ERDHEIM CHESTER DISEASE: CLINICAL PHENOTYPE AND OUTCOME. A MULTICENTRE SURVEY ECDCO01

Study coordinator
Dr Augusto Vaglio,
Dipartimento di Clinica Medica e Nefrologia
Università degli Studi di Parma
Via Gramsci 14
43100 Parma (Italy)

Tel +39 0521 702345
Fax +39 0521 033185
Email: avaglio@ao.pr.it

Participants
Dr Zahir Amoura
Service de Medecine Interne 2,
Hôpital Pitié-Salpêtrière,
Paris, France

Dr Julien Haroche,
Service de Medecine Interne 2,
Hôpital Pitié-Salpêtrière,
Paris, France

Dr Paul Scheel Jr,
Nephrology,
Johns Hopkins University,
Baltimore, USA

Background

Erdheim-Chester disease (ECD) is a rare non-Langerhans cell histiocytosis, characterized by infiltratation by xanthogranulomatous CD68+ CD1a- histiocytes, which typically affects the connective and adipose tissues[1].

ECD is characterised by heterogeneous manifestations which largely depend on the involved sites. ECD typically affects the long bones, causing non-inflammatory juxtaarticular pain mainly involving the knees and the ankles with characteristic radiological findings; other frequently involved sites include the central nervous system (e.g. diabetes insipidus, ataxia, pyramidal syndrome), retro-orbital tissues (e.g. painless exophthalmos), the lungs (e.g. interstitial fibrosis, pleural thickening), the heart (e.g. heart failure, pericarditis, tamponade), the retroperitoneum (peri-aortic, perirenal and

peri-ureteral fibrosis with or without urinary obstruction), the endocrine system (e.g. adrenal infiltration, hypogonadism) and the skin (xanthomatous lesions mainly on the eyelids). Some patients may also present with soft-tissue nodular masses (e.g. peri-vertebral, intramuscular) [1-4].

The severity of the disease varies widely, as it may range from a from pauci-symptomatic form limited to the bone to a multisystemic, life-threatening disease with poor prognosis (in a retrospective analysis of 59 published cases, 60% died within 32 months of presentation)[2]. There are no established predictors of a poor outcome, although it is believed that patients with severe central nervous system, cardiovascular or lung involvement are at higher risk of death[2, 5]. In addition, it cannot be excluded that part of the reported deaths are attributable to treatment-related complications, particularly when aggressive chemotherapy approaches are used.

The diagnosis of ECD is based upon clinical, radiological and histological findings. Although the diagnostic criteria are not well defined, the following histological characteristics and bone abnormalities on imaging studies are usually considered to be diagnostic[6]:

- Histology shows infiltration by "foamy" histiocytes, which are typically $CD68^+$ and $CD1a^-$, and lack Birbeck granules on electron microscopy; they are usually negative for $S\text{-}100^-$; positive staining for the macrophage/monocyte lineage marker CD163 and the Langerhans histiocyte marker Langerhin have also been reported. These histiocytes are usually nested among polymorphic inflammatory cells which may also be arranged in granulomatous formations; marked fibrosis is also usually found[1].
- Typical radiological features are cortical osteosclerosis of the dyaphyseal and metaphyseal region of the long bones mainly of the lower extremities but sometimes also of the upper limbs; lytic lesions can also be found; bone scanning with technetium 99 is probably the most useful examination showing symmetric and increased labelling of the distal extremities of the long bones[2] .

The pathogenesis of ECD is controversial. It is still unknown whether the infiltrating histiocytes are a clonal population, as different studies performed using the human androgen receptor gene (HUMARA) clonality assay have demonstrated clonality in a variable proportion of the patients studied[7-9]. Therefore, it is not known whether ECD is a primitive proliferative disorder or a "reactive" process, nor if there is any correlation between histiocyte clonality and disease severity.
Immunohistochemical studies have shown that a peculiar inflammatory infiltrate accompanies, and probably "drives" histiocyte accumulation in the diseased sites: the infiltrate is rich in CD4+ T cells, which are polarized towards a Th1 phenotype, given their strong expression of IFNγ; interestingly, a fraction of the infiltrating histiocytes express the chemokines CCL19/MIP-3beta and CXCL10/IP-10, which are induced by IFNγ. Other chemokines and their receptors have also been found in ECD lesions, thus supporting the hypothesis that an *in situ* cytokine and chemokine network participates in histiocyte recruitment and accumulation[10].

