Case Report

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Erdheim-Chester Disease With Multisystem Presentation With 20 Months Follow-Up: One Case Report And Literature Review In Molecular Era

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1. Abstract

Erdheim-Chester disease (ECD) is a rare non-Langerhans cell histiocytosis involving CD1a-negative histiocyte accumulation, primarily in adults. Diagnosis is challenging due to its rarity and diverse features. Molecularly, ECD is now understood as a hematopoietic tumor driven by oncogenic mutations, primarily within the mitogen-activated protein kinase (MAPK) pathway, and characterized by significant inflammatory components. Targeted therapies have shown robust clinical benefits. for the substantial proportion of patients, approximately 50-60%, BRAF inhibitors such as vemurafenib and dabrafenib have demonstrated remarkable and often rapid efficacy across diverse disease manifestations. We present a BRAF-V600E-mutant, multisystemic ECD case with 20 months follow-up, and review epidemiology, etiology, diagnosis, treatment, and surveillance. We highlight molecular-era new understandings and the importance of dynamic imaging monitoring for this complex disease. Our objective is to transform the clinical management model of ECD into one that facilitates early detection and prompt intervention, with the ultimate goal of achieving long-term disease control.

2. Keyword: Erdheim-Chester disease, BRAF V600E Mutation, Targeted Therapy,
18F-FDG PET/CT

3. Backgroud

Erdheim-Chester disease (ECD) is a rare non-Langerhans cell histiocytosis characterized by the accumulation of CD1a-negative histiocytes in bones, kidneys, retroperitoneum, heart, lungs, skin, orbits, and brain [1,2]. ECD primarily affects adults, a slight male predominance in reported cases, with the mean age ranging from 46 to 56 years at diagnosis. Diagnosis of ECD is challenging due to its rarity and the diversity of its clinical and radiographic features, therefore interdisciplinary approach with imaging and histological and clinical data is crucial. Advances in molecular biology have reclassified ECD as a hematopoietic tumor, revealing that most patients harbor MAPK-ERK or PI3K-AKT pathway mutations [3,4]. This discovery of driver mutations has led to targeted therapies that demonstrating robust clinical benefits, although challenges like resistance and toxicity remain [5]. In this paper, we present one case of BRAF-V600E-mutant male ECD patient with multisystemic involvement with a follow-up of 20 months, and provide a comprehensive summary of the diagnosis, clinical features, treatment strategies and disease surveillance. Our findings emphasize new understanding and strategies in molecular era and the necessity of dynamic monitoring of imaging.

3. Case Presentation

On August 23, 2023, a 60-year-old male presented to a local hospital due to proptosis, where an orbital mass was identified. The patient had a preceding history from June 2023 of chest tightness, which worsened with activity and relieved by rest. Histopathological examination of a biopsy specimen from the patient's orbital mass revealed abundant lymphohistiocytic infiltration, immunohistochemistry (IHC) showed: CKpan (-), Vimentin (+), SMA (-), Desmin (-), CD68 (+), CD34 (focally +), Ki-67 (+, approx. 5%), S-100 (-), SOX-10 (-), ALK (-), EMA (-), CD21 (-), CD23 (-), CD3 (positive in lymphocytes), CD20 (positive in lymphocytes), CD1a (-), CD163 (+), and BRAF-V600E (weakly +). Molecular genetic testing confirmed the BRAF V600E mutation, leading to a presumptive diagnosis of Erdheim-Chester disease (ECD).

