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# Erdheim-Chester disease complicated by Septic arthritis: A rare disease and uncommon association.

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**Case Report**

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# Abstract

Erdheim-Chester disease (ECD) is a predominantly male form of non-Langerhansian histiocytosis, the pathophysiology of which is poorly understood. The clinical picture is heterogeneous. The presence of hairy kidney images on CT scan is pathognomonic. Diagnosis is anatomopathological. We report the case of a diabetic patient, aged 60, who presented with acute monoarthritis of the left knee in a context of notion, fever and chills. Clinical examination revealed flatus and swelling of the knee with functional impotence of the limb and palpebral xanthelasma. Radiological and biological investigations were in favour of septic arthritis with underlying asymptomatic non-Langerhansian histiocytosis. ECD is an extremely rare entity. Systemic forms generally have a poor prognosis and are refractory to treatment, unlike our asymptomatic case.


# Introduction

Erdheim-Chester disease (ECD) is a rare non-Langerhans cell histiocytosis, the aetiology of which is unclear. The diagnosis is most often made during the fifth decade of life, although paediatric and geriatric forms have also been reported. The disease was first described in 1930 by the Viennese pathologist Jakob Erdheim and his American student William Chester under the name lipoid granulomatosis. Between then and 2013, more than 500 cases were published in the global medical literature (1). ECD results from xanthogranulomatous infiltration consisting of foamy histiocytes, sometimes with Touton giant cells (2). The immunological characteristics of ECD histiocytes allow them to be differentiated from those of Langerhans cell histiocytosis (LCH); in ECD, immunolabelling is positive for CD68 and negative for CD1a, whereas in LCH, CD68 and CD1a are positive; in addition, S100 protein is negative in most cases (80%) of ECD. ECD is a true multisystemic disease with highly variable clinical manifestations: infiltration of long bones causing pain, exophthalmos, diabetes insipidus, xanthelasma, interstitial lung disease, bilateral adrenal infiltration, retroperitoneal fibrosis with infiltration perirenal or ureteral, causing hydronephrosis and renal failure, testicular infiltration, and damage to the central nervous system (CNS) and cardiovascular system (2), (3). Erdheim-Chester disease (ECD) is a rare, non-Langerhans cell histiocytosis. Recent findings suggest that ECD is a clonal disorder, characterised by recurrent mutations in the BRAFV600E gene in more than 50% of patients, and in which uncontrolled chronic inflammation plays an important role in its pathogenesis (4). Two highly suggestive diagnostic signs are hyperfixation of long bones on 99Tc bone scintigraphy (almost constant) and the ‘hairy kidney’ appearance on abdominal computed tomography. An ‘elegant’ diagnostic method for the disease is ultrasound-guided biopsy of perirenal infiltration. Cardiovascular involvement, which affects both the aorta (‘periaortic sleeve’) and all the cardiac tunics, is responsible for one-third of deaths. Central neurological involvement (particularly cerebellar) is severe and difficult to treat. The prognosis, which varies greatly from one form to another, is often poor in the presence of cardiovascular and/or central neurological involvement (1). We report the case of a 60-year-old female patient, discovered incidentally following treatment for acute septic arthritis in the Rheumatology Department of the Mohammed V Military Teaching Hospital in Rabat.

## Patient and observation

We report the case of a 60-year-old female patient with non-insulin-dependent diabetes treated with a combination of insulin therapy, sulphonylureas and biguanides. The patient consulted the emergency department for monoarthritis of the left knee, which had been developing for a week, accompanied by fever, but with no obvious signs of infection or deterioration in her general condition. On clinical examination, the patient was oriented in time and space and remained in a stable general condition. Examination of the left lower limb revealed painful swelling, local heat, redness, significant functional impairment with a flexion deficit of 20° and pain on pressure of the left knee.

The rest of the osteoarticular and spinal examination showed no notable abnormalities, and no infectious entry point was identifiable. She had non-pruritic periocular papules. Dermatological examination revealed multiple orange-yellow papules, grouped in symmetrical patches around the eyes. A diagnosis of xanthelasma (Fig. 1) was made for our patient. Cardiac and pulmonary auscultation, abdominal examination, and neurological examination were also clinically normal, with no additional sounds, murmurs, or organomegaly.