As a consequence of an uncertain etio-pathogenesis, the treatment of ECD is still largely empirical. The main therapeutic options for ECD are glucocorticoids, chemotherapy, immune-modulating therapy (IFNa) and radiation therapy.

- Steroids: the initial dose is usually 1 mg/Kg/day of prednisone, with its tapering varying widely among reports; steroids are useful for reducing general symptoms and in the forms with exophthalmos[2, 11].
- Chemotherapy: for patients with heavy systemic involvement. The most frequently drugs used are vinca alkaloids, cladribine, anthracyclin or cyclophosphamide[2].
- IFNa: probably the most widely used drug, it is given at the dosage of 3-9 X 10(6)U three times per week in patients with multisystemic infiltration[5]. In the largest series of patients analysed so far (8 patients treated with the same IFNa schedule), IFNa was partially effective on bone lesions, xanthelasma, exophthalmos, and systemic symptoms. However, two patients died after a median follow-up of 23 months; additionally, the treatment had to be discontinued in one case because of severe depression[5]
- Radiation therapy: it is used to treat bone pain with good but transient effect; in anecdotal cases, central nervous system lesions have been reported to respond to radiation
- Other therapies: sirolimus is being tested in an ongoing trial[12]; imatinib was used as a second-line agent for ECD patients refractory to IFNa, but without encouraging results[5]; bisphosphonates were used to treat skeletal ECD with improvement of symptoms[13].

Rationale and aims of the study

Given its protean clinical manifestations and the varying severity of the disease, identification of the different disease subsets is warranted; this could help establish the different prognosis associated with particular subsets or disease localisations. In addition, it is crucial to investigate which parameters can predict response to therapy, and whether or not certain disease localisations/complications respond better than others to specific therapies. Finally, it is important to investigate whether clinical responses correlate with improvement in ECD lesions on imaging studies and viceversa.

The study, therefore, will aim to answer questions such as a)what are the frequencies of the clinical manifestations of ECD and what are its main clinical subsets? b) are specific disease localisations/ subsets predictors of a poor outcome? c) what are the rates of response of ECD to different therapies, and do specific disease complications respond better than others? d) Do responses on imaging studies correspond to an improvement/remission of symptoms?

Methods

The project aims to collect the clinical data of about 120 patients with ECD. The clinical data will be provided by three experienced centres (Paris, Parma, Baltimore) as well as by the patients or their

relatives/caregivers who joined the ECD Global Alliance (www.erdheim-chester.org), an association of patients whose main scope is to support research and diffusion of knowledge regarding ECD.
We will review the case history of the patients, their laboratory tests and imaging studies where available. Data obtained will be used to create an electronic database.
We will also prospectively include in the study all the new ECD patients referred to the participating centres during the study period.

Inclusion criteria

- Diagnosis of ECD based on typical histological or radiological findings, as described above
- if clinical data are provided by the patients themselves→ Availability of detailed report written by the treating physician (either primary care physician or a specialist) summarising the patient's medical history
- Availability of a minimum set of imaging studies (see Appendix 1) used as tools for screening the sites most frequently involved by ECD
- Minimum follow-up of 6 months (if the patient survived >6 months); if the follow-up lasted > 12 months, a re-evaluation of the main involved sites must be available

If available, electronic or hard copies of the imaging studies (especially CT and MRI scans, X-rays, bone scintigrams) should be sent for a centralised review, in order for the study coordinators to ascertain whether the lesions are actually secondary to ECD (and not due to other comorbidities). If the data are provided by one of the main participating centres, the review of the imaging studies will be performed on site.