For further management, he was admitted to our institution on September 11, 2023. The 18F-FDG PET/CT scan revealed multisystem involvement, heterogeneous soft tissue densities with increased FDG uptake involving the pericardium, great vessels, perirenal regions, bilateral intraconal spaces of the orbits, mesenteric area, right frontal lobe apex, right scapula, left humeral head, right clavicle, T10 vertebral body, bilateral iliac bones, right

Annals of Clinical and Medical Case Reports

femoral neck, and left pubis (Figure1A). These lesions demonstrated invasion and encasement of adjacent structures, consistent with ECD manifestations. Also, there were pleural and pericardial effusions. Baseline vascular endothelial growth factor (VEGF) was 441.9 pg/mL (normal range: 6.25-142.2 pg/mL), and C-reactive protein (CRP) was 52.7 mg/L (normal range: 0-8 mg/L). We also performed additional Langerin staining on the biopsy specimen from orbital mass and the negative result further supported the diagnosis (Figure1B). Integrating these comprehensive findings, a definitive diagnosis of ECD was established. He was then prescribed with dabrafenib 150 mg twice daily on September 14, 2023. Follow-up assessments, including chest and abdominal CT scans and laboratory tests, were conducted every 2-3 months. The patient tolerated the treatment well with no unanticipated events, reported symptomatic relief of chest tightness and dyspnea. VEGF and CRP levels gradually decreased and subsequently stabilized (Figure1C,1D). Imaging confirmed the resolution of pleural and pericardial effusions after the first month of treatment. Subsequently, lesions in the bilateral intraconal spaces of the orbits became smaller (Figure1E), while the remaining lesions stayed stable. This improvement and stability persisted for 20 months until the latest follow-up. (Figure2).

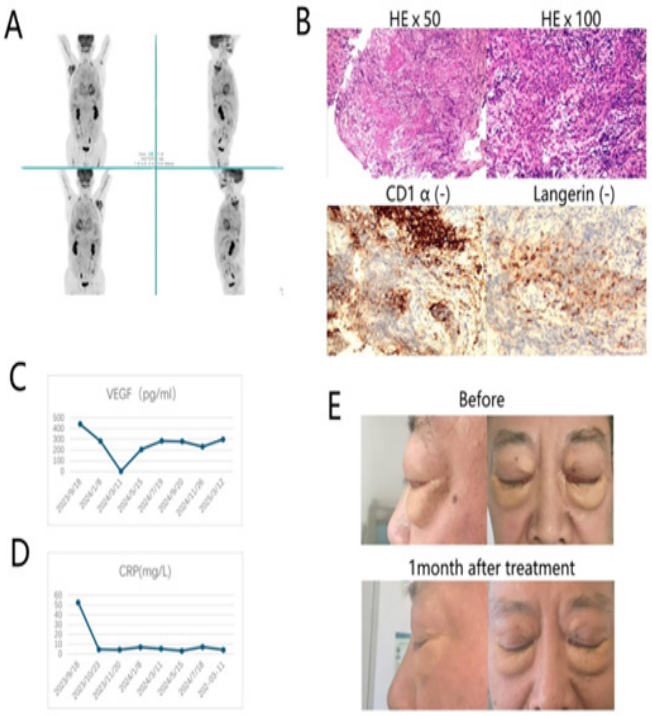

Figure 1: Patient Findings at Baseline and After Treatment. A, 18F-FDG PET/CT scan revealed multisystem involvement with increased FDG uptake. B, Pathological examination findings of orbital mass. Top, foamy or rich in lipid tissue cells, fibrosis with inflammatory cells infiltration. HE stainx50 and HE stainx100, (left/bottom) CD1-α immunohistochemical stain (-)x100,(right/bottom) Langerin immunohistochemical stain (-)x100. C and D, the profile of VEGF and CRP in serum. VEGF normal range: 6.25-142.2 pg/mL, and CRP normal range: 0-8 mg/L. E, photographs taken before and after treatment demonstrate a considerable regression of the orbital mass. Top two were before treatment, bottoms were taken one month after treatment.

