, the incidence of subclinical and undiagnosed neurosarcoidosis (NS) is much higher *(2)*. Furthermore, up to 50% of all patients with NS present with isolated nervous system dysfunction *(1,3,4)*, usually within the first 2 yr of systemic illness, making the diagnosis difficult. NS has a predilection for the base of the brain, although any part of the central nervous system (CNS) or peripheral nervous system (PNS) may be affected. CNS involvement is frequent in the acute stages of the disease, whereas PNS involvement occurs later and prognosticates a chronic course *(5)*.

The most common presentation is cranial nerve involvement (50–70% of cases) affecting one or more cranial nerves *(1,6)*, most frequently unilateral lower motor neurone involvement of the facial nerve *(7)*. Other manifestations include seizures, aseptic meningitis, parenchymatous disease of the CNS, hydrocephalus, polyneuropathy, spinal cord involvement, and myopathy *(1,6)*. Diffuse encephalopathy and vasculopathy can also be associated with cerebral sarcoidosis, presenting with psychiatric illness and short-term memory deficit. Infrequently, NS presents as an intracranial mass lesion, mimicking a glioma or meningioma. Hypothalamic involvement in NS is uncommon; pituitary involvement is also recognized, and an empty sella may supervene.

An infiltrative process in the hypothalamo-hypophyseal region may be caused by granulomatous diseases, infection, or metastatic tumor *(8)*. Granulomatous lesions are uncommon and usually form part of a systemic, generalized granulomatous process with multiorgan involvement, such as tuberculosis, Wegener's granulomatosis, syphilis, Crohn's disease, and sarcoidosis *(9)*. Such infiltrative processes in the hypothalamus may lead to neuroendocrinological dysfunction *(10)*, a primary pituitary defect occurring only rarely *(11)*. The most frequent abnormality involves hypothalamic vasopressin release resulting in either the syndrome of inappropriate secretion of anti-diuretic hormone (ADH) or diabetes insipidus in over 30% of cases *(12,13)*. Hyperprolactinaemia is reported to occur in 3–32% of patients *(14)*; however, other endocrinopathies, including a hypothalamic syndrome, occur in less than 10% of patients with NS *(15)*.

The diagnosis of NS ideally requires evidence of systemic disease, a compatible clinical or neuroradiological picture of sarcoidosis, and histological confirmation of a noncaseating granuloma *(2)*. However, when the initial and perhaps the sole lesion is restricted to the CNS, the differential diagnosis includes histiocytosis X, giant cell granuloma, other granulomatous disorders (tuberculoma, histoplasmosis, brucellosis, coccidiomycosis), lymphoma, and systemic vasculitides, to name but a few. Cerebrospinal fluid (CSF) examination, gallium scanning, serum angiotensin-converting enzyme

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(SACE) and CSF angiotensin-converting enzyme (CACE) may be of help in supporting the diagnosis but lack both sensitivity and specificity.

Corticosteroids, despite significant side effects at high dosages, remain the cornerstone of therapy *(16)*, although conclusive proof of efficacy is lacking. There have been various reports of adjuvant or alternative treatment with immunosuppressive therapy and the effects of irradiation in refractory NS, but these are controversial *(17)*.

We describe a patient without evident systemic involvement in whom the diagnosis of neurosarcoidosis was only confirmed on biopsy, and we review the recent advances in the management of this condition.

Case Report

A 57-yr-old Asian lady, from Nairobi (Africa), presented with a 6-mo history of arm and leg stiffness, lethargy, generalized weakness, weight gain, and poorly controlled insulin-requiring diabetes mellitus. Six months previously, she was seen in Nairobi for investigation and management of irregular menses ascribed to menopausal changes. A hard swelling involving the left mons pubis region, measuring 2.5 × 1.5 × 1.0 cm, was discovered on examination and biopsied; histology reported to be consistent with "active" tuberculosis. A Mantoux test (1 in 1000) performed was weakly positive. Antituberculosis therapy was commenced: 600 mg Rifampicin, 150 mg Pyrazinamide, and 300 mg Isoniazid, daily. A partial ptosis of her right eye was noted and in view of this and her history of transient left-sided weakness 3 mo previously, she underwent a contrast-enhanced computerized tomography (CT) scan of her head. This serendipidously showed enhancement in the region of the pituitary fossa, suggestive of a macroadenoma. She was referred for full pituitary evaluation in the United Kingdom.

