Erdheim-Chester disease (lipoid granulomatosis) is a rare type II (non-Langerhans cell) histiocytosis with systemic manifestations. The disease causes nonspecific disturbances in the function of multiple extraosseous organs, most commonly the eyes, lungs, pituitary gland, and kidneys. Diagnosis is usually made on the basis of radiologic evidence of cortical expansion of long bones. While the osseous and systemic changes have been well documented in the current literature, pathologic changes in the myocardium have not been well characterized since Erdheim and Chester’s first description of this disease in 1930. In the 2 autopsy cases from Dartmouth-Hitchcock Medical Center (Lebanon, NH) reported in the present study, myocardial involvement was severe and had contributed significantly to the patients’ morbidity and death. We describe the autopsy results and correlate them with Erdheim’s original descriptions of this disease. In neither of our cases was bony involvement characteristic of the disease, and the diagnosis was made postmortem on the basis of soft tissue findings at autopsy.

Report of Cases
Case 1
A previously healthy 61-year-old woman presented to her primary care physician with an insidious onset of ataxia, weakness, and dyspnea. On the basis of positive serology for anti-nuclear antibodies and double-stranded DNA antibodies, she was diagnosed with lupus erythematosus and treated accordingly. During the next 1½ years, she developed, in sequence, pericardial effusion requiring the placement of a pericardial window, pancycopenia, diplopia and a right superior-lateral visual field defect, hypothyroidism, congestive heart failure with left ventricular hypertrophy and intermittent pulmonary and peripheral edema, diabetes insipidus, and worsening ataxia and muscle weakness. A bone marrow biopsy showed noncaseating granulomata with no evidence of fungi or mycobacteria. Head imaging studies showed bilateral periorbital masses. The biopsy showed that these peri-orbital masses consisted of xanthogranulomatous tissue. At this time, the diagnosis of Erdheim-Chester disease was suggested, but radiographic studies of the long bones failed to show the characteristic cortical changes of Erdheim-Chester disease; therefore, the diagnosis was not made. Chest radiographs showed interstitial markings consistent with interstitial pulmonary fibrosis, and a repeat bone marrow biopsy showed myelofibrosis with no evidence of granulomatous disease. The patient’s final hospitalization was characterized by refractory serum chemistries, pulmonary and peripheral edema, fever, elevated white blood cell counts, anemia, thrombocytopenia, and finally, hypotension and acidosis.

At autopsy, there were pleural effusions (250 mL right; 500 mL left), ascites (750 mL), and anasarca. There were multiple irregular, sharply demarcated, rubbery, pale yellow plaques and nodules scattered throughout the pericardium and on the epicardial surface. A 5.0 × 3.0 × 2.5-cm yellow rubbery mass extended from the ostium of the right coronary artery to the posterior aspect of the heart, surrounding the right coronary artery on its path through the atrioventricular sulcus but not involving the right coronary artery wall or lumen. The soft tissues around the aortic and pulmonary trunk roots, the thoracic and abdominal aorta, the pulmonary arteries, and the thoracic and abdominal arteries were replaced by dense, yellow fibrous tissue. Similar tissue replaced the retroperitoneal fat and surrounded the adrenals and pancreas. The larynx, thyroid, and parathyroid glands were also encased by the sclerotic, yellow tissue. A yellow plaque on the dura of a thoracic vertebra extended into the narrow space, where it formed a 4.0 × 3.0 × 1.0-cm nodule. There were scattered yellow plaques on the dural leaflets and falx.

In all the areas in which they occurred, the dense, rubbery yellow lesions consisted histologically of aggregates of foamy histioocytes and sparse collections of lymphocytes in a dense, fibrous stroma (Figure 1). This xanthogranulomatous tissue involved the adventitia of large-caliber vessels and infiltrated the atrial myocardium (Figure 2). It also infiltrated the thyroid, pancreas, spleen, and adrenal glands. The neurohypophysis was replaced...
by fibrotic tissue containing perivascular macrophages and activated microglia, and in the cerebellum, there were large areas of myelin pallor. The histiocytes in all the lesional sites stained positively with CD68 (Figure 3) and weakly and variably for S100 but showed no reactivity for CD1a (Figure 4). Electron microscopy did not show Birbeck granules.

**Case 2**

A 69-year-old man with a history of atherosclerotic coronary artery disease, peripheral vascular disease, and idiopathic diabetes insipidus controlled by desmopressin acetate for several years was admitted for evaluation and treatment of light-headedness, dyspnea on exertion, easy bruising, and edema. Echo-cardiography showed pericardial effusion with tamponade, hypertrophy of the right atrium with a right atrial mass, and dilatation of the aorta from the bulb to the iliac bifurcation. The erythrocyte sedimentation rate and partial thromboplastin time were elevated, and serologic studies were positive for anti-nuclear antibody and lupus anticoagulant. A work-up of iron-deficiency anemia led to the discovery and subsequent resection of a T2 N2 M0 moderately differentiated adenocarcinoma of the colon. The patient's postoperative course was complicated by severe tachycardias and bradyarrhythmias. The day after a permanent cardiac pacemaker was inserted, he developed large pleural effusions, refused thoracentesis, and died.

