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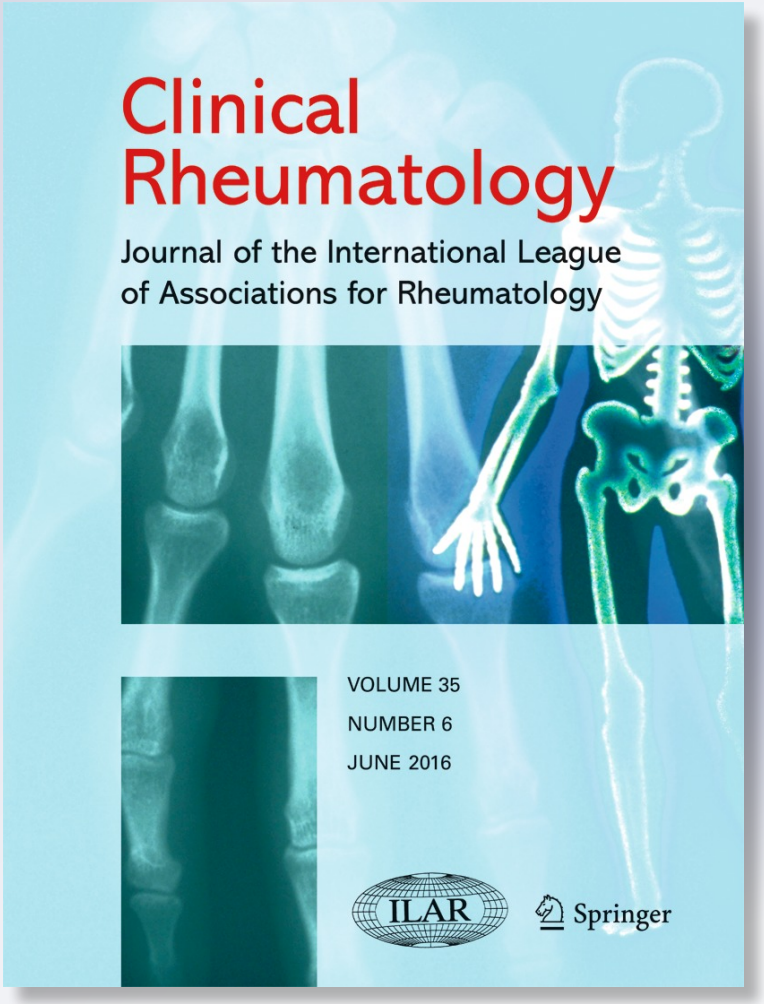
Clinical Rheumatology
Journal of the International League of Associations for Rheumatology

ISSN 0770-3198
Volume 35
Number 6

Clin Rheumatol (2016) 35:1625-1629
DOI 10.1007/s10067-016-3269-y



Springer

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BRIEF REPORT

Erdheim-Chester disease: description of eight cases

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Received: 17 February 2016 / Revised: 5 April 2016 / Accepted: 7 April 2016 / Published online: 23 April 2016

Abstract Erdheim-Chester disease, although rare, has a wide range of manifestations. It is characterized by the xanthomatous infiltration of tissues by spumous histiocytes, surrounded by fibrosis. The symptoms can vary from bone pain, diabetes insipidus, exophthalmos, xanthelasmas, cardiovascular involvement, bilateral adrenal enlargement, renal impairment, testis infiltration, interstitial lung disease to retroperitoneal fibrosis with perirenal and/or ureteral obstruction. We present eight cases, four of them with only breast involvement and the others with bone, cardiovascular, central nervous system, and renal involvement. All showed infiltrates of histiocytes and fibrosis on microscopic evaluation and positive CD68 and negative CD1a on immunohistochemical stains.

Keywords Erdheim-Chester · Non-Langerhans histiocytosis · Xanthomatous tissue infiltration

Introduction

Erdheim-Chester disease was first described as the "lipoid granulomatose" by Jakob Erdheim and his pupil William Chester in 1930 [1]. It is categorized as a non-Langerhans' cell histiocytosis, of unknown origin, with a wide range of manifestations and is rare: up to 2015, only 700 cases had been reported [2]. Due to the better recognition of this entity, the number of cases reported has increased over the last years.

It is characterized by the xanthomatous infiltration of tissues by spumous histiocytes, "lipid-laden" macrophages of histiocytes, surrounded by fibrosis. The symptoms can vary from bone pain, diabetes insipidus, exophthalmos, xanthelasmas, cardiovascular involvement, bilateral adrenal enlargement, renal impairment, testis infiltration, interstitial lung disease to retroperitoneal fibrosis with perirenal and/or ureteral obstruction [3, 4]. The clinical course depends on the extent and the distribution of the disease, ranging from asymptomatic bones lesions to life-threatening forms.