The study will directly involve the patients or their caregivers, who will actively participate through completing a symptom questionnaire form (see Appendix 2); this form will be returned to the coordinating centre along with a signed consent form, which will allow the study coordinators to use the patient clinical data.

Expected results

The objective of the study is to get a "picture" of the characteristics of the patient at the diagnosis basing our observation on the largest population of ECD patients ever reached. This study should expand the knowledge on this rare disease, thus allowing earlier diagnosis, better classification of the different disease forms, and improved prediction of the patient prognosis.
In addition, the results of the study will probably provide, for the first time, systematic data concerning the efficacy of the different treatment approaches attempted so far, with particular emphasis on the responsiveness of certain disease complications to specific treatments.

Statistical analysis

The clinical data of different subgroups of ECD patients will be compared using t test for unpaired data and Mann Whitney U test as appropriate for continuous variables; Fisher's exact test will be used for categorical variables.

Patient survival will be analysed in the different subgroups and in the whole cohort by the log-rank test according to the Kaplan Meier method.

The data will be analysed using SPSS statistical software version 17.0

Ethical considerations

The study will be submitted to the Ethics Committee of the University Hospital of Parma (Italy). A consent form will be generated and every participating patient will have to sign a consent form. The identity of the patients will always remain anonymous, and their names will be replaced in the database by an alphanumeric code.

References

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Appendix 1

Required screening studies

- Bone scintigram (Bone Technetium^{99} scan) and /or X-rays of the long bones
- Brain MRI
- Chest CT scan
- Abdominal CT scan
- Dermatological examination (performed by a specialist or a short report by the primary care physician)
- Clinical diagnosis of diabetes insipidus (Yes/No); if available, MRI of the brain should include scans of the pituitary gland
- Echocardiography and/or cardiac MRI
- Clinical diagnosis of hypogonadism (central/peripheral) (Yes/No) and other hormonal disorders
- Clinical diagnosis of exophthalmos and/or MRI or CT scans of the orbits

Desirable tests

- PET or PET-CT scans
- CT scan of the paranasal sinuses
- Serum levels of: prolactin, testosterone, ADH, ACTH, TSH.

Appendix 2

Symptom questionnaire form

Patient Name (last, first, middle initial):

Phone Number:

E-mail address:

_____

Address:

Date Completed:

Patient Demographics

Date of Birth (mm/dd/yy): _____

Residence (city, state/region, country): _____

Sex: ☐ Female ☐ Male

Ethnic Background (choose all that apply, make notes as you feel appropriate):

- ☐ American Indian/Eskimo _____
- ☐ Asian _____
- ☐ White/Caucasian _____
- ☐ Black/African _____
- ☐ Hispanic/Latino _____
- ☐ Pacific Islander _____
- ☐ Middle Eastern _____
- ☐ Other _____

ECD Specifics

Date ECD Symptoms Began (mm/dd/yy): _____

Date ECD Diagnosed (mm/dd/yy): _____

Known Organ Involvement.

(If possible, please place numbers in the leading blanks to denote the suspected evolutionary sequence of the involvement with lower numbered items representing earlier involvement. If this is not possible, please just check which organs have been affected by ECD. Trailing blanks are for any special notes you would like to include.)

_____ Bones

Which bones (if known) _____

_____ Eyes _____

- ☐ Orbital mass
- ☐ Nerve compression

_____ Pituitary _____

_____ Adrenal _____

_____ Kidney _____

- ☐ Artery
- ☐ Ureter
- ☐ Kidney infiltration

_____ Brain _____

- ☐ Mass
- ☐ Lesions

_____ Cardio-Vascular _____

- ☐ Heart
- ☐ Arteries

_____ Lung _____

_____ Retroperitoneal Area _____

_____ Thyroid _____

_____ Spine _____

_____ Skin _____

_____ Endocrine deficiencies (for example, hypogonadism) _____

_____ Other (please explain) _____

Treatments Tried

Please check those treatments the patient has tried. Provide as much data as you have related to each treatment tried.

