Erdheim–Chester disease of the central nervous system

Report of two cases

RAMESH P. BARU, M.D., THOMAS A. LANSEN, M.D., AMY CHADBURN, M.D., AND SAMUEL S. KASOFF, M.D.

Department of Neurosurgery, New York Medical College, Valhalla, New York; and Department of Pathology, New York Hospital, Cornell University Medical Center, New York, New York

The authors report two cases of Erdheim–Chester disease (ECD), an illness of unknown pathogenesis. Generally, this disease process involves the metaphyseal and diaphyseal portions of the long bones, the lungs, and the retroperitoneum; however, other tissues may be involved including the central nervous system (CNS). To date only two cases of CNS-related ECD have been reported. The present report adds to the literature by documenting two more recent cases of ECD involving the CNS. The clinical presentations of these cases, their radiological findings with special reference to magnetic resonance imaging, pathological determination, and clinical management are briefly reviewed.

KEY WORDS • eosinophilic granuloma • Langerhan’s cell histiocytosis • Erdheim–Chester disease • magnetic resonance imaging

Erdheim–Chester disease (ECD), often referred to as lipogranulomatosis, is a rare disorder that was identified as a separate and distinct entity by William Chester and Jacob Erdheim in 1930. This condition is characterized by infiltration of the viscera and bones by foamy lipid-containing histiocytes that are associated with fibrosis. In addition, Touton-like giant cells are usually present. In 1973, Jaffe reported a case of lipogranulomatosis and coined the term “Erdheim–Chester disease” to differentiate it from Hand-Schüller-Christian disease (HSCD), Farber’s disease, and familial lipidosis. Although the condition most frequently involves the skeleton, extraskeletal involvement, as evidenced by the presence of lipid-laden histiocytes, has been observed in the heart, lungs, mediastinum, pleura, liver, spleen, small bowel, kidneys, peritoneum, and pelvis. Retroorbital lesions and cerebral parenchymal lesions are extremely rare. Specifically, we have not identified a single report of ECD with central nervous system (CNS) involvement in the neurosurgical literature. In this communication, we present the clinical findings, radiological features, and management of two patients with ECD treated at the New York Medical College.

Case Reports

Case 1

This 22-year-old man noted some numbness in his feet and mild difficulty in walking and running following a fall that occurred 4 months prior to admission.

History. After exhibiting initial temporary improvement, the patient developed progressive weakness in both lower extremities with stiffness of gait 1 month prior to admission. On physical examination at that time he had a spastic paraparesis of 3/5 with a sensory level at T-6.

First Examination. Magnetic resonance (MR) imaging revealed an extradural mass placed dorsally, extending from T-5 to T-11, which exhibited enhancement after administration of gadolinium (Fig. 1).

First Operation and Pathological Investigation. The patient underwent a T5–12 laminectomy with decompression of the spinal cord. At surgery, an epidural mass was encountered, which was thick, white, rubbery, and densely adherent to the dura. A pathological diagnosis of an exuberant inflammatory scar, thought to be secondary to an epidural hematoma that probably resulted from his trauma, was made.

Second Admission and Examination. Approximately 6 months after surgery on his spine, the patient developed periorbital swelling and proptosis with increased tearing. An axial computerized tomography (CT) scan of both orbits showed bilateral intraconal infiltrative masses causing severe proptosis. The tissue in the orbit was excised at biopsy and the slides were compared to the slides of the epidural mass that was obtained during the laminectomy. They were found to be identical and consistent with ECD.

