A 55-year-old man with liver failure, delirium and seizures - Diagnosis: Neurosarcoidosis

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JUNE 2007 CASE 2

A 55-YEAR-OLD MAN WITH LIVER FAILURE, DELIRIUM AND SEIZURES

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CLINICAL HISTORY

A 55-year-old African-American man with an 8-month history of poorly controlled seizures and longstanding history of cirrhosis, diabetes and hypertension was brought to the emergency department for progressively worsening confusion, memory loss and increasing frequency of seizures. On the day of presentation, the patient had a prolonged generalized tonic-clonic seizure. The patient was being treated for a hepatic encephalopathy with lactulose. Within the last 8 months he had had a transjugular intrahepatic portal system shunt for management of his end-stage liver disease and was awaiting a liver transplant. A non-contrast computed tomography of the head revealed no acute intracranial process. A magnetic resonance imaging (MRI) was subsequently obtained. After admission, the patient's mental status continued to decline and ultimately progressed to multisystem organ failure. He suffered a cardiopulmonary arrest and expired.

NEUROIMAGING

Gadolinium-enhanced T1-weighted MRI revealed multiple small punctate foci of leptomeningeal enhancement in the sulci between the folia of the superior cerebellar hemispheres, the flocculi and the ventral medulla (Figure 1A). On FLAIR sequence, the inferomedial left frontal lobe and the right gyrus rectus both demonstrated an area of increased signal intensity (Figure 1B). There was no enhancement of these areas with gadolinium.

POSTMORTEM EXAMINATION

Autopsy revealed enlargement of mediastinal lymph nodes with evidence of sarcoidosis, a cirrhotic liver with thrombosis of the transjugular intrahepatic portal system shunt and kidneys with evidence of hypertensive nephrosclerosis. Microscopic examination of the lungs demonstrated numerous granulomas in the mediastinal lymph nodes.

Gross examination of the brain revealed normal gyral pattern, unremarkable dura and leptomeninges. There was no evidence of uncal or tonsillar herniation. The Circle of Willis had symmetrical vessels without evidence of aneurysms or plaques. Coronal sections (5 mm) demonstrated a normal cortical ribbon, a well-demarcated gray/white matter and a normal ventricular system. Brain stem cerebellum and spinal cord showed no abnormalities on gross examination.

Microsections of the brain showed multifocal non-necrotizing granulomas in the leptomeninges covering the cerebral cortex (Figure 2), cerebellar hemispheres (Figure 3) and the brain stem (Figure 4). A predilection for the perivascular location was evident. These granulomas contained numerous multinucleated giant cells admixed with lymphocytes. Special stains for microorganisms including mycobacteria and fungi were negative. Hippocampal sclerosis consistent with metabolic/hypoxic ischemic type injury was also observed.

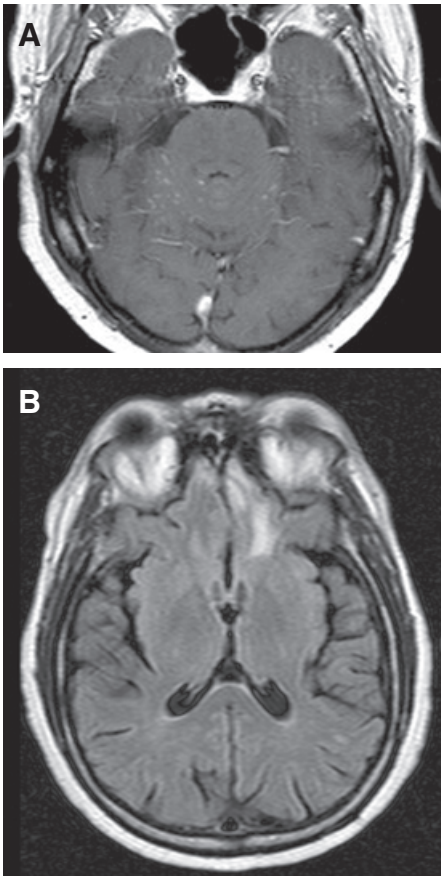

Figure 1.

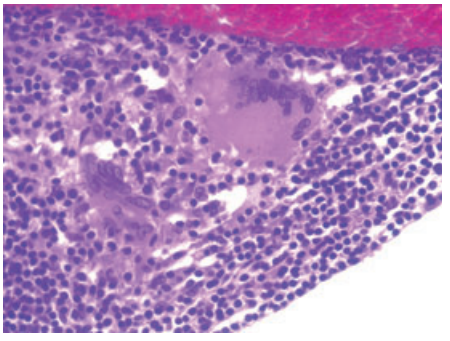

Figure 2.