The patient was a nonsmoker and drank no alcohol. She was married with two children aged 18 and 27 yr; there was no significant family history. At presentation, her blood pressure was 130/80 mm Hg with no postural hypotension. She had a mild ptosis of the right eye, with a normal pupillary reaction. Visual fields were full to red pin confrontation and to Goldmann's perimetry. Fundoscopy was normal, and examination otherwise unremarkable. A peripheral blood film showed an eosinophilia of 1.17 (0–0.4) and the HbA1c elevated at 7.8% (3.5–6.5). The erythrocyte sedimentation rate (ESR) was 52 (0–15) mm/h and C-reactive protein (CRP) was 30 (0–8) mg/L. Renal, liver, and other hematological indices were normal. Basal (0.900 h) pituitary tests revealed: LH 0.6 (20–65) IU/L, FSH 1.1 (27–139) IU/L, estradiol 73 (up to 200) pmol/L, PRL 1218 (up to 425) mU/L, TSH 0.2 (0.5–4.7) mU/L, free T4 7.1 (10–25) pmol/L, and plasma cortisol 142 (200–650) nmol/L. Hormone replacement was commenced with hydrocortisone initially, then thyroxine. Desmopressin was initiated when cranial diabetes insipidus became clinically evident.

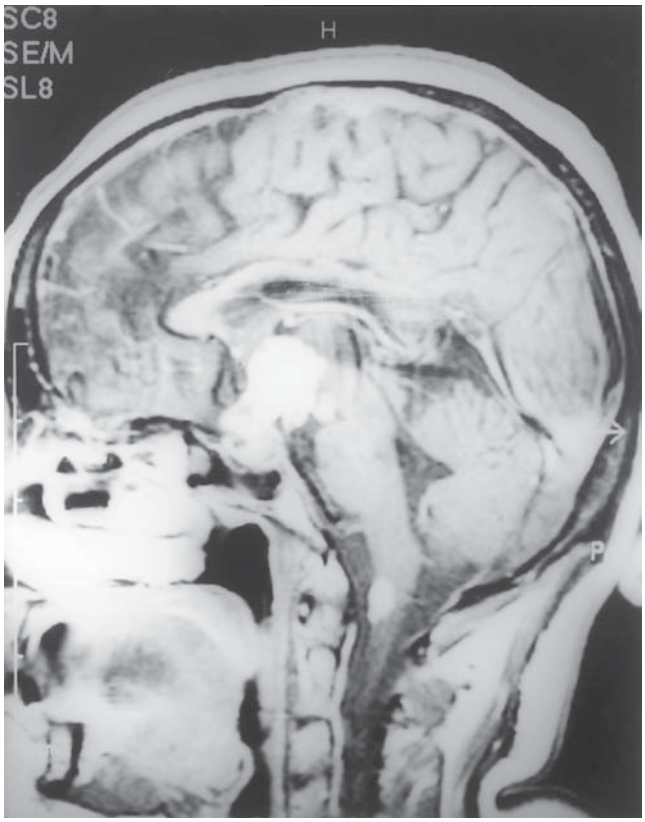

Fig. 1. Magnetic resonance imaging (sagital section) showing a hypothalamic mass with intracranial and spinal deposits. The hypothalamic mass is seen to extend toward, but not involve, the pituitary gland.

Table 1
Cerebrospinal Fluid Analysis

	Admission	6 wk post-admission	4 wk post-treatment	Reference range
Protein (g/L)	2.24	6.89	1.16	(0.1–0.4)
WCC (cells/mL)	15	38	2	< 5
ACE (IU/L)	7	11	<1	(0–7)

Note: WCC: white cell count; ACE: angiotensin-converting enzyme.

