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Diagnosis delay, phenotypic variety, and therapeutic outcome of Erdheim-Chester disease

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Abstract

Erdheim-Chester disease (ECD) is a non-Langerhans histiocytic that typically affects middle-aged adults between the fifth and seventh decades of life. It is characterized by systemic xanthogranulomatous infiltration by histiocytes CD68+/CD1a–. In this paper, we collect the main clinical characteristics of eleven patients, diagnosed with ECD at the Virgen del Rocio Hospital in Seville. After first medical contact, it has been possible to reduce the misdiagnoses and this has shortened the time to diagnosis and initiation of treatment, which has resulted in fewer complications.

Keywords: Erdheim-Chester disease. Non-langerhans histiocytosis. Bone tumor. Rare disease.

Introduction

Erdheim Chester disease is a rare pathology, and it is one of the systemic histiocytosis, classified as a non-Langerhans cells histiocytosis. It is a multisystemic involvement with high morbidity due to infiltration with foamy histiocytic cells in the form of xanthogranulomas that are distributed throughout the body. The most frequent involvement occurs at the osteoarticular level, with osteosclerosing lesions predominantly at the metaphysis and diaphyses of long bones[1]. The etiology of the disease is unknown and is associated with an intense immune response mediated by Th1 lymphocytes, as well as the mutation of the V600E BRAF gene[2,3]. The definitive diagnosis is established by the appearance of CD68+/CD1a– histiocytes in the tissue biopsy[1]. In its absence, the presence of the BRAF V600E mutation or MAPK pathway modification has become the gold standard[1,2].

Materials and methods

The present study describes the form of presentation, main clinical manifestations, as well as the diagnostic and therapeutic methods used in ECD, through a series of 11 patients collected at the Rare Disease Unit at Virgen del Rocio University Hospital in Seville, at third level hospital in Spain.

We performed an intelligent search in our patient database from the year 2000 to the present, including in the search: non-Langerhans cells and Erdheim-Chester disease.

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We have omitted the personal data of the patients and their identification in the images. Informed consent has been requested for the conduct of this study. The Helsinki WMA guidelines were followed.

Results

Onset characteristics of the patients

We have obtained information from 11 patients (six men and five women) with a median age of onset and diagnosis of 41 years and 44 years, respectively, with a mean diagnostic delay of 3 years.

The most characteristic onset in our series of patients is a presentation with general symptoms such as constitutional symptoms with arthralgias, fever, and lymphadenopathy. In only two cases, the debut was considered severe, as it included cardiovascular involvement (periaortitis and heart failure). A summary of the patient's characteristics is given in table 1.

Table 1. Characteristics of patients

Patient	Sex	Onset	Diagnosis	Exitus
1	Male	34 year	43 years	Yes
2	Male	58 year	66 years	Yes
3	Male	39 year	41 years	No
4	Male	20 year	27 years	No
5	Male	50 year	51 years	No
6	Female	23 year	23 years	No
7	Male	49 year	49 years	No
8	Female	36 year	36 years	No
9	Female	50 year	52 years	No
10	Female	64 year	64 years	Yes
11	Female	27 year	29 years	No

Clinical features

In our patients, bone involvement was the most frequently found after diagnostic positron emission tomography-computed tomography (PET-CT) (nine of the 11 patients).

In terms of frequency, the most common involvement after bone disease was nephrourological and endocrine, with the appearance of typical disease manifestations such as hairy kidneys, retroperitoneal fibrosis, and diabetes insipidus.

The most severe involvement was cardiovascular manifestations; four patients presented the classic periaortic fibrosis (Fig. 1). In one patient, pericardial effusion was detected, and he even suffered cardiorespiratory arrest with an etiology not fully identified, which was attributed to sudden cardiac rhythm disturbances (during his admission to the intensive care unit (ICU), the patient had several episodes of bradycardia and supraventricular tachycardia).

A summary of the patient's clinical manifestations is given in table 2.

