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Erdheim-Chester Disease Successfully Treated with Front-Line Single-Agent Dabrafenib

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Patient: Female, 30-year-old
Final Diagnosis: Erdheim-Chester disease
Symptoms: Abdominal pain • fatigue
Medication: —
Clinical Procedure: —
Specialty: Hematology

Objective: Rare disease

Background: Erdheim-Chester disease (ECD) is a clonal disease characterized by histiocytic infiltration of multiple organ systems. As ECD is a rare disorder with variable presentations, its diagnosis and management can present a significant clinical challenge. The diagnosis of ECD requires several clinical, radiological, and histological criteria. Since approximately 75% of ECD patients harbor a mutation in the proto-oncogene *BRAF V600E*, inhibition of BRAF activation by BRAF inhibitors has significantly improved the management of ECD. Vemurafenib was approved by the U.S. Food and Drug administration for treatment of *BRAF*-mutated ECD. Another BRAF inhibitor, dabrafenib, has been used in some cases as a single agent and was associated with a lower toxicity profile.

Case Report: We report the case of a 30-year-old Saudi Arabian woman who initially presented with a history of diffuse abdominal pain and fever. The patient had elevated inflammatory markers, and radiological investigations revealed hypermetabolic regions in the frontoparietal brain lobe, anterior pericardium, kidneys, and the anterior abdominal wall. Histological investigations from the right perinephric soft-tissue mass revealed foamy histiocytes associated with mild chronic inflammation. Furthermore, *BRAF V600E* was mutated in the biopsy sample, leading to a diagnosis of *BRAF*-mutated ECD. The patient began single-agent dabrafenib therapy at 75 mg twice daily and experienced an excellent clinical and radiological response with no reported toxicity.

Conclusions: Single-agent dabrafenib is effective and well tolerated among ECD patients; therefore, it might be considered as a first-line option for the treatment of *BRAF*-mutated ECD.

Keywords: Dabrafenib • Erdheim-Chester Disease • Histiocytosis, Langerhans-Cell

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/935090

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Background

Erdheim-Chester disease (ECD) is a rare disease that was first described by Jacob Erdheim and William Chester in 1930 [1]. It is characterized by histiocytic infiltration of multiple organ systems. The diagnosis of ECD is frequently challenging and requires an appropriate clinical presentation, along with characteristic radiological features and consistent histological findings. Tissue biopsies from the involved sites show infiltration with foamy histiocytes that stain positively for CD68 and negatively for CD1a and S100. The proto-oncogene *BRAF V600E* is mutated in 75% of ECD patients, and approximately 15% of patients have *PIK3CA* and *NRAS* mutations [2]. The use of BRAF inhibitors such as vemurafenib and dabrafenib demonstrated promising results in improving outcomes for ECD. However, BRAF inhibitors have not been effective in all patients with the BRAF V600E mutation. Moreover, BRAF inhibition can lead to several adverse effects and treatment resistance. Dabrafenib was found to be less toxic than its counterpart, vemurafenib [3,4]. Here, we report a case of multisystem ECD with brain and cardiac involvement that had an excellent response to the use of single-agent dabrafenib, without any reported toxicity.

Case Report

A 30-year-old Saudi Arabian woman presented with non-specific diffuse abdominal pain. She had no significant past medical history. According to the patient, the pain had started 3 months prior to her presentation, and appeared to have an intermittent course with no specific aggravating or relieving factors. She was initially admitted at a general hospital where she underwent an explorative laparotomy, the result of which was unremarkable. After the procedure, the patient developed a pulmonary embolism and was diagnosed with hospital-acquired pneumonia. The patient then presented to our hospital with persistent abdominal pain and recent-onset fever.

On examination, the patient was febrile and in pain. Abdominal examination revealed a laparotomy scar with diffuse dark-brown skin hyperpigmentation. She had abdominal tenderness with no palpable organomegaly. Apart from tachycardia, the cardiovascular examination was unremarkable. In addition, neurological and respiratory examinations did not reveal any abnormalities.