A cranial magnetic resonance imaging (MRI) scan showed an infiltrating hypothalamic mass extending, but not involving, the pituitary, with intracranial and spinal dissemination (Fig. 1). CSF examination revealed a raised protein level, along with lymphocytosis (Table 1), and a low CSF glucose of 1.7 (blood glucose 2.7) mmol/L. Gram staining, cytology, Venereal Disease Reference Laboratory (VDRL), Indian ink and culture, and polymerase chain reaction (PCR) for tuberculosis (TB) were all negative. Serum taken for tumor and infection markers (α-feto protein, β-HCG, carcino-embryonic antigen, carbohydrate antigen [CA 125 and CA 19.9], protein electrophoresis, autoantibody screen, antineutrophil cytoplasmic antibodies, syphilitic serology, schis-

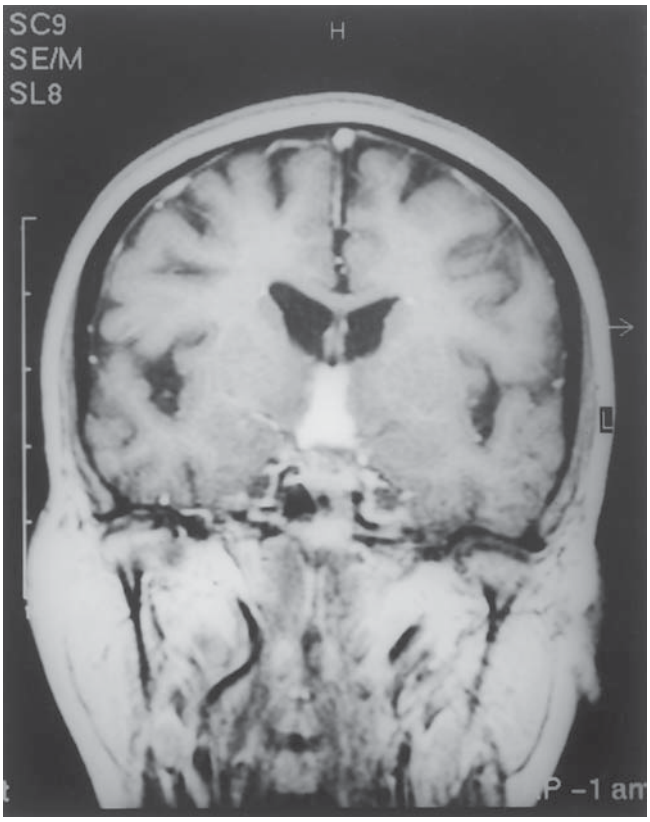

Fig. 2. Magnetic resonance imaging (coronal section) showing the hypothalamic lesion encroaching the third ventricle and optic chiasm.

tosomal and histoplasma antibodies) showed no abnormalities. Her HIV antibody status was negative. Serum angiotensin-converting enzyme (SACE) was 55 (11–55) IU/L and both her chest X-ray and bone scintigraphy were unremarkable. Stool cultures for ova, cysts, and parasites were negative. A tentative diagnosis of cerebral tuberculomata was made, and antituberculosis therapy continued.

Over the next 6 wk, her clinical state deteriorated. She became aggressive, confused, immobile, and unable to cope at home, culminating in admission. On examination, in addition to the right ptosis, a left-sided pyramidal weakness was evident. Repeat MRI showed the lesions to have increased in size, encroaching the third ventricle and optic chiasm (Fig. 2), and a repeat lumbar puncture showed worsening indices (Table 1). Repeat CSF tuberculous culture was negative, as was the PCR, cytology, and syphilitic serology. A single monoclonal band was noted in the CSF. In addition, the hematological and biochemical parameters had worsened, with an ESR of 90 (0–50), CRP of 114 (0–8), and deranged liver function tests, the latter having previously been normal. Hepatitis serology and liver ultrasound were normal. With the worsening clinical, radiological, and biochemical picture, despite antituberculosis therapy, and with a slightly raised CACE, a diagnosis of NS was entertained, even though a liver biopsy revealed no granulomatous lesions and the gallium scan was negative.