## *Diagnostic approach*:

The patient was admitted to hospital for further investigations. Joint puncture revealed purulent fluid with a cytobacteriological study showing 8,000 white blood cells/mm³, 81% of which were neutrophils. The joint fluid culture was sterile. The complete infectious assessment, including blood cultures, was unremarkable. The blood count revealed hyperleukocytosis and hypochromic microcytic anaemia. We observed a significant biological inflammatory syndrome with elevated C-reactive protein (CRP). Renal and hepatic function tests were normal. Phosphocalcic function tests were normal. Diabetes was uncontrolled, with hyperglycaemia and elevated glycated haemoglobin (Hb1AC: 10%). Hormone tests showed hypogonadism with decreased luteinising hormone (LH) and follicle-stimulating hormone (FSH), elevated prolactin at more than three times the normal level, and normal antidiuretic hormone (ADH).

An osteoarticular ultrasound of the left knee, performed during the puncture, revealed significant effusion in the quadriceps recess, as well as infiltration of the soft tissues. In addition, standard X-rays of the knees (Fig. 2) showed images of bilateral cortical and lytic osteosclerosis, symmetrical at the metaphysis-diaphysis of the long bones, particularly marked on the right (healthy knee) compared to the left knee, suggesting non-Langerhans cell histiocytosis.

Due to the suggestive nature of these radiological images, a bone scan was performed, revealing bilateral and quasi-symmetrical hyperfixations in the forearm bones, tibias, and lower thirds of the femurs, as well as a hyperfixation focus in the left humeral head, accompanied by increased fixation in the mandible. This scintigraphic profile is typically observed in Erdheim-Chester disease (Fig. 3). A thoraco-abdominal-pelvic (TAP) computed tomography (CT) scan (Fig. 4) revealed osteoarthritis of the left knee, as well as peri-pyelic and peri-ureteral thickening, causing ureteropelvic-calyceal dilatation of the right pyelon relative to the left pyelon, and slight infiltration of the right perirenal fat. A brain MRI

showed thickening of the pituitary stalk (Fig. 5), reinforcing our diagnostic hypothesis of Erdheim-Chester disease. Abdominal ultrasound revealed no abnormalities. Bone mineral density (BMD) showed osteopenia.

A bone biopsy (Fig. 6) was performed with immunohistochemistry showing diffuse CD68 staining and weak, focal CD1a staining, confirming our diagnostic hypothesis. We were unable to perform BRAF mutation analysis.

The diagnosis of septic arthritis developing on a background of asymptomatic non-Langerhans cell histiocytosis was retained. The patient received intravenous dual antibiotic therapy with good clinical and biological response to the joint infection, and oral maintenance treatment was recommended for a total treatment duration of 6 weeks. For the underlying disease, a wait-and-see approach with close monitoring was initially adopted. However, given the persistence of the biological inflammatory syndrome and the thickening of the pituitary stalk, uretero-pylo-calyceal dilatation, and infiltration of the right perirenal fat, treatment with infliximab was initiated with an unfavourable biological outcome, then switched to anakinra with a favourable clinical and biological outcome and close monitoring.

