

## CASE REPORT

# Indolent renal involvement with BRAF<sup>V600E</sup> mutation: Erdheim-Chester, a rare disease with a wide spectrum of clinical manifestations

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## Abstract

We present the case of a patient with three-year indolent bilateral ureteral and perirenal masses. Clinical presentation, radiological context, and histopathological findings with detection of BRAF<sup>V600E</sup> mutation confirmed the diagnosis of Erdheim-Chester disease (ECD). A review of current knowledge regarding diagnosis, clinical assessment, management, and treatment of ECD is also presented.

## KEYWORDS

BRAF<sup>V600E</sup>, Erdheim-Chester disease, histiocytosis, retroperitoneum, review

## 1 | INTRODUCTION

Erdheim-Chester disease (ECD) is an orphan form of non-Langerhans cell histiocytosis (LCH) with multifaceted clinical presentations that vary from single organ lesion to systemic disease<sup>1</sup>. Bones, central nervous system, cardiac system, and retroperitoneum are mostly involved, and the prognosis is generally poor. Due to the rarity of ECD and the diversity of its presentations, the diagnosis

is often delayed. A multidisciplinary approach regarding the diagnostic workup, the treatment, and the follow-up is usually required<sup>2</sup>.

## 2 | CASE REPORT

A 69-year-old man was admitted to the emergency department for severe left back pain, acute kidney

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failure, and inflammatory syndrome. His medical history was remarkable for arterial hypertension and bilateral xanthogranulomatous pyelonephritis (XGP) diagnosed two years ago after a complete work up: An abdominal computed tomography (CT) demonstrated diffuse, bilateral, irregular perinephric soft tissue thickening leading to bilateral pyelic dilatation (Figure 1), and a percutaneous renal biopsy showed foamy xanthomatous histiocytes, chronic inflammatory cells, surrounding fibrosis without evidence of malignancy or immunoglobulin G4 (IgG4)-related disease (IgG4-RD). After this, kidney function (creatinine 95,9  $\mu\text{mol/l}$ , MDRD 72 ml/min/1,73 m<sup>2</sup>) and clinical status remained stable.

Two years later, on admission, physical examination was remarkable for blood pressure of 180/90 mmHg and temperature of 38°C. The rest of physical examination was normal.

CT of abdomen showed an increase in tissue surrounding the kidneys with ureteral stenosis responsible for the acute kidney injury (creatinine 337  $\mu\text{mol/l}$ , MDRD 17 ml/min/1,73m<sup>2</sup>) Figure 2. Bilateral ureteral stents were placed and up until this point are regularly changed. Complete auto-immune and bacteriological tests were negative.

Magnetic resonance imaging (MRI) of abdomen was performed (Figure 3) showing perinephric infiltration iso-intense on T1-weighted images and slightly hypo-intense on T2-weighted images. Slow enhancement was visible

after injection of contrast agent. These features did not confirm the previous diagnosis of XPG, but rather favored the diagnosis of systemic disease.

A <sup>99m</sup>Tc bone scintigraphy revealed bilateral and symmetric abnormal increased fixation of the distal ends of the long bones at the level of the lower limbs and pathognomonic of ECD (Figure 4).

A review of histopathology's renal biopsy performed two years earlier was performed showing foamy histiocytes with small nuclei, reactive lymphocytes, few neutrophils, and surrounding fibrosis (Figure 5A, B). On immunohistochemistry (IHC), histiocytes were positive for CD163 (Figure 5C). Targeted-capture «Next Generation Sequencing» (NGS, using Ion Torrent Personal Genome Machine with Kit AmpliSeq) is used to analyze exome sequences and DNA copy number in 50 genes linked to cancer.

NGS revealed *p.V600E mutation* on BRAF gene (BRAF(NM\_004333.6):c.1799T>A (p. Val600Glu)).