A CT-guided stereotatic biopsy of the hypothalamic lesion revealed a chronic noncaseating granulomatous inflammatory infiltrate with no mycobacteria, fungi or parasites present (Fig. 3). High-dose corticosteroid therapy, first intravenously then orally, was instituted. The patient made a gradual clinical improvement and a repeat MRI scan, 1 mo after corticosteroid therapy, showed marked regression of abnormally enhancing cerebral and hypothalamic lesions (Fig. 4). In addition, CSF examination showed improving indices (Table 1). Azathioprine, as a form of adjuvant therapy, was commenced and the dose of prednisolone was tapered to 10 mg/d. The patient is presently asymptomatic on a maintenance dose of immunosuppressive therapy.

Discussion

The protean manifestations of NS make diagnosis a challenge, particularly when presented with an isolated CNS disorder, as in our case. In such instances where neurological involvement is the first or only manifestation of sarcoidosis, the diagnosis is one of exclusion. There are no specific investigations for sarcoidosis or NS at present. In about 50% of patients with NS, CSF examination reveals characteristic but nonspecific abnormalities such as increased protein and a mild pleocytosis, mostly lymphocytes; hypoglycorrhachia is occasionally seen *(18)*. Normal results of CSF analysis do not exclude NS.

Serum ACE (SACE) and CSF ACE (CACE) are helpful in supporting the diagnosis of NS in only a small group of patients. In particular, SACE is often normal in isolated NS; elevation is usually associated with active pulmonary disease. Elevated SACE and CACE reflect an activated disease state, with a sensitivity from 50% to 86% and 80%, respectively *(19,20)*. CACE is normally much lower than SACE. In our case, SACE was within the normal range and CACE raised, highlighting the fact that a normal SACE may be misleading and does not exclude the diagnosis of NS. CACE, which is elevated in 50% of patients with NS, lacks specificity and may be raised in other conditions, such as Guillain-Barre syndrome, multiple sclerosis (MS), Behcets' disease, degenerative brain disorders, and medulloblastoma. Although the usefulness of CACE in the diagnosis of NS has been questioned *(21)*, we feel that raised CACE levels may be useful in cases where the CSF does not contain large amounts of inflammatory cells and where SACE is not elevated, as in our case. Elevation of CSF lysozyme and β_2-microglobulin have been reported in some patients with NS *(22)* and are the result of local CNS secretion rather than leakage through the blood-brain barrier. However, in the diagnosis of NS, they are less specific than elevation of ACE *(23)*. Determination of CSF lymphocyte subpopulations (increased T4:T8), oligoclonal bands, and IgG index have been used to diagnose and differentiate NS from other diseases, such as MS, but lack specificity *(24)*. Furthermore, there have been conflicting reports on the presence or absence of intrathecal synthesis of oligo-

