

ERDHEIM-CHESTER DISEASE

DEFINITION

The histopathologic characteristics of ECD overlap xanthogranuloma and distinctions between the two are made on clinical and radiologic findings. Lipid-laden histocytes with foamy or eosinophilic cytoplasm infiltrate bones and various organs and generate a fibroblastic response that leads to critical organ failure. The histocytes are CD68+, Factor XIIIa+ CD1a-, S100-, and lack Birbeck granules. Touton-like giant cells are commonly found.

EPIDEMIOLOGY/ETIOLOGY

The mean age of ECD patients is 53 years with a range of 7-84 years. (1). The cause of ECD is unknown. Biologic features include clonal proliferation of cells in 3 cases and polyclonality in 2 by the HUMARA PCR assay. (2-4) Elevated levels of osteopontin in ECD tissue have been found at diagnosis and then declined after treatment with prednisolone. (5) A variety of chemotactic factors identified by Immunohistochemical staining include CCL2 (monocyte chemotactic protein 1), CCL4 (macrophage inflammatory protein 1 β - MIP1 β), CCL5 (RANTES), CCL20 (MIP-3 α) and CCL19 (MIP-3 β) along with their receptors CCR1, CCR2, CCR3, CCR5, CCR6, and CCR7. (6). Elevated expression of an interferon- γ -inducible protein, IL-6 and RNAKL has been described. The latter two are important for bone remodeling. Biopsies of 32/37 ECD biopsies had prominent staining for the platelet derived growth factor receptor-beta (PDGFr- β)

CLINICAL FEATURES

Patients frequently have fever, weakness, and weight loss. Symmetric osteosclerosis of long bones with infiltrating and encasing masses around various organs are characteristic of ECD. Patients present with bone pain, especially in the lower extremities. The second most common presenting symptom is diabetes insipidus. Some patients have cerebellar signs and focal neurologic deficits. (6) Bilateral painless exophthalmos may also occur. Fifty percent of patients have extraskeletal disease. It is unusual for the lymph nodes, liver, spleen or axial skeleton to be affected in ECD, whereas these areas are frequently affected in LCH and RDD. Retroperitoneal and renal involvement occurs in one third of ECD patients and causes abdominal pain, dysuria, and hydronephrosis. Pulmonary involvement may present in 20% of patients and causes dyspnea. Skin manifestations of ECD include xanthomatous lesions that may begin as reddish-brown papules similar to xanthoma disseminatum. Cardiac dysfunction occurs because of circumferential sheathing of the aorta, aortic branches, including coronary arteries. There may also be endocardial, myocardial, or pericardial involvement leading to pericardial effusions with risk of tamponade. (7)

LABORATORY FEATURES

There are no specific laboratory findings, but elevated sedimentation rate and alkaline phosphatase have been reported in about one fifth of cases. Radiographs show bilateral patchy osteosclerosis of the metaphysis and diaphysis of femur, proximal tibia, and fibula. Lytic lesions are found in approximately one third of patients. Chest CT

findings include diffuse interstitial infiltrates, pleural and interlobular septal thickening.(8). Characteristic findings on an abdominal CT are peri-renal infiltration extending through the fat of the anterior or posterior para-renal spaces leading the classic “hairy kidney” appearance and circumferential sheathing of the aorta.

DIFFERENTIAL DIAGNOSIS

Although histologically distinct, the clinical features may suggest LCH, RDD, juvenile xanthogranuloma or xanthoma disseminatum. Some clinical features overlap with sarcoidosis, amyloidosis, Paget disease, Ormond’s Disease (idiopathic retroperitoneal fibrosis), and Whipple’s Disease. The histologic features can be confused with Gaucher’s disease, Niemann-Pick Disease, mucopolysaccharidoses, or Malakoplakia. (9).

THERAPY

In a review of 37 patients, steroids (usually 1mg/kg/d) decreased exophthalmos or general symptoms in 20 patients. (1) Among these patients steroids were effective in 6 patients, transiently in 4, and not effective in 8. Of 8 patients treated with a variety of chemotherapy agents and steroids. 4 had improvement. Radiation was not effective for orbital masses and transiently relieved bone pain. Long term responses occurred with alpha-interferon in three ECD patients. (10) These patients had marked decrease in their fatigue, improvement of bone films, and in one case nearly complete resolution of diabetes insipidus. Treatments continued for months or years. Another ECD case with favorable response to interferon-has been reported (3). A series of 8 ECD cases treated with interferon- α was reported with 4 patients failing and 4 improving after several months of treatment. (11) The same group published a series of 6 ECD patients treated with imatinib mesylate. (12) Two patients had stable disease and one initial response before worsening.

COURSE AND PROGNOSIS

Nearly 60% of ECD patients die of their disease, 36% within 6 months. The mean survival duration is less than 3 years. Cardiac, pulmonary, or renal failure are the primary causes.

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Multifocal Reticulohistiocytosis (MFRH)

Also known as Multicentric reticulohistiocytosis, MFRH affects the skin and bones of adults with only rare pediatric cases being reported (1,2). MFRH is associated with malignancy, hyperlipidemia (over half the cases) and autoimmune diseases. (1,3) The destructive arthropathy mimics rheumatoid arthritis with symmetric destruction of finger joints primarily. A variety of cytokines including TNF α , IL-1 β and others in activated macrophages have been described. (1)

Clinical Features

Hyperplastic skin nodules are prominent on the hands and fingers, but may be found in any location. Some patients have vermicular lesions near the nose (4) The destructive joint lesions lead to debilitating deformities. Some patients have fever, weight loss, and malaise.

Treatment

Responses with methotrexate (5), cyclophosphamide (2,5), prednisone and azathioprine or cyclosporine have been reported. A case treated by the author with thalidomide had nearly complete resolution of skin lesions, but no effect on the bony destruction.

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