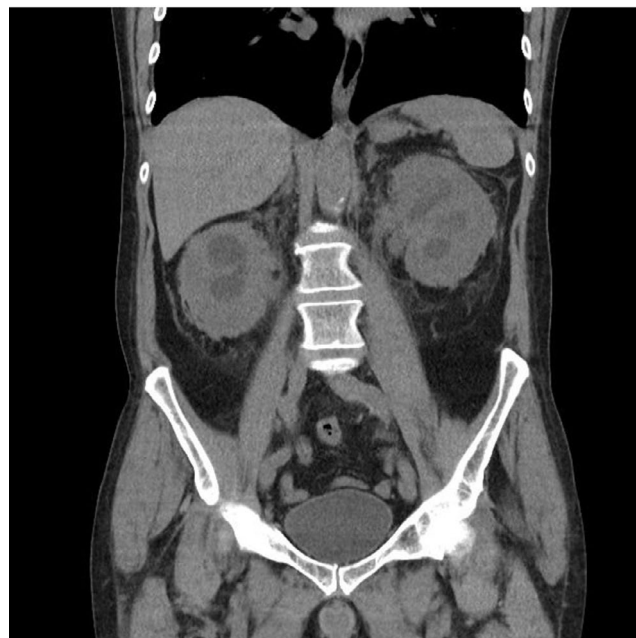
Other mutations like ALK, KRAS, NRAS, and PIK3CA were tested but were negative.

These histopathology findings combined with typical infiltration of perirenal fat, symmetric diaphyseal and metaphyseal osteosclerosis in the legs and the presence of BRAF<sup>V600E</sup> were highly suggestive of ECD. Supplementary examinations were performed, and no other organs were involved.

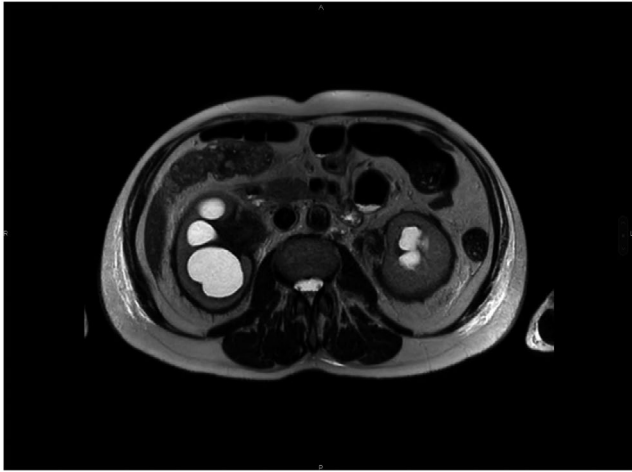
At this stage, the patient was considered to have ECD with kidney and asymptomatic bone involvement.



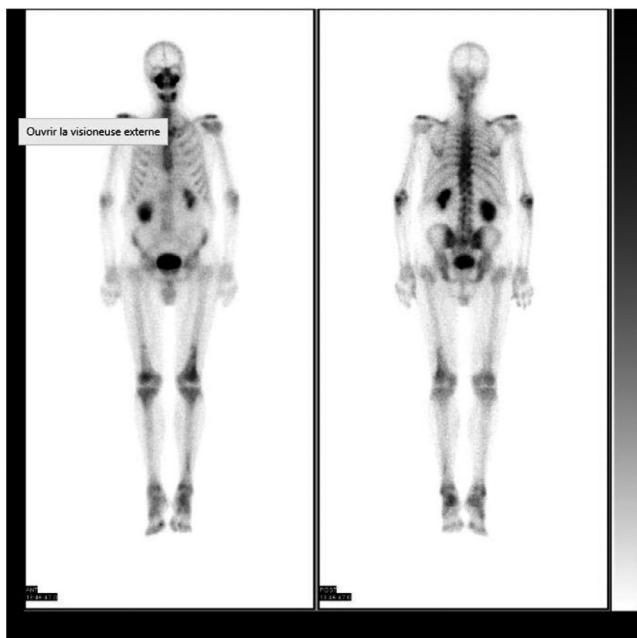
**FIGURE 1** Axial contrast-enhanced CT scan shows perinephric infiltration (white arrow) and pyelic dilatation (blue arrow)



**FIGURE 2** Coronal CT scan showing increasing perinephric soft tissue around proximal ureters and bilateral hydronephrosis (white arrow)



