ORBITAL MANIFESTATIONS OF ERDHEIM-CHESTER DISEASE*

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IN 1930, WILLIAM CHESTER, AN AMERICAN POST-DOCTORAL STUDENT WORKING IN the laboratory of the well-known Viennese pathologist, Jakob Erdheim, published a paper in Virchow's Archives of Pathology entitled "Lipoid-granulomatosis."[1] Included in his presentation were the case histories and autopsy findings observed in two patients with lipogranulomatosis that he considered quite distinct from both the primary lipidoses (Gaucher's disease, Neiman-Pick disease, Tay-Sachs disease) and Schüller-Christian disease.

The condition was characterized by invasion of foam cells containing cholesterol in the viscera of one patient and in the bones of both. Jaffe in 1973[2] reported an additional case and coined the eponym "Erdheim-Chester disease" to differentiate it from Schüller-Christian disease, Farber's disease (lipoglycoprotein storage disease) and familial lipidosis (Table I).

In our review of the world literature through 1982[2-10] there were at least 47 cases reported. None of these patients had ocular or orbital manifestations. It is our purpose to report what may be the first description of orbital involvement in two patients with this rare disease.

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TABLE I: REPORTED SYMPTOMS AND SIGNS OF ERDHEIM-CHESTER DISEASE

1.	May be asymptomatic
2.	Pain over skeletal abnormality
3.	Expansile lesions of ribs
4.	Spontaneous discharging sinus from cortical defect in femur
5.	Symmetrical patchy sclerosis and thickening of metaphyses of long tubular bones with sparing of axial skeleton
6.	Patchy sclerosis of calcaneus
7.	Symmetrical radionuclide uptake in areas of bony abnormality
8.	Dyspnea
9.	Pulmonary infiltration and pleural effusion
10.	Cardiac decompensation and pericardial effusion
11.	Pulmonary fibrosis
12.	Congenital megacalices, hydronephrosis, and hydroureter
13.	Chronic lipogranulomatous pyelonephritis
14.	Retroperitoneal xanthogranuloma
15.	Hyperlipidemia

CASE REPORTS

CASE 1

History of Present Illness: A 70-year-old man was first seen in consultation on November 17, 1978, because of painless, progressive protrusion of both eyes for the previous 3 months. Foreign body sensation, lacrimation, and diplopia had been present for 2 months.

Past Medical History: In January 1973, he had been hospitalized because of dyspnea and weight loss of 20 pounds. Pleural effusion and hepatosplenomegaly were noted at that time. A tuberculin skin test was positive. Venous pressures were repeatedly normal. Bronchial and pleural biopsy showed fat-laden macrophages. Cultures of both pleural fluid and bronchial washings were negative. Chest roentgenograms showed diffuse pulmonary fibrosis. Needle biopsy of liver showed mild venous congestion. A definite diagnosis was not established. No specific treatment was given. On February 26, 1974, he was readmitted to the hospital with fever and congestive heart failure. Acid-fast organisms were found in his sputum, but proved not to be tuberculous. Ethambutol and isoniazide were started. In March 1974, he was rehospitalized with further congestive heart failure. Alkaline phosphatase, serum glutamic-oxaloacetic transaminase (SGOT), and serum glutamic-pyruvic transaminase (SGPT) were elevated. An open lung biopsy was performed. Chronic pleural and pulmonary fibrosis were demonstrated. The previously noted fat-laden macrophages were absent. Prednisone was started and he enjoyed a remarkable recovery. After 1 month ethambutol was stopped but isoniazide therapy was continued for another 18 months. During this

period his chest roentgenogram remained unchanged. He became mildly diabetic. Prednisone was gradually tapered and discontinued in November 1977. A pulmonary volume study was normal. Sincel breath diffusion test was normal. He remained well until onset of the present illness in August 1978.

Ophthalmologic Examination: On November 17, 1978, the following findings were recorded: Corrected vision: OD = 20/25; OS = 20/40. The right eye was more proptosed than the left. The right lower lid was 2 mm below the limbus. Hertel exophthalmometry measurements were: OD, 23.5 mm; OS, 20.5 mm. Chemosis was present in each lower cul-de-sac. Limitation of extraocular motility of each eye was noted. No palpable masses were present. There was poor retropulsion of each eye. Forced duction testing of the right eye was positive in all fields of action but was negative in the left eye (Fig 1). Slit-lamp examination showed incipient nuclear and cortical cataracts in each eye. Ophthalmoscopic examination revealed striae in the posterior pole of the retina and choroid of the right eye. Intraocular pressure of the right eye became elevated to 30 mm Hg by applanation tonometry on upgaze, but returned to 14 mm Hg in primary gaze. The intraocular pressure of the left eye was 14 mm Hg in all fields of gaze. Visual fields in each eye were full to 1_2 isopter test targets upon Goldmann perimetry testing. B-scan ultrasonography revealed in the right eye a rounded anechoic area within the muscle cone and enlarged extraocular muscles. In the left eye a smaller anechoic area was present within the muscle cone and the extraocular muscles were enlarged (Fig 2). Computed tomographic (CT) scanning demonstrated bilat-

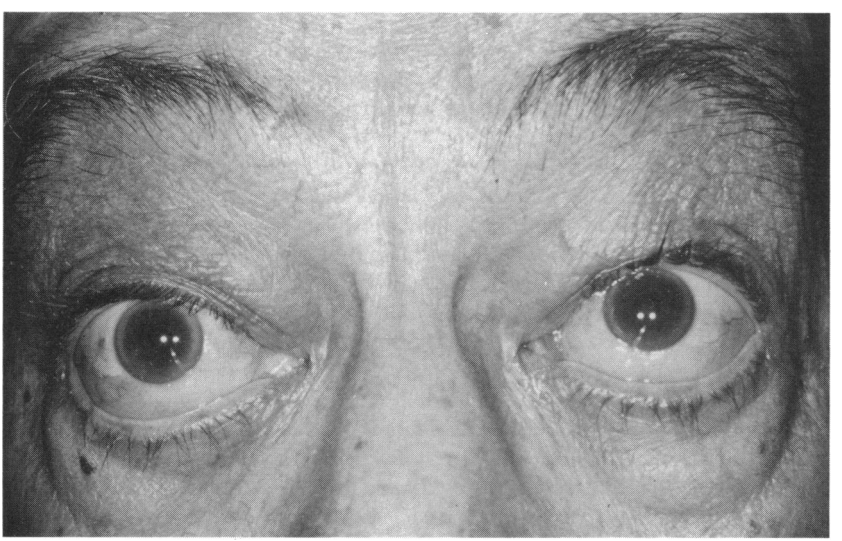

FIGURE 1

CASE 1. Patient attempting to elevate eyes. Note chemosis of each eye and inability to elevate right eye. Ophthalmoplegia was present in other fields of gaze. A forced duction test was positive in right eye only. Increased resistance to retropulsion was present in each eye.