## Discussion

Erdheim-Chester disease (ECD) is a form of non-Langerhans cell histiocytosis affecting multiple systems, the pathophysiology of which is poorly understood. The most common sites of involvement are the bones, kidneys, eyes, endocrine system, nervous system, and cardiovascular system (5). Men are affected in 70% of cases. It has been described in all age groups, with a peak between 50 and 70 years of age. The time to consultation often exceeds one year, as in our case (6). Clinical signs depend on the organs affected. Indolent forms exist with simple asymptomatic bone lesions. Systemic forms are aggressive, with a risk of life-threatening complications if vital organs are affected. Bone manifestations are common and pathognomonic in ECD, reported in 40% of cases according to Haroche et al. In a series of 53 patients, they are asymptomatic in 50% of cases of disseminated forms, similar to our patient, and particularly affect the diaphysis and metaphysis of long bones, as in our case. Imaging is characteristic, with the presence of osteosclerosis and bone condensation on CT scans, and obvious hyperfixation on bone scintigraphy (5), (7). Central nervous system involvement, present in our patient, is described in 40 to 50% of cases, depending on the series. The most common locations are hypothalamic-pituitary, pituitary, cerebellar (observed in our patient) and meningeal (8). The clinical picture is non-specific and marked by major disability. Imaging shows multifocal and non-specific involvement. Pituitary involvement is responsible for endocrinopathy, particularly hypogonadism, diabetes insipidus and hyperprolactinemia, which is similar to our case. Retro-orbital infiltration and facial involvement are concomitant in the majority of cases with neurological involvement and suggest the diagnosis (9). Retroperitoneal fibrosis is described in one-third of cases. It often affects the adrenal glands, kidneys (appearing hairy on abdominal CT scans) and excretory tract, with a risk of obstructive renal failure and renovascular hypertension (10). The prognosis for MEC depends on whether or not the disease is symptomatic. The progression of symptomatic forms depends on the organs affected. Neurological

involvement is a poor prognostic factor affecting survival. ECD is a multisystemic condition whose pathophysiology was poorly understood. The pathophysiology of ECD was poorly understood until recently, with most studies involving only a few patients. Stoppacciaro et al. demonstrated in an immunohistochemical study based on biopsies from three patients the existence of a complex network of cytokines and chemokines, responsible for the recruitment and accumulation of histiocytes within tissues. Dagna et al. studied the spontaneous production of interleukin (IL)-6 and IL-8, and after stimulation, tumour necrosis factor-alpha (TNFα) by mononuclear cells from biopsy fragments from a single patient. Depending on the series, overall, 5-year survival in ECD can reach 60%, with mortality estimated at 26% in the series by Haroche et al. ECD is a multisystemic condition whose pathophysiology was poorly understood. The pathophysiology of ECD was poorly understood until recently, with most studies involving only a few patients. Stoppacciaro et al. demonstrated in an immunohistochemical study based on biopsies from three patients the existence of a complex network of cytokines and chemokines, responsible for the recruitment and accumulation of histiocytes within tissues. Dagna et al. studied the spontaneous production of interleukin (IL)-6 and IL-8, and after stimulation, tumour necrosis factor-alpha (TNFα) by mononuclear cells from biopsy fragments from a single patient (11). The particularity of our case lies in the favourable outcome under Anakinra treatment after failure of infliximab, with satisfactory long-term results despite the aggressive nature of the disease.

## Conclusion

Non-Langerhans cell histiocytosis is a very rare condition. The prognosis depends on the organs affected. Thorough examination and recognition of the images of condensed lytic osteosclerosis will allow the incidental discovery of several asymptomatic cases.

This case illustrates the diagnostic complexity of rare diseases such as Erdheim-Chester disease, where an apparently mundane clinical presentation (in this case, knee arthritis accompanied by fever) may reveal a serious underlying systemic pathology. It emphasises that clinicians must remain alert to atypical features and pursue further investigation when standard hypotheses fail to fully explain a patient's condition. Early recognition of ECD is essential, as prompt intervention can prevent target organ damage and improve outcomes.

## Abbreviations

ADH
antidiuretic hormone.
BMD
Bone mineral density
BRAFV600E
genetic mutation where the amino acid valine (V) is replaced by glutamic acid (E) at position 600 of the BRAF protein

CNS
central nervous system
CRP
C-reactive protein
CT scan
computed tomography scan
ECD
Erdheim-Chester disease
FSH
follicle-stimulating hormone
HbA1c
Hemoglobin A1c or glycated hemoglobin
HL
Langerhans cell histiocytosis
IL-
interleukin
LCH
Langerhans cell histiocytosis
LH
luteinising hormone
TAP
thoraco-abdominal-pelvic
TNFα
tumour necrosis factor-alpha

## Declarations

**Funding**: ‘not applicable’ -Consent to participate: All participants gave their informed written consent to publication in accordance with the Declaration of Helsinki

**Ethical approval and reference number**: The Biomedical Research Ethics Committee of Mohammed V University granted approval (approval number: 86/26).