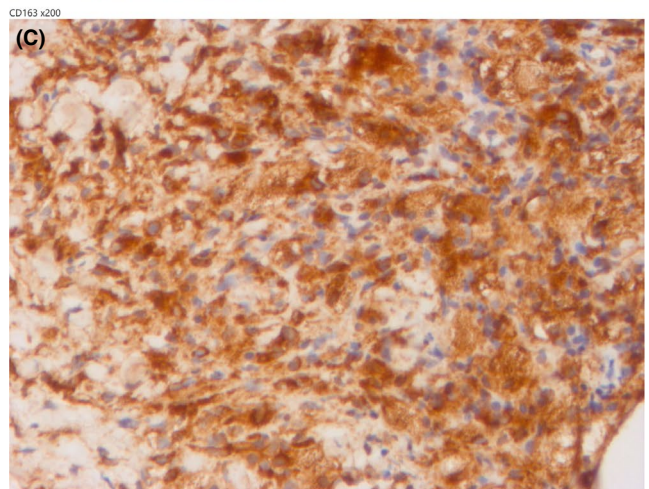
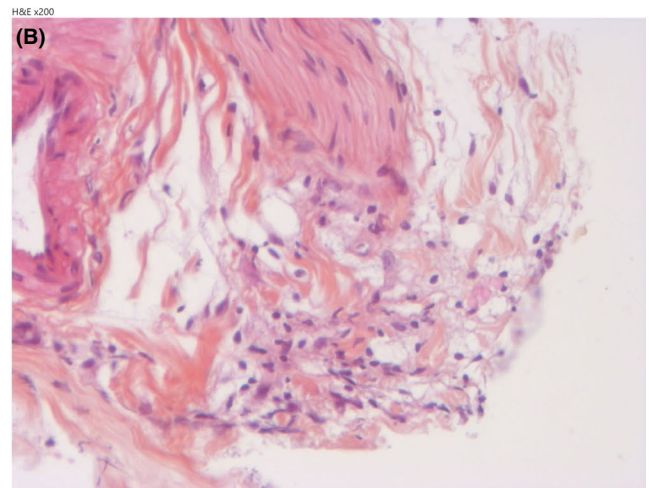
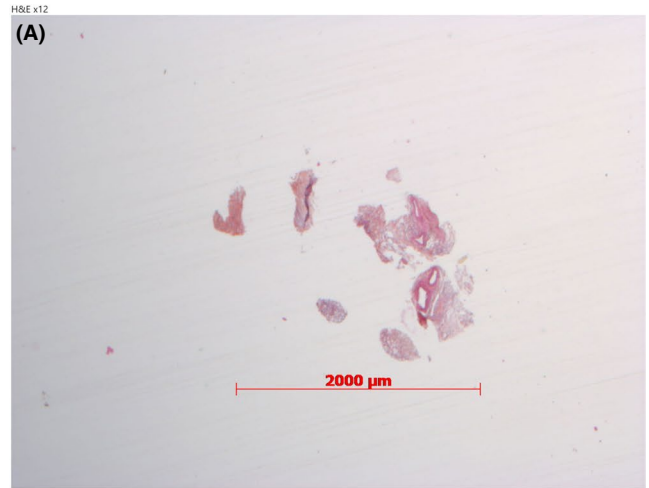
**FIGURE 3** Axial T2-weighted abdominal MRI shows bilateral mild perinephric soft tissue (arrow). Perinephric infiltration appeared iso-intense on T1-weighted images and slightly hypointense on T2-weighted images. Slow enhancement was visible after injection of contrast agent



**FIGURE 4**  $^{99m}\text{Tc}$  Technetium bone scintigraphy revealed bilateral and symmetric abnormal increased captation in the diaphysis and metaphysis of the long bones of legs and arms (black arrow)

## 2.1 | Outcome and follow-up

He has been doing well except for complaints of asthenia. His renal function has remained stable (creatinine  $133,7 \mu\text{mol/l}$  and MDRD  $49 \text{ ml/min/1,73m}^2$ ). He was addressed to a specialized ECD center in France. Bone marrow biopsy showed no neoplastic infiltration. In front of bilateral obstructive uropathy and inflammatory syndrome, medical experts propose to treat with pegylated



**FIGURE 5** A, B, Histopathology's renal biopsy showing foamy histiocytes with small nuclei, reactive lymphocytes, few neutrophils and surrounding fibrosis. C, On immunohistochemistry (IHC), histiocytes were positive for CD163

interferon- $\alpha$  (PEG-IFN- $\alpha$ ) and evaluate response in six months with  $^{18}\text{F}$ FDG-PET scan.