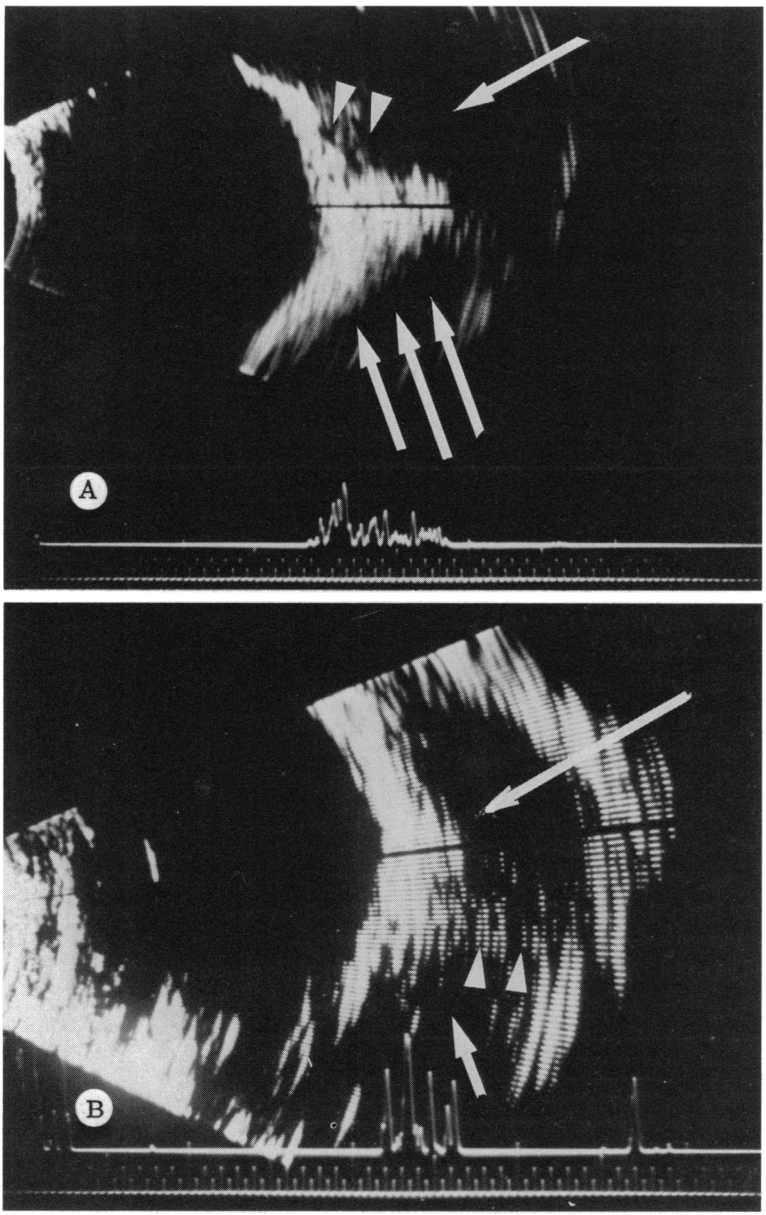

FIGURE 2

CASE 1. A: Ultrasonogram of right orbit demonstrates anechoic mass (1 arrow) surrounding optic nerve (2 arrowheads) and enlargement of inferior rectus muscle (3 arrows) seen in this view. All other muscles appeared enlarged in other views. B: Ultrasonogram of left orbit demonstrates a smaller anechoic mass than in right orbit (1 arrow). Note optic nerve (2 arrowheads) surrounded by anechoic mass (1 arrow).

eral enhancing retrobulbar masses (Fig 3). In the right orbit the mass filled the entire retrobulbar space and obscured the normal architecture. In the left orbit the mass was lateral to the optic nerve but did not reach the apex. The extraocular muscles appeared normal in size. Laboratory studies demonstrated normal complete blood count and urinalysis. Alkaline phosphatase and SGOT were slightly elevated. Blood cholesterol and triglycerides were normal. Iodine-123 uptake in 2 hours measured 3% and in 24 hours, 17.8%. Tc 99m-pertechnetate demonstrated thyromegaly of both lobes. T-3 (resin uptake) was 40% (normal range, 25% to 35%); T-4 (RIA) was 3.9 ng/dl (normal range, 5.6 to 12.6 ng/dl); FT4 index was 1.6 (normal range, 1.4 to 4.4); T-3 (RIA) was 55 ng/dl (normal range, 70 to 215 ng/dl); TSH (RIA) was 9.8 μIU/ml (normal range, < 10 μIU/ml). TRH test resulted in a TSH rise to high levels as follows: 15 minutes, 24.4 μIU/ml; 30 minutes, 27.1 μIU/ml; 45 minutes, 27.6 μIU/ml; and 60 minutes, 25.1 μIU/ml. These studies were consistent with mild tertiary (hypothalamic) hypothyroidism. Thyroid antibodies were normal.

On January 10, 1979, the patient underwent a right lateral orbitotomy by the Wright approach. A large mass measuring 30 mm in diameter was removed from within the muscle cone (Fig 4). It was carefully dissected from its association with the extraocular muscles and the optic nerve. The orbital tissue was studied at the

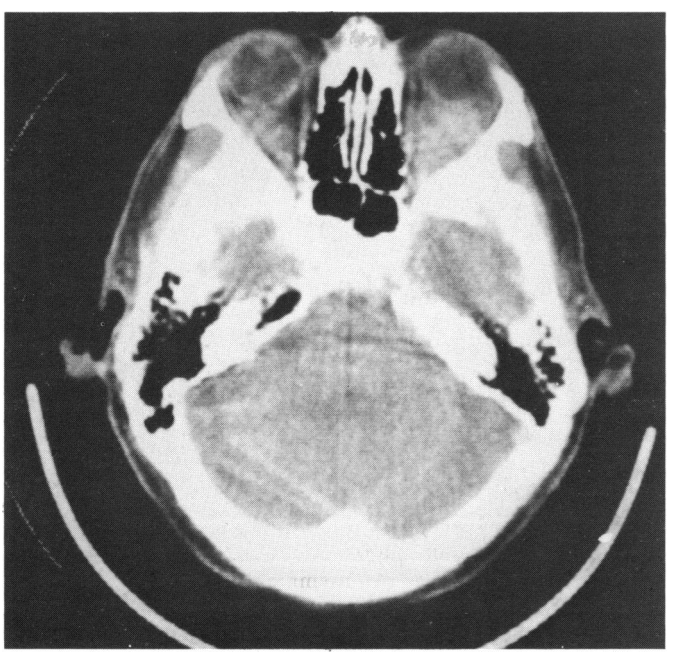

FIGURE 3

CASE 1. Computed tomogram demonstrates presence of enhancing masses within muscle cone of each orbit.

FIGURE 4
CASE 1. Right orbital mass noted at Kronlein orbitotomy. Eyebrow is noted to viewer's left.