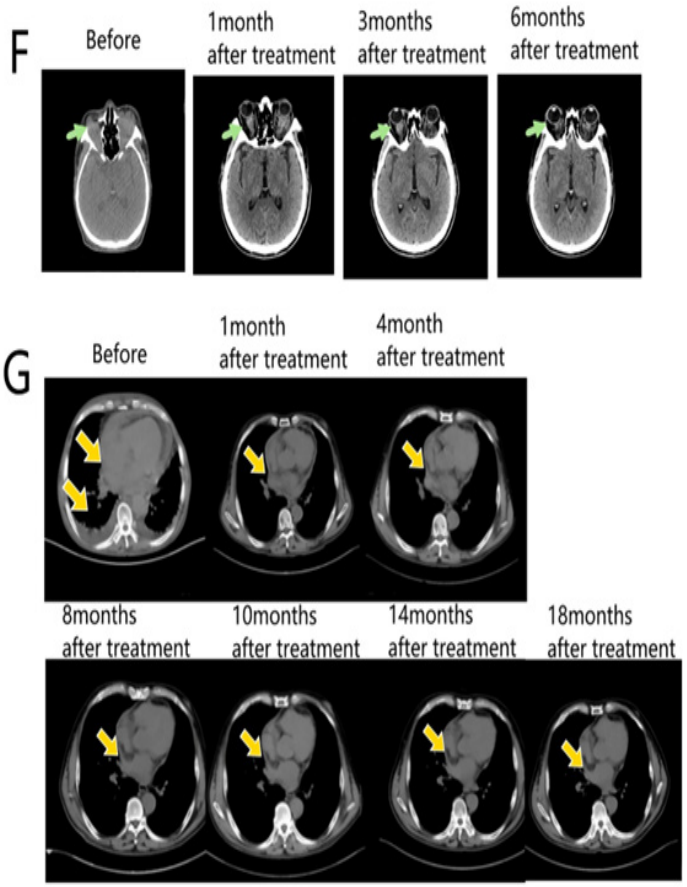

Figure 2: Follow up Computed tomography (CT) scans. F, CT scans showed the lesion became smaller after 1 months,3 months,6 months of targeted treatment. G, CT scans before and after treatment. The pre-treatment scan (left/top) shows a mediastinal mass with pericardial and pleural effusions. One month after treatment (middle/top), the effusions have resolved and the mass is smaller. The disease remained stable after 4,8,10,14,18 months follow-ups.

4. Discussion and Conclusions

Erdheim-Chester disease (ECD) is a rare non-Langerhans cell histiocytosis, characterized by the infiltration of tissues by cells originating from the macrophage and dendritic cell lineages1. Epidemiologically, ECD has seen a substantial increase in reported diagnoses over the last two decades, a trend largely attributed to growing awareness among clinicians. By 2006, only about 240 cases were documented in English literature, whereas current estimates suggest the number of diagnosed cases worldwide exceeds 1500. Despite this increase, the exact incidence remains unknown due to the lack of population-based mandatory reporting, though a study in Italy and France estimated an average disease incidence of 0.35 cases per 1,000,000 adult residents per year between 2018 and 2020, likely an underestimation6. ECD predominantly affects middle-aged adults, cohort studies report median ages at

diagnosis in the mid-50s to early 60s. Data from various cohorts support this, with a mean age at diagnosis reported as 46 years in a United States cohort (range 20-74), 56 years in a large French cohort (range 29-86), and median ages of 56.5 years (range 19-81) in an Italian cohort and 62 years (range 21-86) in a French cohort from a geoepidemiological study. A consistent male preponderance is observed, with a male-to-female ratio of approximately 3:1 [2]. The occurrence of pediatric ECD is rare, it sometimes present as BRAF-V600E mutated juvenile xanthogranuloma affecting the central nervous system.Geo-epidemiological research in Italy and France has identified geographic clustering of ECD cases, with an inverse correlation to the Human Development Index (HDI) of these regions, suggesting potential roles for socioeconomic or environmental factors alongside genetic predispositions, although genetic predispositions within these populations are not excluded [6].