In conclusion, this 69-year-old man with a three-year history of stable chronic kidney disease and bilateral



“hairy kidney” was found to have two pathognomonic imaging findings and the presence of BRAF<sup>V600E</sup> mutation consistent with the diagnosis of ECD.

### 3 | DISCUSSION

ECD is an orphan non-LCH with multi-organ involvement<sup>1,2</sup>. Histiocytic neoplasms are rare and include several heterogeneous disorders like ECD, LCH, and Rosai-Dorfman disease<sup>2</sup>. It is characterized by spumous CD68<sup>+</sup> CD1a<sup>-</sup> histiocytic infiltration of tissues and xanthogranulomatous inflammation found in long tubular bones, skin, heart, kidneys, retroperitoneal space, orbit, and pituitary gland<sup>2,3</sup>.

Since 2016, ECD is included in the “L” group of histiocytic and dendritic cell neoplasms in the 2016 World Health Organization classification of hematopoietic and lymphoid tumors since recurrent clonal activating mutations in MAP kinase pathway alterations were found in ECD patients<sup>4,5</sup>.

In 2010, BRAF<sup>V600E</sup> mutation which is known to occur in about 50% of cutaneous melanomas was identified in patients with ECD and LCH<sup>6</sup>. The BRAF<sup>V600E</sup> mutation is present in ECD around 50% and is associated with more severe prognosis<sup>7</sup>.

More recently, recurrent activating kinase mutations and fusions involving the MAPK and PI3K-AKT pathways have been discovered in ECD genome: *MAP2K1* (30%), *KRAS* (27%), *NRAS* (27%), *PIK3CA* (11%), and more recently *CSF1R*<sup>8,9,10,11</sup>. These mutations are associated with to develop myeloproliferative or myelodysplastic syndromes<sup>9,12</sup>.

ECD patients are adults (median age, 50 years), predominantly males<sup>4</sup>. The clinical course and the prognosis are highly heterogeneous, ranging from asymptomatic to multi-organ failure, often leading to a delay in the establishment of a diagnosis<sup>13</sup>. Similarly, our patient was diagnosed 3 years after the first clinical presentation due to the relative indolent course. The first symptom differs considerably between patients: bone pain, diabetes insipidus, ataxia, or constitutional symptoms<sup>13</sup>.

The diagnosis of ECD depends on the combination of clinical presentations, imaging features, and presence of MAPK and PI3K-AKT pathway mutations<sup>4</sup>. The most frequent lesion is bilateral symmetrical osteosclerosis of the metadiaphyseal bones around the knees which is pathognomonic of ECD and is present in our patient and as found in 80–95% of ECD's patients. Bone manifestations is symptomatic in 38%<sup>3,4</sup>. “Coacted aorta” is the second classic feature of ECD with peri-aortic infiltration. Retroperitoneal and urologic involvements are the third

most frequent manifestations (50 – 68%) and may occur alone or as a component of disseminated disease<sup>14</sup>. This « hairy kidney» appearance is pathognomonic and characterized by a perinephric halo of soft tissue at abdominal CT and MRI<sup>15</sup>.

In 2019, the multidisciplinary Histiocytosis Working group within Mayo Clinic presented the formulation of the consensus guidelines for the diagnosis of ECD<sup>2</sup>.

Full body <sup>18</sup>FDG PET scan (vertex to toe) is recommended as the first point when ECD is suspected, because it can evaluate simultaneously multiple organ involvement, orientate tissue biopsy and now used to follow-up patients every 3 to 6 months<sup>4</sup>.