Armed Forces Institute of Pathology (AFIP) and interpreted as showing a xanthogranulomatous inflammatory pseudotumor (Fig 5), an unusual type of orbital pseudotumor with many Touton giant cells that were conspicuously present in some areas (Fig 6). The reviewers in the AFIP's departments of Ophthalmic and Pulmonary Pathology could not readily relate the changes observed in the orbital tissue to those previously seen in the pulmonary biopsies.

Because of the xanthogranulomatous nature of the orbital mass, evaluation of blood lipids was performed and was found to be normal. The patient was treated postoperatively with oral prednisone. The orbital masses diminished in size and ocular motility improved. He remained stable and prednisone was tapered.

On March 13, 1981, he was readmitted to the hospital in cardiac decompensation. Cardiomegaly and pulmonary fibrosis were noted (Fig 7). Bone scan with technetium demonstrated unusual symmetrical increased activity in both humeral heads extending to the midportion of the humerus bilaterally. In addition, increased symmetrical activity was seen through the proximal one-third of both femurs as well as the distal one-third. A similar finding was seen in the proximal and distal portions of the tibias. An asymmetrical increased activity was seen in the left S-1 joint and in the left sternoclavicular junction. Plain roentgenograms of the bony skeleton revealed symmetrical mottling and sclerosis in the long tubular bones. These changes were most prominent in the proximal and distal metaphyses of the humerus, femur, and tibia (Figs 8 and 9). The patient was treated for cardiac decompensation and recovered. His eyes and lungs remained stable. On

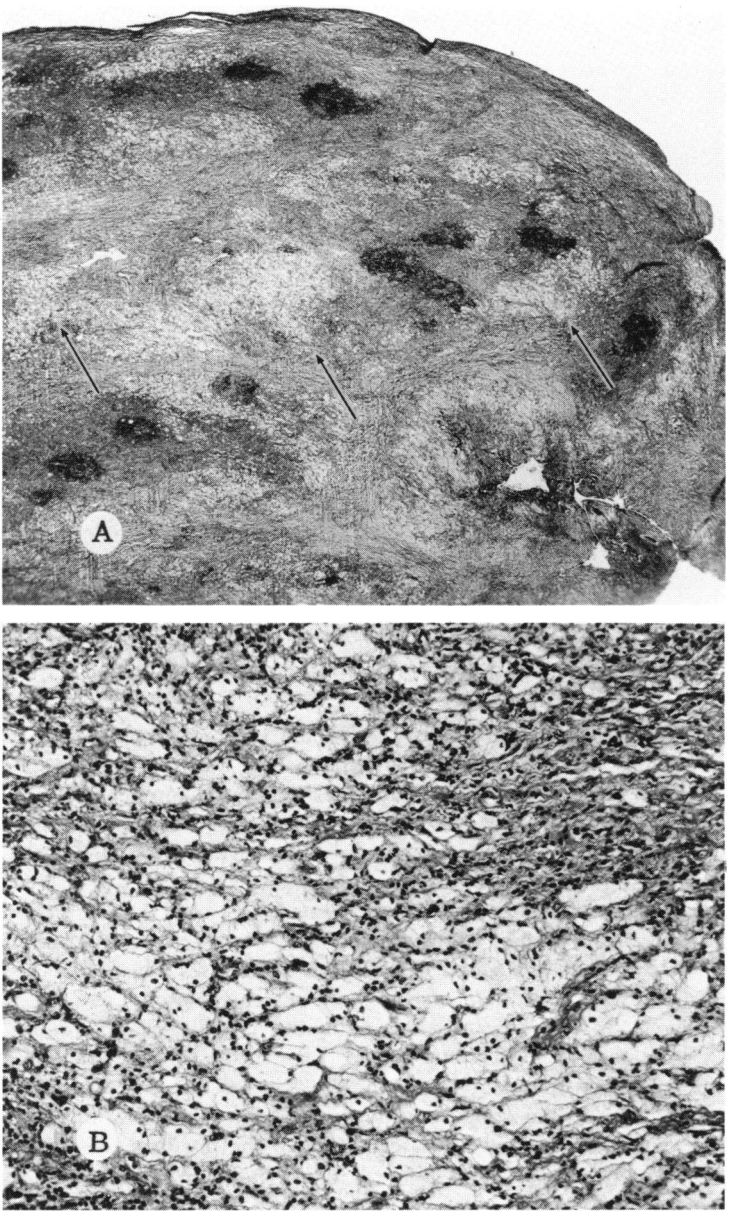

FIGURE 5

CASE 1. A: Much of orbital mass resembles an ordinary sclerosing inflammatory pseudotumor except that within pale areas (arrows) there are massive accumulations of xanthomatous histiocytes (× 15). B: One of pale-staining areas as shown by arrows in A, composed of huge xanthomatous histiocytes with abundant pale-staining cytoplasm and small round nuclei (× 160).

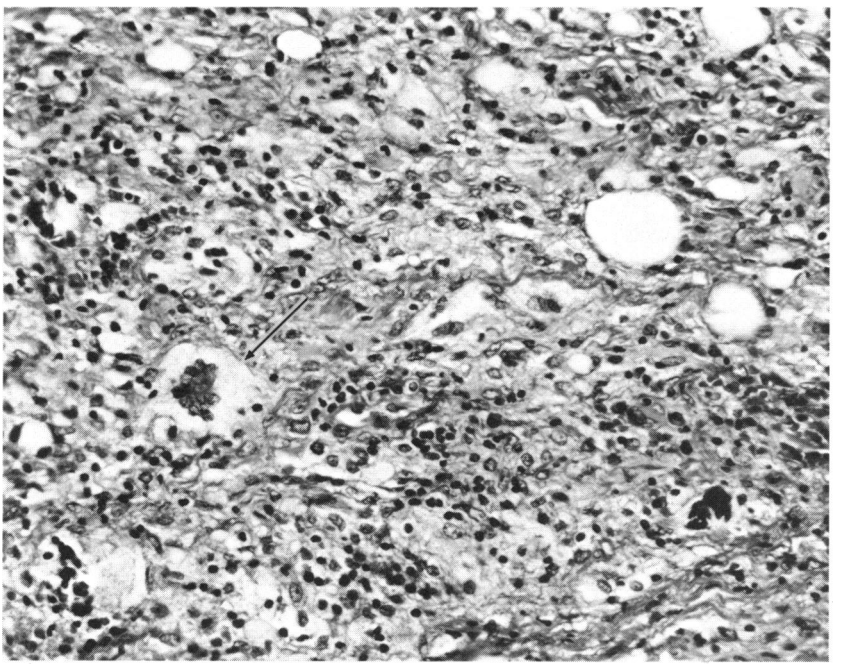

FIGURE 6
CASE 1. Arrow indicates a Touton giant cell within xanthomatous inflammatory infiltrate (×250).