Objective

The objective of this study was to present eight cases of Erdheim-Chester disease.

Cases

Case 1

A 41-year-old man was admitted because of pain in arms and legs lasting 2 years and nodules that appeared 20 years earlier. The patient had a history of hypercholesterolemia. On physical examination, there were bumps in elbows, hands, knees, and ankles, xanthelasmas in the upper and lower eyelids (Fig. 1), and submaxillary lymph node enlargement. His vital signs were normal and the remainder of his physical examination was unremarkable.

Laboratory investigation showed hypercholesterolemia and hypertriglyceridemia, with normal results of uric acid in the serum and urine. Rheumatoid factor, antinuclear

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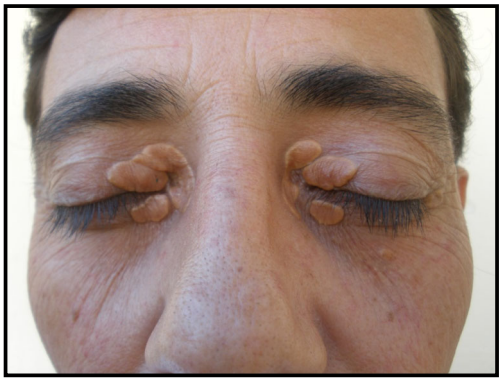

Fig. 1 Xanthelasmas in upper and lower eyelids

antibodies, anti-cyclic citrullinated peptide antibody, and ds-DNA antibody were negative. Radiographs of hands, feet, and long bones (humerii, ulnae, radii, femora, tibiae, and fibulae) were normal. Nodule histology demonstrated the presence of multiple granulomas surrounded by histiocytes, giant cells, lymphocytes, and plasmocytes and scattered urate crystals. Computed tomography scan of head, neck, thorax, abdomen, and pelvis showed tiny submandibular and axillary lymph nodes. Bibasal bronchiectasias were also seen. Technetium-99 bone scintigraphy showed bilateral and symmetrical increased uptake in proximal humerus. A new biopsy of the nodules was performed. Hematoxylin-eosin staining revealed foamy histiocytes that were positive for CD68 but negative for S100 and citoqueratin. During the follow-up, he developed an acute thoracic pain. The electrocardiogram showed a myocardial infarction and coronary involvement (right coronary artery and left coronary trunk) was demonstrated by coronary angiogram.

Case 2

A 30-year-old woman came to consultation because of the presence of a brain mass that resolved spontaneously a year ago. On physical examination, she had arterial hypertension. At the time of the brain mass, she presented with right fasciobrachial and crural paresia, associated with headaches. Both computed tomography scan and magnetic resonance of the brain informed the presence of a frontal mass, surrounded by edema. Histological results of the lesion showed necrosis, interstitial edema, macrophages, and thrombosed vessels. She was treated with prednisone 10 mg/day. A new brain magnetic resonance failed to demonstrate the presence of the mass.

Later on, the patient developed paresthesias and Raynaud phenomenon. An X-ray of long bones showed normal results, but technetium-99 bone scintigraphy showed bilateral and symmetrical increased uptake in elbows, knees, and distal femurs.

Brain biopsy was reviewed, and histiocytes, foamy macrophages, and leukocytes were seen. The histiocytes were positive for CD68 and S100 but negative for CD1a.

Case 3

A 55-year-old man came to consultation with loss of weight and abdominal pain (left side). He underwent surgery due to the presence of an apparent benign renal mass. Physical examination was unremarkable. An X-ray of long bones was normal, but technetium-99 bone scintigraphy showed bilateral and symmetrical increased uptake in knees, ankles, and proximal tibiae. Brain magnetic resonance and echocardiogram were normal. Abdominal computed tomography scan showed pyelocalyceal augmentation and perirenal involvement with "hairy kidney" appearance (Fig. 2). Malignancies were ruled out. Microscopically, the renal mass showed infiltrates of histiocytes, plasmocytes, and fibrosis. Immunohistochemical stains for CD68 and S100 were positive but negative for CD1a.

