CLINICAL IMAGE*

Significant response to dabrafenib in a patient with Erdheim–Chester disease with *BRAF*^{V600E} mutation

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Introduction Erdheim–Chester disease (ECD), initially described by Jakob Erdheim and William Chester in 1930, is a rare nonfamilial xanthogranulomatous non–Langerhans cell histiocytosis. The disease is classified by the World Health Organization as a lymphoproliferative disorder, although its etiology has been elusive for a long time.

Since 1930, 500 to 750 cases of ECD have been reported. The disease is usually diagnosed a few years after the initial onset. The median age at diagnosis is 53 years. The disease is more prevalent in men (62%) than in women (38%).

Skeletal involvement (sclerosis of long bones) is the most frequent manifestation (74.1%), but the involvement of the central nervous system (55.6%), retroperitoneum (36.2%), skin (27.8%), cardiovascular system (27.0%), lungs (18.5%), pleuropericardial membrane (8.9%), and kidneys (6.0%) is also often described. The prognosis is poor, with a mean overall survival of only 2.3 year after diagnosis.[1]

In recent years, following the discovery of the *BRAF*^{V600E} and *RAS* mutations in ECD, the clonal origin of the disease has gained increasing attention. Since 2012, it is known that the *BRAF*^{V600E} mutation is present in more than 50% of ECD cases.[2]

According to the 2014 guidelines,[3] the diagnosis is based on immunohistochemistry in addition to clinical and radiological features. The disease is characterized by an abnormal proliferation of CD68-positive tissue macrophages loaded with lipids, which add them a foamy aspect on histology. In contrast to Langerhans cell histiocytosis, patients with ECD are negative for CD1, and rarely positive for CD207.[3]

Although many different treatment regimens have been proposed, only a few are based on evidence from randomized controlled trials. Only vemurafenib was approved by the Food and Drug Administration in November 2017 for patients with *BRAF*^{V600E}-mutant ECD. The treatment regimens proposed in the literature include corticoids, interferon alfa, anakinra, infliximab, tocilizumab, cyclophosphamide, anthracyclines, vinca alkaloids, vemurafenib, dabrafenib, and a combination therapy of dabrafenib and trametinib. A large case series has been published that supports the interferon alfa treatment.[4]

The efficacy of interferon α differs among patients, depending on the site of disease involvement. In addition, interferon alfa has little or no impact in cases of severe disease, multiorgan disease, or specific organ involvement including the central nervous system as well as pulmonary and cardiovascular systems.[5]

Case report We report a case of a 57-year-old man managed in a tertiary care hospital, with a disease lasting more than 10 years and characterized by arthralgias, retroperitoneal fibrosis (negative for immunoglobulin G4 [IgG4] after biopsy), bilateral hydronephrosis, recidivating pancreatitis, and serositis with pericardial effusion complicated by tamponade with waxing and waning symptomatology. The disease was further complicated by arteritis with periaortic soft tissue infiltration, carotid stenosis, and bilateral renal and femoral artery stenosis. Bone scintigraphy performed in 2009 revealed peripheral osteoblastic lesions, which were located at the humeral shafts. A presumptive diagnosis of idiopathic retroperitoneal fibrosis with concomitant