Second Pathological Investigation. The lesions were histologically composed of numerous bland-appearing lipid-laden histiocytes associated with fibroconnective tissue (Fig. 2 upper left). A mild, mixed, chronic inflammatory infiltrate was also noted. Touton-like multinucleated giant cells were readily identified (Fig. 2 upper right). Im-
munophenotypical analysis of the tumor was performed using the three-step immunoperoxidase method described by Hsu, et al.3 The sections were stained using antibodies to CD1a (Immunotech, Marseille, France), CD45 (Becton-Dickinson, San Jose, CA), CD68 (KP-1), S-100 protein, and Mac 386 (Dakopatts, Copenhagen, Denmark). The tumor cells displayed a positive reaction to CD68 (Fig. 2 lower left) but a negative one to CD1a and S-100 protein (Fig. 2 lower right). The CD68 positivity was consistent with a histiocytic origin of the tumor cells. The lack of S-100 protein and CD1a reactivities effectively ruled out the diagnosis of Langerhans’ cell histiocytosis.

Radiological Findings. After the histopathological diagnosis was obtained, the patient was studied for signs of skeletal and systemic involvement. A bone scan showed increased uptake in the right supraorbital ridge, the mandible, the left seventh rib, and the bones of both legs. A CT scan of the abdomen revealed enlarged kidneys containing multiple cysts. All these radiographic findings were compatible with ECD.

Follow-Up Treatment and Course of the Disease. The patient received radiation therapy (8 Gy) to the orbits and was started on a course of prednisone with tapering doses. Fourteen months after he underwent laminectomy and approximately 8 months after he was diagnosed as having ECD, the patient developed recurrent back pain. An MR image of the spine obtained at the time showed postoperative changes and repeated orbital CT scans showed no change in the intraorbital pathology.

Approximately 18 months postlaminectomy the patient again began to experience slight weakness in his lower extremity. An MR image of the thoracic spine showed enhancing epidural tissue consistent with recurrent tumor. The patient was given a total of 16 Gy of external-beam radiation to the spine. He also underwent surgery for decompression of the orbital lesions. At his most recent follow-up examination, which occurred 4 years postoperatively, the patient was neurologically intact and an MR image showed a small amount of epidural tissue with no evidence of spinal cord compression.

Case 2

This 65-year-old right-handed woman with a history of Hashimoto’s thyroiditis was first seen 2 years prior to admission for complaints of periorbital swelling.

First Examination. Ophthalmological examination showed that the patient had a visual acuity of 20/20 in the right eye and 20/25 in the left. There was minimal restriction of extraocular movements in extreme gazes. Results of a slit-lamp examination were reported to be normal. On physical examination, the patient was noted to have waxy, soft, and nodular skin. Within the periorbital skin, fatty lesions extended from the frontal area superiorly to the bridge of the nose and to the malar areas on each side. Computerized tomography scanning showed large bilateral retroorbital soft-tissue masses with a total encasement of both optic nerves. There was also diffuse thickening of the superficial soft tissues of the orbits including the iris.

First Biopsy and Treatment. Biopsy samples revealed histological features consistent with ECD. The patient was treated with a course of prednisone following which the retroorbital swelling diminished to some extent. She later received interferon α-2b, which was discontinued because her skin lesions and orbital and periorbital pathology continued to progress. She was then treated with cyclosporin A, which resulted in significant regression of the periorbital lesions.

Second Admission. Four weeks prior to her current admission, the patient developed symptoms of congestive heart failure. On investigation she was noted to have a pericardial effusion that was interpreted to be of ECD etiology. She underwent pericardiocentesis and window placement.

Third Admission and Examination. Two weeks before her current admission to our institution, the patient developed paraparesis and urinary incontinence. On physical examination she was found to have multiple fatty subcutaneous lesions that extensively involved the chest, abdomen, and infraorbital areas bilaterally. She had a Grade 3/5 upper motor neuron type of paraparesis with extensor plantars, but no sensory changes. Magnetic resonance imaging of the head and the cervicothoracic spine revealed an isointense lesion at the anterior foramen magnum (Fig. 3 upper left) and multiple white matter lesions in the cerebral hemispheres and the brainstem. These lesions enhanced significantly after administration of gadolinium (Fig. 3 upper right and lower left and right). In view of the patient’s previous orbital biopsy, which yielded results histologically consistent with ECD, these lesions were also judged to be of a similar nature. Because ECD lesions are known to retain gadolinium for long periods of time, MR imaging without gadolinium enhancement was performed at the end of 6 days. The lesions continued to appear hyperintense, confirming the diagnosis of ECD (Fig. 4). A skeletal survey showed radiographic changes consistent with ECD and a CT scan of the chest showed residual pericardial effusion.