(Often times it is difficult to tell if a symptom is a side effect of medication, if it is a symptom of the disease, or if it is totally unrelated to either. In noting the issues the patient is facing, please make a 'best guess' as to the root cause of the issue. If your Doctors believe it is a side effect of medication, please note the symptom as a side effect in the table immediately below. If your Doctor believes it is a symptom of the disease or even think it is unrelated to the disease in any way, please note it in the symptom table following this table.)

Treatment	Tried? Yes/No	Approx. Date Started	Approx. Date Ended	Side Effects	Results (if known) No Change? Slowed Progression? Stopped Progression? Reduced Masses?	Notes (Dosage, protocol, etc.)
☐ Interferon						
☐ Cladribine (2CDA)						
☐ Imatinib (Gleevec)						
☐ Tamoxifen						
☐ Methotrexate						
☐ Vinblastine						
☐ Mycophenolic acid (Cellcept)						
☐ Sirolimus (rapamycin, Rapamune)						
☐ Azathrioprine(Imuran)						
☐ Inflixomab(Remicade)						
☐ Steroids						
☐ Surgery						

Treatment	Tried? Yes/No	Approx. Date Started	Approx. Date Ended	Side Effects	Results (if known) No Change? Slowed Progression? Stopped Progression? Reduced Masses?	Notes (Dosage, protocol, etc.)
☐ Radiation						
☐ Long term antibiotics						
☐ Other: _____						

Symptoms & Issues the Patient is Facing

Please check those symptoms the patient has experienced, even if they no longer are experiencing the symptom. Provide as much data as you have related to each symptom experienced.

(Often times it is difficult to tell if a symptom is a side effect of medication, if it is a symptom of the disease, or if it is totally unrelated to either. In noting the issues the patient is facing, please make a 'best guess' as to the root cause of the issue. If your Doctors believe it is a symptom of the disease or even think it is unrelated to the disease in any way, please note it in the table immediately below. If your Doctors believe it is a side effect of medication, please note it in the treatment table above as a side effect.)

Neurological Symptoms

Neurological Symptom	**Impact Level:** **Minimal** (no impact to dialing living) **Moderate** (slows down patient and limits activity) **Excessive** (prevents patient from performing daily living activities required to care for oneself)	**Approximate Date Symptom First Noticed**	**Status of Symptom at the moment (improve, stable, worsened)**	**Notes** (please include any treatments that have been successful in combating the symptom or to better localize the symptoms, i.e. witch kind of balance is involved (static or dynamic?))
☐ Balance				
☐ Speech				
☐ Short term memory loss				
☐ Depression				
☐ Nerve Pain – Location _____				
☐ Other – _____				

Bone Symptoms

Bone Symptom	**Impact Level:** **Minimal** (no impact to dialing living) **Moderate** (slows down patient and limits activity) **Excessive** (prevents patient from performing daily living activities required to care for oneself)	**Approximate Date Symptom First Noticed**	**Status of Symptom at the moment (improve, stable, worsened)**	**Notes** (please include any treatments that have been successful in combating the symptom or to better localize the symptoms, i.e. which bones are involved)
☐ Pain				
☐ Fracture				
☐ Other _____				

Eye Symptoms

Eye Symptom	**Impact Level:** **Minimal** (no impact to dialing living) **Moderate** (slows down patient and limits activity) **Excessive** (prevents patient from performing daily living activities required to care for oneself)	**Approximate Date Symptom First Noticed**	**Status of Symptom at the moment (improve, stable, worsened)**	**Notes** (please include any treatments that have been successful in combating the symptom or to better localize the symptoms, i.e. which eye is involved)
☐ Loss-Reduction of sight				
☐ Double vision				
☐ Other – _____				

Abdominal Symptoms

Abdominal Symptom	**Impact Level:** **Minimal** (no impact to dialing living) **Moderate** (slows down patient and limits activity) **Excessive** (prevents patient from performing daily living activities required to care for oneself)	**Approximate Date Symptom First Noticed**	**Status of Symptom at the moment (improve, stable, worsened)**	**Notes** (please include any treatments that have been successful in combating the symptom or to better localize the symptoms)
☐ Diarrhea				
☐ Constipation				
☐ Vomiting				
☐ Other – _____				

