Erdheim-Chester disease with long-standing diabetes insipidus and generalized edema

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Abstract

Erdheim–Chester disease (ECD) is a rare non-Langerhans disease. This report describes a 51-year-old woman with a history of weakness, bone pain, xanthelasma palpebrarum, diabetes insipidus, and hypothyroidism. ECD is a multisystemic condition with a poor prognosis. This disease should be considered in patients with diabetes insipidus and multiorgan involvements.

Key clinical message

ECD is a rare and aggressive type of non-Langerhans histiocytosis with an unknown etiology. This disease should be considered in patients with longstanding diabetes insipidus and multiorgan involvements.

Introduction

Erdheim–Chester disease (ECD) is a rare, non-familial, and non-Langerhans histiocytic disorder with an unknown etiology. It was named after description of two "lipoid granulomatosis" cases by William Chester and Jakob Erdheim in 1930 (1). The real prevalence of ECD is unknown, but based on a multicenter 53-patient case-series, it is more common to be diagnosed between the ages of 40 and 70 years with a median of 57, and it's 3 times more prevalent among men (2, 3).

While it is seemed to be a reactive or neoplastic disorder, recent studies detected a mutation in the BRAF gene in most of ECD patients. This recent identification of the clonal nature of the disorder has changed our understanding of the pathogenesis of the disease (4). Few attempts had been made to determine the clonality of the non-Langerhans' cell histiocytes in ECD (5). ECD is diagnosed based on clinical manifestations and imaging features confirmed by histopathologic and immunohistochemical findings, such as positive CD68 and negative CD1a and S-100 (4, 6).

ECD is most common in middle-aged men. The disease initially affects the skeletal system, leading to an abnormal increase in bone density and fibrosis, followed by severe pain. About 95% of patients develop skeletal symptoms in which bone pain is the first (4). The most common sites involved are distal of the femur and proximal of tibia and fibula (7). Symmetric bilateral long bone lesions found in magnetic resonance imaging (MRI) and technetium-99m bone scintigraphy can be used for confirmation of the diagnosis (8), these lesions are also obvious in 18fluoro-2-deoxy-d-glucose (18FDG) positron emission tomography/computed tomography (PET)/CT scanning, but sometimes it is hard to be diagnosed based on plain radiographs (9). PET scan seems to be a proper choice for the assessment of disease activity because of extraskeletal signs and symptoms of the disease. These extraskeletal involvements include diabetes insipidus, neurologic symptoms like cognitive impairment or seizure, pulmonary symptoms such as dyspnea or cough, cutaneous lesions and xanthelasma, pericardial effusion, and retroperitoneal involvement (10, 11).

Currently, there are lots of evidence to support Interferon-α (IFN-α) and Pegylated IFN-α as first-line therapy for the disease. Other medications such as anakinra, an anticytokine agent, have been shown to be effective, especially in patients without CNS involvement (3).

Although the 5-year survival of ECD patients treated with IFN-α is reported 68%, but the overall disease prognosis is considered poor (3).

In this paper, we present a patient with ECD, who revealed a history of prolonged DI, generalized edema, and xanthomas. We describe its clinical presentations and discuss in this rare entity, clinical course, and its treatment.

Case report

A 51-year-old woman was admitted to our endocrinology ward with a history of weakness, anemia, bone pain (since 2 years ago), xanthelasma palpebrarum (Figure 1), and ulcerative skin lesions (since 5 years ago), and progressive generalized edema (since 1 month ago). She has had diabetes insipidus (DI) since 12 years ago treated with desmopressin. She is also under treatment for hypothyroidism by levothyroxine. The patient was aware and awake with normal vital signs. Thyroid examination was remarkable of a right lobe nodule, deep tendon reflexes of lower limbs were absent, and left lower limb had decreased muscular force (3/5).

Laboratory findings revealed inflammatory disease anemia (Hb=9.1 g/dL), elevated serum alkaline phosphatase (155 U/L), lactate dehydrogenase (174 U/L), and 24h urine protein (594 mg), and low serum albumin (2.2 g/dL) and total protein (3.8 g/dL). Anterior pituitary hormones were within normal range except prolactin that was 1447Miu/ml.

Thyroid ultrasonography study showed a 3*3.2mm non-calcified nodule on the left lobe and a 48*50*73mm heterogeneous solid mass with calcified foci on the right lobe of the thyroid. Pathology study of the specimen from the right lobe mass reported a benign follicular lesion and BRAFV600E mutation was negative in Immunohistochemistry study.

Humeral and femoral plain x-ray showed bilateral symmetric metaphyseal and diaphyseal sclerosis (Figure 2).

On chest CT scan mild pericardial effusion, bilateral pleural effusion, few mediastinal lymph nodes (SAD=10 mm), thyroid nodule (35×37mm with calcification), and small sclerotic lesions in left bilateral humerus meta-diaphysis were seen. In echocardiography, mild pericardial effusion and normal LV systolic function were reported.

An MRI examination of the brain showed empty sella and flattening of the pituitary gland over the sellar floor. Abnormal enhancement of pituitary stalk was obvious, which maximum thickness was about 6mm. There was also severe abnormal thickening and enhancement of tentorium cerebelli with maximum thickness about 17mm.

Axial T2 and post-contrast T1 weighted images of skull base show low T2 signal, enhancing soft tissue in the right maxillary sinus and left cheek subcutaneous fat. Indeed, axial T2 FIESTA and post-contrast T1 weighted images of the abdomen show low T2, enhancing soft tissue around abdominal aorta faintly infiltrate along renal vascular pedicle, renal sinuses and perinephric spaces leading to bilateral hydronephrosis (Figure 3).

Whole-body bone scan revealed symmetrical increased radiotracer uptake in the mandible, pelvic bones, bilateral femora, bilateral tibiae, and metatarsi. There was also a focus of activity in the proximal right tibial diaphysis. Myocardium plus pericardial space shadow was thickened. Bilateral dilated pyelocaliceal system was noted (Figure 4).

