Erdheim–Chester disease mimicking a primary brain tumor

Case report

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Erdheim–Chester disease (ECD) is a rare systemic histiocytic disease. The authors present a case report detailing the presentation and treatment of a 26-year-old man diagnosed with seizures and a well-circumscribed temporoparietal mass that had been demonstrated on imaging studies. Both preoperative and intraoperative diagnoses were consistent with a low-grade astrocytic neoplasm. Subsequent pathological examination indicated a histiocytic proliferation positive for CD68 and factor VIII, and negative for CD1a and S100, with Touton giant cells characteristic of ECD. This case represents the first isolated occurrence of intracranial ECD and its potential to mimic glial neoplasms.

KEY WORDS • Erdheim–Chester disease • histiocytosis • seizure • tumor

Erdheim–Chester disease is a rare, idiopathic, non-Langerhans cell histiocytosis with widespread systemic manifestations.1,4,8,10 The disease appears to be nonfamilial and mainly affects middle-aged adults. Typical systemic features include osteosclerotic lesions of the metaphyseal regions of long bones, retroperitoneal and pulmonary fibrosis, cutaneous lesions, fever, and exophthalmos.3,13,15,19,25,31 Neurological involvement is most commonly heralded by hypothalamic/pituitary involvement with resultant diabetes insipidus, and occasionally cerebellar symptoms.7,14,16 Involvement of other intracranial regions such as the cerebral cortex and leptomeninges is uncommon.23,29,30,32 By the time the intracranial lesion is discovered, most patients demonstrate evidence of systemic disease. To our knowledge, no similar case of ECD isolated to the cerebral cortex and characterized by seizures has been previously described.

Case Report

History. This previously healthy 26-year-old man presented for evaluation after experiencing two generalized tonic-clonic seizures. Results of the neurological and general physical examinations were normal. Computerized tomography and MR imaging studies of the head revealed a 1.2 × 1.3–cm solitary, well-delineated, subcortical, homogeneously enhancing mass in the left temporoparietal region (Fig. 1). The lesion demonstrated low signal intensity on T1-weighted MR images and had minimal surrounding edema without mass effect. A positron emission tomography scan was most consistent with a low-grade neoplasm. Results of the metastatic workup were negative. During the course of 3 months, the lesion enlarged slightly. The differential diagnosis included low-grade glial neoplasm such as astrocytoma or pleomorphic xanthoastrocytoma and less likely metastasis or lymphoma.

Operation. The patient underwent a left temporoparietal awake craniotomy and receptive speech mapping with the aid of frameless stereotactic localization of the lesion. A corticectomy was performed through an adjacent sulcus located anterior to the mapped eloquent cortex. A firm, yellowish, almost rubbery lesion was identified at a depth of approximately 1.5 cm. This mass was easily dissected from surrounding parenchyma, with the majority of the lesion appearing well circumscribed. A gross-total resection was achieved. The surgeon’s intraoperative characterization of the mass was a well-circumscribed superficial lesion, possibly PXA.

Representative tissue samples were received fresh from the operating room. Intraoperative so-called squash preparations and cryostat sections were examined for frozen-section analysis. The sections showed numerous multinucleated cells in a background of densely fibrillar astrocytes. A diagnosis of glial neoplasm was made on intraoperative consultation. Microscopic examination of permanent sections revealed two sheets and loosely aggregated clusters of foamy/xan-
thomatous histiocytic cells in a dense, gliotic background (Fig. 2a). Many of the xanthoma cells were multinucleated, with a wreathlike nuclear arrangement typical of Touton giant cells (Fig. 2b). The inflammatory background was composed primarily of mature lymphocytes, with rare neutrophils and eosinophils. Reticulin and trichrome stains revealed fibrosis. Special stains were negative for microorganisms. Immunohistochemical stains demonstrated strong cytoplasmic expression of CD68 (KP1) and negative reactions for S100 protein and CD1a in the histiocytic cells. Glial fibrillary acidic protein staining was intense in reactive astrocytes flanking the histiocytic infiltrate, but negative in the giant cells. The CD45 immunostain highlighted the accompanying reactive lymphoid infiltrate. Electron microscopy was not performed.

Postoperative Course. Postoperatively, the patient made a good recovery and his seizures were well controlled. Shortly after surgery, he experienced the onset of bilateral wrist pain. Additional laboratory results were significant for an elevated alkaline phosphatase (mean 217 U/L, range 3–126 U/L). The patient was referred for a bone scan, which revealed multiple foci of abnormal increased signal in the upper thoracic costovertebral junctions.

Discussion

In addition to ECD, other notable histiocytic disorders that involve the central nervous system and are rarely characterized as a solitary mass lesion include sarcoidosis, RDD, and LCH. In the absence of the characteristic extracerebral manifestations, the diagnosis of these disorders is often challenging and is one of exclusion. Awareness of the clinicopathological spectrum of these entities can be helpful in sorting out the differential diagnosis of cerebral histiocytic lesions that may mimic neoplastic or infectious diseases.