May 7, 1982, he again developed pleural effusion and cardiac decompensation and died on May 11, 1982.

Autopsy Findings: At autopsy, bilateral exophthalmos was still present. The pleural cavities were obliterated by dense adhesions, but the pericardial cavity contained about 500 ml cloudy, tan-yellow fluid. The enlarged (480 gm) heart had a roughened focally thickened pericardial surface. There was severe atherosclerosis of the aorta with focal ulceration of the atherosclerotic plaques. The atherosclerotic pulmonary artery contained a thrombus that partially obliterated the left branch. Both lungs were much firmer than normal. Moderate atherosclerotic thickening was observed in the cerebral vessels. The final anatomical diagnosis after histologic studies of the tissues obtained postmortem was right-sided heart failure secondary to extensive bilateral pulmonary fibrosis. The autopsy report made no mention of xanthomatous or lipogranulomatous lesions, but, at our request, some tissue was obtained from the head of the right femur. It revealed focal infiltration by large, clear xanthomatous histiocytes and discrete collections of cholesterol clefts surrounded by multinucleated foreign body giant cells (Fig 10).

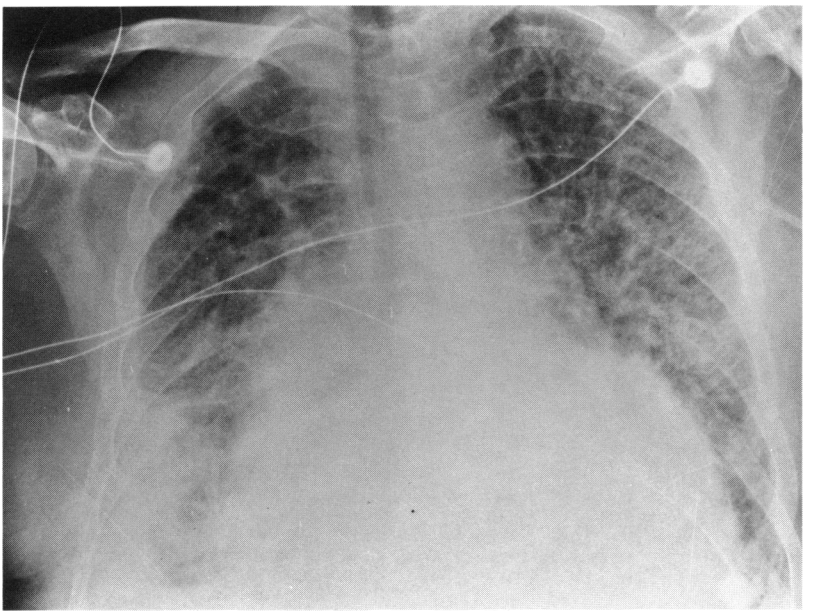

FIGURE 7
CASE 1. Chest roentgenogram taken 1 year before death demonstrates pulmonary fibrosis, cardiomegaly, and pleural and pericardial effusions.

CASE 2

The patient was a white woman born in 1933. In 1953, she developed hyperthyroidism and was treated with "iodine," subsequently becoming euthyroid. In 1960, strabismus surgery was performed on the left eye and labile hypertension was controlled with propranolol hydrochloride (Inderal). In 1967, diabetes insipidus required treatment with chlorpropamide (Diabinese), clofibrate (Atromid S), and lypressin (Diapid) nasal spray. In 1973, she developed swelling and redness of her legs and stiffness of her ankles and knees. In 1975, lesions were detected in the radius, ulna, tibia, and fibula. Roentgenograms were characterized by increased density of the spongiosa, intramedullary scarring, reactive new bone formation, areas of rarefaction, and osteosclerosis. In 1977, she became aware of decreased perception of color and transient loss of portions of the visual field. By 1978, bilateral proptosis, "xanthelasma" and thinning of the right and left lower lids (Fig 11) and papilledema had developed. Examination revealed visual acuity 20/20+ OU; normal pupils; weakness of abduction and adduction of both eyes; and bilateral papilledema. Hertel exophthalmometry measured: OD = 18 mm; OS = 19.5 mm with an interorbital base of 98 mm. Optic canals were normal. CT scan demonstrated a "large symmetrical uniformly densely enhanced soft tissue mass filling the muscle cones of both orbits, displacing the globes forward and

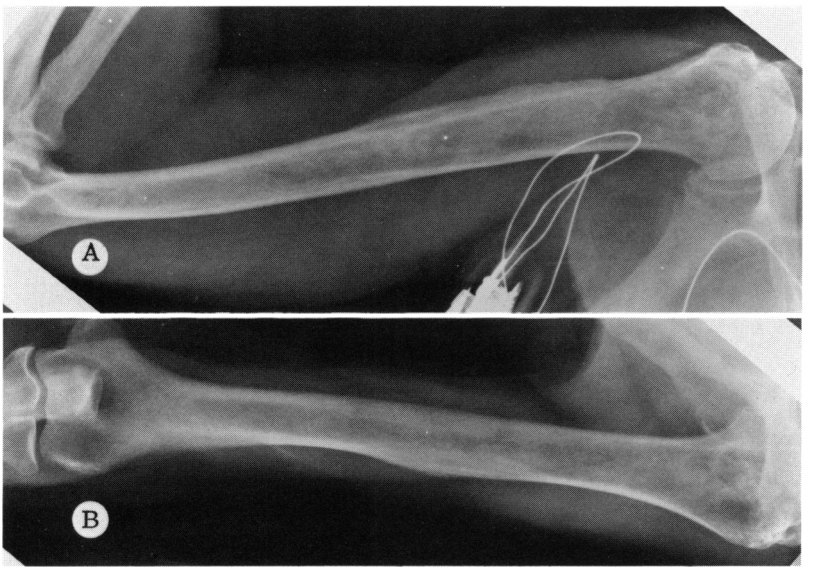

FIGURE 8
CASE 1. A: Radiograph of right humerus. Note mottled sclerosis of metaphyses with sparing of mid-shaft. B: Radiograph of left humerus demonstrates mottled sclerosis of metaphyses of head.

surrounding enlarged optic nerves" (Fig 12). Ultrasonography of right and left orbits revealed dense, highly absorptive masses obliterating the optic nerve outline. Bone scan revealed increased uptake in the distal portions of both femurs. Biopsy of the mass in the left orbit (Fig 13) by Kroenlin orbitotomy and resection of a lid lesion led to a diagnosis of "unusual xanthomas" (Fig 14). Osseous lesions were also biopsied (Fig 15). Samples of these lesions and radiographs of the bones were submitted in consultation to the AFIP by Dr Milton Boniak of Houston, Texas. A working diagnosis of Erdheim-Chester disease was suggested by the AFIP's experts in orthopedic pathology. Blood lipid analyses revealed no abnormalities.