The initial laboratory investigation showed white blood cells 32.100/uL, platelets 989 000/uL, and hemoglobin 86 gm/L. The renal profile and liver function were within normal ranges. Furthermore, inflammatory markers were elevated, with erythrocyte sedimentation rate (ESR) 49 mm/h and C-reactive protein (CRP) 218 mg/L.

An enhanced computed tomography (CT) scan of the abdomen revealed bilateral perinephric hyper-dense soft-tissue attenuation (57 HU in average). There were also multiple splenic infarctions. Whole-body positron emission tomography/CT (PET/CT) showed hypermetabolic activity involving the frontoparietal brain lobe, anterior pericardium, and both kidneys, in addition to the anterior abdominal wall (**Figure 1**). Moreover, there was a notable increase in bone marrow activity, with multiple foci of high bone marrow uptake, mainly at the appendicular skeleton. A portion of these foci were correlated to mixed lytic/sclerotic lesions, whereas others were purely lytic, and most regions displayed only cortical sclerosis. These changes were mainly seen on the lower limb, with extensive involvement of the bilateral proximal and distal tibia, fibula, and tarsal bones. There was also involvement of the distal radius and carpal bones. Brain magnetic resonance imaging (MRI) revealed a hyper-intense lesion arising from the left parietal convexity, as well as hyper-intense signal changes in the dorsal pons. There was no pituitary involvement, and the patient did not have clinical or laboratory findings indicative of diabetes insipidus. Moreover, a cardiac MRI illustrated multiple non-obstructive masses attached to the right atrium.

CT-guided tissue biopsy from the right perinephric soft-tissue mass revealed foamy histiocytes associated with mild chronic inflammation. These cells reacted positively for CD68 and CD163 markers and negatively for CD1a and S100 markers (**Figure 2**). Additionally, *BRAF V600E* was mutated in the biopsy sample. Therefore, a diagnosis of ECD was established based on the clinical, radiological, and histological findings.

Due to unavailability of vemurafenib at our institution, single-agent targeted therapy using dabrafenib was initiated at a dose of 75 mg twice daily. After 2 months on dabrafenib, the patient experienced a dramatic clinical and biochemical response, as is evidence by decreases in white blood cells to 9.5/UL, platelets to 400 000/UL, hemoglobin to 14.1gm/L, and CRP to 12 mg/L. The PET-CT showed significant improvement of metabolic activities (**Figure 3**). Moreover, the cardiac MRI displayed a significant regression in size of the cardiac masses. The regression in cardiac masses was expected given that presence of the BRAFV600E mutation is strongly associated with cardiac involvement [5]. A follow-up PET-CT conducted 6 months after treatment with dabrafenib revealed complete resolution of all hypermetabolic- activity (**Figure 2**). The patient has currently been on dabrafenib for 18 months without any evidence of disease recurrence or drug-related toxicity.

Discussion

Erdheim-Chester disease (ECD) is a very rare disorder with less than 800 cases reported in the literature, but the number of