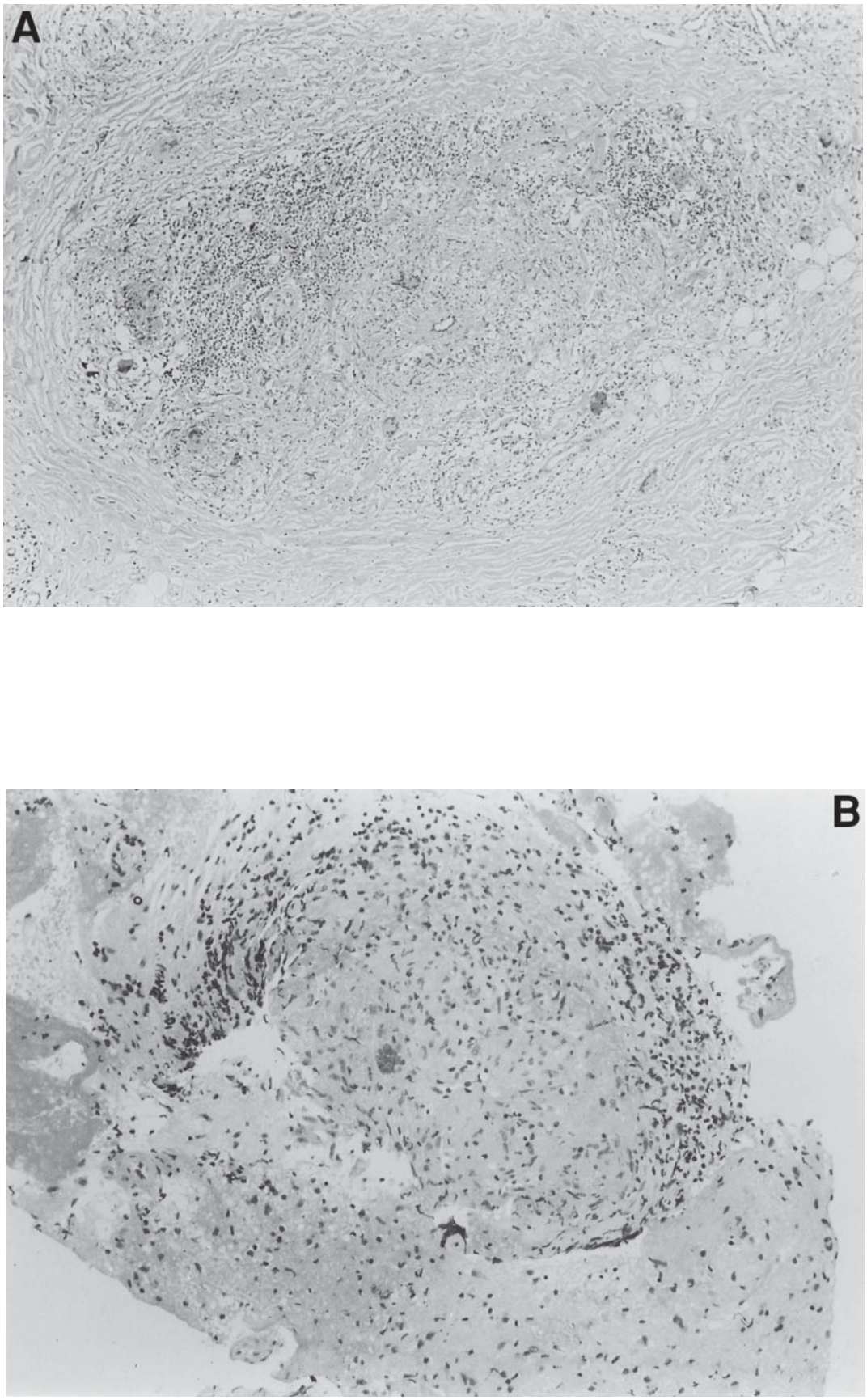

Fig. 3. Photomicrographs of the histology of the hypothalamic lesion. Hematoxylin–eosin staining. (**A**) Noncaseating granulomatous infiltrate in the absence of mycobacteria, parasites, or fungi; (**B**) Same as (a) at higher power. Histology consistent with sarcoidosis.