Treatment and Course of Disease. Because the patient had multiple lesions and was in poor health, surgical intervention either for biopsy or for decompression was deferred and a trial course of radiation followed by chemotherapy was planned. She received 18 Gy of radiation treatment to the cervicomедullary area. The lesions remained unchanged radiologically, but her paraparesis improved. The patient was started on a course of interferon and the subcutaneous fatty lesions around her eyes...
showed significant regression. However, she suffered a sudden cardiac arrest and died within 10 weeks after the CNS lesions were discovered.

**Discussion**

The clinical presentation of ECD ranges from an asymptomatic to a widespread multisystem disease with symptoms related primarily to the organs involved. A thorough review of the literature revealed that ECD occurs more frequently in men. The median age of patients at diagnosis is 56.6 years (range 7–78 years). Orbital involvement previously has been documented and cerebral involvement with multiple parasagittal masses has been reported in the radiological literature. Skeletal and extraskeletal involvement of the disease is very well known.Extraskeletal involvement has been described in the kidneys, adrenal glands, myocardium, pericardium, lungs, liver, spleen, small bowel, pancreas, mediastinum, testes, pituitary, and retroperitoneum.

**Radiological Investigation**

In ECD skeletal lesions can be asymptomatic and thus radiological identification of these lesions is extremely important for diagnosis of this disease. In both cases reviewed here, the skeletal lesions were asymptomatic and did not constitute a presenting complaint. Radiological examination often reveals bilateral symmetrical sclerosis or increased radiodensity of the metaphyseal regions of the long bones with epiphyseal sparing. The metaphyses of long tubular bones followed by those of the ribs are most commonly involved. The type of bone activity varies from osteoclastic to osteoblastic patterns and, occasionally, patients may be misdiagnosed as having Paget’s disease.

Magnetic resonance imaging is of enormous value in diagnosing ECD. Gadolinium-enhanced MR imaging shows retention of enhancement even after several days as demonstrated in previously reported cases, as well as in one of our cases. The prolonged retention (more than 24 hours) of gadolinium may be due to the abnormal histiocyte content of the lesions (intact gadolinium complex-
es, phagocytosed by these cells, would give prolonged enhancement). Alternatively, the complex may be demetalized because of the presence of a competitive chelate.

Tien, et al., reported prolonged lesion enhancement 8 days after administration of gadolinium; Kujat and coworkers noted enhancement 14 days after its initial administration. In one of our cases (Case 2), gadolinium enhancement was present 1 week after administration of the contrast agent. Not only is demonstration of prolonged gadolinium enhancement important in confirming a clinical diagnosis of ECD, it also obviates the need for a diagnostic biopsy in a medically unstable patient as well as in cases of deep-seated lesions.

Pathological Investigation

The pathogenesis of ECD, as well as its relationship with other lesions composed primarily of histiocytes, is not known. Although most investigators feel that ECD is a distinct entity, some authors have suggested that ECD represents the end stage of a progression of histiocytic lesions: the earliest lesions being composed of histiocytes and eosinophils associated with osteolytic lesions, as seen in HSCD, with a progression to lesions consisting of foamy histiocytes and fibrosis and sclerosis, as seen in ECD. However, this is unlikely, because it is now definitely known that HSCD is actually part of the spectrum of Langerhans’ cell histiocytosis in which the histiocytes are distinctly different from those seen in ECD (by virtue of their immunoreactivity for the S-100 protein and the CD1 antigen as well as by the presence of Birbeck granules seen on electron microscopy). In Case 1, although the original diagnosis was primarily based on classic clinical and histological findings, paraffin-embedded tissue that had been subjected to immunophenotyping confirmed the diagnosis of ECD. The tumor cells expressed a phenotype consistent with a macrophagic/histiocytic origin, but proved negative for both CD1a and S-100 protein, effectively ruling out a diagnosis of Langerhans’ cell histiocytosis, histiocytosis X, or HSCD.