Considering hypoalbuminemia, upper and lower endoscopies were performed to rule out the protein-losing enteropathy, but they were normal. Unfortunately, the patient did not agree to push enteroscopy.

Bone marrow biopsy revealed 40% cellularity and decreased trilineage population of hematopoietic elements replaced by histiocytic infiltration exhibiting abundant foamy cytoplasm and bland looking nuclei. Scattered eosinophils also noted.

Flow Cytometric Immunophenotypic study showed cellular bone marrow with reactive changes and marked shift to the left at myeloid series. Immunohistochemistry study results include CD68 (+, diffuse), Fascin (+), MPO (highlights myeloid series), CD20 (occasional scattered positively), CD3 (occasional scattered positively), TDT (no excess of blast), CD34 (no excess of blast), CD1a (-), S100 (occasional scattered positively), and Ki67 (+) (Figure 5).

Therefore, considering the diagnosis of Erdheim-Chester disease, the patient was prescribed weekly 1mg/m2 vinblastine for 8 weeks and daily 50mg prednisolone. Seeing the stability and alleviation of the patient's symptoms, she was discharged after 2 weeks of treatment; unfortunately, she died in her living town a few days after the discharge due to acute pulmonary edema.

Discussion

This study reports a case of Erdheim-Chester disease. ECD is a rare non-Langerhans histiocytic disorder with systemic manifestations, from an asymptomatic disease to a fulminant multiorgan damage. Our patient had diabetes insipidus for a long time, as the only symptom of the disease, and hence the diagnosis was delayed. On this admission, complementary investigations were done due to the presence of xanthelasma and skeletal symptoms and the results led us to the diagnosis. Based on the literature, the involvement of long bones is the only specific presentation of ECD, in which the lower extremities long bones are more common to be involved than the uppers; however, up to 50% of patients may have asymptomatic bone lesions (12). Neurological involvement is the most common after the skeletal system. It can be presented as diabetes insipidus, cerebellar ataxia, panhypopituitarism, and papilledema. Half of the ECD patients have extra-skeletal manifestations; the most common are diabetes insipidus, hypothyroidism, and skin involvement which are reported in our case (13). Involvement of other organs in order of prevalence include cardiovascular (pericardial pain, cardiac tamponade, cardiac failure, and myocardial infarction), renal (dysuria, abdominal pain, chronic kidney failure, and nephrovascular hypertension), skin (xanthelasma), orbital (exophthalmos, diplopia, and visual impairment), constitutional (fever, fatigue, and weight loss), pulmonary (cough and chest discomfort), and endocrine (hyperprolactinemia, gonadotropin insufficiency, and IGF deficiency) (14). Cardiovascular infiltration is reported in 40% of ECD cases. Periaortic fibrosis is the most frequent vascular involvement with sometimes a "coated aorta" aspect. Other arteries infiltrations are described in this disease like renal artery stenosis or life-threatening ischemic manifestations like myocardial infarction or mesenteric angina. Some patients may present with pericarditis, pericardial effusion, and bilateral hydronephrosis (15). Available literature suggests corticosteroids, cytotoxic agents, and immunosuppressive drugs as the promising treatment for ECD patients, while IFN-α and Pegylated IFN-α have been introduced recently and showed hopeful results, as far as being the only major predictor of survival in these patients (16). So, we treated our patient by vinblastine 1mg/m2 weekly and prednisolone 50mg daily. The prognosis of this histiocytosis is relatively poor and common causes of death are cardiac failure and pulmonary fibrosis (17). Our patient was in a relatively good situation after starting the treatment; edema reduced moderately and was discharged from the hospital. Unfortunately, she died in another town within a few days with acute pulmonary edema.

In conclusion, ECD is a very rare non-Langerhans histiocytosis. The cause and pathogenesis of this disorder remain unclear, and further studies are warranted. It has nearly pathognomonic radiographic features and is comprised of lipid-storing CD68 (+), S100 (variable), CD1a (-) histiocytes. ECD is a multisystemic and heterogeneous clinicopathological condition with a poor prognosis and should be considered in patients with diabetes insipidus and multiorgan involvements.

DISCLOSURE

The patient consented to the publication of her data.