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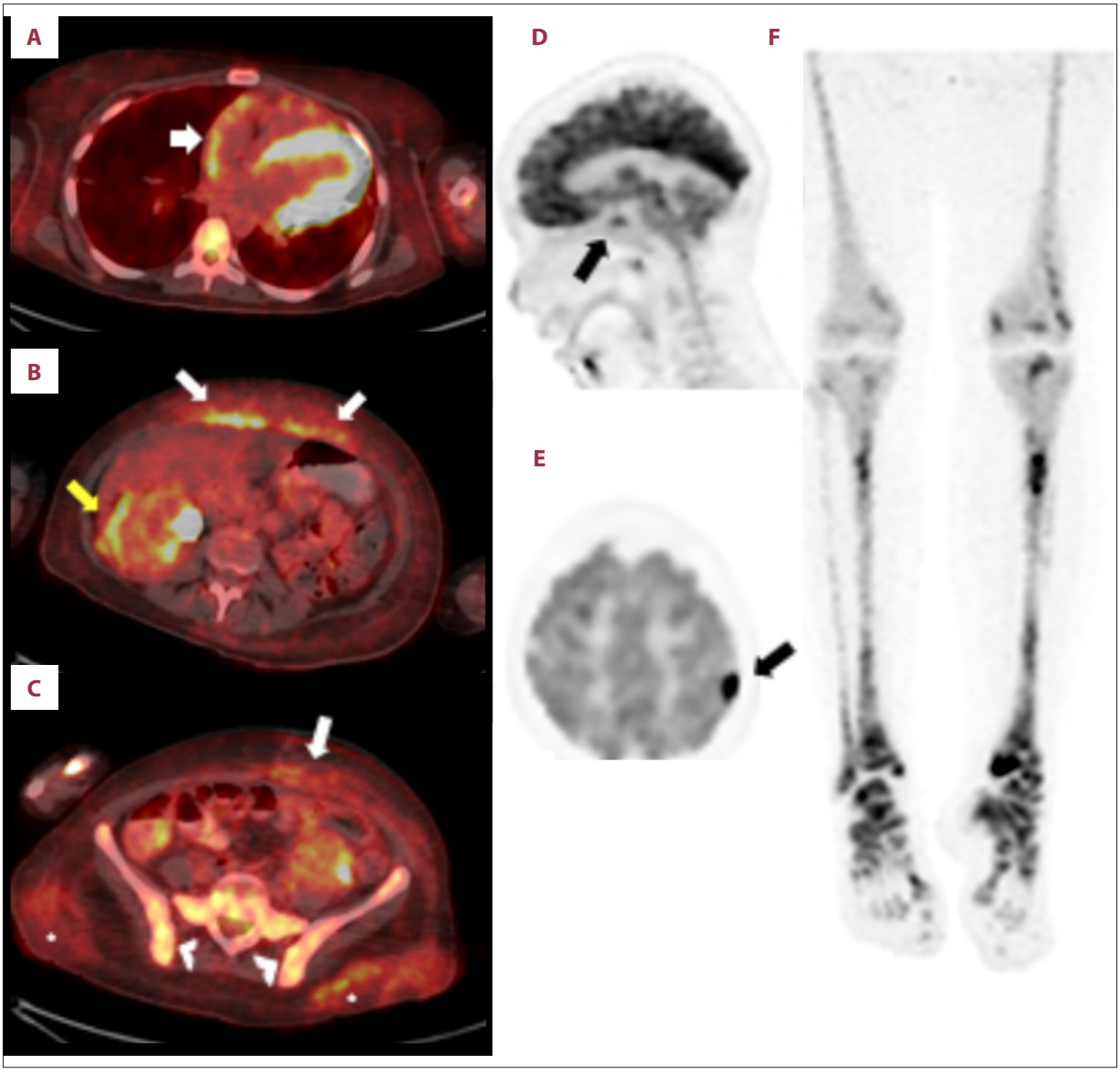

Figure 1. Baseline FDG PET-CT. (**A**) Transaxial fused image at the level of the heart shows moderate pericardial hypermetabolism overlying the right atrium (arrow). Transaxial fused images at level of abdomen (**B**) and pelvis (**C**) show hypermetabolic (SUV 7.7) right perinephric soft-tissue infiltration (yellow arrow), heterogeneous hypermetabolism in sacrum and iliac bones (arrow heads), and fat stranding and soft-tissue thickening in anterior abdominal wall (SUV 13.4) (white arrows) and bilateral gluteal regions (stars). (**D**) Sagittal brain PET image shows hypermetabolic pituitary lesion. (**E**) Transaxial brain PET image shows hypermetabolic dural-based extra-axial left parietal lesion (SUV 26.5). (**F**) Anterior maximum-intensity projection (MIP) image of lower extremities shows areas of heterogeneous hypermetabolism in multiple bilateral bones related to symmetrical metaphyseal and diaphyseal sclerosis (not shown).

cases increased dramatically during the past few years owing to increased disease recognition and availability of diagnostic methods. The disease affects males more than females and the mean age of diagnosis is 50 to 60 years [6].