Once the biopsy is performed, BRAF<sup>V600E</sup> mutation testing should be pursued. In cases without the BRAF<sup>V600E</sup> mutation, targeted-capture “NGS” is recommended to test alterations of the MAPK-ERK and PI3K-AKT pathways<sup>4</sup>. Simultaneously, initial evaluation includes laboratory tests including complete blood cell, hepatic function, renal function, markers of inflammation, and evidence of endocrinopathy. Radiological studies are recommended such as brain and cardiac MRI.

Misdiagnosis and mistreatment are common because of the multifaceted presentation of this disease. The spectrum differential diagnoses of proliferative tumors and pseudotumors of the perirenal space are wide<sup>16,17</sup>. In our patient, many diagnoses involving kidneys bilaterally were discussed before ECD, as well as XPG, mycobacterial infections and other granulomatous diseases, histiocytosis X, malignancy, and idiopathic retroperitoneal fibrosis (iRPF).

XPG is a rare form of unilateral chronic pyelonephritis, affecting mostly peri-menopausal women, associated with obstructive renal calculi and a history of recurrent urinary tract infections, mostly *Proteus Mirabilis* and *Escherichia Coli*<sup>18</sup>.

Infiltration of foam cells with lipid inclusions and chronic granulomatous inflammation infiltrates the kidney parenchyma and leads to its destruction. This disease often affects one kidney and is characterized by a unilateral renal mass at CT scan, resulting in a multiloculated appearance known as the “bear's paw sign”<sup>18</sup>.

Renal involvement by lymphoma is usually seen in advanced stage extranodal non-Hodgkin disease due to its contiguous spread<sup>16</sup>. Primary renal lymphoma is extremely rare and mostly mimics conditions like histiocytosis or iRPF<sup>17</sup>. Unlike XGP, bilateral kidney involvement is generally more common in urogenital tuberculosis (TB)<sup>19</sup>. Patients with renal TB are often asymptomatic for several months and then develop constitutional symptoms like fever, flank pain, or weight loss. The presence of sampled *Mycobacterium tuberculosis* is

the gold standard for diagnosing TB. This was negative in urine samples of our patient. Renal TB often shows granulomatous interstitial nephritis at histology with caseous material, which was not present at kidney biopsy of our patient. Throughout the follow-up period, the patient has never had a documented urinary tract infection.

iRPF and IgG4-RD are two important differential diagnoses of retroperitoneal involvement in ECD<sup>3</sup>. iRPF may be idiopathic or secondary to a systemic process and is characterized by a proliferation of fibrosis around the aorta. Pelvic ureters and inferior vena cava are spared in ECD and frequently involved in iRPF<sup>20</sup>. Imaging and histopathological data do not enter into this disease in our patient.

This report describes a usual case of ECD involving an insidious course of disease with no specific treatment for a long period of time. For patients who are asymptomatic and without evidence of organ dysfunction, it is suggested that a period of observation should be respected rather than immediate treatment<sup>4</sup>. This is because there is no known cure for ECD and in some patient's disease presents itself with an indolent clinical course. During this observation period, examinations are organized similar to those used for the follow-up for patients undergoing active treatment.

Recommendations about treatment have changed drastically over the last few years. BRAF inhibitors are the first-line treatment for BRAF<sup>V600E</sup>-mutant ECD patients with cardiac or neurologic involvement. For BRAF<sup>V600E</sup>-mutant ECD without end-organ dysfunction, either BRAF inhibitor or conventional therapies (such as PEG-IFN- $\alpha$ ) may be considered. For patient without BRAF<sup>V600E</sup> mutation, NGS must be performed to consider a treatment with MEK-inhibitor<sup>4</sup>.

ECD is a rare disease, with heterogeneous and extremely diverse clinical manifestations. This case is unique because of its atypical presentation with bilateral kidney involvement.

ECD diagnosis and management is challenging and requires a multidisciplinary approach.

## CONFLICT OF INTEREST

The authors declare no competing financial interests.

## AUTHOR CONTRIBUTIONS

C.V. designed and wrote this case. F.M., D.F., S.H., S.T., and C.R. critically reviewed and approved the final version of this manuscript.

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