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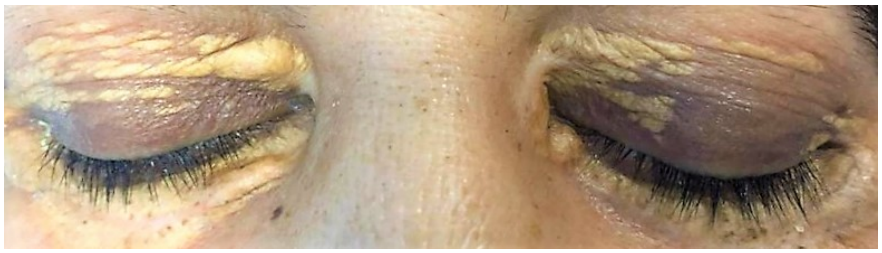
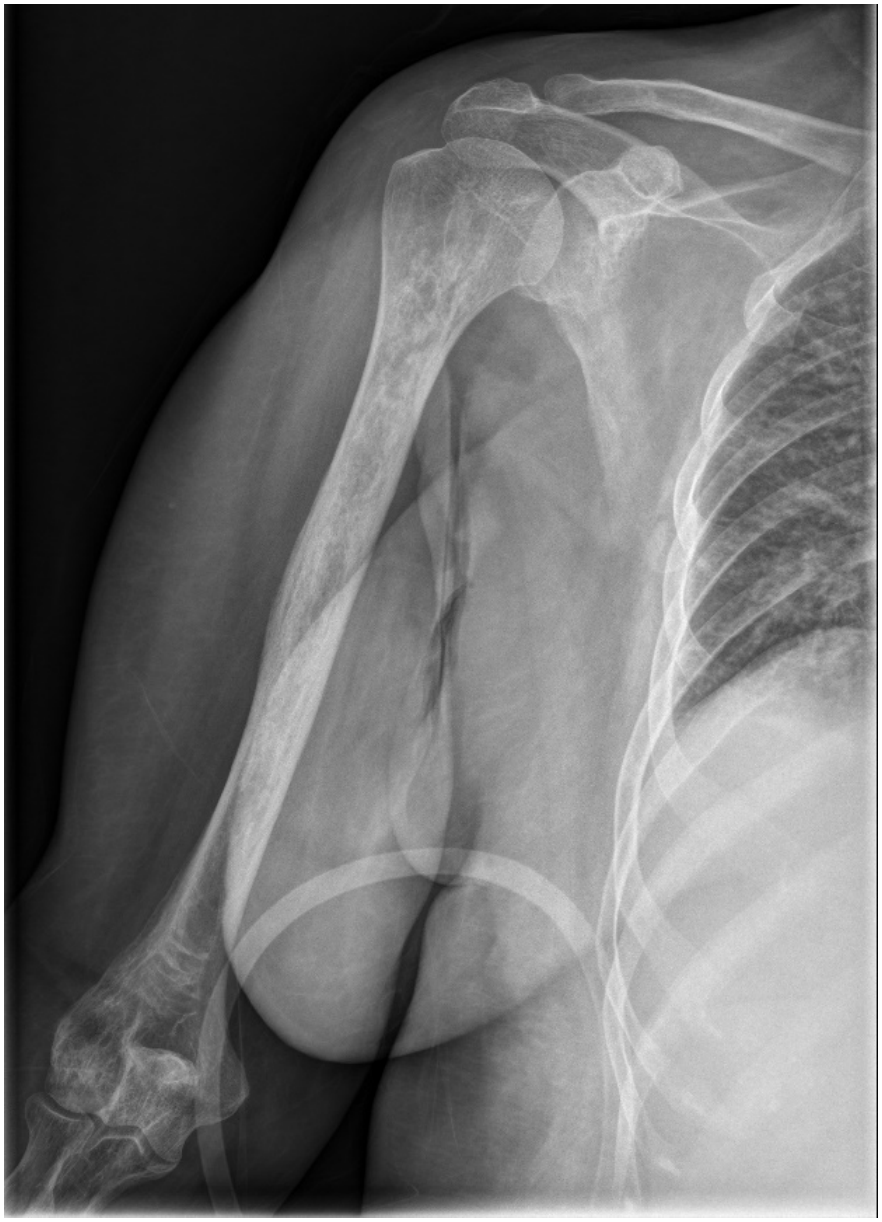


Figure 1 - Photograph of the eyes revealing xanthelasma palpebrarum.