The orbital lesions were judged non-resectable and not otherwise treatable. In 1980, the patient developed back and flank pain. Intravenous pyelogram revealed bilateral hydronephrosis and CT scan demonstrated a retroperitoneal mass. Vision began deteriorating in 1980. In January 1981, visual acuity was: OD = 20/60; OS = 20/50. By June, the visual acuity had decreased to hand motion at 2 feet in the right eye and 6 inches in the left eye. Pupils were equal but only sluggishly reactive. There was 4+ resistance to retropulsion. Xanthelasma-like lid lesions were present bilaterally and there was decreased ability to elevate the left eye. The optic discs were gray and elevated without spontaneous venous pulsations.

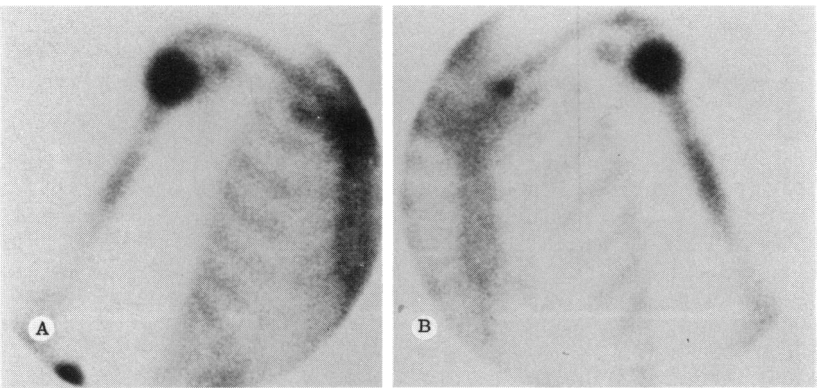

FIGURE 9
CASE 1. A: Increased radionuclide uptake in abnormal head of right humerus. B: Increased uptake in left clavicle.

Visual evoked response (VER) was non-recordable from both eyes. By July 1981, visual acuity was reduced to light perception in both eyes.

Laboratory Data:

Cholesterol	150 mg/dl	Triglycerides	163 mg/dl
Hemoglobin	10.2 gm/dl	Hematocrit	31.7 TBV
Alkaline phosphatase	73 IU/l		

By March 1982, the patient had lost all vision and had developed diabetes mellitus. In October 1982, increased right-sided weakness and slurred speech were noted. Over the next several weeks, she became comatose and died in November 1982.

A very complete postmortem study made by Dr Michael J. Dickerson revealed massive lipogranulomatosis of the orbit, retroperitoneal tissues, mesentery, pericardium, and skin. The extensive pericardial lesions which were associated with severe retroperitoneal fibroxanthogranulomatous disease, had encased the kidneys and adrenals and produced partial ureteral obstruction bilaterally. The orbital lesions completely engulfed both optic nerves and some of the extraocular muscles. The process extended intracranially, enveloping the pituitary gland. Histologic study of the many different areas of involvement revealed the full spectrum of fibrosing xanthogranulomatous infiltration.

The immediate cause of death was a massive hemorrhagic infarction of the left cerebral hemisphere, right cerebellar peduncles, and right mid-brain believed to have been secondary to carotid artery compression. Histologic study did not reveal evidence of xanthogranulomatous disease of the brain itself.

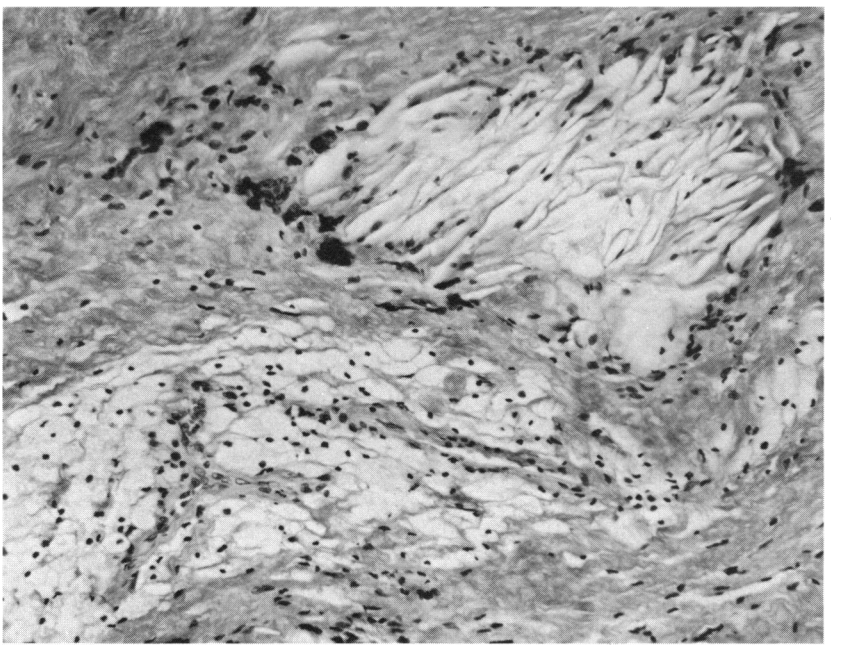

FIGURE 10

CASE 1. Specimen from head of right femur demonstrates focal infiltration by large clear xanthomatous histiocytes and discrete collections of cholesterol clefts surrounded by multinucleated foreign body giant cells (magnification, × 160).

DISCUSSION

Both patients reported herein developed lipogranulomatous masses that filled each orbit and produced exophthalmos and ophthalmoplegia. Following biopsy, the orbital disease process became arrested in our first patient who was treated with prednisone. He maintained useful vision throughout his life and was relatively unhandicapped by the ophthalmoplegia. Our second patient developed progressive exophthalmos and ophthalmoplegia. Both of her optic nerves became encased by the lipogranulomatous process. She developed optic disc swelling and ultimate atrophy and blindness.

The first patient had initially presented with pulmonary and pericardial effusions. He developed pulmonary fibrosis and right ventricular decompensation. Open pulmonary biopsy and autopsy, however, failed to reveal evidence of foam cells containing cholesterol in either the lung or heart. There is a striking tendency for these xanthogranulomatous lesions to

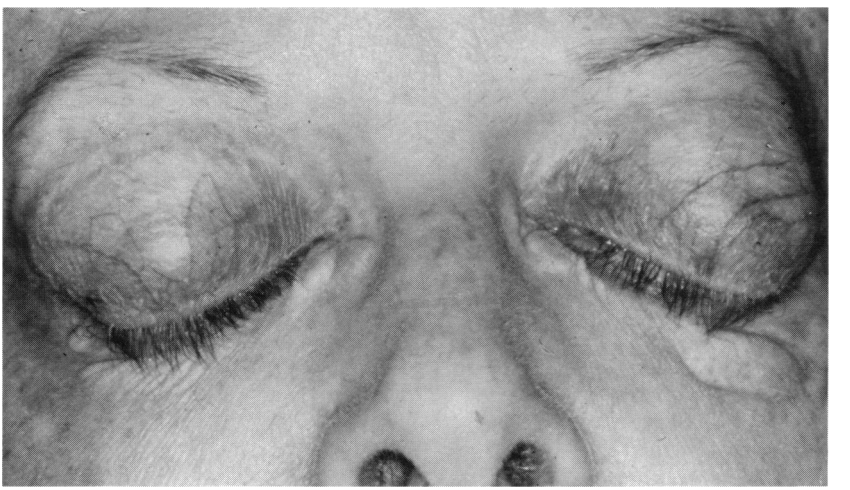

FIGURE 11
CASE 2. Thinning and xanthelasma of eyelids.

become fibrotic and densely collagenized, so perhaps the pulmonary fibrosis and densely obliterated pleural cavities were the result of xanthogranulomatous lesions that were missed by the initial biopsy.