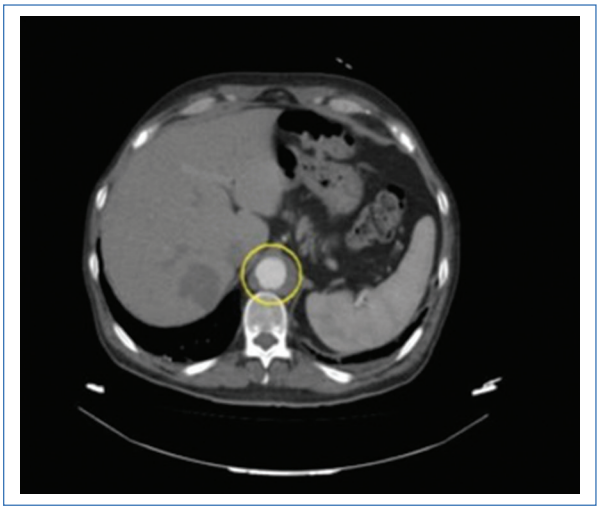

Figure 1. Inflammatory cuff suggestive of periaortitis.

Diagnosis and its difficulties

It has already been mentioned that ECD is an entity with very diverse clinical manifestations and that a high clinical suspicion is required for its diagnosis. In our series of patients, the diagnostic delay in the very first patients diagnosed in our unit (patients 1-4) was about 7.5 years; however, in the last patients (4-11), the diagnostic delay has decreased, and it is frequent that ECD is among the clinical judgments to be discarded in the first visits. At present, the average delay is < 2.5 years.

The most frequent misdiagnosis at debut includes metastasis of non-infiltrative primary tumor, idiopathic retroperitoneal fibrosis, eosinophilic granuloma, and lymphoma. In most of the patients, the appearance of key images on PET-CT simplified the differential diagnosis. In three of the patients, the diagnosis was reached after histopathological and immunohistochemical reinterpretation of biopsy specimens.

Table 2. Organ involvement and clinical features

Patient	Cardiovascular	Neurologic	Pulmonary	Bone	Nephrological	Endocrine	Ophthalmic	Dermatologic
1	No	Piramidalism, Cerebral tumors	No	Yes	No	No	No	No
2	Periaortitis	Frontal cerebral tumor Parcial seizures	No	Yes	Hairy kidneys	Diabetes insipidus Hypogonadotropic hypogonadism	No	No
3	No	No	Condensative infiltrates	Yes	Obstructive uropathy	Diabetes insipidus	No	Lichen pigmentosum
4	Periaortitis Pericardic effusion Sinusal bradycardia and cardiac arrest Supraventricular tachycardia	Seizures	No	Yes Myositis ossificans	Obstructive uropathy Hairy kidney	Diabetes insipidus Hypogonadotropic hypogonadism Hyperprolactinemia Secondary hypothyroidism	No	No
5	No	No	No	Yes	Obstructive uropathy Hairy kidney	Hypogonadotropic hypogonadism	No	No
6	No	No	No	Yes	No	No	No	No
7	No	No	No	Yes	No	Autoimmune hypothyroidism	No	No
8	No	No	Micronodular infiltrate	Yes	No	Diabetes insipidus	No	No
9	Sinusal bradycardia	No	No	Yes	No	Diabetes insipidus	No	No
10	No	No	No	No	No	Primary hypothyroidism	No	No
11	Periaotitis and coronary stenosis	No	No	No	No	No	No	No

The rest of the patients were diagnosed with a suspicion oriented toward the symptoms once the sample was taken. The biopsies obtained from the lesions were: brain by surgical excision figure 2, renal capsule of Gerota and retroperitoneal fibrous tissue by intraoperative biopsy, skin biopsy by punch, bone biopsies, bone marrow, or lymphatic biopsies.

