Sarcoidosis is a multisystemic granulomatous disease that affects the CNS in 5–9% of patients with the disease. In patients with known sarcoidosis who develop neurological signs and symptoms, neurosarcoidosis should be a diagnostic consideration. Such a diagnosis is difficult to make in the absence of systemic disease, but is rather apparent in patients with biopsy specimen proof of obvious systemic multiorgan involvement, concomitant CSF abnormalities, and contrast-enhancing meningeal or parenchymal lesions. Although we have some understanding of this disease, its natural history, etiopathogenesis, diagnosis, treatment, and prognosis remain unclear. Hypothalamic-pituitary sarcoidosis occurs in less than 10% of patients with neurosarcoidosis and has been previously reported in association with profound endocrinological dysfunction. The authors report the case of a patient with isolated pituitary sarcoidosis who was first evaluated for visual symptoms and showed no preoperative endocrinological dysfunction or evidence of multisystemic or other CNS involvement. To the authors’ knowledge, only 1 other such presentation is previously reported in the English literature. Such presentations are diagnostically and therapeutically challenging, and definitive diagnosis requires obtaining a biopsy specimen of the lesion with histological proof of noncaseating epithelioid granuloma, as well as the exclusion of other possible entities.

**Key Words** • hypothalamus • macroadenoma • neurosarcoidosis • pituitary • sarcoidosis

**Case Report**

This 62-year-old Caucasian man was first examined because of a 3-month history of progressive bilateral visual loss. His visual examination revealed bitemporal hemianopsia with reduced visual acuity in both eyes. The patient had previously undergone coronary artery bypass grafting for ischemic heart disease. Ophthalmological assessment revealed a bitemporal field defect consistent with involvement of the optic chiasma. Magnetic resonance imaging revealed a large, homogeneously enhancing, dumbbell-shaped pituitary lesion approximately 24 mm long extending into the suprasellar region, findings consistent with a pituitary macroadenoma (Fig. 1). Results of endocrine function evaluations were normal, and he was informed of the likely diagnosis of a nonsecreting pituitary tumor. The pituitary lesion was decompressed via transsphenoidal approach with the aid of frameless stereotactic surgery and intraoperative MR imaging. Intraoperative analysis of several biopsy frozen sections yielded a preliminary diagnosis of an inflammatory granulomatous lesion. Intraoperatively, the lesion was unusually rubbery and firm. Postoperatively, the patient experienced transient diabetes insipidus that was treated with desmopressin acetate nasal spray (Aventis). Histopathological examination revealed multiple circumscribed nonnecrotizing granulomata composed of epithelioid histiocytes, lymphocytes, and multinuclear giant cells (Fig. 2). Special stains as well as cultures for acid-fast bacilli and fungal organisms were negative. Immunohistochemical staining with CD45 antigen (leukocyte common antigen) showed lymphocytes at the periphery of the granulomata (Fig. 3 right), and staining with CD68 (macrophage marker) demonstrated that histiocytes were apparent at the center of the granulomata (Fig. 3 right). Systemic disease was ruled out using computed tomography and radiography of the chest and abdomen, as well as ophthalmologi-
A

B

C

Fig. 1. Gadolinium-enhanced T1-weighted MR images. The axial view (A) shows the diffusely enhancing pituitary lesion, whereas the sagittal (B) and coronal (C) views show the homogeneously enhancing dumbbell-shaped pituitary mass with suprasellar extension.

cal and ear, nose, and throat examinations. The patient was started on immunosuppressive therapy with prednisolone after the diagnosis was established and has been regularly followed up since that time. On MR imaging of the brain obtained at the 3-month follow-up, the lesion was found to be stable with no significant morphological changes.

Discussion

Sarcoidosis is a systemic inflammatory disease of unknown origin that is characterized by noncaseating epithelioid cell granulomata. The lungs and reticuloendothelial system are typically involved, but virtually any organ system may be affected. Sarcoidosis involving the CNS is relatively uncommon, occurring in an estimated 5–9% of patients with sarcoidosis. Neurological manifestations of the disease include peripheral or cranial neuropathy, spinal cord lesions, parenchymal granulomata, granulomatous meningitis, and hypothalamic-pituitary dysfunction. In a series of 68 patients, the most common manifestation was disease of the optic nerve in 38%, followed by disease of the spinal cord in 28% and of the facial nerve in 19%; 10% showed cognitive decline. Optic nerve involvement was attributed to granulomata of the nerve head, papillitis, papilledema caused by increased intracranial tension, optic atrophy, pressure from adjacent granulomata, optic neovascularization caused by long-standing uveitis, or retinal periphlebitis.

Although Mycobacterium and Propionibacterium have been implicated in the pathogenesis of sarcoidosis, the etiological factors inciting these inflammatory responses remain unknown. The pathogenesis of neurosarcoidosis is considered leptomeningeal and vascular, and results in the elicitation of a chronic inflammatory response. Disruption of the blood–brain barrier permits the granulomatous infiltration of the brain parenchyma along the Virchow–Robin spaces, with characteristic vasculitis and perivascular infiltration.

Zajicek and colleagues have proposed a 3-point classification of neurosarcoidosis based on the certainty of diagnosis of multisystemic sarcoidosis, the pattern of neurological disease, and response to therapy as follows:

1) Possible. The clinical syndrome and neurodiagnostic evaluation suggest neurosarcoidosis. Infection and malignancy have not been completely excluded, or systemic sarcoidosis has not been pathologically confirmed.