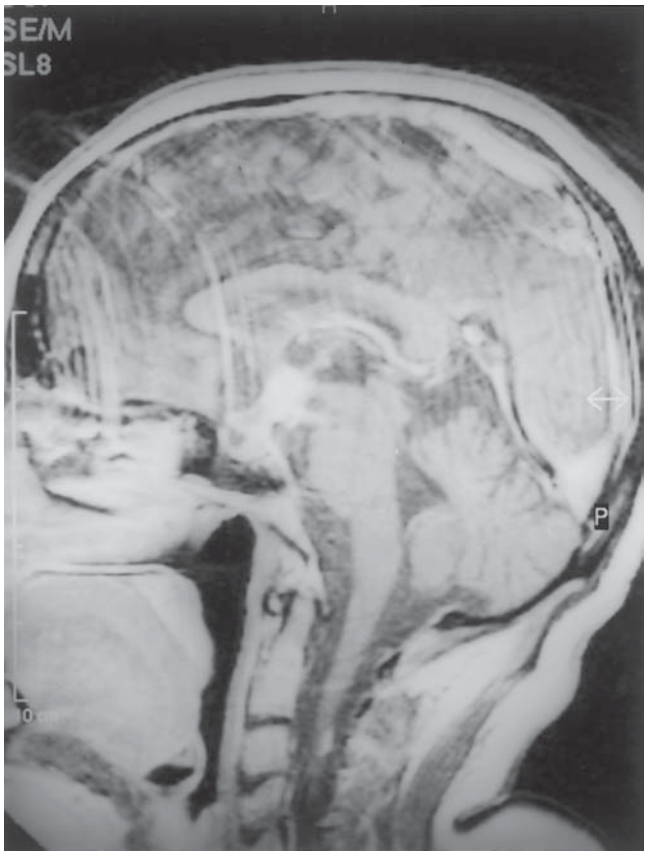

Fig. 4. Magnetic resonance imaging (sagital section) demonstrating marked regression of cerebral and hypothalamic lesions 1 mo after corticosteroid therapy.

clonal IgG *(25,26)*; if local synthesis of oligoclonal bands does occur in NS, it is uncommon.

The radiographic findings of NS are as variable as the clinical manifestations. In patients with NS, the chest x-ray (CXR) is abnormal in only 30% of cases at presentation, as compared to patients with sarcoidosis, where over 90% have an abnormality. Granulomatous lesions within the cerebral parenchyma may be isodense or hypodense on CT and typically enhance with contrast. Although CT scanning may be helpful in demonstrating life-threatening complications of NS, namely hydrocephalus and intracranial mass lesions, MRI is superior in aiding in the diagnosis of NS. MRI is highly sensitive, with abnormalities in 31 of 34 patients NS patients when 2 series are combined *(27,28)*. Miller et al. *(28)*, reported that parenchymal lesions were seen in 17 of 21 (81%) patients with MRI, compared with 9 of 18 (50%) with CT.

The most common MRI pattern was one of periventricular and multifocal white-matter lesions, which appeared hyperintense on T2-weighted scans. Other abnormalities, such as infiltrations of the hypothalamo-pituitary region, granulomatous masses within the brain tissue and leptomeningeal infiltration have been described *(29)*. Use of gadolinium greatly enhances the sensitivity of MRI, as it demonstrates lesions that are not visible on conventional T1- and T2-weighted spin-echo sequences. In a study of 17 patients, Sherman and Stern *(27)* demonstrated meningeal involvement in all patients on the gadolinium-enhanced T1-weighted images; in contrast, unenhanced images were helpful in only three patients, highlighting the importance of gadolinium-enhanced MRI. MRI can also be used to follow therapeutic response. As in our patient, the study by Miller et al. *(28)* demonstrated regression of MRI lesions during steroid therapy; however, despite an improvement of symptoms with steroid therapy, an increase in the number of cerebral lesions has been documented by others *(30)*.

Neurosarcoidosis has a prediliction for the optic nerve, second only to the facial nerve. A neuro-ophthalmological workup is required and should include slit-lamp examination, fluorescein angiography, and visual evoked potentials (VEP). Multimodality evoked potentials (MEP), VEP, and brainstem auditory evoked potentials (BAEP) have been shown to be abnormal in 48% of patients with multisystem sarcoidosis but normal CNS examination, indicating subclinical NS *(31)*. In the study by Gott et al. *(31)*, contrast-enhanced MRI of the brain in patients with abnormal evoked potentials revealed no supportive structural lesions. Given these findings, MEP may be an important adjunct to neuroradiology in the diagnosis and monitoring of NS, particularly in patients with subclinical disease.

To confirm a suspicion of sarcoidosis, and thereby add diagnostic probability of NS, documentation of multisystem involvement is of prime importance. To demonstrate multisystem disease, the Kveim test was considered the most useful investigation, gallium scanning and histological confirmation now being most commonly used. The Kveim antigen skin test, which is still used and reported by some authors as a useful investigation and aid in the diagnosis of NS *(32)*, has its drawbacks. The KT antigen is not widely available, and negative results may occur with concomitant steroid therapy, but, most importantly, a 4- to 6-wk time interval is required before biopsy can be performed. More recently, the use of Mantoux test (MT) site biopsy as an alternative to the KT has been advocated by some, arguing that the MT antigen is well standardized, easily available, and cost-effective *(33)*. The biopsy and histologic interpretation are similar to procedures adopted for the KT. However, in a study by Gupta and Dutta *(34)*, the MT site biopsy was reported as positive in only 94 patients in a series of 146 patients with sarcoidosis (64.3%).