In case 2 the patient developed multifocal changes involving many body systems in the course of her disease. Retroperitoneal lipogranulomatous masses were present in association with bilateral hydronephrosis. Lipogranulomas encased both optic nerves, extended into the chiasm, and surrounded the pituitary gland. In our review of the literature, there was no other report involving lipogranulomatous invasion of the pituitary.

Both of our patients demonstrated characteristic radiologic changes in the long tubular bones attributed by Jaffe[2] to bony reaction to lipogranu-

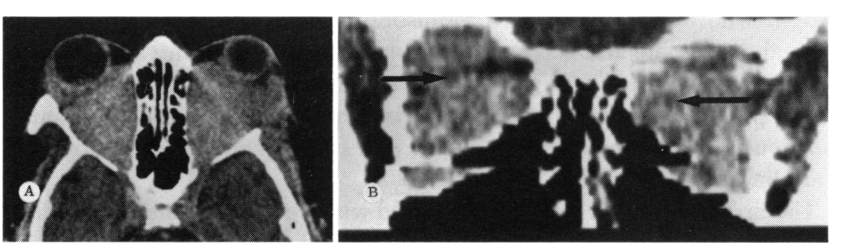

FIGURE 12
CASE 2. A: Transaxial computed tomogram demonstrates bilateral enhancing orbital masses. B: Coronal view computed tomogram demonstrates enhancing orbital masses which surround optic nerves seen as a negative shadow in each orbit.

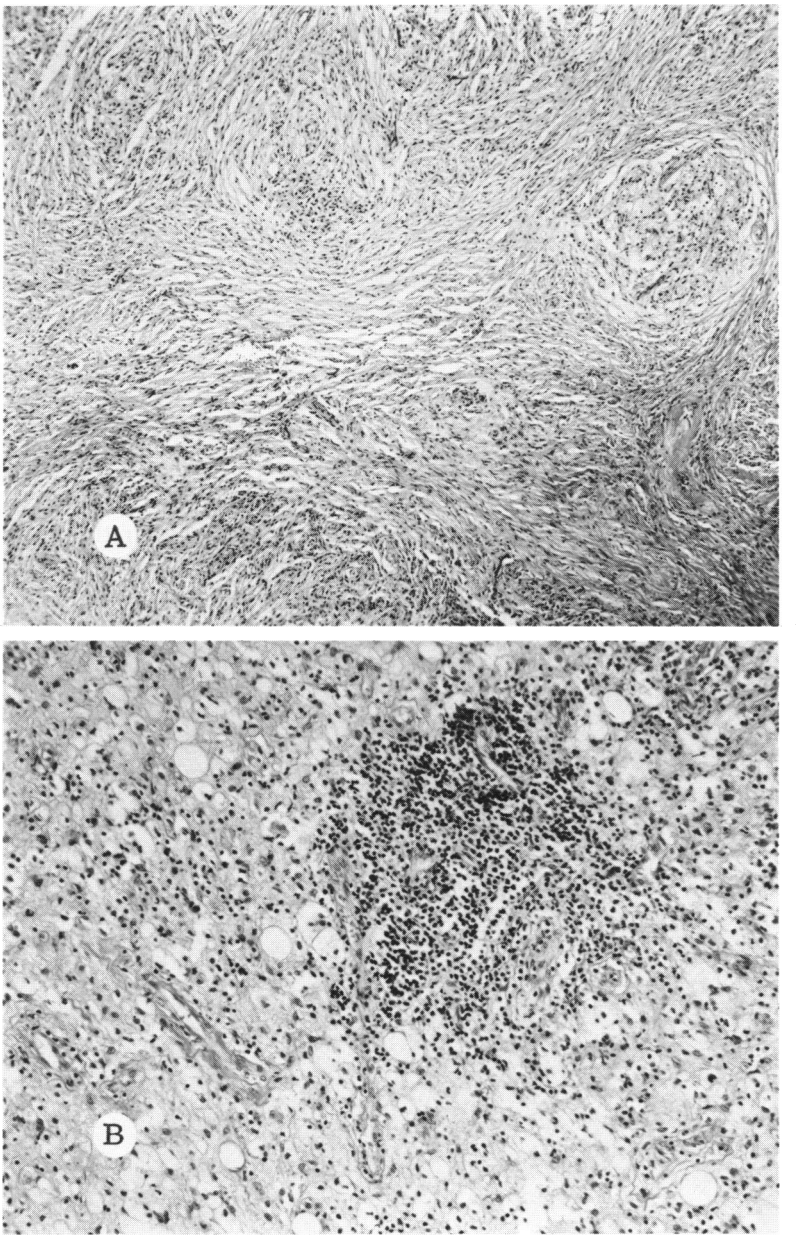

FIGURE 13
CASE 2. Sclerosing fibroxanthomatous inflammatory pseudotumor of orbit. A: (×60). B: (×160).

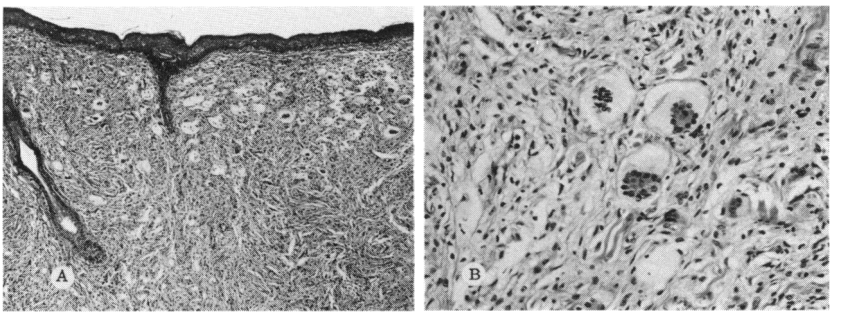

FIGURE 14
CASE 2. A: Xanthogranulomatous dermal infiltrate of eyelid. There is massive thickening of dermal tissues by fibrohistiocytic cells and many Touton giant cells containing an abundance of clear or vacuolated cytoplasm (×60). B: Three conspicuous Touton giant cells are present in center of field (×250).