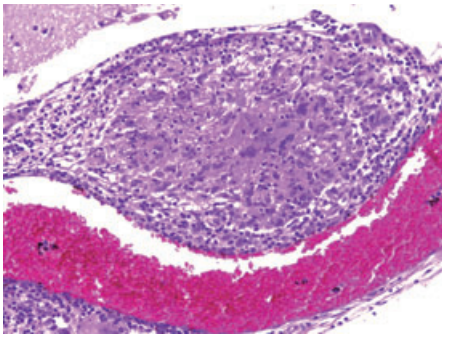

Figure 3.

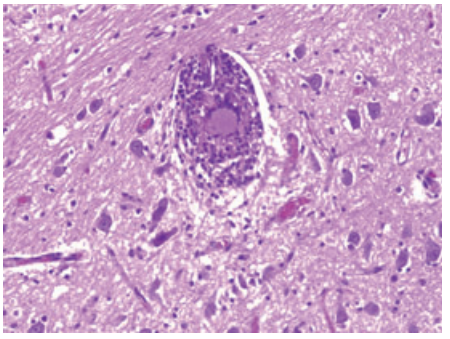

Figure 4.

FINAL DIAGNOSIS

Neurosarcoidosis.

DISCUSSION

Postmortem studies have demonstrated that central nervous system involvement of sarcoidosis is more common than the actual clinical manifestations of this disease would suggest (3, 4, 5). In fact, clinically silent neurosarcoidosis may also be demonstrated radiographically in up to 10% of patients with known systemic sarcoidosis (6) Despite this, only approximately 5% of all patients who suffer from sarcoidosis will report neurological symptoms (7). Patients who present with neurosarcoidosis in the absence of systemic manifestations are exceedingly rare (2)

Recognizing neurosarcoidosis in the absence of systemic disease is a diagnostic challenge as there are no clinical or radiographic features unique to this disease. Meningitis, encephalopathy, seizures and hydrocephalus are only a few of the nonspecific presentations neurosarcoid patients may exhibit. Signs and symptoms of central nervous system involvement classically mimic other disease processes such as autoimmune, vascular or demyelinating processes (1).

The imaging findings of neurosarcoid are also nonspecific and may involve any part of the neuroaxis. Lesions may be either enhancing or non-enhancing in the parenchyma, meninges and bone. Nevertheless, there are findings that may favor neurosarcoid. Leptomeningeal enhancement, diffuse or nodular, is the most common radiographic finding in neurosarcoid, present in 40% of cases (6). Intraparenchymal lesions are seen as non-enhancing periventricular white matter lesions that have high signal intensity on T2 and FLAIR, as seen in this patient (please see images on the web at http://path.upmc.edu/divisions/neuropath/bpath/cases/case141.html). These findings may be difficult to distinguish from demyelinating or vascular processes. Mass lesions within the parenchyma may also enhance, mimicking a primary or metastatic tumor (2). The literature suggests that in the context of known systemic disease, MRI may be up to 97% sensitive for central nervous system involvement (2, 3). In the absence of known sarcoidosis, the specificity and sensitivity of the above mentioned findings are substantially less. MRI remains the study of choice for monitoring progression of disease.

As there are no individual clinical or pathologic features specific for this disorder, the diagnosis of sarcoidosis requires clinicopathologic correlation and the exclusion of other causes of granulomatous inflammation. Non-necrotizing granulomas, often perivascular in location with relatively sparse lymphocytic infiltration (ie, naked granulomas), are the histologic hallmark of sarcoidosis. As tuberculosis, fungi, spirochetes and other disorders may cause identical pathology, a purely histologic diagnosis of sarcoidosis cannot be made (7). Hence, most pathologic specimens should not be signed out more definitively than "non-necrotizing granulomatous inflammation consistent with sarcoidosis". In contrast with meningitis or cerebritis caused by microorganisms, the clinical course of neurosarcoidosis is typically more indolent and the CSF glucose is usually normal. A history of systemic sarcoidosis is also very helpful in the diagnosis of neurosarcoidosis. When the diagnosis of neurosarcoidosis is suspected in the absence of systemic findings, tissue biopsy from enhancing lesions should be strongly considered to direct further treatment.