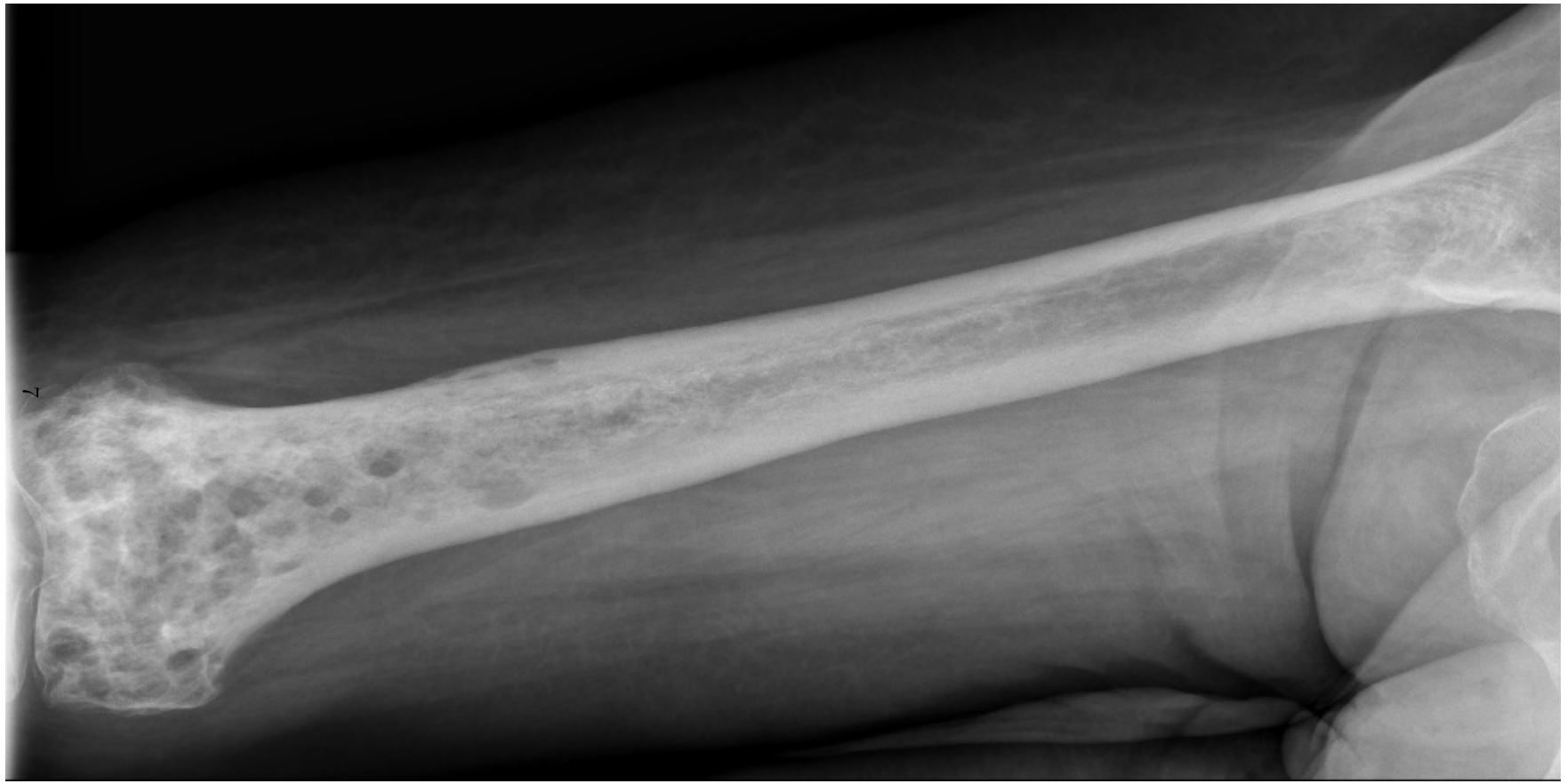
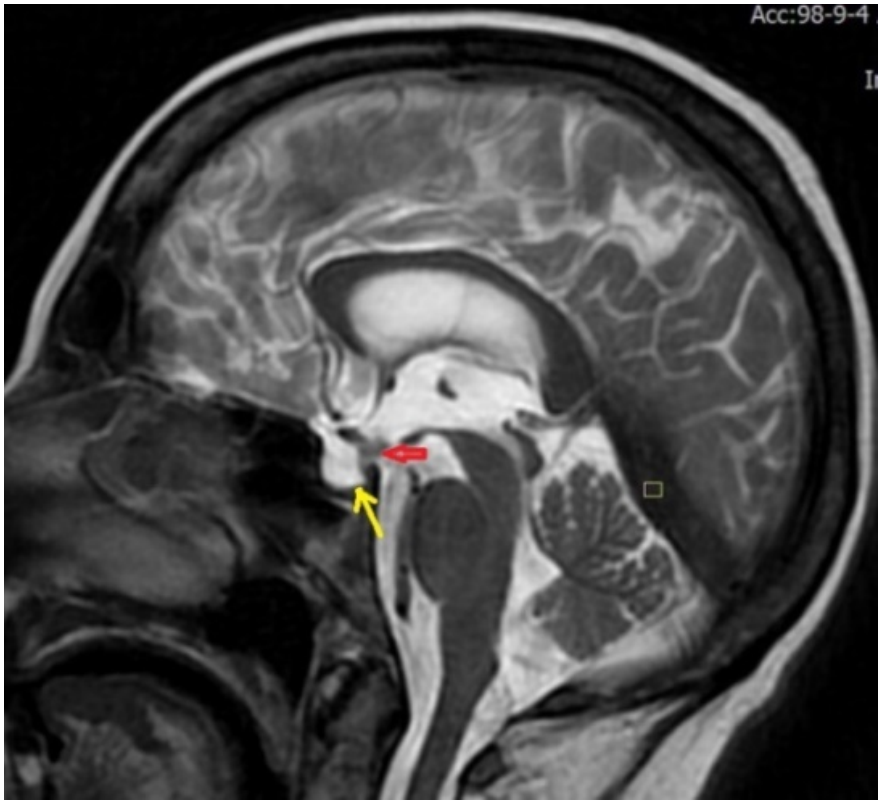
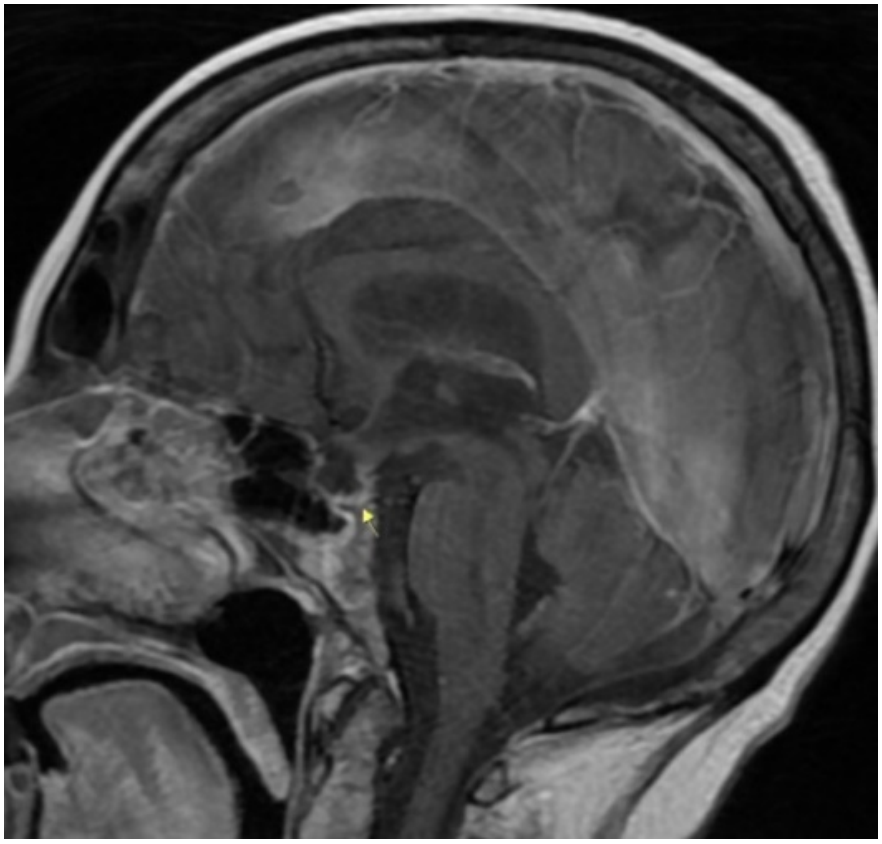