lomatosis. These changes were asymptomatic in our first patient, but were associated with pain, swelling, and redness of the legs in the second patient. Symptoms in the second patient led to roentgen ray evaluation and radionuclide studies which demonstrated typical diagnostic findings

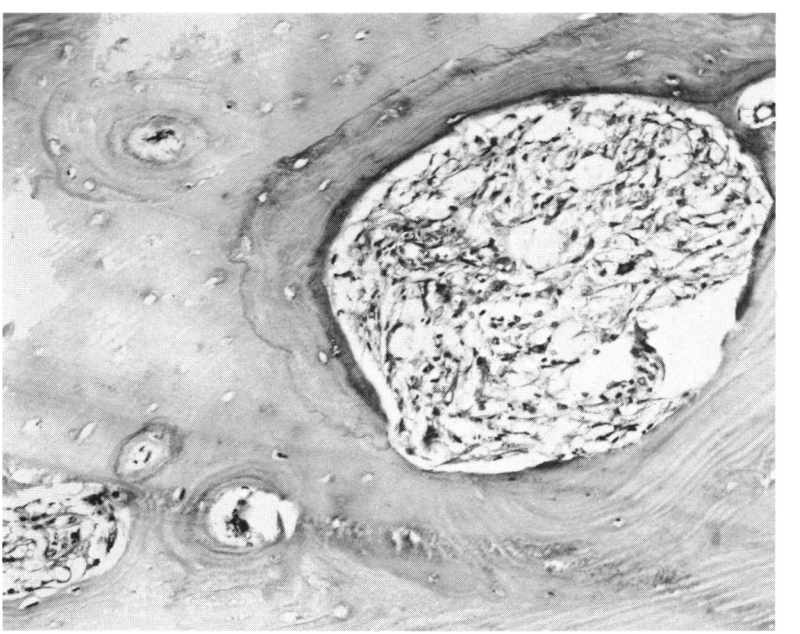

FIGURE 15
CASE 2. Marrow space is filled by large, pale-staining histiocytes (×160).

in the long bones. The final diagnosis of Erdheim-Chester disease in our first patient, however, was not established until one of us (MGA) became aware of identical orbital changes in both patients. This led to performing roentgenograms and radionuclide studies of the bony skeleton that demonstrated typical diagnostic features of metaphysial radiopacities and epiphysial sparing in the long tubular bones.

Even though blood lipid studies were normal in both of our patients, autopsy revealed moderate to severe atherosclerotic disease. The aorta and pulmonary and cerebral arteries were involved in the first patient. The second patient demonstrated atherosclerosis in the coronary and carotid arteries with death due to hemorrhagic infarction of the left cerebral hemisphere.

Jaffe[2] has thoroughly described the roentgenographic and pathologic findings in the bones. The long tubular bones show the most striking abnormalities characterized by diffuse and/or spottly increased radiopacities involving the spongiosa especially in their metaphyses. Symmetrical involvement is the rule and radionuclide uptake is increased in the areas of abnormality.[10] Pathologic changes, according to Jaffe, demonstrated conspicuous osteosclerosis in the metaphyses bordered by discrete lipid granulomata. The marrow present in the mid-shaft also displayed lipid granulomata.

Involvement of the lungs and heart by foam cells containing cholesterol was reported in one of Chester's[1] cases. Death was due to cardiac failure and bony involvement was noted only at autopsy. Others[3,10] have reported involvement of the lungs and heart manifested clinically by pleural and pericardial effusions. Foam cells containing lipid were identified from the fluid of the effusions.

Renal involvement,[10] retroperitoneal granulomatosis,[6,10] and congenital megacalices[5] have also been reported in association with the bony changes noted above. None of the reported cases had orbital or ocular changes.

Jaffe[2] described Erdheim-Chester disease as quite distinct from Schüller-Christian disease, Farber's disease, and familial hypercholesterolemia. Schüller-Christian disease affects older children and young adults with initial inflammatory lesions that resemble those of eosinophilic granuloma. Later in the course of the disease, secondary changes of cholesterol deposition occur which convert the pathologic process into xanthogranulomas. The complete diagnostic triad of calvarial defects, diabetes insipidus and exophthalmos may or may not be present. More recently it has been shown that in Schüller-Christian disease, eosinophilic granuloma of bone, and Letterer-Siwe disease (the histiocytosis X group) there is con-

sistently present within the histiocytes an intracytoplasmic organelle identical to the Birbeck granules of the epidermal Langerhans' cells. These are not present in other xanthogranulomatous lesions such as juvenile xanthogranuloma (formerly called nevoxanthogranuloma).[11,12] While the Birbeck or Langerhans' granule itself can only be demonstrated by electron microscopy, immunoperoxidase staining for S-100 protein has also proven useful in differentiating the histiocytes of histiocytosis X from those of other xanthogranulomatous diseases.[13-15] In histiocytosis X the histiocytes stain intensely positive for S-100 protein, sharing this feature with Langerhans' cells and other derivatives of the neural crest. In both of our cases the histiocytes did not stain for S-100 protein even though the "built-in controls" such as epidermal Langerhans' cells and dermal nerves gave the expected positive staining (Table II). These results support the view expressed by Jaffe[2] that Erdheim-Chester disease is not a variant of Schüller-Christian disease.

Farber's disease is a lipoglycoprotein storage abnormality which occurs shortly after birth and is dominated by progressive involvement of joints with development of nodular swellings in the subcutaneous and periarticular tissues. Death occurs in infancy with lipid infiltration of the lungs.

Essential familial hypercholesterolemia is an hereditary disorder of cholesterol utilization characterized by cholesterol deposits in connective tissue. Skeletal roentgenograms are usually normal and total serum cholesterol values are markedly elevated in contradistinction to changes described above in our patients.

Our two patients demonstrated the widespread nature of involvement of many of the body's tissues by this unusual xanthogranulomatous process (Table III). Clinical manifestations were produced which were nonspecific and highly variable. Although the orbital involvement was similar in the two patients (Table IV), the final diagnosis of Erdheim-Chester disease depended upon demonstration of pathognomonic radiographic changes in the skeleton consisting mostly of diffuse sclerosis of the metaphyses of the long tubular bones. A high index of suspicion with knowledge of these diagnostic criteria may be helpful in determining the proper diagnosis in other patients with a similar clinical picture (Table V).

TABLE II: HISTOPATHOLOGY IN ERDHEIM-CHESTER DISEASE

Fibrosing xanthogranulomas which exhibit:
A. Xanthomatous histiocytes
B. Touton and other giant cells
C. Fibrosis with collagenization

TABLE III: SUMMARY OF OTHER FINDINGS IN ERDHEIM-CHESTER DISEASE

1) Pleural and pericardial effusion
2) Pulmonary fibrosis
3) Cardiac decompensation
4) Atherosclerosis and cerebrovascular accidents
5) Retroperitoneal xanthogranulomas
6) Bilateral hydronephrosis
7) Normal blood fat studies
8) Characteristic long tubular bone changes
   a. Symmetrical bilateral patchy sclerosis and thickening of metaphyses
   b. Symmetrical bilateral radionuclide uptake in areas of bony abnormality
   c. Pain and redness over long bones
   d. May be asymptomatic

SUMMARY

1. The ophthalmological changes in two patients with Erdheim-Chester disease are described. These consist of exophthalmos, ophthalmoplegia, xanthelasma, optic disc swelling, blindness due to optic atrophy, retinal striae, and bilateral enhancing orbital masses on CT scan.