2) Probable. The clinical syndrome and neurodiagnostic evaluation suggest neurosarcoidosis, and alternative diagnoses—especially infection and malignancy—have been excluded. There is pathological evidence of systemic sarcoidosis.

3) Definite. a) Clinical presentation suggests neurosarcoidosis, other possible diagnoses are excluded, and there is supportive pathology of the nervous system; or b) the criteria for “probable” diagnosis are met, and the patient has responded well to therapy for neurosarcoidosis over 1–2 years of observation.

According to these criteria, in our patient, the clinical presentation and histopathological evidence of sarcoidosis enabled a definitive diagnosis of sarcoidosis to be made.

Hypothalamic-pituitary sarcoidosis, which occurs in less than 10% of patients with neurosarcoidosis, continues to present diagnostic and therapeutic challenges. Although a rare entity, pituitary sarcoidosis has been reported, typically associated with profound endocrinological dysfunction that may include any combination of obesity, psychosis, diabetes insipidus, amenorrhea, hypoglycemia, or other significant pituitary insufficiency. Originally, the neuroendocrine dysfunction was attributed to a destructive process affecting the pituitary gland, but recent studies have indicated that it is caused by hypothalamic insufficiency; hence, the term hypothalamic-pituitary sarcoidosis is often used for lesions involving this area. The infiltrative process involves the patchy destruction of the hypothalamic-pituitary tract, which results in various combinations of anterior and posterior pituitary dysfunctions. Diabetes insipidus, one of the most frequent symptoms, results from direct infiltration of the pituitary stalk. Our patient’s endocrine function was
normal despite a large lesion that involved the pituitary gland and pressed on the anterior optic pathway. Because this pituitary involvement was not accompanied by endocrinological dysfunction or systemic disease, our case is unique and can be considered as a solitary pituitary sarcoidosis. We have found only 1 other similar report in the English literature, in which Arle and colleagues reported 2 cases of pituitary sarcoidosis with normal endocrine studies, 1 of which showed evidence of systemic sarcoidosis. The clinical presentation of this entity is indistinguishable from that of a nonsecreting pituitary adenoma.

These examples highlight the diversity of presentation of this rare clinical entity and the possibility of isolated involvement of the pituitary gland that does not affect endocrine function. Imaging findings from these entities are often indistinguishable from those of macroadenomas, which can be relatively unenhancing or enhancing, midline, and inhomogeneous, especially in the case of an isolated lesion as in our patient.

In the absence of a known etiological agent, diagnosis of sarcoidosis remains one of exclusion and requires comprehensive evaluation of the patient. When isolated neurological symptoms provoke suspicion of neurosarcoidosis, systematic evaluation should be performed to establish a diagnosis of systemic sarcoidosis. When neurological or neuroophthalmological symptoms occur in the course of established systemic sarcoidosis, the diagnosis of neurosarcoidosis is often straightforward, but in the absence of established multisystemic involvement, diagnosis is often difficult. The diagnosis of solitary pituitary sarcoidosis is even more complex if the lesion is not accompanied by endocrine dysfunction, because the disease mimics other infectious, demyelinating, granulomatous, neoplastic, and connective tissue disorders that affect the nervous system. The diagnosis is particularly difficult in the absence of leptomeningeal or parenchymal lesions elsewhere in the CNS or systemic manifestations of sarcoidosis. Patients should undergo complete ophthalmological examination to rule out ocular manifestations of the lesion. In addition, examination of the CSF may be abnormal in as many as 80%
of the patients with neurosarcoaidosis; however, there is emerging consensus that the CSF angiotensin-converting enzyme level should not be routinely used as a diagnostic criterion because of poor specificity and sensitivity.

Definitive diagnosis requires biopsy specimen evidence of noncaseating necrotizing granulomata. Nonnecrotizing epithelioid granulomata are the hallmark of sarcoidosis. Inflammation is often perivascular, and the outer aspect of the media and the adventitia may be involved. Fibrosis and thickening of the intima and media of blood vessels can develop, which lead to ischemic injury.

Because of the relative rarity of neurosarcoaidosis, its diverse spectrum of presentation, and the absence of any randomized studies, there are no clear treatment guidelines for this disease. Recommendations are generally based on reported case series and expert opinion. Most authorities recommend corticosteroid administration as first-line therapy for most patients if there are no contraindications. Increasingly, adjunctive therapy with other immunosuppressive and immunomodulatory agents is used. Therapeutic decisions should be guided by the patient’s clinical course, expected natural history of the patient’s clinical manifestations, and any adverse response to treatment. Patients with hypothalamic-pituitary sarcoidosis often require anterior and posterior pituitary hormone replacement because of endocrine dysfunction. Use of MR imaging with the contrast agent gadolinium is the preferred modality for monitoring the treatment of neurosarcoaidosis.

Conclusions

Neurosarcoaidosis can present with diverse neurological manifestations that make its diagnosis difficult, especially when systemic disease is absent. Our patient’s case of solitary pituitary sarcoidosis without preoperative endocrine dysfunction and with no systemic evidence of sarcoidosis represents 1 example of the diversity of presentation of this rare clinical entity, and underscores the need to obtain biopsy specimens of such lesions and perform histological analysis to establish a definitive diagnosis.

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References


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