Neurosarcoidosis is known to develop in 5 to 7% of patients with sarcoidosis, usually during the first 2 years after onset of the disease. Various neurological manifestations may be encountered, including seizures, cognitive dysfunction, hypothalamic and pituitary involvement, and hydrocephalus frequently associated with asymptomatic lymphocytic meningitis. In one series, 13 (15%) of 79 patients experienced seizures; in eight patients (10%), seizure was the first manifestation of neurosarcoidosis. Cranial nerve palsy, particularly of the seventh cranial nerve, occurred less often. Pathological findings consisted of characteristic noncaseating granulomatous inflammation accompanied by scattered multinucleated giant cells of foreign-body type. Special stains for visualizing microorganisms rule out an infectious origin.

Typical clinical features of RDD include bilateral painless lymphadenopathy, fever, and polyclonal hypergammaglobulinemia. In approximately 43% of cases, extranodal sites may be involved and occasionally represent the initial or sole manifestation of the disease. Huang, et al., reported on a 38-year-old man who had presented with a generalized tonic-clonic seizure and whose radiological findings had indicated meningioma. Based on microscopic studies, the lesion consisted of a histiocytic proliferation exhibiting emperiplois coupled with the characteristic cytoplasmic staining against S100 protein. More recently, Konishi and colleagues described a case of isolated intracranial RDD in a 68-year-old woman who had presented with new-onset seizures and a dural-based lesion. In another published case, a 39-year-old man presented with an isolated well-circumscribed brain mass in the right temporal lobe, which subsequently proved to be RDD.

Langerhans cell histiocytosis represents a neoplastic proliferation of Langerhans cells that occurs in a range of nodal and extranodal sites. Similar to ECD, LCH has an affinity for the hypothalamic–pituitary axis. Unifocal brain involvement in LCH without concomitant osseous involvement is rare, but such cases have been documented in the literature. The diagnosis of LCH can be substantiated or excluded by performing appropriate immunohistochemical staining (LCH cells are CD1a- and S100-positive) or, when available, electron microscopy studies to identify pathognomonic Birbeck granules.

The most common central nervous system manifestations of ECD in descending order are diabetes insipidus, cerebellar syndromes, orbital lesions, and extraaxial dural-based masses. Spinal and extradural masses have also been documented in the literature. In general, ECD evolves in a slowly progressive manner and may mimic multiple sclerosis because of the multifocal nature of involvement. Martinez reported on a patient with symptoms of paraparesis, urinary incontinence, visual loss, ataxia, vertigo, poptosis, and nystagmus. Analysis of imaging results revealed cerebral hemispheric infiltrates as well as intraaxial and extraaxial brainstem involvement. In another study, eight patients harbored lesions in the cerebellum, often involving...
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Adle-Biassette, et al.,1 detailed the neuropathological findings from three autopsy cases. One patient who had demonstrated characteristic radiological and pathological bone changes was found on postmortem examination to have multiple characteristic xanthogranulomas disseminated in the cerebral hemispheres, hypothalamus, cerebellum, and brainstem. The second patient had presented with cutaneous lesions characteristic of LCH. Subsequently, she had developed bone abnormalities indicative of ECD, which was confirmed on autopsy. This case raised the possibility of a common spectrum of histiocytosis including both diseases. Microscopic examination of the brain showed infiltrates characteristic of non–Langerhans cell xanthogranulomas. The third patient had presented with systemic features characteristic of ECD. Neurological signs had included gait disturbance, seizures, and confusion. Postmortem examination of the brain revealed no histiocytic infiltration, but did show changes indicative of Hallervorden–Spatz syndrome. The significance of the association of these two disease entities remained unclear.1

The biological behavior of systemic ECD is variable.11 The overall disease course is indolent. In one study, 22 (59%) of 37 patients with follow up died, eight within a 6-month period.22 The presence of widespread systemic disease appears to be an ominous prognostic feature. Because no study involving a large series of cases has been undertaken, the role of adjuvant therapy is unclear. In one report, Mascalchi and colleagues24 documented the failure of radiation therapy in a patient with brainstem involvement. In another publication, Pautas, et al.,27 reported on two patients with progressive cerebellar dysfunction and pyramidal signs. Both patients had kidney and bone involvement, but only one experienced improvement with steroid therapy. Esmaeli, et al.,13 described a 55-year-old man with ECD characterized by bilateral orbital infiltration and visual loss who was successfully treated using interferon-α. In patients with a circumscribed mass lesion in the brain and neurological symptoms, resection may be indicated.

Important to the case in the present study is the intraoperative pathological consultation. The preoperative imaging characteristics and the surgeon’s intraoperative impressions were consistent with a low-grade glial neoplasm such as a PXA. The presence of giant cells and a densely fibrillar glial background on smear and frozen-section preparations supported initial impressions. Permanent sections and immunohistochemical stains demonstrated the histiocytic nature of these cells, excluding a diagnosis of PXA. The characteristic immunohistochemical examination of this xanthogranulomatous lesion revealed CD1a-negative, CD68-positive histiocytic cells. Histiocytic lesions must therefore be considered in the differential diagnosis on frozen-section analysis for any lesion containing multinucleated giant cells.

Conclusions

In general, ECD is rarely found intracranially; thus given the more frequently occurring disorders in the intracranial region, ECD’s potential to mimic primary brain tumors underscores the need for a broader differential diagnosis in evaluating patients who present with new-onset seizures. With so few reported cases of intracranial involvement, more experience is necessary to ascertain the scope of ECD’s clinical presentation, therapeutic intervention, and prognosis.

References


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