Case 4

A 37-year-old woman came to consultation because of headaches and right brachial and crural paresia which evolved in paralysis 24 h later. Her past medical history was unremarkable, except for a birth of a low-weight baby and a peripheral facial paralysis. She was admitted in hospital and high blood pressure was found on physical examination. A brain computed tomography scan was performed showing displacement of the left lateral ventricle but without evidence of a mass. A brain magnetic resonance informed the presence of a left subcortical periventricular mass. Laboratory investigation showed increased erythrosedimentation rate (50 mm/1°h), ANA (HeP-2) 1/2560 with negative anti-Ro, anti-La, and RNP antibodies. Anticardiolipins antibodies and lupus anticoagulant were also negative. A brain biopsy was carried on, and

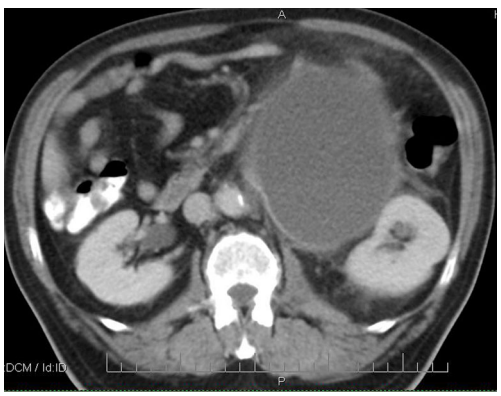

Fig. 2 Abdominal computed tomography scan showing pyelocalyceal augmentation and perirenal involvement with "hairy kidney" appearance

microscopic examination showed necrosis and vacuolated histiocytes. Immunohistochemical stains for CD68 and S100 were positive but negative for CD1a.

Cases 5 to 8

There were four women of 38, 32, 38, and 35 years who had been evaluated by the Gynecology Department due to the presence of an erythematous and painful breast mass (size ranging 0.18 × 0.05 to 3 × 5 cm). They underwent mass drainage and received antibiotics, suspecting a breast abscess. Due to the lack of improvement, biopsies of the masses were carried on. Bacteriologic studies were negative for fungus and common germs. Microscopic evaluation showed in all cases similar histopathologic features: breast tissue with ductal ectasia, extensive infiltrates of lymphocytes, polymorphonuclear and plasma cells, with giant multinucleated cells and scattered granulomas. Final diagnosis was granulomatous mastitis. Due to the recurrence of the lesions, the biopsies were reviewed.

A diffuse infiltration by epithelioid cells with abundant foamy cytoplasm, multinucleated cells with the appearance of Touton-type giant cells (Fig. 3), and patchy mature lymphoid infiltrate were found. On immunohistochemical staining, the cells were positive for CD68 and negative for CD1a, S100, and IgG4.

Discussion

Erdheim-Chester disease (ECD) is a non-Langerhans'cell histiocytosis of unknown etiology that affects middle-aged individuals (50–70 years old) with no sex predilection. However, in the study of Arnaud et al. [5], a strong male predominance was found among 53 patients.

There are typical radiographical and pathological features which can lead to the diagnosis but the clinical spectrum shows a broad variation, ranging from asymptomatic tissue infiltration to fulminant multisystem organ failure [6]. This entity is defined by a xanthomatous or xanthogranulomatous tissue infiltrate consisting of foamy histiocytes and "lipid-laden" macrophages and can be distinguished from Langerhans' cell histiocytosis based on the immunohistologic characteristics of histiocytes, as cell staining is positive for CD68 and negative for S100 (80 % of the cases) and CD1a in ECD [3, 7].

The scarcity of patients serves as an obstacle in medical science's endeavor to better understand this condition, rendering the formulation of controlled randomized trials impossible to perform.

Although skeletal involvement is extremely frequent (96 % of the 53 patients included in the 2011 series) [5], only 50 % of patients suffer bone pain. It is often mild, mostly affects the legs, and can start at any time during the course of the disease. X-ray evidence of bilateral and symmetrical cortical osteosclerosis of the diaphyseal and metaphyseal regions of the long bones is typical of ECD. The axial skeleton and mandible are often involved in Langerhans' cell histiocytosis, but not in cases of ECD. Also, symmetric and abnormally strong labeling of the distal ends of the long bones of the legs (and sometimes the arms) is often revealed by technetium-99 bone scintigraphy. Only one of our patients complained of bone pain and long bone X-ray was normal in all of them. Nevertheless, technetium-99 bone scintigraphy showed bilateral and symmetrical increased uptake in four.

Magnetic resonance may also be valuable in the rare cases of ECD for which abnormalities are not detected by bone CT scans [3, 4]. Recently, positron emission tomography (PET) with 18F-labeled fluorodeoxyglucose (PET-CT) has been used in place of bone CT scans [8, 9].

Eyelids xanthelasmas were seen in only one of our patients and was reported in 28 % of Haroche's series. Other classical, but less frequent lesion is papulonodular lesion and infiltration of the vulva and clitoris [1].