Researchers now identify the pathogenesis of ECD as a clonal disorder with inflammation playing a critical role in disease progression [5]. The BRAF-V600E mutation is the most common driver identified in approximately 50-60% of ECD patients, with some specific cohorts showing frequencies like 59.3% in Italian patients and 50.8% in French patients. The variant allele frequency (VAF) of BRAF-V600E in tissue samples can be very low, often less than 5%, underscoring the need for highly sensitive detection methods, immunohistochemical analyses have shown that the mutated BRAF-V600E protein is expressed in histiocytes and Touton giant cells but not in other surrounding cells like lymphocytes or fibroblasts. Beyond BRAF-V600E, MAP2K1 (MEK1) mutations are found in up to 30% of patients, particularly those with BRAF wild-type ECD, accounting for roughly another 25% of cases [8]. Less frequent are mutations in NRAS, KRAS (reported in up to 27% collectively in some series, though lower in specific cohorts like 0.8-1.7% for KRAS and 0.4-0.8% for NRAS in the Italian/ French study), and ARAF, translocations leading to gene fusions involving BRAF, ALK, and NTRK1 have also been identified. The PI3K-AKT pathway is also implicated, with PIK3CA mutations found in about 11% of patients. Despite these advances, about 10-15% of ECD cases lack an identified driver mutation. ECD cell is believed to originate from mutated hematopoietic stem cells or myeloid progenitors and then migrate to tissues and differentiate into characteristic histiocytes [9]. Oncogene-induced senescence is one proposed mechanism, BRAF-V600E mutated histiocytes expressing p16Ink4a and potentially releasing a senescence-associated secretory phenotype (SASP) [10]. Furthermore, oncogene-induced maladaptive activation of trained immunity can lead to immunometabolic reprogramming and epigenetic changes enhancing cytokine production, resulting a hyperinflammatory state. Inflammation is a critical co-driver of ECD pathology. Systemic inflammation is common, with over 80% of patients exhibiting elevated C-reactive protein (CRP) levels. Studies have identified increased serum levels of various pro-inflammatory cytokines and chemokines, including interferon-α (IFNα), IL-1/IL-1RA, IL-6, IL-12, and MCP-1, suggesting a Th1-skewed immune response. Tumor necrosis factor-α (TNFα), IL-6, and IL-8 have been shown to be secreted by mononuclear cells from ECD lesions, with IL-8 acting as a chemoattractant for polymorphonuclear cells and monocytes. Chemokine ligand 18 (CCL18), involved in fibrosis, is also significantly increased in ECD patients and its high levels correlate with disease severity. The mechanistic link between oncogenic mutations and inflammation is an area of active research, one hypothesis involves oncogene-induced senescence, BRAF-V600E mutated histiocytes in ECD have been shown to express the senescence marker p16Ink4a, and senescent cells are known to secrete a complex array of inflammatory mediators (senescence-associated secretory phenotype or SASP), thus potentially driving systemic inflammation and recruiting other immune cells11. Finally, there is study showing that up to 20% of cases ECD coexists with Langerhans cell histiocytosis (LCH), in such mixed cases, patients are often younger, and there's a higher frequency of BRAF-V600E mutations in both the LCH and ECD components compared to when these diseases occur in isolation. ECD has also been observed in association with the extranodal form of Rosai-Dorfman-Destombes disease (RDD), predominantly in men, and these cases frequently harbor MAP2K1 mutations. This highlights the complex interplay of shared molecular drivers and potential common cellular origins across different histiocytic disorders [18].

The diagnosis of ECD is challenging due to its rarity and diverse clinical manifestations, which often mimic other conditions, leading to significant diagnostic delays. The histopathological findings may show non-specific inflammation and fibrosis, or atypical features such as florid lymphohistiocytic infiltration, rather than the classic foamy histiocytes with Touton giant cells [2]. Consequently, integrating clinical, radiographic, and molecular supports is essential, as ECD is not solely a pathologic diagnosis.