2. The clinical and histopathologic findings of Erdheim-Chester disease are reviewed and the manifestations in two patients with orbital change are presented.

3. This is believed to be the first report describing the ophthalmological manifestations of Erdheim-Chester disease.

4. Our observations support the view that Erdheim-Chester disease is unrelated to the histiocytosis X group.

TABLE IV: OPHTHALMOLOGICAL FINDINGS IN ERDHEIM-CHESTER DISEASE

A. Lids	Xanthelasma
	Thinning
B. Orbit	Exophthalmos
	Ophthalmoplegia
	Enhancing masses on CT scan
C. Globe	Optic disc swelling
	Optic atrophy
	Retinal striae

TABLE V: DIFFERENTIAL DIAGNOSIS OF SCHÜLLER-CHRISTIAN DISEASE — FARBER'S DISEASE — FAMILIAL HYPERCHOLESTEROLEMIA

SCHÜLLER-CHRISTIAN DISEASE	FARBER'S DISEASE	FAMILIAL HYPERCHOLESTEROLEMIA
Affects older children and young adults	Lipoglycoprotein storage disease	Hereditary disorder of cholesterol utilization
Pathognomonic triad: calvarial defects, diabetes insipidus, exophthalmos	Occurs shortly after birth	Cholesterol deposits in connective tissue ("xanthoma tuberosum multiplex")
Initial lesion inflammatory	Death occurs in infancy	Skeletal roentgenograms usually normal
	Progressive involvement of joints	
	Roentgenograms show distention of articular capsules and juxta-articular erosion	
	Lipid infiltration of lungs	

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DISCUSSION

DR MYRON YANOFF. I congratulate the authors on bringing to our attention a most interesting entity, namely, Erdheim-Chester disease. The condition is characterized by cholesterol-containing foam cells infiltrating or invading the viscera and bones. The widespread multifocal lipogranulomatous involvement may or may not be asymptomatic. Of the 47 previously reported cases, none had orbital involvement.

The authors now present two patients both of whom had orbital involvement in the form of bilateral exophthalmos secondary to infiltrative orbital lesions. We now have yet another entity to add to our long list of the differential diagnosis of exophthalmos. In addition, we need to consider Erdheim-Chester disease in patients who have lid lesions resembling xanthelasma.

The orbital pathology is intriguing in that it is most unusual to find Touton giant cells in this region except in juvenile xanthogranuloma (JXG) and liposarcoma, in the latter being most rare. I would like to know how the authors distinguish the pathology in their patients from JXG? Also, in general, what is the significance of Touton giant cells?

In case 1, acid-fast organisms, stated not to be tuberculosis, were found in sputum. Were the organisms further classified by culturing? Were the tissues from the lung and orbital biopsies in case 1 and orbital, tibial, and lid biopsies in case 2 cultured? Do the authors think that the acid-fast organisms could have been causative of the disease or played a role in it?

Also, inasmuch as some people have suggested that Erdheim-Chester disease might be a member of the histiocytosis X group, what do the authors feel about this? Have they performed or contemplated any electron microscopic and immunochemistry studies that might elucidate the conundrum?

Finally, I wish to thank the authors for allowing me the privilege of discussing this fascinating paper.

DR DENNIS M. ROBERTSON. I was struck by the similarity of the histopathologic characteristics of the cases presented with the histopathologic characteristics of lesions representing what has recently been described with necrobiotic xanthogranuloma and paraproteinemia. First reported by Kossard and Winkelmann, and later by Windelmann, and most recently by Cordere and associates, the lesions of necrobiotic xanthogranuloma have distinct clinical and histopathologic features. We are presently reviewing 15 cases of necrobiotic xanthogranuloma with paraproteinemia. This entity is associated with lesions that look very much like xanthelasma in distribution and color but the lesions are almost always indurated. Some become inflamed and crusted while others invade the orbit. The cases in our review are associated with abnormalities of the serum proteins, usually a paraproteinemia in the form of a monoclonal gammopathy. When further studies have been conducted, abnormal changes in the bone marrow are frequently recognized. These include multiple myeloma and other plasma proliferative disorders. I ask if either of the two patients with Erdheim-Chester disease were studied with serum protein-immunoelectrophoresis or if bone marrow studies were done? I wonder also if the authors were aware of the descriptions of necrobiotic xanthogranuloma? I might add that necrobiotic xanthogranuloma appears to be responsive in some instances to low-dose chemotherapy.

DR MELVIN ALPER. I would like to thank Doctors Yanoff and Robertson for discussing this paper. In answer to Doctor Yanoff's question, tuberculosis cultures were done and were negative in patient 1, although there were acid-fast non-tuberculous bacilli. There was no report of such cultures in the records of patient 2. I would like to call on Doctor Zimmerman at this time, if I may, to answer questions regarding the pathology studies.

DR LORENZ ZIMMERMAN. As Doctor Yanoff quite properly pointed out, for the ophthalmic pathologist the presence of a histiocytic lesion with Touton giant cells should suggest juvenile xanthogranuloma (JXG). There is no reason to believe that a relationship exists between the disease that our two patients had and JXG despite the fact that in both conditions Touton giant cells may be conspicuous.

First of all, in JXG we are dealing with a patient population that is characteristically very young, while our patients were much older. In JXG it is very rare for the patients to have serious systemic involvement. Histologically there are also some differences even though they share the presence of these Touton giant cells. The histiocytic cells in JXG are characteristically not as large and not xanthomatous even though they do contain lipids just as do the Touton giant cells, which are loaded with lipids.

In answer to Doctor Robertson's question, the lesions here are quite different histologically from those of necrobiotic xanthogranuloma in that the typical areas of necrobiosis that characterize the latter were not present in the lesions of either of these two patients; furthermore, in necrobiotic xanthogranuloma the discrete areas of necrobiosis are surrounded by a palisade of histiocytes, so they are zonal granulomas whereas in the lesions of Erdheim-Chester disease there is a diffuse proliferation of the xanthomatous histiocytic cells without the formation of discrete granulomas having central areas of necrosis or necrobiosis. I think the pathologist should be able to make that differential diagnosis rather easily.

Dr Melvin G. Alper. In final closing, I would like to thank my co-authors and all of the doctors involved in the prolonged treatment of these patients reported today. Without their cooperation in gathering the clinical material, this report could not have been made.