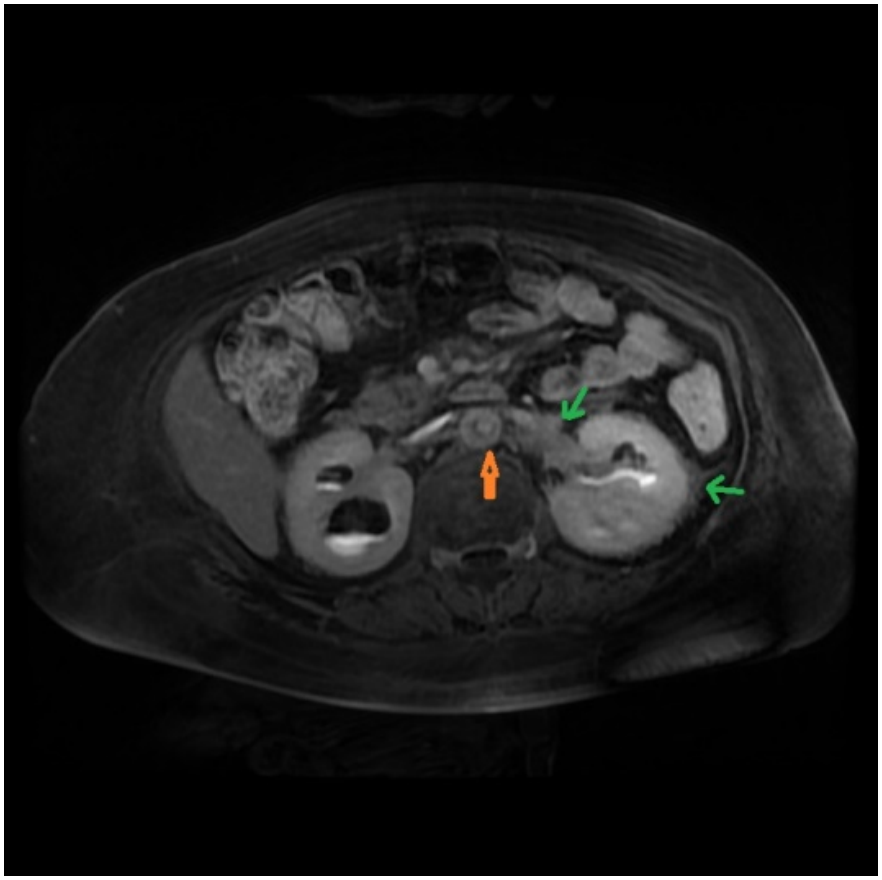
Figure 2 - Humeral and femoral plain X-ray revealing bilateral symmetric metaphyseal and diaphyseal sclerosis.