18F-FDG PET/CT has emerged as a crucial imaging modality in the diagnostic procedure and follow-up assessment [19]. It is preferred for its ability to assess systemic involvement, including visceral and soft tissue disease, and to guide biopsy to the most metabolically active and accessible sites. A full-body PET-CT scan is recommended at baseline for all patients to define disease extent, as it can reveal characteristic patterns of FDG avidity in bones, kidneys, central nervous system (CNS), cardiovascular system, and other organs [2,19]. Notably, PET/CT results influenced patient management in nearly half of the cases in one large study, contributing to initial diagnosis, directing biopsies, or guiding therapy decisions. Furthermore, PET/CT findings, such as FDG-avid CNS disease and higher overall SUVmax, may act as non-invasive biomarkers suggesting the presence of a BRAF-V600E mutation, a critical factor for therapeutic decisions. For instance, FDG-avid CNS disease demonstrated high specificity and positive predictive value for BRAF positivity in one cohort [17].

Molecular testing of biopsy material using Droplet Digital Polymerase Chain Reaction (ddPCR) or Next Generation Sequencing (NGS) can increase diagnostic confidence, especially in cases with ambiguous histopathology or absent classic bone lesions, and also identify targetable mutations. The identifications of BRAF-V600E (present in 50-60% of cases) or MAP2K1 (in

25% of cases) strongly support an ECD diagnosis and distinguishes it from other histiocytoses that typically lack these specific alterations [8].

The advent of molecular testing has profoundly reshaped therapeutic strategies for ECD [11]. BRAF inhibitors such as vemurafenib and dabrafenib have demonstrated remarkable and often rapid efficacy in patient outcomes. But before achieving complete remission, disease recurrence is observed frequently, then re-challenge of these agents often recaptures clinical benefit [10,11]. Vemurafenib was first reported in 2013 for 3 BRAF-V600E-mutant ECD patients with multi-system involvement, all of whom achieved partial response [12]. In the subsequent phase II VE-BASKET clinical trial, 22 patients with BRAF-V600E mutant ECD were treated with vemurafenib (15 patients had previously received systemic treatment and 7 patients were treatment-naive). The overall response rate (ORR) was 54.5% (RECIST 1.1 criteria), all 15 patients evaluated by FDG-PET/CT achieved a metabolic response, including 12 patients (80%) with a complete metabolic response. The 2-year progression-free survival (PFS) rate and 2-year overall survival (OS) rate were 83% and 95%, respectively [13]. Based on this study, vemurafenib was approved by the U.S. Food and Drug Administration (FDA) in 2017 for the treatment of ECD patients with BRAF-V600E mutation. In recent years, some researchers have proposed that vemurafenib is effective for ECD patients with orbital involvement, but ineffective for those with multi-organ involvement [14].

For individuals with BRAF wild-type ECD, particularly the 25-30% with MAP2K1 mutations or other non-BRAF MAPK pathway aberrations, or those intolerant to BRAF inhibitors, MEK inhibitors like cobimetinib or trametinib have emerged as effective alternatives [8,18]. Further investigations into mTOR inhibitors for patients with PIK3CA mutations and other rarer oncogenic drivers like ALK or RET fusions reflect increasingly personalized therapeutics [18].

Prognostic monitoring in ECD has correspondingly evolved, heavily relying on 18F-FDG PET/CT imaging to assess metabolic and structural responses to treatment, long-term surveillance and detection of relapse. Clinical evaluation, including symptomatic improvement and organ function assessment, remains paramount. Inflammatory markers, notably C-reactive protein have been correlated with patient outcomes and disease activity. While still an area of development, molecular monitoring using techniques like circulating tumor DNA analysis for specific mutations may offer a non-invasive method to track therapeutic response and detect treatment resistance. At last, these monitoring techniques will improve the prognosis for many patients, turning ECD into a more manageable, long-term multidisciplinary care disease.

ECD is an infrequent histiocytosis driven by various genetic mutations. Here, we present a BRAF-V600E positive case with multisystemic involvement. We further review recent literature, new insights into ECD's epidemiology and its etiology, then highlighting new diagnostic and therapeutic breakthroughs for ECD in the molecular era, including advances in targeted therapies and prognostic monitoring.

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