Data are available

# Author Contribution

SK, et HT drafted the main text of the manuscriptAAG et MS analysed the imagesAB made corrections to the form and content of the manuscriptAll the authors have proofread the manuscript

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# Figures

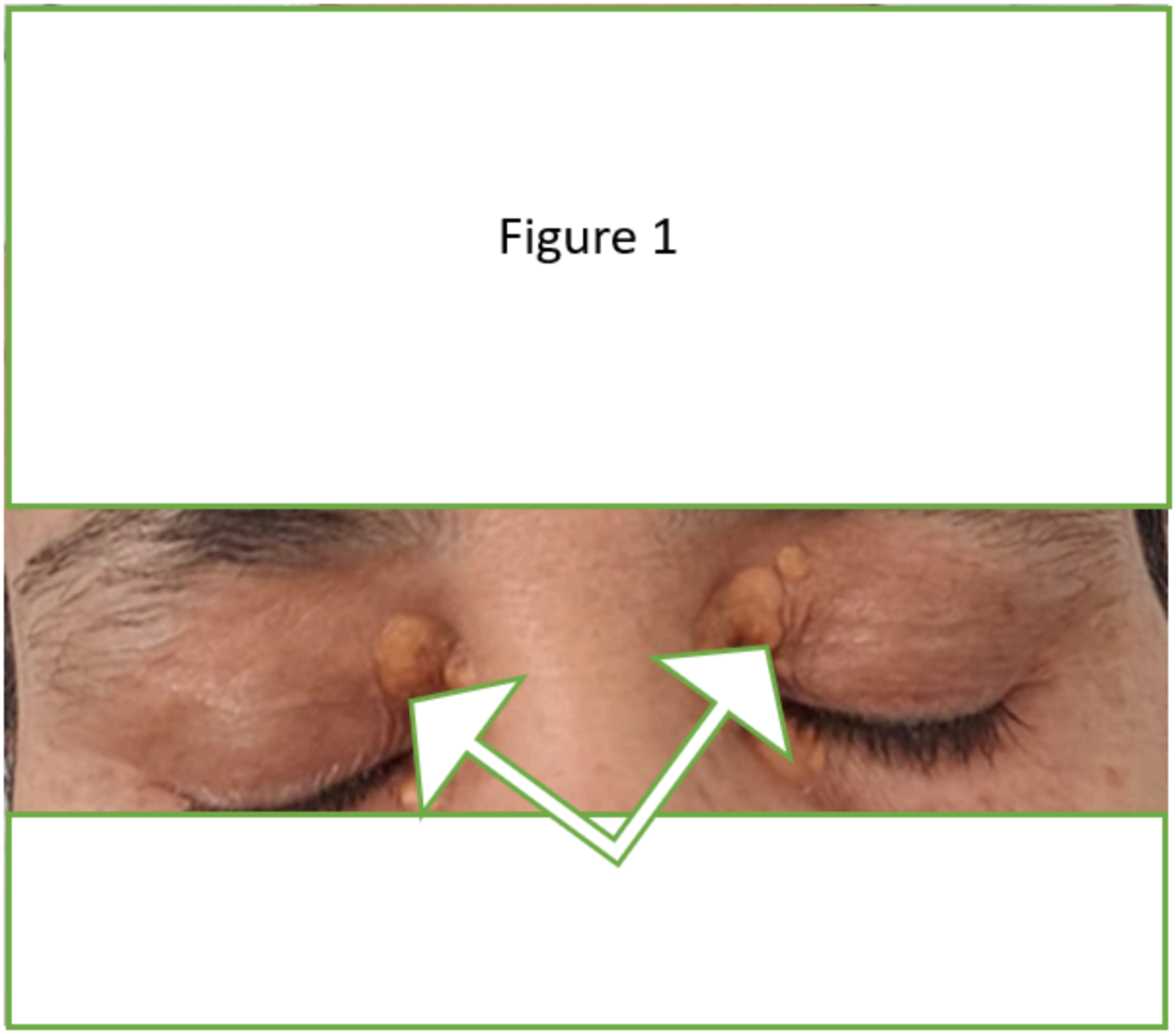



**Figure 1**

showing xanthelasma




**Figure 2**

Anteroposterior radiograph of the knees showing bilateral mixed sclerotic and lytic lesions at the distal femurs and proximal tibias. The lesions involve the diaphyses, metaphyses, and extend to the epiphyses, accompanied by cortical thickening (white arrows). These findings are characteristic of Erdheim-Chester disease.