In one patient, histological samples were not obtained due to the patient's own refusal; the diagnosis in this patient was made based on the clinical manifestations present (periaortitis and retroperitoneal fibrosis) and the PET-CT images (epicardial tissue infiltration involving proximal areas of the coronary arteries, axillary hypercaptant lesions suspicious for adenopathy). Other pathologies such as IgG4 disease and chronic Kawasaki lesions were ruled out.

In those patients with histopathological samples, BRAF V600 gene analysis was performed to determine, whether they were candidates for third-line specific immunotherapy in the event of failure of interferon and MEK inhibitors (cobimetinib). In the sample of patients, four of them were positive for the BRAF V600 gene mutation, five were negative, in one, there was not enough histological sample, and in another patient, a biopsy was not performed by choice.

Treatment and clinical course

Once the diagnosis was oriented or concluded, the treatment was started. All patients received glucocorticoids in addition to the basic treatment.

Table 3. Diagnosis and treatment procedure

Patient	Pathology	BRAF V600E	General symptoms	Treatment
1	Cerebral biopsy	Positive	No	Alfa interferon + Pegylate interferon+prednisone
2	Kidney and retroperitoneum biopsy	Positive	Fever Retroperitoneum fibrosis	Pegylate interferon + prednisone
3	Skin biopsy	Negative	Retroperitoneum fibrosis	Pegylate interferon + cobimetinib
4	Kidney biopsy	Positive	Retroperitoneum fibrosis	Pegylate interferon + prednisone + Anakinra
5	Adenopathy biopsy	Positive	Retroperitoneum fibrosis Fever	Alfa interferon + Pegylate interferon + cobimetinib
6	Bone biopsy	Negative	Retroperitoneum fibrosis	No treatment
7	Bone/retroperitoneum biopsy	No performed	No	Anakinra
8	Bone biopsy	Negative	Retroperitoneum fibrosis	Pegylate interferon
9	Bone biopsy	Negative	No	Pegylate interferon + Anakinra + vinblastine+cobimetinib
10	Adenopathy biopsy	Negative	No	Anakinra + cobimetinib
11	No performed	No performed	Retroperitoneum fibrosis	No

The most commonly used dose of glucocorticoids comprised between 60 and 40 mg of prednisone per day. On some occasions if the general clinical condition worsened, methylprednisolone pulses were used at doses between 0.5 and 1 mg/kg on three consecutive days with good response. The most used treatment regimens are those including pegylated interferon 130.000-180.000 ug (some patients started treatment with interfering alpha 2b with poor tolerance). In addition to this treatment, immunomodulators such as Anakinra (used in four of the patients) and Cobimetinib (in another four patients) were used as second line treatment.

For the control and follow-up of the disease, PET-CT was used in eight of the patients on an annual basis or when there was suspicion of disease progression to decide on the continuation or change of treatment. PET-CT showed in these patients a partial metabolic response in soft tissues and a greater response at bone level, although disease activity persisted.

It is worth to notice the great improvement with complete disappearance of the skin lesions in a short time and with almost complete response in one of the patients when starting interferon.

In our registry, three of the patients died. The first patient with brain involvement was admitted to our department for respiratory failure, and a new PET-CT scan showed progression of brain lesions. The patient was dead due to respiratory insufficiency of infectious etiology.

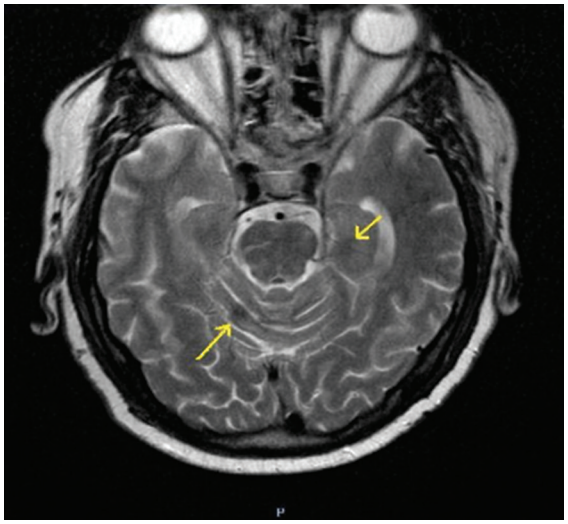

Figure 2. Hypointense lesions in temporal lobes.