We have presented a patient with subclinical systemic sarcoidosis, who presented with progressive encephalopathy and seizures thought to be secondary to hepatic failure. Autopsy revealed clear evidence of systemic sarcoidosis also involving the central nervous system. The patient's hepatic failure may have overshadowed the clinical consideration of other potential underlying etiologies. A history of mediastinal lymphadenopathy was discovered only after extensive review of the patient's medical records. In the absence of clinical pulmonary disease, this finding was not further evaluated. While hepatic encephalopathy may have accounted for the patient's confusion and seizure disorder, it is less likely that it could account for MRI findings in the cerebellum and leptomeninges, both of which were suggestive of neurosarcoidosis. As encephalopathy and seizures have a reported incidence of 5%–10% in patients with neurosarcoidosis, this disease process could have accounted for this patient's presentation (7). In fact, the postmortem studies demonstrated leptomeningeal involvement of the cerebral cortex, cerebellum and midbrain by sarcoidosis, which may be compatible both with the imaging studies and clinical findings in this patient.

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CASE OF THE MONTH: ABSTRACTS

April 2007—Case 1. **Supratentorial meningeal-based neoplasms are a frequent indication for intraoperative frozen sections. An otherwise well 57-year-old man presented with a 6-month history of worsening headaches, hearing difficulties and personality changes. No sensory or motor deficits were found on clinical examination. Imaging showed a dural-based, contrast-enhancing, lobulated left parasagittal mass and a clinicoradiologic diagnosis of meningioma was made. Frozen sections showed a cellular, predominantly solid-appearing tumor composed of sheets of cells with amphophilic cytoplasm and moderately pleomorphic nuclei, on the basis of which a definitive diagnosis was not possible. Smears of fresh tumor tissue were moderately cellular and showed capillary-sized vessels admixed with cohesive groups of pleomorphic cells with foamy cytoplasm in a bloody background. The provisional diagnosis of supratentorial hemangioblastoma was confirmed with paraffin sections and immunohistochemistry. Hemangioblastomas in supratentorial locations are rare tumors, but their importance lies in the fact that they, along with meningioma, renal cell carcinoma and anaplastic astrocytoma, comprise the differential diagnosis of supratentorial meningeal-based neoplasms. The recognition of hemangioblastoma on frozen sections is difficult because of its morphologic similarities with metastatic carcinoma and glioma, and is rendered even more challenging when the tumor is dural-based and supratentorial (a location where the entities in the differential diagnosis occur more commonly). These difficulties are compounded by the artifactual cytomorphologic changes induced by freezing. Cytologic evaluation of smear preparations is extremely useful (and superior to frozen sections) in the intraoperative diagnosis of hemangioblastoma and in its distinction from other tumors in the differential diagnosis.**

April 2007—Case 2. **Lafora body disease is a rare metabolic disorder marked by the accumulation of polyglucosans. Mutations in the EPM2A gene cause up to 80% of Lafora body disease and are inherited in an autosomal recessive manner. The gene has been localized to the long arm of chromosome 6 (6q24), and encodes for a dual phosphatase 331 amino acid protein, laforin, normally located at the plasma membrane and rough endoplasmic reticulum. Various mutations (mostly deletions) result in loss of function of the laforin protein. The overexpressed non-functional protein aggregates with glycogen-microsomal complexes, and may cause cell death by non-apoptotic neuronal degeneration. A second gene causing Lafora body disease, NHLRC1, was identified in 2003 on chromosome 6p22.3, and encodes for malin, an E3 ubiquitin ligase involved in proteolysis cascades. We report a case in which Lafora body disease was diagnosed on a skin biopsy in a 12-year-old girl. She presented at age 7 years with seizures. Over the next several years her clinical course was marked by increased seizure frequency, developmental regression and movement abnormalities including chorea and myoclonus. A skin biopsy was eventually performed to evaluate for metabolic or mitochondrial disease; the biopsy showed globose, non-membrane bound filamentous inclusions within sweat gland epithelial cells resembling Lafora bodies. The filaments comprising the inclusions measured 10 nm and had a randomly intersecting felt-like pattern.**

May 2007—Case 1. **A 63-year-old man presented in February with recurrent syncope. Two months later he developed progressive dementia, cerebellar ataxia, myoclonus, alternating hemiparesis, right VI nerve palsy, somnolence and weight loss. In August, CT scan revealed vascular encephalopathy and mild cerebral atrophy. In October, parasellar masses were detected. At this time, tumors were also seen in the left kidney and both adrenal gland. The patient died of cardio-respiratory insufficiency in November, showing the clinical picture of brainstem encephalitis. Neuropathological macroscopic examination showed an intrasellar gray-white mass with a maximal diameter of 4 cm involving the clivus and pituitary gland. Histological analysis revealed atypical lymphoid cells in the sellar mass and blood vessels with only focal infiltration of the leptomeningeal space and the brain parenchyma. Nearly all organs were involved, with conspicuous sparing of the bone marrow, spleen and peripheral lymph nodes. By immunohistochemistry, the neoplastic cells were positive for LCA and B-cell markers, respectively. Molecular pathology using PCR for immunoglobulin gene rearrangements proved that it was a B-cell neoplasm. The diagnosis of intravascular large B-cell lymphoma with predominant cerebral manifestation was made. This is the first report of an intravascular B-cell lymphoma manifesting as a large tumor mass involving the sella and clivus.**