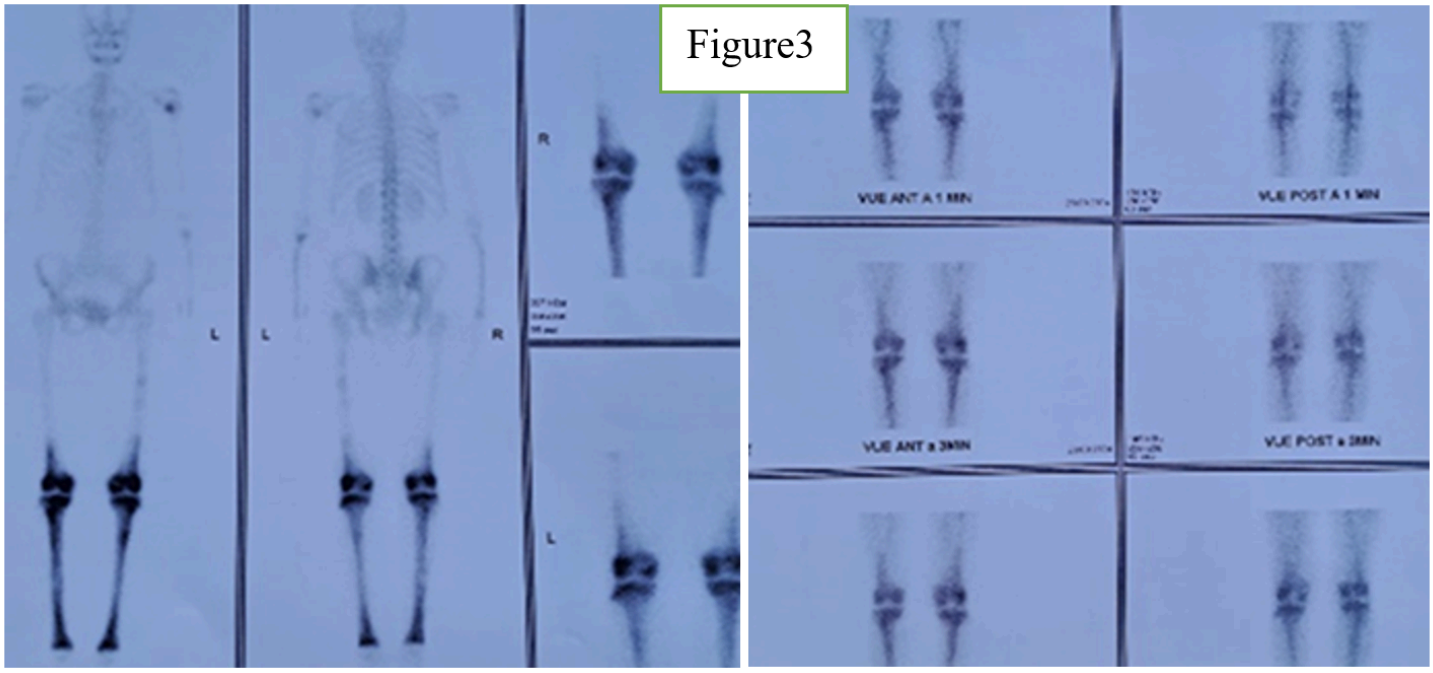



**Figure 3**

***TEP-Scan*** Technetium-99m bone scintigraphy revealing bilateral, nearly symmetrical increased uptake in the long bones. There is intense tracer uptake in the forearm bones, tibiae, and distal femurs, as well as in the left humeral head and mandible (arrowheads). Notably, there is no significant uptake in the axial skeleton (spine or pelvis), a pattern typical of Erdheim-Chester disease.