ECD is a clonal disease. About 60% of ECD patients harbor the *BRAFV600E* mutation [7]. Due the therapeutic implication of the *BRAF V600E* mutation, accurate determination of the mutational status is very essential. Thus, it is highly advised to confirm cases which are negative for the presence of BRAF mutation through repeating BRAF testing on biopsy from another anatomic site or using an alternate genotyping modality [8]. Recurrent activating kinase mutations involving *MAPK* and *P13K* pathways have been identified in some ECD patients [8].

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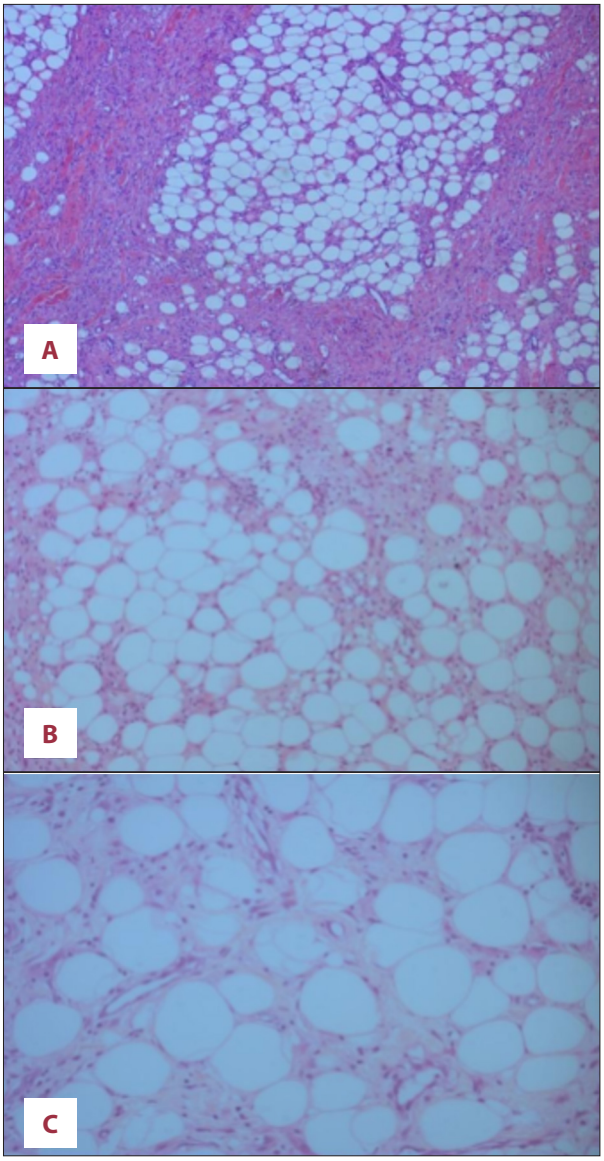

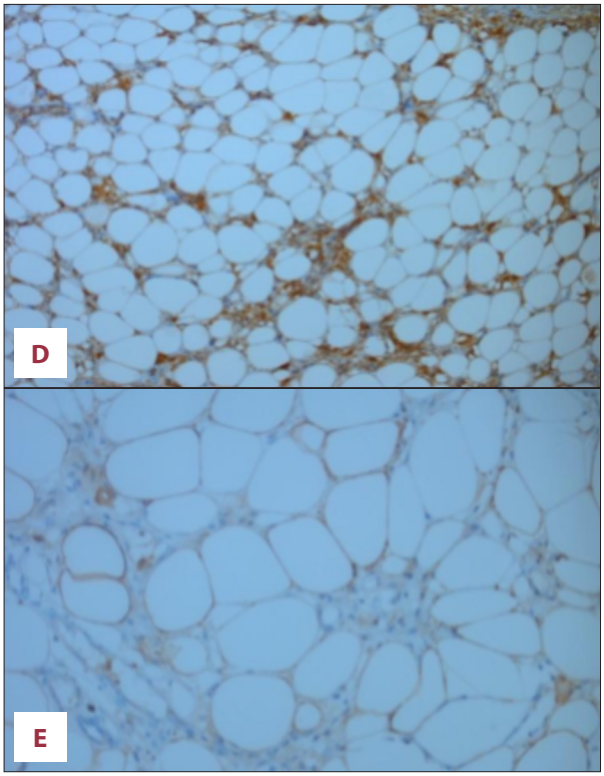

Figure 2. Perinephric mass tissue biopsy. The hematoxylin and eosin (H&E) stain in Figure **A** (100×), **B** (200×) and **C** (200×) shows collection of histocytes with abundant pale and foamy cytoplasm embedded within a fibrotic background. The histocytes stained positive for CD68 (**D**) and negative for S100 (**E**).