Whereas the lesions of Langerhans’ cell histiocytosis are composed of histiocytes with reniform nuclei showing linear nuclear grooves admixed with a variable number and type of inflammatory cells, including eosinophils, ECD is characterized histologically by xanthomatous histiocytes with relatively small, bland nuclei, Touton giant cells, fibrosis, and a relatively scant amount of inflammatory infiltrate with a minimal number of eosinophils (Fig. 2). In addition, Birbeck granules have not been identified in the histiocytes of ECD. Thus, in those instances in which it is difficult to separate ECD from Langerhans’ cell histiocytosis clinically and by routine staining with hematoxylin and eosin, electron microscopy and immunophenotypical studies usually resolve the problem.

However, whether ECD is really a distinct clinicopathological entity or merely a part of the spectrum of histiocytosis akin to HSCD has not been determined, particularly because some investigators have found S-100 protein reactivity on the part of the histiocytes in ECD.

Differential Diagnosis. Although clinically there is some overlap between HSCD and ECD, such as the presence of diabetes insipidus, in general the clinical presentation of HSCD differs from that of ECD. Radiologically, patients with HSCD tend to display osteolytic lesions occurring randomly. This is distinctly different from the bony lesions that occur in ECD, which tend to be both osteolytic and osteoblastic and are symmetrically distributed. However, the histological findings as described previously are definitive.

Both pseudotumor cerebri and inflammatory pseudotumor may also occur in the orbit and should be included in the clinicopathological differential when considering a diagnosis of ECD. In pseudotumor cerebri, a biopsy usually shows normal tissue; however, on rare occasions acute inflammatory changes may be present. Chronic inflammatory pseudotumor is more difficult to separate clinically and pathologically from ECD. In inflammatory
pseudotumor, a variable degree of fibrosis and inflammation, including foamy histiocytes, is seen. However, bilateral lesions containing many xanthoma cells and Touton giant cells with only a scant amount of lymphocytic infiltrate should suggest the diagnosis of ECD rather than chronic inflammatory pseudotumor.23

Management of ECD

Because not much is known about this rare disease, little information is available regarding the management of ECD. Obtaining a biopsy specimen is helpful to establish the histological diagnosis but no definite modality for cure is known. If there is significant mass effect, however, surgery should be an option.

Patients may show some response to a course of steroid medications.1 Radiation seems to be the treatment of choice based on its usefulness in similar lesions like eosinophilic granuloma, histiocytosis, and HSCD.1,16,18 Chemotherapy consisting of vincristine, vinblastine, interferon, cyclosporin, or steroid medications has also been tried.6,15,19,20,22 In many instances, the disease is relentlessly progressive and often fatal because of renal or cardiovascular complications.

Conclusions

Erdheim–Chester disease is a rare and potentially fatal entity that can involve any part of the body and has no known successful cure. It bears a striking resemblance to other histiocytic disorders. Thorough skeletal and systemic survey and ophthalmic examination are necessary for treatment planning. Delayed gadolinium-enhanced MR imaging may be pathognomonic. Typical radiographic findings and the presence of bilateral subcutaneous fatty lesions with diffuse orbital masses should alert the clinician to this potentially fatal disease.

In ECD, a multisystem involvement including the long bones can be asymptomatic. In a patient who has had ECD confirmed at biopsy elsewhere in the body, a thorough systematic search needs to be performed to determine the extent of disease. Surgery is an option in treating mass-producing lesions or for histopathological verification. Other modalities of treatment, namely radiation and/or chemotherapy, need further evaluation. Although few cases have been reported, the treatment plan may be patterned after existing protocols for the histiocytosis group.

References


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Address reprint requests to: Ramesh P. Babu, M.D., New York University Medical Center, 400 East 34th Street, Suite #605, New York, New York 10016.