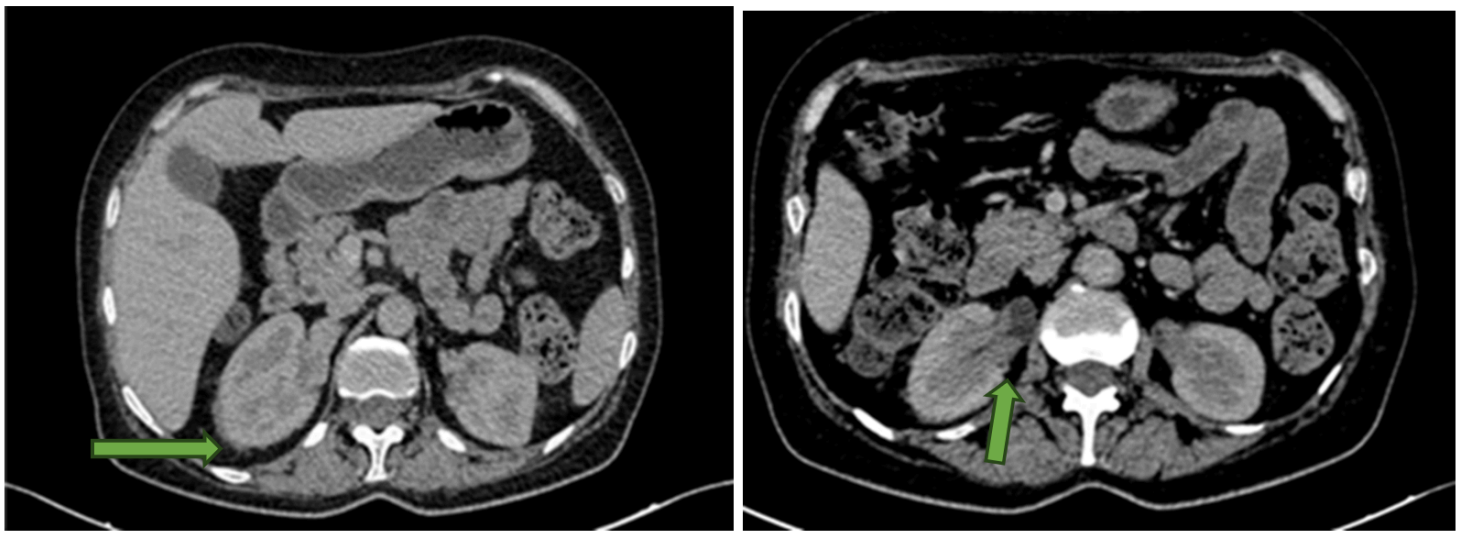


**Figure 4**

Abdominal CT scan

Abdominal CT scan (coronal view) showing mild infiltration of the perirenal fat (more pronounced around the right kidney, red arrow) and a concentric soft-tissue rind around both renal pelvises (peri-pyelic

fibrosis, white arrow). This fibrosis has led to dilation of the collecting systems – the right renal pelvis measures 23 mm and the left 13 mm (hydronephrosis). These findings reflect retroperitoneal involvement by ECD. The lesions did not enhance with contrast in delayed phases and were not detectable on ultrasound.