Two of our patients developed brain masses with paresias, paralysis, and headaches. The location, size, and nature of the lesion will determine whether the

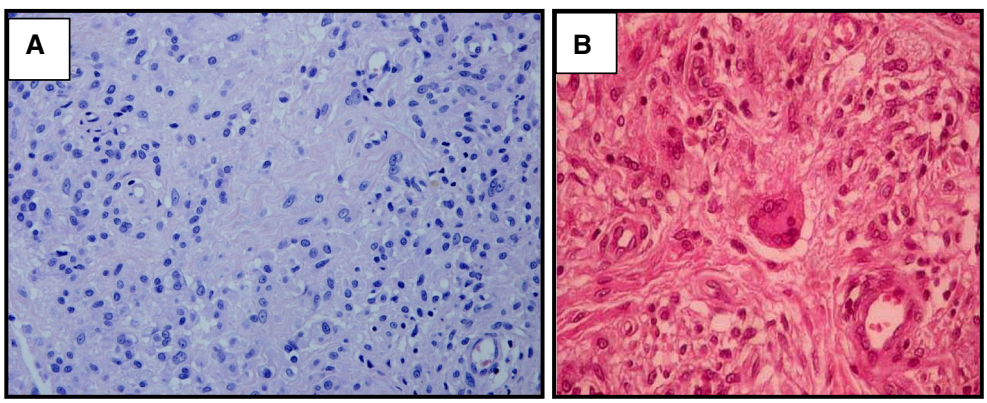

Fig. 3 Xanthomatous histiocytes (**a**) and Touton cell (**b**)

patient will be completely asymptomatic, suffer from various neurological deficits and severe disability, or succumb to this disease. CNS involvement appears in approximately 51 % of ECD patients and accounts for 29 % of all deaths [5]. In another retrospective analysis of 33 patients with confirmed ECD, performed by Drier et al., 45 % of the patients had symptoms related to CNS and/or orbital manifestations at presentation. These manifestations, by order of frequency, were diabetes insipidus, exophthalmos, cerebellar ataxia, panhypopituitarism, and papilledema [10]. Other involvements reported in the literature include thickening of face and skull bones, intracranial peri-arterial infiltration, intraluminal involvement of the superior sagittal sinus, involvement of the choroid plexus, and masses involving the cerebral hemispheres [10] (as occurred in case 2, who presented brain pseudotumor with neurological symptoms that reverted with glucocorticoids). Although this case was asymptomatic in other systems, magnetic resonance and technetium-99 bone scintigraphy showed the presence of bone involvement by ECD.

Approximately 75 % of ECD patients suffer from cardiovascular manifestations and about 60 % of them will perish due to cardiovascular complications [11]. These lesions account for various clinical consequences (congestive heart failure, myocardial infarction, thromboembolism, cardiac remodeling, valvular dysfunction, ischemia, peripheral edema, and others). Our patient developed an acute coronary syndrome, characterized by acute thoracic pain and electrocardiographic alterations. Imaging studies detected coronary obstruction. However, pericardial infiltration is the most frequent cardiac manifestation in ECD [3, 11]. Both aortic and pericardial involvements of ECD are seen well on computed tomography and echocardiography. Periaortic fibrosis appears as a "coated aorta" on CT scans, but it is not limited to the aorta. It has been identified in the brachiocephalic trunk, left common carotid artery, left subclavian artery, coronary arteries, pulmonary, and celiac trunk and renal arteries [3, 11]. The clinical consequences are not classically severe, except for reno-vascular hypertension.

Renal and perirenal involvement was found in almost 30 % of the patients reported [12, 13]. An aspect of pseudo "retroperitoneal fibrosis" may be seen, and sometimes this situation may complicate with bilateral hydronephrosis. As opposed to idiopathic retroperitoneal fibrosis, the pelvic ureters are always spared in ECD and the inferior vena cava is usually not affected [3]. Also, the fibrosis completely and circumferentially sheaths the aortic walls, as opposed to idiopathic retroperitoneal fibrosis in which the posterior aortic wall is usually spared [14]. Renal involvement is usually asymptomatic (as occurred in patient 3) and is revealed on CT, which shows hypoattenuated homogeneous tissue infiltration with weak contrast enhancement in the renal fossae. The "hairy kidney" appearance, due to symmetric and bilateral infiltration of both the perirenal and posterior pararenal space, is highly suggestive of the diagnosis [15].

A variety of general symptoms may accompany ECD. This are relatively unspecific and do not appear globally in all patients. Among them are fever, weakness, weight loss, and night sweats. Fatigue may be associated with a microcytic anemia, which occasionally accompanies ECD [16].

The wide clinical spectrum and the poor knowledge of this entity make its diagnosis extremely difficult. The majority of the patients of this report took years to be diagnosed. Even so, it was necessary to carry out numerous biopsies to attain the diagnosis. In other cases, biopsies (nonspecific at onset) should be reviewed. After immunohistochemical staining (CD68, CD1a, and S100), a correct diagnosis was reached.

Compliance with ethical standards

Disclosures None.

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