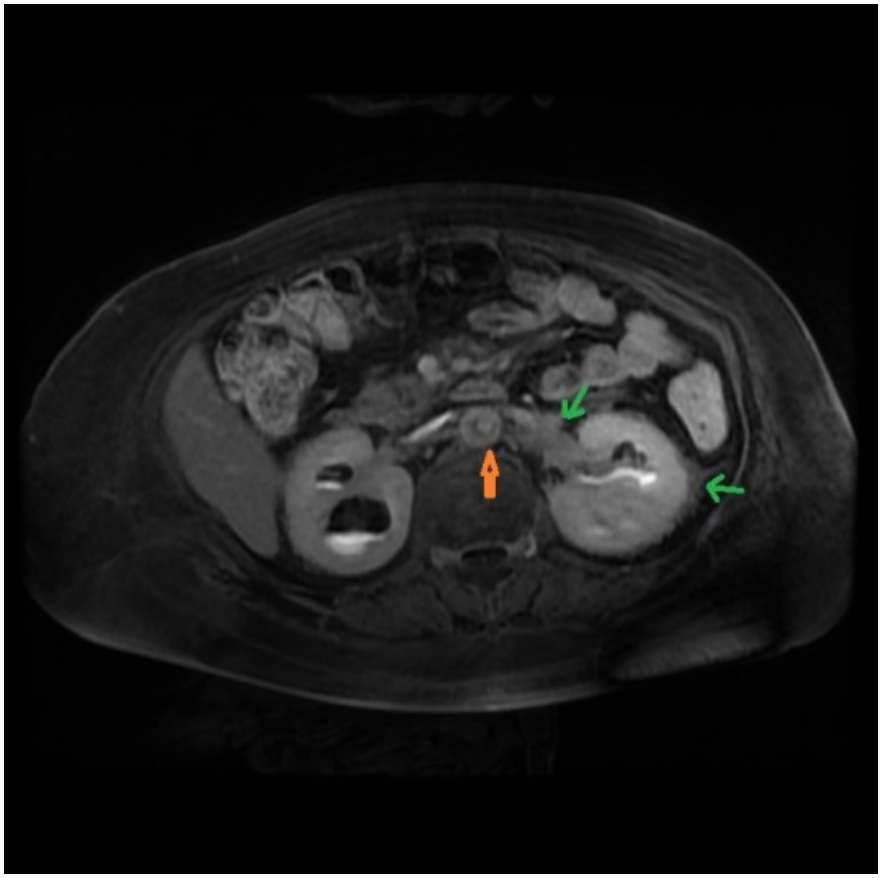


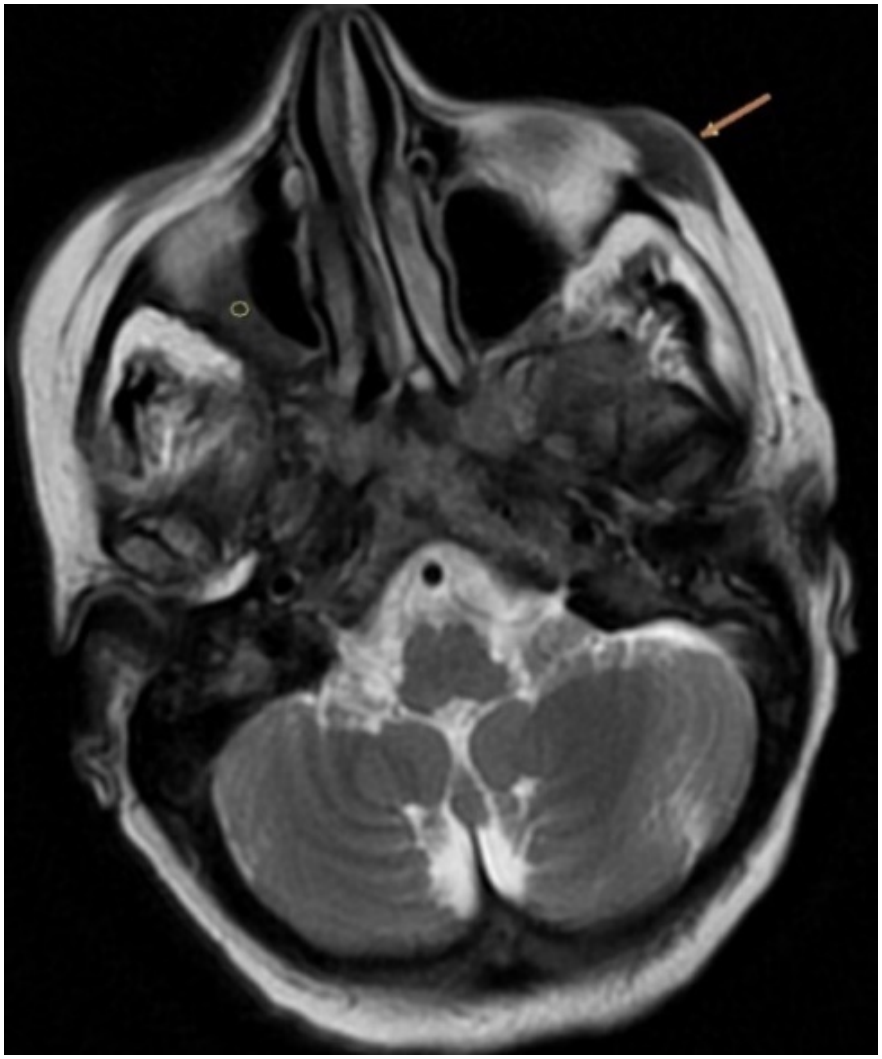


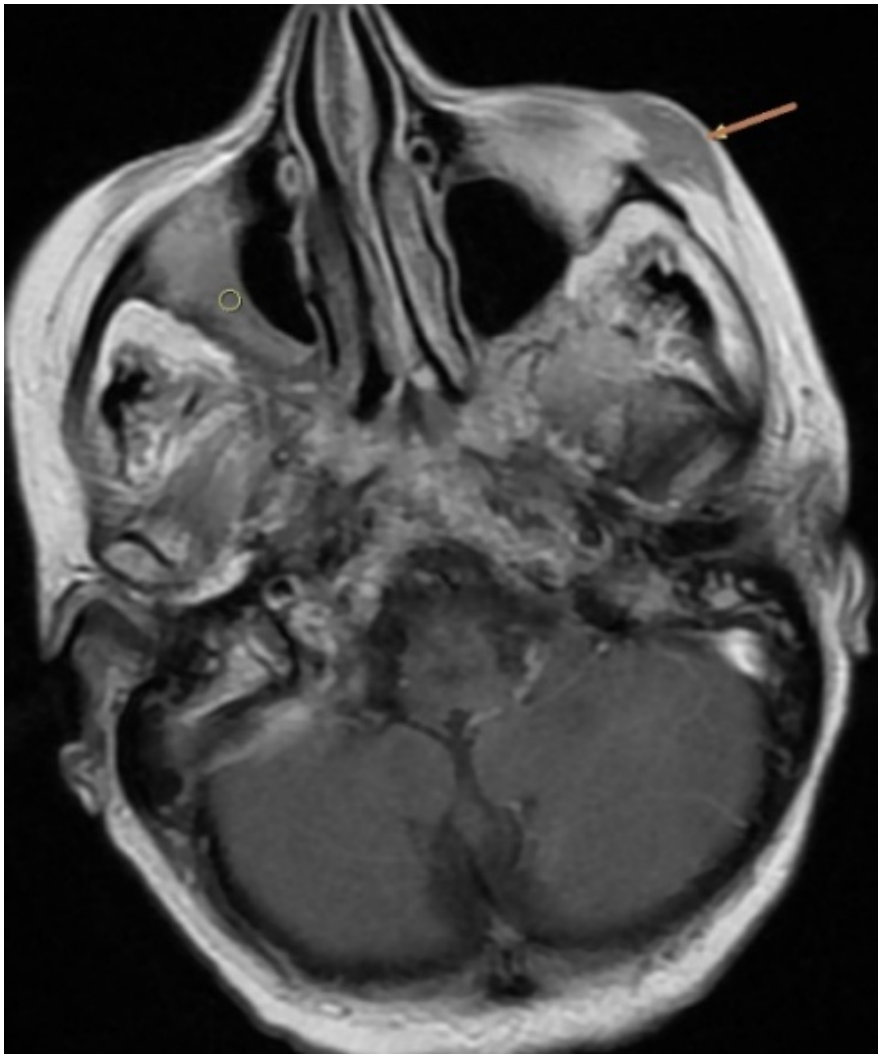
A B

C D









E F

Figure 3 - A and B; sagittal T2 weighted and coronal contrast-enhanced T1 weighted images of brain show low T2 signal, enhancing thickening of tentorium cerebelli and falx cerebri (rectangle) along with empty sella and flattening of compressed pituitary gland along the sellar floor (thin yellow arrow) and faint enhancing thickening of the pituitary stalk (thick red arrow). C and D; axial T2 and post-contrast T1 weighted images of skull base show low T2 signal, enhancing soft tissue in the right maxillary sinus (circle) and left cheek subcutaneous fat (brown arrow). E and F; axial T2 FIESTA and post-contrast T1 weighted images of abdomen show low T2, enhancing soft tissue around abdominal aorta faintly infiltrate along renal vascular pedicle, renal sinuses and perinephric spaces leading to bilateral hydronephrosis.