Lung Symptoms

Lung Symptom	**Impact Level:** **Minimal** (no impact to dialing living) **Moderate** (slows down patient and limits activity) **Excessive** (prevents patient from performing daily living activities required to care for oneself)	**Approximate Date Symptom First Noticed**	**Status of Symptom at the moment (improve, stable, worsened**	**Notes** (please include any treatments that have been successful in combating the symptom or to better localize the symptoms)
☐ Shortness of breath				
☐ Oxygen requirement				
☐ Other – _____				

Skin Symptoms

Skin Symptom	**Impact Level:** **Minimal** (no impact to dialing living) **Moderate** (slows down patient and limits activity) **Excessive** (prevents patient from performing daily living activities required to care for oneself)	**Approximate Date Symptom First Noticed**	**Status of Symptom at the moment (improve, stable, worsened**	**Notes** (please include any treatments that have been successful in combating the symptom or to better localize the symptoms, i.e. leg or nose)
☐ Rashes				
☐ Unusual bumps or knots				
☐ Itching				
☐ Other – _____				

Urinary Tract Symptoms

Urinary Tract Symptom	**Impact Level:** **Minimal** (no impact to dialing living) **Moderate** (slows down patient and limits activity) **Excessive** (prevents patient from performing daily living activities required to care for oneself)	**Approximate Date Symptom First Noticed**	**Status of Symptom at the moment (improve, stable, worsened**	**Notes** (please include any treatments that have been successful in combating the symptom or to better localize the symptoms)
☐ Urgent need to urinate				
☐ Reduced urination				
☐ Other – _____				

Dental Symptoms

Dental Symptom	**Impact Level:** **Minimal** (no impact to dialing living) **Moderate** (slows down patient and limits activity) **Excessive** (prevents patient from performing daily living activities required to care for oneself)	**Approximate Date Symptom First Noticed**	**Status of Symptom at the moment (improve, stable, worsened**	**Notes** (please include any treatments that have been successful in combating the symptom or to better localize the symptoms)
☐ Tooth loss				
☐ Jaw loss				
☐ Other - _____				

Hearing Loss Symptoms

Hearing Loss Symptom	**Impact Level:** **Minimal** (no impact to dialing living) **Moderate** (slows down patient and limits activity) **Excessive** (prevents patient from performing daily living activities required to care for oneself)	**Approximate Date Symptom First Noticed**	**Status of Symptom at the moment (improve, stable, worsened**	**Notes** (please include any treatments that have been successful in combating the symptom or to better localize the symptoms)
☐ Hearing loss				
☐ Other - _____				

Cardio Vascular Symptoms

Cardio Vascular Symptom	**Impact Level:** **Minimal** (no impact to dialing living) **Moderate** (slows down patient and limits activity) **Excessive** (prevents patient from performing daily living activities required to care for oneself)	**Approximate Date Symptom First Noticed**	**Status of Symptom at the moment (improve, stable, worsened**	**Notes** (please include any treatments that have been successful in combating the symptom or to better localize the symptoms)
☐ Irregular heart rate				
☐ Chest Pain				
☐ Other - _____				

Muscle Symptoms

Muscle Symptom	**Impact Level:** **Minimal** (no impact to dialing living) **Moderate** (slows down patient and limits activity) **Excessive** (prevents patient from performing daily living activities required to care for oneself)	**Approximate Date Symptom First Noticed**	**Status of Symptom at the moment (improve, stable, worsened**	**Notes** (please include any treatments that have been successful in combating the symptom or to better localize the symptoms)
☐ Muscle Pain				
☐ Muscle cramps				
☐ Other - _____				