As a result, the treatment landscape for ECD has changed with the introduction of targeted agents. Treatment is recommended for all ECD patients with the exception of asymptomatic patients without vital organ involvement.

For ECD patients with *BRAF V600E* mutation, targeted therapy with a BRAF inhibitor is the recommended initial treatment. Vemurafenib is the first-line therapy for this group of patients [9]. The *VE-BASKET* trial was a non-randomized open-label trial including 22 patients with BRAF-mutated ECD, treated with vemurafenib, demonstrating that 100% of the patients had complete metabolic response as analyzed by FDG-PET/CT [10]. Based on that study, vemurafenib was approved by the U.S. Food and Drug Administration (FDA) for treatment of BRAF-mutated ECD.

Dabrafenib is another BRAF kinase inhibitor that can be used interchangeably with vemurafenib. In a report from Memorial Sloan Kettering Cancer Center, dabrafenib was offered as a single agent to 11 patients with *BRAFV600E* mutation. Of those 11 patients, 7 had ECD and 4 had overlapping ECD and Langerhans cell histiocytosis (ECD/LCH). Almost all patients responded well, and with limited toxicity [11]. The recommended dose for dabrafenib is 50-75 mg twice a day [11].

Adverse events for BRAF inhibitors include fatigue, QT interval prolongation, arthralgia, fluid retention, and cutaneous complications. A study of 24 patients receiving vemurafenib showed that all patients presented with at least 1 adverse skin reaction [12]. Dabrafenib has a lower skin toxicity profile and is thought be better tolerated than vemurafenib. The risk of cutaneous adverse events reported with vemurafenib is 44%, in comparison to 32% with dabrafenib [13]. In our case, the patient tolerated dabrafenib well without any reported toxicity.

For ECD patients with un-mutated *BRAFV600E*, it is recommended to perform next-generation sequencing (NGS) to look for other *MAPK-ERK* alterations that can be targeted with MEK