May 2007—Case 2. **A 15 year-old female patient presented with headache and vomiting for a 3-week duration. MRI disclosed a cystic mass with a mural nod-**

ule in the right temporoparietal region. Microscopic examination and diagnostic immunohistochemistry revealed pleomorphic xanthoastrocytoma (PXA) with typical features including spindle-shaped neoplastic astrocytes in fascicular arrangement intermixed with astrocytes displaying marked pleomorphism and bizarre cytologic and nuclear features, xanthomatous changes, perivascular patchy lymphocytic infiltrates, dense reticulin staining around single or clusters of tumor cells and eosinophilic granular bodies. Interestingly, the neoplastic astrocytes in the current case showed occasional immunoreactivity to neurofilament protein (NFP), which may support the speculations of a possible relationship between PXAs and neuronal tumors. In contrast to the classic PXAs which show no mitotic activity with a very low Ki-67 index (0%–1%), the case in hand showed increased mitotic activity (up to five mitoses per 10 high power fields) with a high Ki-67 index (3%). WHO recommends describing PXAs featuring high mitotic activity with or without accompanying necrosis as "PXA with anaplastic features" rather than "anaplastic PXA". Moreover, upgrading such cases from WHO grade II to grade III or IV is also not recommended. Such designations to the PXAs featuring high mitotic activity may indicate a false correlation with a potentially more aggressive clinical behavior and thus provoke inappropriately aggressive treatment. Studies showed that PXA should be always distinct from diffuse astrocytoma in regard to the grading and description as PXAs have more favorable prognosis and different genetic pathways. Therefore, the criteria used in describing or grading diffuse astrocytomas showing anaplastic features should not be applied to PXA with the same anaplastic features. Although PXA with anaplastic features is uncommon, neuropathologists should be aware about the terms used in the description of such cases.

***June 2007—Case 1*. A 31-year-old woman was admitted for evaluation and treatment of leg weakness. Neurological examination revealed marked decreased strength and sensation to light touch and hyperesthesia in the lower extremities. Her past medical history was significant for an orthotopic liver transplant performed three and half months prior to the admission, fungal meningitis and diabetes mellitus. She also underwent placement of a ventriculoperitoneal shunt for a diagnosis of acute communicating hydrocephalus approximately 1 month after the liver transplantation. The spinal MRI with contrast showed the cord to be compressed both anteriorly and posteriorly, which was greatest at the level of T12-vertebral body, with diffuse abnormal enhancement throughout the spinal leptomeninges. She underwent a thoracic laminectomy and decompression with removal of the intradural mass, and was begun on amphotericin B. Microscopically, the mass lesion showed multiple epithelioid and giant cell granulomata with central suppuration and necrosis. The granulomata contained scattered large round spherules filled with endospores, highlighted with special stains (PAS and GMS stains). These features were diagnostic of coccidioidomycosis. Clinical suspicion was high based on the history of previous coccidioidal meningitis. Not only communicating hydrocephalus but also mass formation should be included among the major complications of coccidioidal meningitis.**

***June 2007—Case 2*. A 55-year-old African-American man with a known history of end stage liver disease, presented for progressively worsening seizures. These were believed to be secondary to hepatic encephalopathy, but at autopsy he was found to have neurosarcoidosis. After admission, the patient progressed to multisystem organ failure and expired. Prior to this, MRI of the brain showed diffuse nonspecific areas of enhancement of the leptomeninges. Sections taken from these areas of enhancement at autopsy demonstrated non-necrotizing granulomas. The radiographic correlates with the histological sections are presented. Retrospective review of the patient's records revealed remote radiographic finding of mediastinal lymphadenopathy, but no diagnosis of sarcoid. Patients who present with neurosarcoid in the absence of systemic manifestations are exceedingly rare. The diagnosis of neurosarcoidosis in the absence of systemic findings is a diagnostic challenge as there are no specific radiographic or pathologic findings unique to this disease. This case illustrates the difficulty of establishing the diagnosis of neurosarcoidosis in the presence of severe concomitant disease and subclinical systemic sarcoidosis.**