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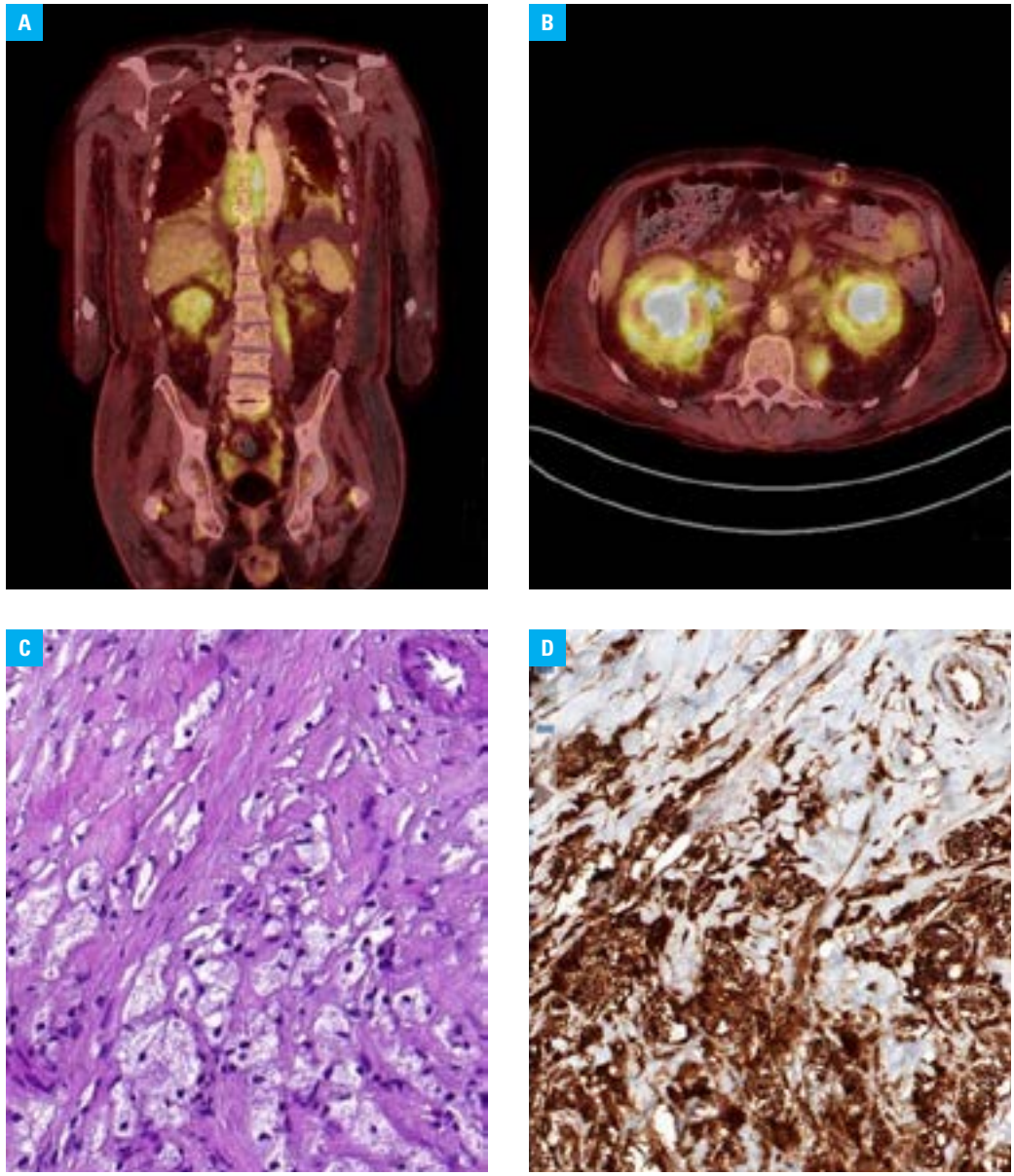

FIGURE 1 Imaging and biopsy results at diagnosis; **A** – ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}FDG-PET) scans: periaortic ^{18}FDG uptake, coronal view; **B** – ^{18}FDG-PET scan: perirenal ^{18}FDG uptake, axial view; **C** – foamy histiocytes on perirenal tissue biopsy (hematoxylin and eosin staining); **D** – CD68 positivity on perirenal tissue biopsy

autoimmune pancreatitis was made by the patient's gastroenterologist.

The patient was transferred to our internal medicine department after a stay of more than 2 months in a secondary care hospital, where he was hospitalized due to dysphagia and speech troubles, weight loss, and cough. A diagnostic evaluation revealed left vocal cord paralysis due to fibrosis around the laryngeal recurrent nerve and candida epiglottitis. His condition was also complicated by herpes simplex virus type 1 infection treated with acyclovir and *Stenotrophomonas maltophilia* pneumonia.

On presentation (December 2015), the patient was treated with mycophenolate mofetil, 1.5 mg twice daily, and methylprednisolone for a corticoid-resistant retroperitoneal fibrosis of unknown origin. The dose of methylprednisolone had been increased shortly prior to the presentation to 32 mg/d due to disease progression.

On physical examination, the patient was tired, cachectic, and pale. He reported dysphonia, dysphagia, dry cough, episodes of cold sweats, as well as episodes of vertigo with an unsteady gate. Pulmonary auscultation revealed bilateral expiratory wheezing.