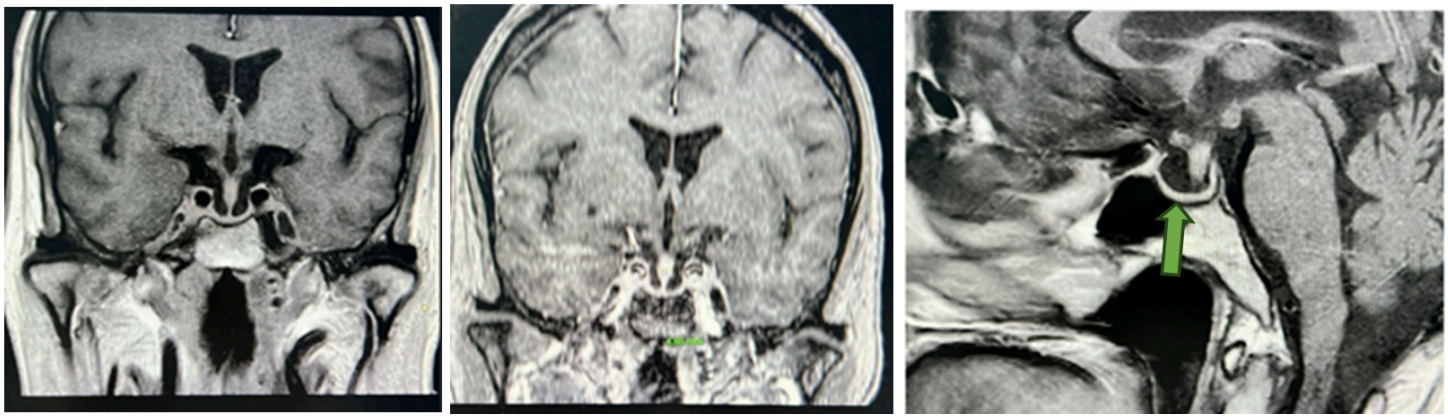


**Figure 5**

IRM cérébrale (pondérée en T1 après injection de gadolinium)

Brain MRI (T1-weighted post-gadolinium) demonstrating a thickened, abnormally enhancing pituitary stalk (yellow arrow). In addition, the normal bright signal of the posterior pituitary on T1 (indicative of stored vasopressin) is absent, consistent with diabetes insipidus. An incidental arachnoid cyst is noted in this image (not marked). Pituitary stalk lesions with enhancement are frequently seen in ECD and often correlate with diabetes insipidus and other pituitary dysfunctions.

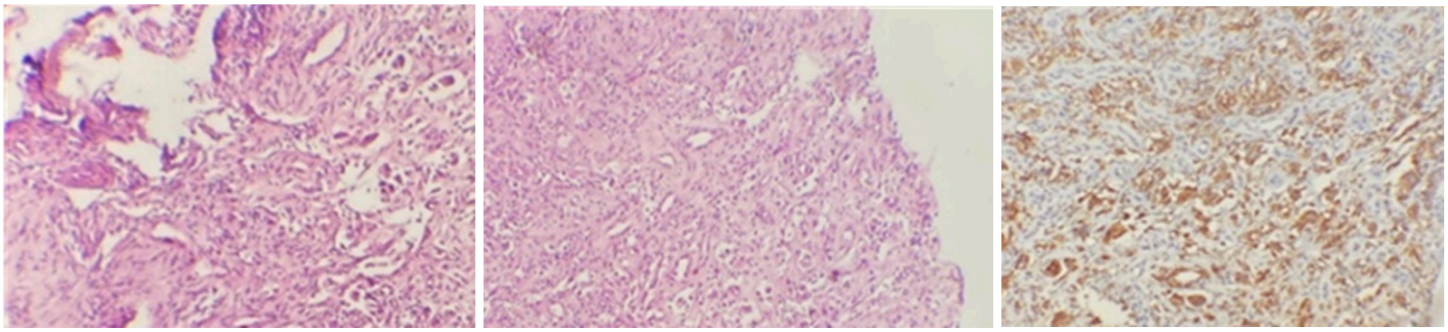


**Figure 6**

Histopathology of a cutaneous xanthelasma lesion from the patient (H&E stain, 200× magnification). The dermis is infiltrated by a dense proliferation of histiocytes with foamy, eosinophilic (“oncocytic”) cytoplasm (black arrow). Scattered lymphocytes and occasional neutrophils are present in the inflammatory background. Immunohistochemical staining of the lesion showed diffuse CD68 positivity in the histiocytes and focal CD1a positivity (not shown in image). The overall morphology and

immunoprofile are consistent with a xanthogranulomatous histiocytic lesion, as seen in Erdheim-Chester disease, with no evidence of malignancy