The second patient was suspended from treatment due to poor tolerance, worsening of performance status index (PS), and progression of the disease to the central nervous system (CNS) and dead during a palliative care admission due to status epilepticus.

The tenth patient developed a recurrent pleural effusion, in which the study was diagnosed as

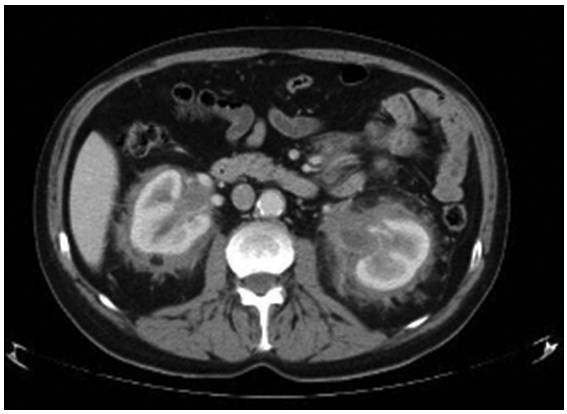

Figure 3. Hairy kidneys sign.

high-grade lymphoma; before starting treatment, she started with respiratory failure secondary to the effusion and complicated infection, being exited during admission to the Internal Medicine Department (Table 3).

Discussion

As we have seen, ECD presents a multitude of different clinical presentations. Whether in pediatric age[1] or in the elderly, the number of manifestations of the disease requires a great deal of knowledge on the part of the clinician and a high degree of suspicion in order to reach a diagnosis. With an incidence between the fifth and seventh decades of life, patients present cardiac, endocrine, pulmonary, neurological, and bone involvement, which requires a differential diagnosis[1,4,5] between pathologies such as lymphoma, osteoblastic metastases, sarcoidosis, or metabolic disorders such as Gaucher disease or Niemann-Pick.

Bone involvement revealed by bone scintigraphy was present in all but one patient, with diaphyseometaphyseal involvement typical of the disease being present in nine of them. In a review of the disease[5,6,7], several bone involvement is found in 96% of the patients, although pain is only manifested in about half of them (in the case of our patients only two). We must be cautious, since, although it is one of the most frequent conditions of the entity described in the study, there are patients who do not present it. Therefore, its absence should not make us ignore the possibility of being before a ECD as already mentioned by Iborra et al.[7] in a study of 12 clinical cases, where there were patients who did not present bone involvement.

Approximately 75% of patients suffer cardiovascular involvement, conferring a worse prognosis to the disease, being the cause of death in 60% of patients[8-10].

Morbidity and mortality depend on the extent and severity of cardiac involvement and magnetic resonance imaging is a very useful test in the diagnosis of cardiac affectation. The ascending and descending aorta are the most frequently affected with fibrosis, also is described cases of stenosis of the renal and cerebral arteries, often requiring a differential diagnosis between Takayasu's arteritis[8]. Nevertheless, these clinical characteristics are rare presentations with high mortality and their management should be considered in future research, since the etiopathogenesis is different from that of atherothrombotic coronary artery disease.

In the study Arnaud et al.,[11] they documented neurological involvement of the disease in 51% of patients, being the direct cause of all deaths in 29%, as well as an independent factor of poor prognosis. The manifestations are multiple, from exophthalmos to cerebellar ataxia, pyramidal syndrome, etc., depending on the sites affected by the disease. Lumbar puncture is not recommended[1] since there is no presence of histiocytic cells in cerebrospinal fluid. Magnetic resource imaging (MRI) is the best test to evaluate central nervous system (CNS) involvement.