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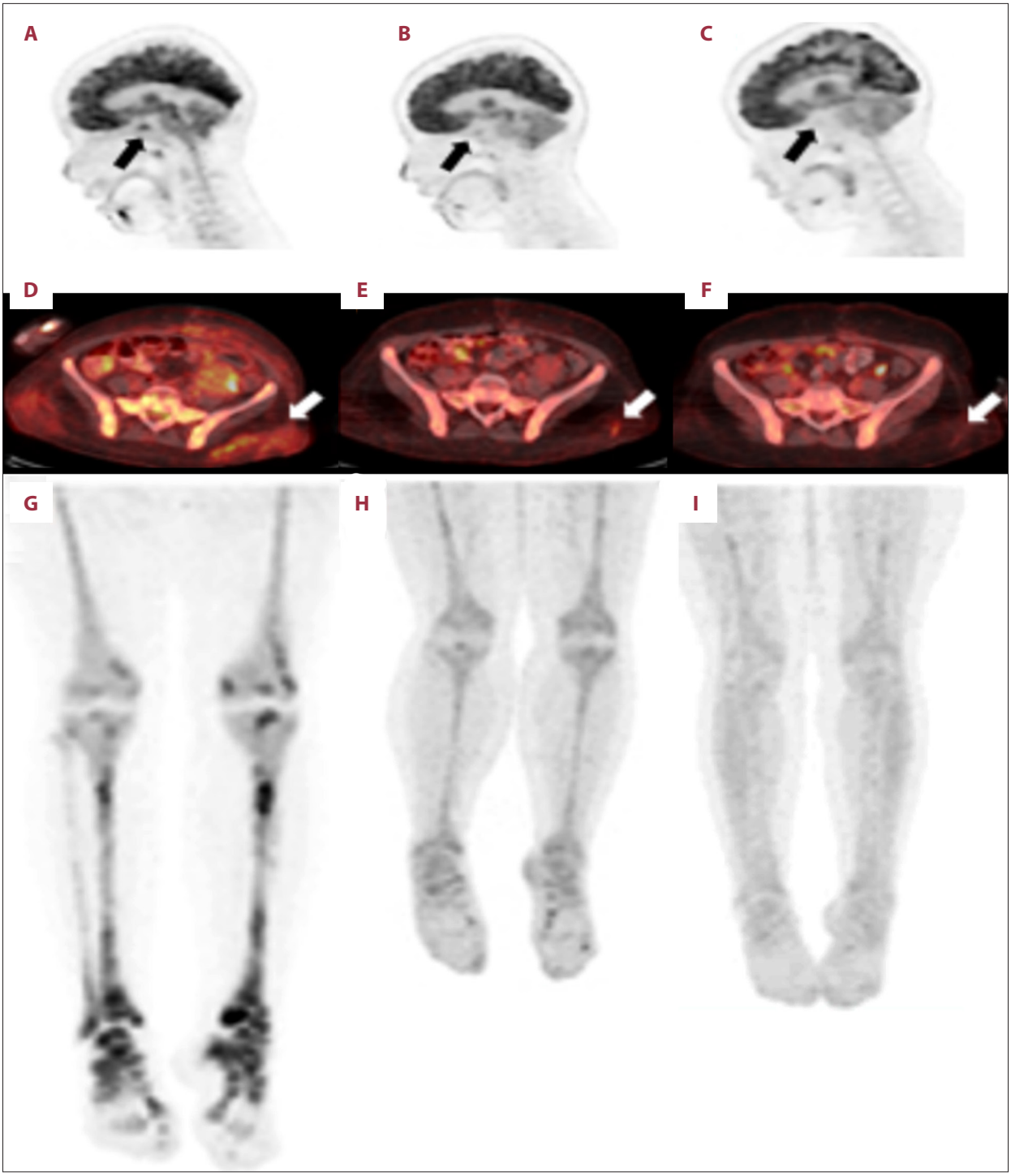

Figure 3. FDG-PET-CT at baseline (**A, D, G**), 2 months (**B, E, H**) and 6 months (**C, F, I**) after dabrafenib treatment. Sagittal brain PET images show a hypermetabolic pituitary lesion (arrow) at presentation (**A**) with metabolic improvement in mid-treatment (**B**) and metabolic resolution at end of treatment (**C**). Transaxial fused PET-CT images at level of S1 show hypermetablolism in sacrum and bilateral iliac bones with hypermetabolic subcutaneous soft-tissue thickening in anterior abdominal wall and bilateral gluteal regions at presentation (**D**) with only moderate residual hypermetablolism in left gluteal subcutaneous nodule (arrow) at mid-treatment (**E**) and metabolic resolution of all lesions at end of treatment (**F**). Anterior maximum-intensity projection (MIP) images of lower extremities show areas of heterogeneous hypermetabolism in multiple bilateral bones at presentation (**G**) with resolution of hypermetabolic lesions in mid- (**H**) and end of treatment (**I**).

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inhibitors. Cobimetinib is a selective MEK1 and MEK2 inhibitor that has marked and durable activity in adults with ECD and is recommended for use in patients with MAPK mutation [14].

Trametinib is another MEK inhibitor that can be used in newly diagnosed ECD with MAPK-ERK. There are some case reports of successful treatment with trametinib after disease reactivation while on dabrafenib [15]. Empiric treatment with MEK inhibitors such as cobimetinib and trametinib should be considered in acutely ill patients or patients with cardiac or central nervous system involvement but no identified MAPK mutation.

Conclusions

Our patient had multisystem involvement with Erdheim-Chester disease. The patient had an excellent and rapid response to dabrafenib with no medication-related toxicity. Our report indicates that given the effectiveness and lower toxicity profile of dabrafenib, it might be considered as a first-line option for BRAF-mutated ECD. However, our report is limited by the short duration of follow-up and limited sample size, and more cases are needed to reach firm conclusions.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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