Sinus Symptoms

Sinus Symptom	**Impact Level:** **Minimal** (no impact to dialing living) **Moderate** (slows down patient and limits activity) **Excessive** (prevents patient from performing daily living activities required to care for oneself)	**Approximate Date Symptom First Noticed**	**Status of Symptom at the moment (improve, stable, worsened**	**Notes** (please include any treatments that have been successful in combating the symptom or to better localize the symptoms)
☐ Sinusitis				
☐ Rhinitis				
☐ Excessive mucus (running nose, sinus drainage, etc)				
☐ Other - _____				

General Symptoms

General Symptom	**Impact Level:** **Minimal** (no impact to dialing living) **Moderate** (slows down patient and limits activity) **Excessive** (prevents patient from performing daily living activities required to care for oneself)	**Approximate Date Symptom First Noticed**	**Status of Symptom at the moment (improve, stable, worsened**	**Notes** (please include any treatments that have been successful in combating the symptom or to better localize the symptoms)
☐ Fatigue				
☐ General Pain or Discomfort, Location: _____				
☐ Fevers of Unknown Origin				
☐ Anxiety				
☐ Weight Loss, Amount _____				
☐ General ill feeling				
☐ Other, _____				

Misdiagnosis

Please note any diseases you may have been diagnosed with earlier in your life that you and/or your doctor now feel were made in error. Please feel free to add in any notes you feel appropriate:

☐ Endocrinological, specific

_____

☐ Hypophysitis

_____

☐ Langerhans's cell histiocytosis

_____

☐ Lymphoma

_____

☐ Cancer

_____

☐ Meningiomas

_____

☐ Metabolic disorders

_____

☐ Multiple Sclerosis

_____

☐ Myelofibrosis

_____

☐ Neurosarcoidosis

_____

☐ Pagets Disease

_____

☐ Pseudotumor

_____

☐ Retroperitoneal Fibrosis or Ormond's Disease

_____

☐ Thyroid abnormalities

_____

☐ Other

_____

Other Diseases Suffered, not directly ECD Related

Please note any other diseases you may have faced at some time or another that did not fit in a category above. Please feel free to add in any notes you feel appropriate:

☐ Coronary Artery Disease, specific

_____

☐ Gall Bladder problems, specific

_____

☐ Uterine Fibroids

_____

☐ Hypo/Hyper-thyroidism

_____

☐ Diabetes (sugar)

_____

☐ High Blood Pressure

_____

☐ Edema/swelling, location

_____

☐ High cholesterol, HDL/LDL levels

_____

☐ Major depression

_____

☐ Psychosis

_____

☐ Bone fractures,
location_____

☐ Severe infections, location and
type_____

☐ Cancer, location and type

_____

☐ Other,

_____

_____

Current Medication

Please list all medicines you are currently taking, including over the counter medication.

Medicine	Dosage Amount (mg, mil, etc.)	How often taken (1/day, 2/day, 1/week, as needed, etc.)

Family History

Please list known diseases of blood relatives. Please be sure to include any autoimmune diseases, blood diseases, cardiac diseases, kidney diseases, eye diseases, cancers, etc.

Disease	Relative (mother, father, male child, female child, grandfather, grandmother,, male grandchild, female grandchild, brother, sister and aunt, uncle, male cousin or female cousin)	Mother or Father's Side (if appropriate)	Notes

Your Doctors

If you feel it appropriate, please give us the name and contact information of your doctor(s). If you want us to contact your doctor to see if (s)he wants us to include her/his name on our website, please note this the appropriate column. If you do not give permission, we will not contact them. Thank you.

Name	Specialty	E-mail address	Phone Number	Permission to Contact?

Your Comments

Please give us your thoughts. Are there any other issues you would like someone to know about your past? Any ideas or suspicions you might have concerning your medical history? Feel free to provide any input you would like here.

Hard copies of imaging studies sent to us:

Imaging study	Date(s)
☐ Bone Scintigram	
☐ X-rays of the long bones	
☐ Brain MRI	
☐ Chest CT scan	
☐ Abdominal CT scan	
☐ Echocardiography	
☐ Cardiac MRI	
☐ MRI scans of the orbit	
☐ CT scans of the orbit	
☐	
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Copy of the blood tests result sent: