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Case report

PRESENCE OF IGG4-POSITIVE CELLS IN ERDHEIM-CHESTER DISEASE. EPIPHENOMENON OR OVERLAP?

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Abstract

Erdheim-Chester disease (ECD) and IgG4-related disease (IgG4-RD) are rare conditions with overlapping clinical and imaging manifestations that complicate their diagnosis. The finding of an infiltrate rich in IgG4-positive plasma cells in ECD lesions adds complexity, raising the question of whether this is an epiphenomenon or a true pathogenic overlap.

We present the case of a 61-year-old man with systemic symptoms and a retroperitoneal mass causing the "hairy kidney" sign on imaging. Histopathology was ambiguous: a perirenal biopsy met the criteria for IgG4-RD, showing storiform fibrosis, phlebitis, and an infiltrate of >50 IgG4+ cells/HPF; however, a sample from the omentum contained foamy histiocytes (CD68+) characteristic of ECD. Molecular analysis was decisive: the BRAF V600E mutation was negative, but an activating mutation in the *MAP2K1* gene was identified, confirming the diagnosis of ECD. The patient had an excellent clinical and radiological response to targeted therapy with the MEK inhibitor, trametinib.

This case underscores the critical importance of molecular biology, beyond the BRAF mutation, in the differential diagnosis of complex fibro-inflammatory lesions. The coexistence of diagnostic criteria for both entities in the same patient suggests that the presence of IgG4 cellularity in ECD should be represent a true pathogenic overlap, where the neoplastic clone triggers a secondary immune response, rather than a mere reactive epiphenomenon.

Key words: Erdheim-Chester disease, immunoglobulin g4-related disease, retroperitoneal fibrosis

Resumen

Presencia de células IgG4 positivas en la enfermedad de Erdheim–Chester ¿Epifenómeno o superposición?

La enfermedad de Erdheim-Chester (EEC) y la enfermedad relacionada con IgG4 (ER-IgG4) son afecciones infrecuentes con manifestaciones clínicas e imagenológicas superpuestas que dificultan su diagnóstico. El hallazgo de un infiltrado rico en células plasmáticas IgG4 en lesiones de EEC añade complejidad, planteando si se trata de un epifenómeno o una verdadera superposición patogénica.

Se presenta un hombre de 61 años con síntomas sistémicos y una masa retroperitoneal que generaba el signo de "riñón peludo" en imágenes. El estudio histopatológico fue ambiguo: una biopsia perirrenal cumplía con los criterios de ER-IgG4, con fibrosis estoriforme, flebitis y un infiltrado >50 células IgG4+/HPF; sin embargo, una muestra del epiplón contenía histiocitos espumosos (CD68+) característicos de la EEC. El estudio molecular fue dirimente: la mutación BRAF V600E fue negativa,

pero se identificó una mutación activadora en el gen *MAP2K1*, confirmando el diagnóstico de EEC. El paciente presentó una buena respuesta clínica y radiológica a la terapia dirigida con el inhibidor de MEK, trametinib.

Este caso subraya la importancia crítica de la biología molecular, más allá de la mutación BRAF, en el diagnóstico diferencial de lesiones fibroinflamatorias complejas. La coexistencia de criterios diagnósticos para ambas entidades en un mismo paciente sugiere que la presencia de celularidad IgG4 en la EEC podría representar una superposición patogénica real, donde el clon neoplásico desencadena una respuesta inmunológica secundaria, más que un mero epifenómeno reactivo.

Palabras clave: enfermedad de Erdheim-Chester, enfermedad relacionada con inmunoglobulina g4, fibrosis retroperitoneal

Erdheim-Chester disease (ECD) is a non-Langerhans cell histiocytosis, recognized as a rare myeloid neoplasm driven by activating mutations in the MAP kinase (MAPK) pathway[1]. In contrast, IgG4-related disease (IgG4-RD) is a systemic fibroinflammatory disorder that can mimic multiple conditions, including malignancies and infections[2]. Both entities are rare, and their diagnosis remains challenging due to overlapping clinical and radiological manifestations, such as retroperitoneal fibrosis. This challenge is compounded when an IgG4-positive plasma cell-rich infiltrate is identified in biopsies from ECD patients– a phenomenon whose nature, whether reactive epiphenomenon or true disease overlap, remains a matter of debate[3,4]. Herein, we present a case that exemplifies this diagnostic complexity.

Clinical case

A 61-year-old man with a past medical history of type 2 diabetes mellitus, heart failure with preserved ejection fraction, and arterial hypertension presented with a three-month history of frontal headache, asthenia, and a 10 kg weight loss (13% of body weight). He was a former smoker (1.25 pack-year index, quit 40 years prior) and worked as a seed handling technician. Over time, he developed a non-productive cough, febrile episodes reaching up to 40°C, and worsening glycemic control. He also reported xerostomia, xerophthalmia, and mild bilateral lumbar pain, without other significant symptoms.

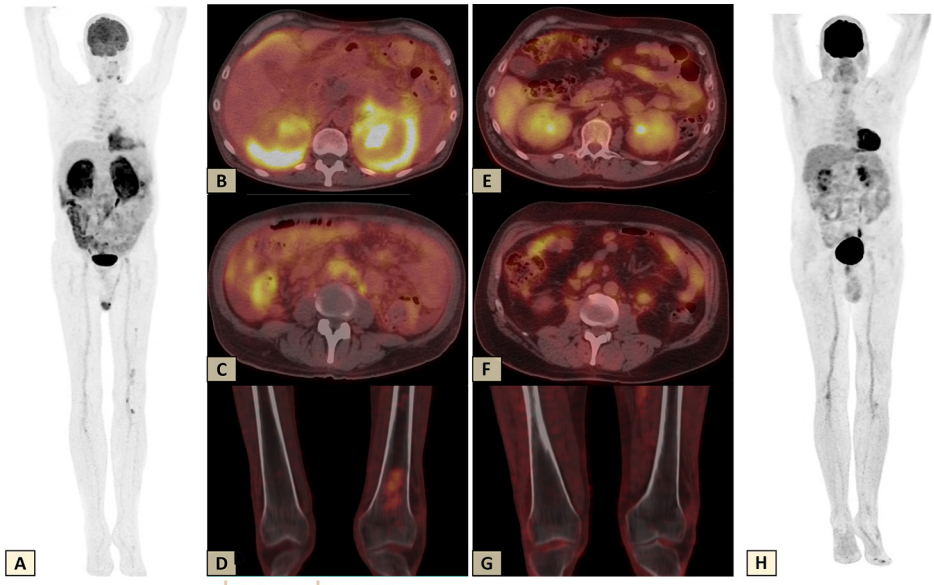
On physical examination, he had lower limb edema, with no other relevant findings. Laboratory tests revealed leukocytosis (15 300/µL with 96% neutrophils), anemia (hemoglobin 11.1 g/dL), and elevated inflammatory markers: erythrocyte sedimentation rate 77 mm/h, C-reactive protein 7.56 mg/dL (normal <0.6), and procalcitonin 6.35 ng/mL (normal <0.5). Serum creatinine was 1.16 mg/dL; urine sediment was unremarkable, with a protein-to-creatinine ratio of 0.66. Notably, serum IgG4 was elevated (221 mg/dL; normal <135 mg/dL). Serologies for hepatitis B and C viruses, HIV, as well as blood and urine cultures, were all negative.

Chest computed tomography (CT) revealed a small ground-glass opacity and a right pleural effusion. Abdominal and pelvic CT showed a soft-tissue density mass circumferentially surrounding both kidneys, infiltrating the perirenal fat without causing vascular or ureteral stenosis producing the characteristic "hairy kidney" appearance. This infiltration extended to the infrarenal abdominal aorta and iliac arteries, with a thickness of 10 mm. Positron emission tomography/CT (PET/CT) confirmed the presence of hypermetabolic tissue (SUVmax 8.5) with an infiltrative pattern involving both kidneys and the perirenal fat, as well as increased uptake in the abdominal aorta (SUVmax 3.4). Heterogeneous bone uptake was observed in the mid and distal thirds of the left femur (SUVmax 2.5), consistent with findings on a prior bone scintigraphy. Brain MRI was normal (Fig. 1 A, B, C, D).

Given these findings, a videolaparoscopic procedure was performed with biopsies taken from the retroperitoneal tissue and omentum. Peritoneal fluid analysis was negative for malignancy and infection. Histopathological evaluation of the perirenal sample revealed adipose tissue with a dense lymphoplasmacytic infiltrate, focal fibrosis with a vaguely storiform pattern, and obliterative phlebitis, findings consistent with IgG4-RD. Immunostaining showed numerous CD138+ plasma cells with a high proportion of IgG4-positive cells (IgG4/IgG ratio >80% and absolute count >50 cells/HPF). On the other hand, the omental biopsy, while also rich in IgG4-positive plasma cells, revealed the presence of foamy histiocytes (CD68+, S100–, CD1a–), a hallmark feature of ECD (Fig. 2).

Given the coexistence of findings meeting diagnostic criteria for both diseases, empirical treatment was initiated with methylprednisolone pulses followed by oral corticosteroids and weekly methotrexate, resulting in clinical improvement and reduction of inflammatory markers. Concurrently, molecular analysis of the tissue was performed. Both immunohistochemistry and PCR for the BRAF V600E mutation were negative. Due to the high suspicion for ECD, next-generation sequencing (NGS) was performed, which identified the c.159T>A (*p.Phe53Leu*)

Figura 1 | Diagnostic and post-treatment follow-up PET/CT (Positron Emission Tomography) with F-18 FDG. A: Maximum intensity projection (MIP). B: Fused PET/CT: Infiltrative and globular appearance of both renal parenchymas, with increased density of the perirenal fat and renal fossae, showing intense hypermetabolism (max SUV 8.5). Also noted is increased density of the anterior peritoneum and greater omentum with multiple micronodules, associated with abdominopelvic free fluid, all of which are hypermetabolic (max SUV 5.3). C: Hypermetabolism of the infrarenal abdominal aortic wall extending to both common iliac arteries (max SUV 3.4). D: Heterogeneous radiotracer uptake with patchy endomedullary density changes in the left femur, demonstrating moderate glucose metabolism (max SUV 2.5) with a distribution pattern similar to that of bone scintigraphy. Follow-up PET/CT post-treatment. E–G) Fused PET/CT images showing resolution of the previously described metabolic and morphological abnormalities: renal and peritoneal (E), vascular (F), and skeletal (G). H: MIP



mutation in the *MAP2K1* gene. This confirmed the diagnosis of ECD, and targeted therapy with trametinib (a MEK inhibitor) at 2 mg/day was initiated. Methotrexate was discontinued due to intolerance, and corticosteroids were tapered and eventually stopped.

The patient showed a favorable clinical course, with symptom resolution, normalization of inflammatory markers, and significant improvement in follow-up PET/CT imaging, which demonstrated complete resolution of hypermetabolism and marked regression of perirenal and periaortic fibrosis after two years of follow-up (Fig. 1 E, F, G, H). He tolerated trametinib well, with only mild peripheral edema responsive to a low-sodium diet, minor nail changes, and a slight reduction in ejection fraction without clinically significant repercussions. Despite the definitive molecular diagnosis of ECD, the presence of both histological and serological criteria for IgG4-RD raises the possibility of a true pathogenic overlap rather than a mere reactive phenomenon.

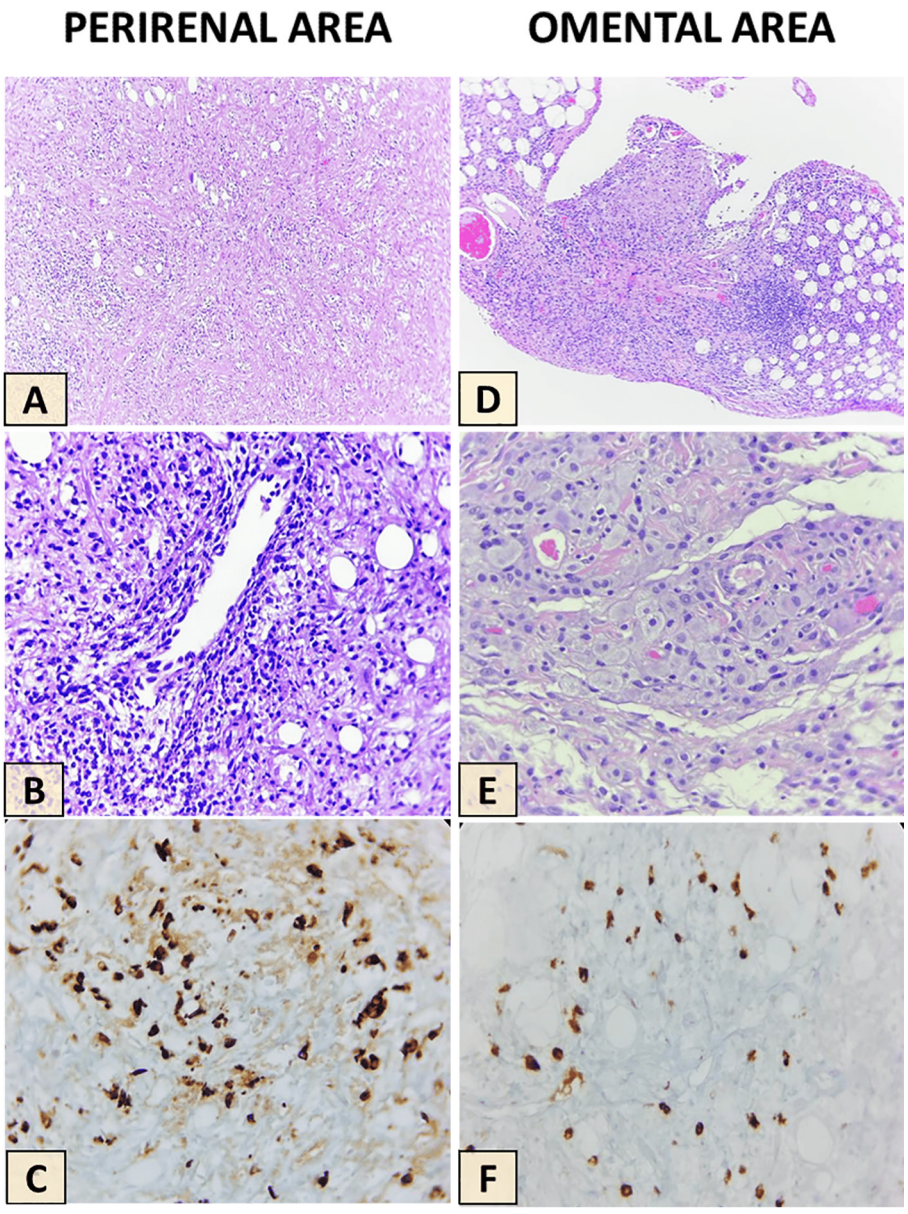
Informed consent was obtained from the patient for the publication of the case.

Discussion

The differential diagnosis between ECD and IgG4-RD remains a major clinical challenge due to overlapping manifestations such as retroperitoneal fibrosis, periaortitis, and orbital involvement[5]. ECD is an exceedingly rare, multisystemic non-Langerhans cell histiocytosis of adulthood, showing a male predominance and typically presenting in mid-to-late adulthood, with nearly 1500 cases reported worldwide[6]. Molecular cohorts consistently demonstrate activation of the MAPK-pathway (most commonly *BRAF V600E*, with *MAP2K1* among non-*BRAF* alterations) supporting the clonal and neoplastic nature of the disease[1,5].

In contrast, IgG4-RD is an underrecognized systemic fibroinflammatory disorder that can mimic a wide spectrum of conditions, from localized head and neck disease to retroperitoneal fibrosis[2]. Population-based studies estimate an incidence of 0.8–1.4 per 100 000 and a point

Figura 2 | Histopathology of perirenal and omental lesions. Perirenal lesion. A: Hematoxylin/Eosin (H&E) 10x: Perirenal adipose tissue with lymphoplasmacytic infiltrate and sectoral fibrosis. B: H&E 40x: Perivenular inflammation (obliterative phlebitis). C: IgG4 immunohistochemistry showing a high count per high-power field (HPF). Omental lesion. D: H&E 10x: Adipose tissue with lymphoplasmacytic inflammation and foamy histiocytes, with mild fibrosis. E: H&E 40x: Foamy histiocytes and inflammation. F: IgG4 immunohistochemistry showing a lower count per high-power field compared to the perirenal lesion



prevalence of nearly 5.3 per 100 000 in the United States[7,8]. Histopathology remains a diagnostic cornerstone, defined by the triad of lymphoplasmacytic infiltrate, storiform fibrosis, and obliterative phlebitis, while isolated tissue IgG4 counts are supportive but not diagnostic[7,8].

Our case exemplifies the diagnostic complexity arising from this overlap. The patient exhibited the classic "hairy kidney" sign and skeletal involvement typical of ECD, together with histological and serological findings fulfilling IgG4-RD criteria[5,9]. ECD typically shows CD68+/

CD1a– foamy histiocytes within a fibrotic stroma; however, histopathologic variability across anatomical sites can obscure the diagnosis[4,10]. Retroperitoneal biopsies, as in our patient, may reveal prominent plasma-cell infiltrates mimicking IgG4-RD. The perirenal specimen demonstrated storiform fibrosis, obliterative phlebitis, and more than 50 IgG4+ plasma cells per high-power field (HPF) with an IgG4/IgG ratio of 80%, hallmarks highly specific for IgG4-RD[2,4,5,9]. Nevertheless, IgG4+ cell fractions exceeding 40% have been documented in confirmed ECD lesions, underscoring the need for clinicoradiologic and molecular correlation.[4-9]. The omental biopsy, which demonstrated foamy histiocytes, was decisive in establishing the final diagnosis.

Advances in molecular biology have transformed the diagnostic approach to ECD. Identification of MAPK-pathway mutations is now fundamental for diagnostic confirmation and therapeutic stratification. *BRAF V600E* mutations occur in approximately 50–60% of cases, while *MAP2K1* mutations (encoding MEK1) are found in 40–50% of BRAF–wild-type patients. Detection of the *MAP2K1 p.Phe53Leu* mutation in our patient was decisive in confirming ECD and explaining the excellent and sustained response to trametinib, consistent with MEK-pathway activation[1,5].

Up to 27% of ECD patients have been reported to exhibit elevated serum IgG4 levels, and a smaller proportion may fulfill histologic thresholds for IgG4-RD, though not the complete diagnostic criteria[4,5,9]. Reports describing apparent overlap between ECD and IgG4-RD are scarce and generally involve retroperitoneal, vascular, biliary, or orbital manifestations later clarified through integrated clinical, radiologic, and molecular analyses[3,5,9,11-14]. These findings suggest that IgG4 overexpression in ECD likely represents a reactive immunologic phenomenon within the lesional microenvironment rather than a true dual pathology. Accordingly, any hypothesis of pathogenic overlap should be regarded as speculative and requires confirmation in larger, systematically phenotyped cohorts.

This case demonstrates molecularly confirmed ECD (*MAP2K1 p.Phe53Leu* mutation) with durable clinical response to trametinib, reinforcing the central role of MAPK-pathway activation in disease pathogenesis and targeted therapy. The IgG4-positive plasma-cell infiltrate observed here most likely represents a reactive and nonspecific immune phenomenon. While a true pathogenic overlap between ECD and IgG4-RD has been occasionally proposed, current evidence is confined to isolated case reports and small series, and cannot substantiate a reproducible mechanism. Future studies integrating standardized histopathologic criteria (e.g., ACR/EULAR) with molecular profiling are needed to clarify the frequency and biological relevance of IgG4-rich signatures within ECD.

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Conflict of interest: None declare

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