At autopsy, there were pleural effusions (700 mL bilaterally) but no appreciable ascites or anasarca. There were yellow, dense, rubbery lesions reaching up to 10 cm in greatest dimension diffusely coating the adventitial surface of the severely atherosclerotic and dilated aorta. The wall of the right atrium was diffusely thickened and stiff, and there were nodules measuring up to 5 cm in greatest dimension scattered throughout the atrial wall (Figure 5). The cut surface of these nodules showed yellow fibrous tissue. The right kidney was atrophic. The hilar fat of both kidneys and the perirenal fat on the right were replaced by dense, rubbery yellow tissue, as were the right adrenal and the pancreas. No pituitary tissue was identified. There were yellow, firm, irregularly shaped plaques scattered diffusely over the dura and aggregating on the falx to form nodules measuring up to 2.5 cm in their greatest dimension. There was a solitary, well-circumscribed, 1.5 x 1.0 x 1.0-cm cavitary lesion in the cranium filled with dense, yellow fibrous tissue.

Histologically, the yellow fibrous lesions consisted of sheets of histiocytes and sparse chronic inflammatory aggregates in a background of dense fibrosis. There were occasional Touton giant cells. The xanthogranulomatous process diffusely infiltrated the pancreas but respected the capsules of the adrenals and kidneys. It diffusely expanded and replaced the adventitia of the aorta, the atrial myocardium, the remnant of the pituitary stalk, and the pleura and interlobular septae of the lungs. Special stains did not yield evidence of infectious organisms. The histiocytes stained positively for CD68 and faintly for S100 but were negative for CD1a. Electron microscopy was not performed.

**COMMENT**

Erdheim-Chester disease is a class II (non-Langerhans cell) histiocytosis in which fibroxanthogranulomatous tis-
Erdheim-Chester disease was made on the basis of histologic and immunohistochemical findings and a characteristic tissue distribution of lesions. Radiologic findings did not contribute to the diagnosis.

An unusual feature of these 2 cases of Erdheim-Chester disease is the involvement of the right atrial myocardium by the fibroxanthogranulomatous infiltrate. Bundles of atrophic, necrotic myocytes diffusely infiltrated by histiocytes remain scattered throughout the myocardium (Figures 2 and 3). Since 1996, when a review of 59 cases of Erdheim-Chester disease reported no cases of myocardial involvement, only a few such instances have been described. As in the cases presented in this study, the cardiac involvement in the previously reported cases was restricted to the right atrium, and in one of them, the infiltrate caused a radiologically demonstrable “tumor” in the right atrial wall similar to that in our second case.

One of the patients in the original report by Erdheim and Chester had lesions in the right atrial wall grossly resembling those of the first patient described in this study: “exclusively in the right heart (there are) lipid granulomas, three in number. One is in the form of an almost finger-thick strand, lying exactly in the coronary sulcus and involving the subepicardial tissue along its entire length. Cut surface is transparent grey with many yellow inclusions. . . . Two further tumor-like inclusions lie in the wall of the atrium, one, 12 mm thick, at the junction of the 2 great veins, the other, 14 mm thick, at the origin of the superior vena cava. Both are elevated from the surface of the heart and shine yellowishly through the epicardium; both involve the entire thickness of the atrial wall from endo- to epicardium; on cut surface the musclecuture of the heart wall is interrupted by the lipoidgranuloma” (personal translation). The observation that the “lipoidgranuloma” involves the entire thickness of the heart wall was borne out by microscopic examination, which, in turn, led to the observation that the process appears to have begun within the subepicardial fatty tissue, extending from this point secondarily into the epicardium and the myocardium.

The protean clinical manifestations of Erdheim-Chester disease have increasingly been recognized in the medical, pathologic, and radiographic literature. The histologic appearance and pattern of distribution of the lesional tissue should alert physicians to the presence of Erdheim-Chester disease, even in the absence of evidence of radiographic changes. In this context, atrial myocardial involvement needs to be recognized not only as yet another manifestation but also as one that can contribute to the affected patients’ morbidity and their deaths. The typical radiologic appearance of symmetric cortical sclerosis of the diaphragm and metaphysis of long bones with sparing of the epiphyses, found in approximately 75% of patients, is a valuable adjunct to histologic diagnosis.

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References

Histologically, the lesions of Erdheim-Chester disease are diffuse, densely collagenous masses in which are nested sheets of histiocytes, sparse pockets of chronic inflammatory cells, and occasional Touton giant cells. With routine stains, the lesions of Erdheim-Chester disease resemble those of class I (Langerhans cell) histiocytosis, but Langerhans and non-Langerhans histiocytes have distinct immunohistochemical phenotypes. As opposed to Langerhans cells, non-Langerhans cells stain with CD68, are negative for CD1a and other dendritic cell markers (FDRC, germin cells, non-Langerhans cells stain with CD68, are masses. Even the involvement of the testis has affected the skeletal muscle in the form of painful soft tissue sive lymphadenopathy (Rosai-Dorfman disease), xantho-