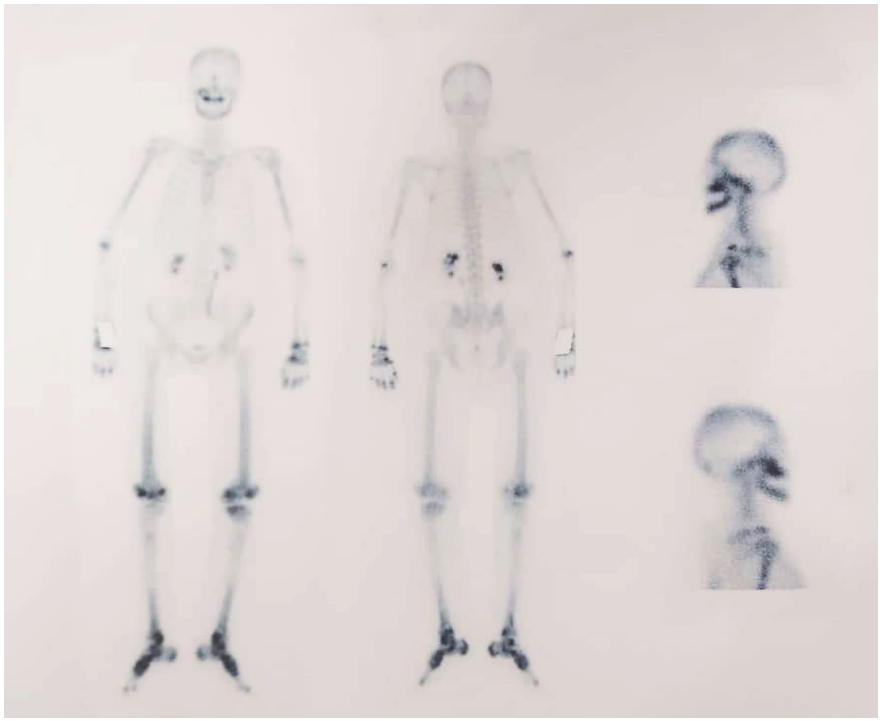
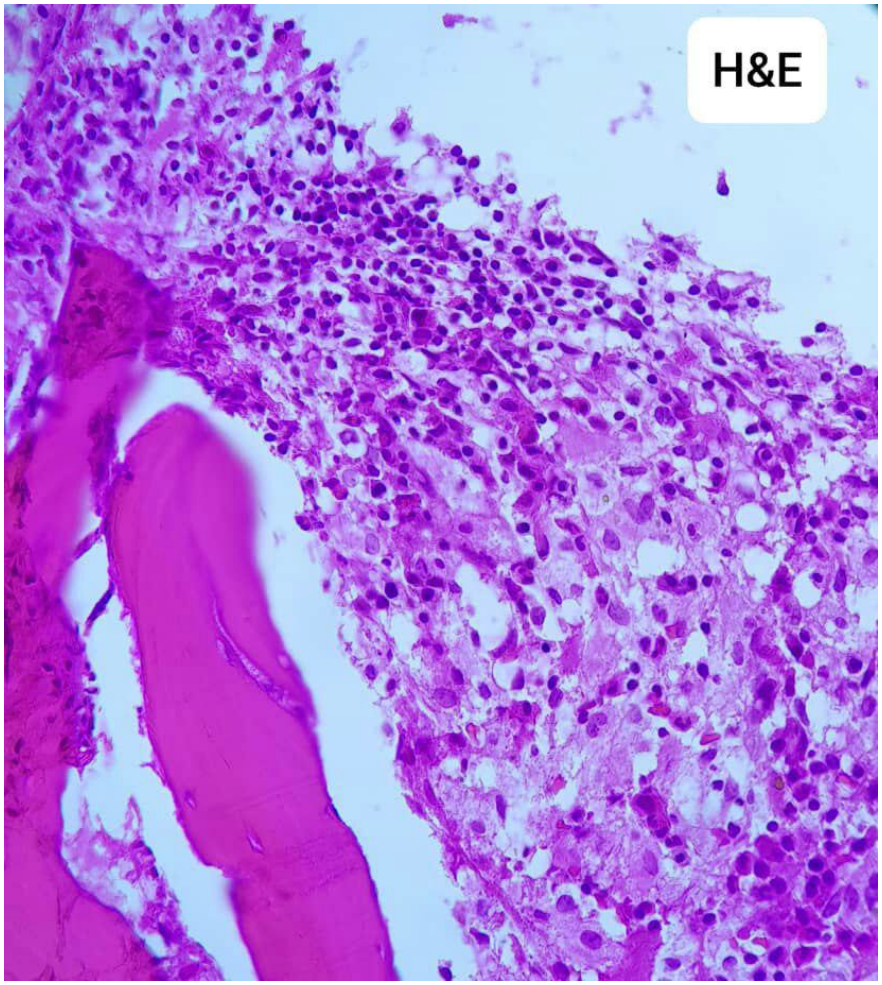
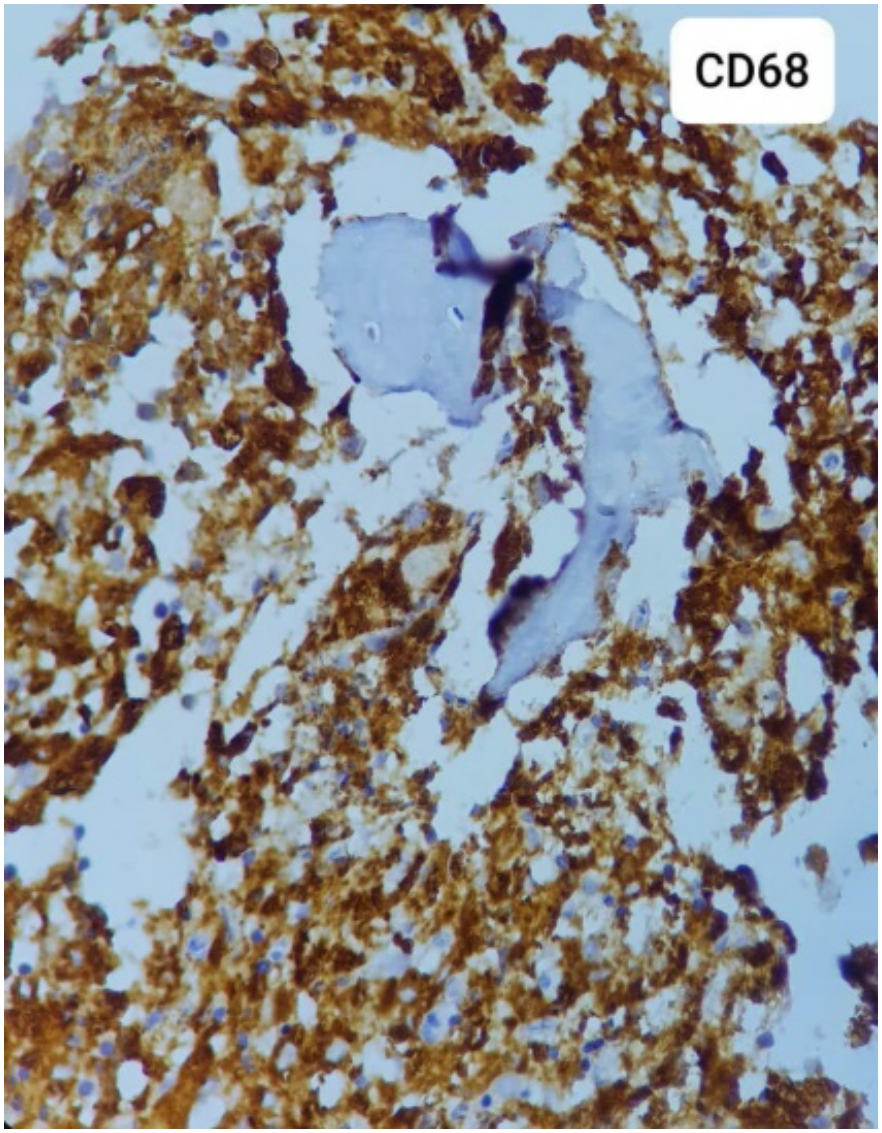
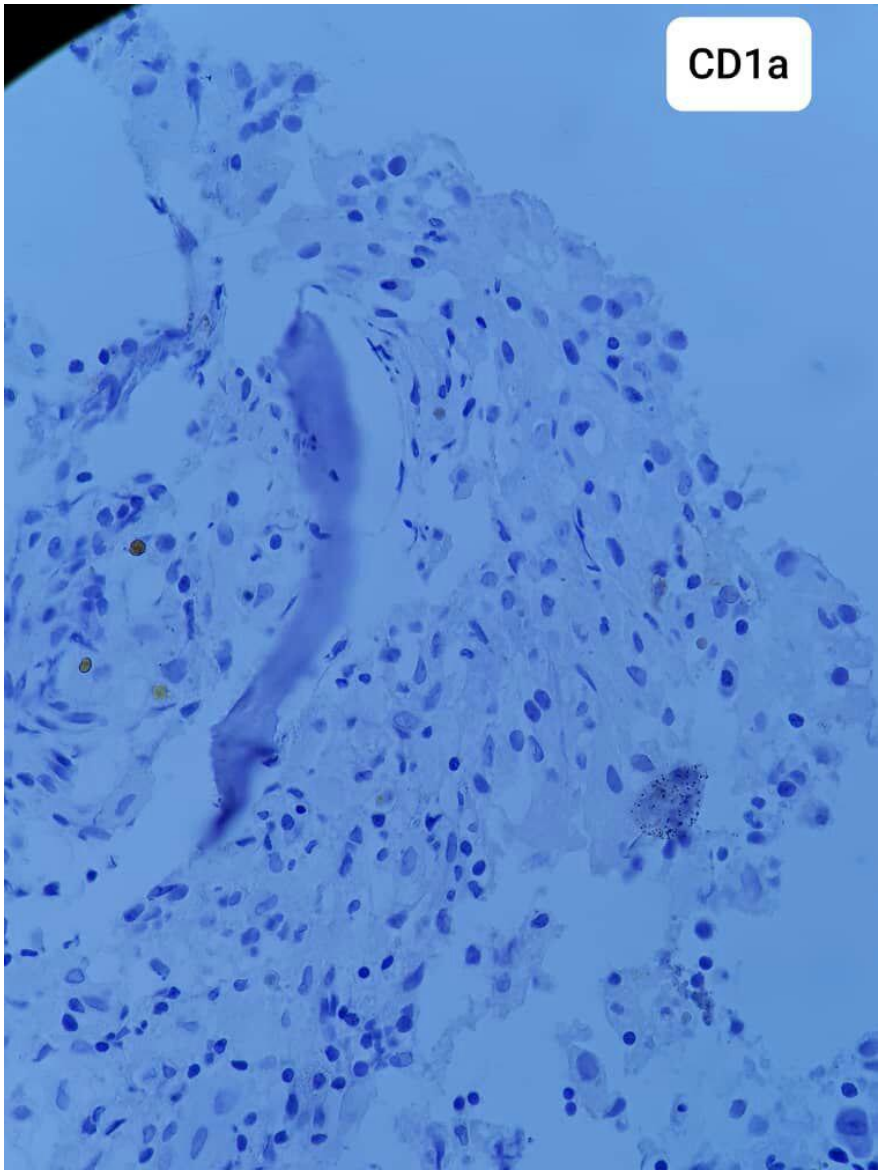


Figure 4 - Whole-body bone scan revealing symmetrical and diffused increased radiotracer uptake.







A B C

Figure 5 - (A) Hematoxylin-eosin–stained bone marrow biopsy revealing lipid-laden histiocytes

histiocytic infiltration exhibiting abundant foamy cytoplasm and bland looking nuclei. (B) IHC stain for CD68 revealing positivity of histiocytes and (C) negativity for CD1a.