The patient was fed through a gastrostomy tube because of the swallowing difficulties. No other abnormalities were observed. On admission, he was apyretic. Blood pressure and heart rate were 162/84 mmHg and 88 bpm, respectively. Oxygen saturation was 98%, with 2 l/min of oxygen.

A methicillin-resistant *Staphylococcus aureus* bacteremia was diagnosed on the second day of admission. Transthoracic echocardiography showed a moderate pericardial effusion without signs of constriction, but no signs in favor of endocarditis. The patient was treated with vancomycin for 2 weeks, without relapse of the bacteremia.

Laboratory test results are listed in Supplementary material, *Table S1*. Additional laboratory tests included autoimmune tests (antinuclear factor), anti-neutrophil cytoplasmic antibody, anti-citrullinated peptide, and IgG4 tests; the results were negative.

Positron emission tomography–computed tomography revealed periaortic thoracic hypermetabolic activity associated with pericardial effusion (FIGURE 1A). Moreover, it showed perirenal and suprarenal hypermetabolic activity, as well as bilateral hydronephrosis (FIGURE 1B).

Due to the typical image of perirenal stranding, which is almost pathognomonic for ECD, in combination with the previously mentioned abnormalities, our radiologist made a presumptive diagnosis of ECD.

A computed tomography–guided biopsy of perirenal hypermetabolic tissue was eventually performed following an episode of progressive renal failure despite bilateral double-J stenting for hydronephrosis. The diagnosis of ECD was confirmed by the typical immunohistochemistry profile (CD68 positivity and CD1 negativity) on renal biopsy, with the presence of foamy macrophages (FIGURE 1C and 1D). A mutation analysis using the Idylla™ *BRAF* Mutation Test revealed the presence of $BRAF^{V600E}$ in a formalin-fixed paraffin-embedded biopsy.

A treatment with dabrafenib, 150 mg twice daily, combined with trametinib, 2 mg/d, was then initiated, based on clinical evidence supporting the increased efficacy and reduction of side effects related to extracellular signal-regulated kinases (ERK) paradoxical activation compared with B-rapidly accelerated fibrosarcoma (BRAF) inhibitors in monotherapy.[6]

Discussion The recent discovery of the activating kinase $BRAF^{V600E}$ mutation in ECD served as the rationale for developing a disease-specific targeted therapy. BRAF inhibitors have demonstrated efficacy in targeting $BRAF^{V600E}$-mutated ECD. A combination therapy with BRAF and mitogen-activated protein kinase/ERK (MEK) inhibitors appears efficient in ECD after disease recurrence with single therapy with BRAF inhibitors and is currently under investigation in a phase II clinical trial.[7]

The patient developed grade 2 arthralgia according to the Common Terminology Criteria for Adverse Events (CTCAE v 4.03) 4 days after initiation of the combination therapy. As arthralgias are common adverse effects related to combination therapy (and, to a lesser extent, dabrafenib monotherapy), trametinib was stopped and dabrafenib monotherapy was continued after dose reduction (75 mg twice daily).

Dabrafenib monotherapy is currently continued and is well tolerated with no adverse events. We noted clinical improvement with total resolution of dysphagia, but also resolution of the neurological signs and stabilization of the kidney function. Moreover, biological and radiological improvement was observed in terms of reduced inflammation and metabolic activity on ^{18}F-fluorodeoxyglucose positron emission tomography 2 years after diagnosis.

Treatment resistance might occur in patients on long-term monotherapy with BRAF inhibtors. Therefore, in the future we might consider restarting the MEK inhibitor in combination with the BRAF inhibitor, in case of resistance to the current BRAF inhibitor monotherapy.[7]

Recently, efficacy of a MEK inhibitor as a single agent (cobimetinib) in patients with *BRAF* wild-type ECD was reported.[8] Moreover, MEK inhibition has been shown to promote the resolution of inflammation by modulating macrophage function in vivo and in vitro.[8] These data suggest that inhibitors may play a broader role independent of the inhibition of the altered mitogen-activated protein kinase signaling pathway.

SUPPLEMENTARY MATERIAL Supplementary material is available with the article at www.pamw.pl.

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