Another frequent location of the disease is the infiltration of the retroperitoneal space. Present in up to 68% of patients[1,8], it gives rise to fibrosis that can involve both kidneys causing the appearance of the characteristic image of "hairy kidneys" (Fig. 3), while it can cause bilateral obstruction at the ureteral level with hydronephrosis and renal failure. One of the most useful tests to demonstrate retroperitoneal involvement and at the same time the involvement of the great thoracic and abdominal vessels is CT.

PET-CT is the test proposed for patient follow-up[7,12] since it is the only one that provides a global vision of the possible affectations that ECD may be causing in the organism. In all our patients, a PET-CT scan was performed which showed both metabolic response with treatment and the appearance of new foci of disease or progression in three of the patients. In patients who in the first instance do not show bone involvement, Arnaud et al. and Goyal et al.[6,13] propose whole body MRI as an alternative test for the follow-up of patients, due to the absence of irradiation of the organism and a good sensitivity to recognize cardiac or visceral involvement of the test.

The pathogenesis underlying the treatment of the disease is still unknown. Through the study of the

BRAF mutation, it has been demonstrated that Langerhans histiocytosis and ECD have a common pathogenic basis[3], evidenced by the premise that this mutation is only found in these two types of histiocytosis, not being present in other forms such as Rosai-Dorfman disease, histiocytic sarcoma, or interdigitating dendritic cell sarcoma. It is this BRAF V600E mutation that opens the door to new therapeutic possibilities. Present in up to 54% of patients,[2,3,14] this mutation not only supports diagnosis, but is also a new window and target for trials of new treatments.

Until now, ECD has been treated using glucocorticoids, with a limited impact on the disease, and interferon alpha the one that demonstrates regression of clinical manifestations and an increase survival in different analyses and studies[11,15]. The response to interferon and other treatments corroborates an underlying immune-based alteration that has yet to be adequately investigate. Other immunosuppressants used with less success are cladribine, imatininb, or sumatinib. Bisphosphonates have been used to try to palliate bone resorption and among the new treatments, the interleukin-1 inhibitor (Anakinra)[16,17] has shown improvement of disease symptoms at doses similar to those of patients with rheumatoid arthritis and without setting an exact time limit for treatment.

Nevertheless, it is the mentioned BRAF mutation that offers us a new drug, vemurafenib, which promises to be an inescapable drug in the treatment of ECD. Based on the premise of increased survival of melanoma patients, Haroche et al.[3] present a new study of three patients with ECD treated with vemurafenib at an initial dose of 1920 mg/day. They demonstrate a dramatic and rapid efficacy of treatment in all three patients, with regression of perivascular and cardiac lesions, as well as skin, visceral, bone, or cranial lesions among others and a more rapid decline in acute phase reactants with respect to interferon alpha, all documented by follow-up with PET-CT and computed tomography[3].

Due to the expansion of the use of MEK inhibitors in the treatment of ECD with progression, in our service, we have started to perform genetic studies of biopsies taken positive for non-LCH of NRAS, PID3CA, or RAS-PI3K-AKT expression.

Conclusion

The incidence of ECD has increased during the last decade. Despite its great clinical variety, the study of the most frequent organic manifestations, as well as a greater knowledge on the part of clinicians of this entity, corroborates this finding. Undoubtedly, ECD is a diagnostic challenge for the physician who must keep in mind the existence of this pathology to be able to make the diagnosis. A high diagnostic suspicion is vital given the heterogeneity that characterizes the disease.

Patients with less diagnostic delay and, therefore, early initiation of targeted therapy, severe complications of the disease have not developed or have decreased in their expressivity, improving the patient's prognosis.

The light shed by new studies on its etiopathogenesis is allowing the discovery of promising targets for treatment and patient survival. Even so, the low incidence of the disease and the widespread ignorance that still persists makes it difficult to carry out adequate clinical trials, which are necessary for a more reliable and in-depth study.

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Conflicts of interest

The authors declare that they have no conflict of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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