Whole-body gallium scanning is a sensitive but nonspecific marker of inflammation and may be taken up by other inflammatory and malignant diseases. Even in the absence of clinical involvement, gallium scanning may be positive with increased uptake in the lungs and also the carotid, lachrymal, and salivary glands, with a 83–99% sensitivity

for the diagnosis of sarcoidosis in the presence of an elevated SACE *(35)*. In a recent series, 45% of patients with NS had increased uptake of gallium in salivary glands or chest, with only 3 out of 31 (9.6%) showing increased uptake in the cranium *(32)*. Although not routinely used in conjunction with gallium, single-photon-emission computed tomography (SPECT) has been shown to improve spatial resolution of radionuclide imaging and facilitate localization of unsuspected lesions *(36)*.

Histological confirmation involves a biopsy of an enlarged lymph node, salivary gland, or cutaneous lesion, or even transbronchial and liver biopsy. It should be emphasized that positive tissue biopsies outside the nervous system are evidence only of systemic disease and are not diagnostic of NS, even in the context of an appropriate clinical picture. Liver biopsy in our patient was unhelpful in supporting the diagnosis of sarcoidosis, as was gallium scanning. In a patient who is seriously ill with progressive disease and in whom there is no history or evidence of systemic sarcoidosis, as in our case, it is vital to ascertain a definitive diagnosis so that appropriate treatment can be initiated. Under these circumstances, guided stereotactic or open biopsy is performed on CNS tissue/lesion, demonstrating noncaseating epitheliod granulomas, the pathologic hallmark of sarcoidosis.

If the diagnosis is certain, corticosteroids remain the mainstay of treatment of NS. Corticosteroids effectively suppress the elevated CD4–CD8 (T4–T8) lymphocyte ratio, decrease interleukin-2 production, and inhibit collagen synthesis, all of which occur at the sites of active disease *(17)*. Treatment is usually prolonged, exposing the patient to significant steroid-related side effects. Those unresponsive to treatment often require higher doses, either orally or using pulsed methylprednisolone. In these patients, adjuvant or alternative treatment with radiotherapy and/or immunosuppressive agents may be necessary. Methotrexate, azathioprine, cyclosporin, chloroquine, and cyclophosphamide have all been tried with variable success. There are very little data on the efficacy of immunomodulatory therapy in sarcoidosis; no prospective data are available. Certain authors recommend methotrexate *(37)* or hydroxychloroquine *(38)* as first-line steroid-sparing agents, whereas others opt for cyclosporine and azatioprine *(17)*. Surgical debulking is effective and indicated in cases of hydrocephalus or expanding mass lesion refractory to corticosteroid or immunotherapy *(39)*.

Our patient presented with features of chronic meningitis and focal neurological dysfunction, in the setting of abnormal CSF examinations. The potential harm of immunosuppressive therapy in infectious chronic meningitis, the latter excluded in our patient, demands that a positive diagnosis be obtained. Although we were able to demonstrate hypopituitarism, a nonspecific feature of sarcoidosis, the unusual aspect of our case was the absence of demonstrable systemic disease. The definitive diagnosis of sarcoidosis was established on stereotactic biopsy of the hypothalamic lesion, which revealed epithelioid noncaseating granulomas.

In conclusion, our case illustrates the diagnostic difficulties posed by NS and that NS remains a diagnosis of exclusion, there being no definitive tests. We have been able to demonstrate CSF and radiological regression of disease with steroid therapy. MRI may be the imaging modality of choice. The importance of obtaining a tissue biopsy for histological examination of inflammatory lesions in the hypothalamo-hypophyseal region *(40)* is highlighted in our case, as the differential diagnosis of lesions in this region can be varied and their treatment modalities different. In addition, an open mind must be kept for dual pathologies, as this case has illustrated. Finally, the case highlights the lack of specificity and sensitivity in ACE levels in diagnosing neurosarcoidosis, and large prospective series are necessary to validate diagnostic criteria and investigations and to develop guidelines for a rational approach to the management of neurosarcoidosis.

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