CASE REPORT

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Differential Diagnosis in a Case with Liver Lesion: Hypereosinophilic Syndrome or Eosinophilic Granulomatosis Polyangiitis

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ABSTRACT Hypereosinophilia is a common hematological abnormality often associated with parasitic infections, allergic diseases, drug reactions and neoplasms. When persistent eosinophilia is accompanied by organ involvement (e.g., heart, lungs, skin) and secondary causes are excluded, it may indicate primary hypereosinophilic syndrome (HES). Eosinophilic granulomatosis with polyangiitis (EGPA), a systemic vasculitis characterized by eosinophilic infiltration, necrotizing vasculitis, and refractory asthma, shares many clinical features with HES, particularly in the early stages. This overlap can make differentiating between the two conditions challenging without clear vasculitic signs. We present a case report highlighting the complex interplay between HES and EGPA, underscoring the diagnostic challenges in distinguishing these conditions.

Keywords: Eosinophilia; eosinophilic granulomatosis with polyangiitis; hypereosinophilic syndrome

The normal range for the peripheral blood absolute eosinophil count is between 0.05 and 0.5×10^9/L. Hypereosinophilia is defined as an eosinophil count exceeding 1500/μL on 2 separate occasions at least 1 month apart. Eosinophilia can result from various causes, including helminthic parasitic infections, allergic disorders like eosinophilic asthma and atopic dermatitis, and adverse drug reactions. It is also associated with solid tumors, Hodgkin lymphomas, myeloid neoplasms, immunoglobulin G4-related disease, and endocrine disorders. High serum eosinophil levels are associated with many immune deficiency or dysregulation disorders such as Hyper immunoglobulin E (IgE) syndrome, DOCK-8 deficiency, Omenn syndrome, Wiskott-Aldrich syndrome, and autoimmune lymphoproliferative syndrome.[1]

When secondary causes are excluded and organ involvement is evident, primary hypereosinophilic syndrome (HES) should be considered.[2] In primary HES, eosinophils infiltrate various tissues, leading to clinical manifestations that often affect the skin, lungs, and gastrointestinal tract. Although cardiovascular and neurological complications are less common, they are associated with significant morbidity and mortality. The clinical course of HES is variable; some patients present with progressive disease, while others experience episodic flare-ups.

Eosinophilic granulomatosis with polyangiitis (EGPA) is categorized as a secondary form of HES, characterized by necrotizing small vessel vasculitis, granulomatous eosinophilic inflammation, and refractory asthma. Clinical manifestations of EGPA

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vary depending on anti-neutrophil cytoplasmic antibodies (ANCA) status. ANCA-positive patients are at a higher risk of developing necrotizing vasculitis and glomerulonephritis. In contrast, ANCA-negative patients are more likely to experience eosinophilic organ infiltration, such as lung and endomyocardial involvement.[3] However, ANCA status alone does not entirely predict clinical presentation.

Distinguishing between primary HES and EGPA can be difficult due to significant overlap in their early clinical presentations (similar high eosinophil count, presence of constitutional symptoms, similar organ involvement). Here, we present a case report illustrating the challenges distinguishing between HES and EGPA.

CASE REPORT

A 59-year-old woman presented a history of myalgia, widespread arthralgia, dry cough, and mild exertional dyspnea. She also reported an unintentional weight loss of 10 kilograms over the past 5 months. The patient had no history of chronic disease, smoking, or drug use.

On physical examination, subcrepitant rales were detected in the bilateral pulmonary bases, but there were no signs of peripheral arthritis, cutaneous lesions, or muscle weakness. Laboratory findings revealed persistent eosinophilia with an eosinophil count of 3200×10^3/μL, confirmed over at least 3 months. Relevant laboratory tests are summarized in Table 1. She and her family had no previous history of frequent infections or recurrent allergies. Viral serologies were negative, and other laboratory results were within normal limits except for elevated serum IgE (659 IU/mL) and mild proteinuria (550 mg/24-hour urine collection). Serum protein electrophoresis and immunoelectrophoresis were unremarkable, with no significant clonality detected at the kappa-lambda light chain levels. Tumor markers were also within normal limits.

Abdominal magnetic resonance imaging (MRI), performed due to elevated liver enzymes, revealed numerous scattered peripheral enhancing liver lesions (Figure 1). Further malignancy screening, including mammography, esophagogastroscopy, and colonoscopy showed normal results and negative fecal parasite examinations. Despite initial suspicion of metastasis, a positron emission tomography-computed tomography (CT) scan demonstrated hypermetabolic liver nodules and focal ground-glass lung lesions with no evidence of malignancy (Figure 2). Bone scintigraphy revealed degenerative changes in the vertebrae, but other imaging findings were nonspecific. Electromyography findings for polyneu-

TABLE 1: Laboratory tests.

	Patient's Value	Normal Value Range
Hemoglobin	12.3 g/dl	12-16
MCV	90 fl	80-99
White blood cells	**12.350/mm³**	4.300-10.300
Neutrophil	3.580/mm³	2.100-6.100
Eosinophil	**3.200/mm³**	50-500
Platelet	210.000/mm³	156.000-373.000
Creatinine	1 mg/dl	0.7-1.2
AST	**100 IU/L**	0-35
ALT	**125 IU/L**	0-50
C- reactive protein	**20 mg/L**	0-5
LDH	210 U/L	0-250
TSH	1 μIU/ml	0.27-4.2
CK	43 U/L	<170
pro-BNP	**206 pg/ml**	60-170
Troponin T	**0.024**	<0.014
Vitamin B12	380	200-900

MCV: Mean corpuscular volume; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; LDH: Lactate dehydrogenase; TSH: Thyroid stimulating hormone; CK: Creatine kinase; pro-BNP: pro-brain natriuretic peptide.

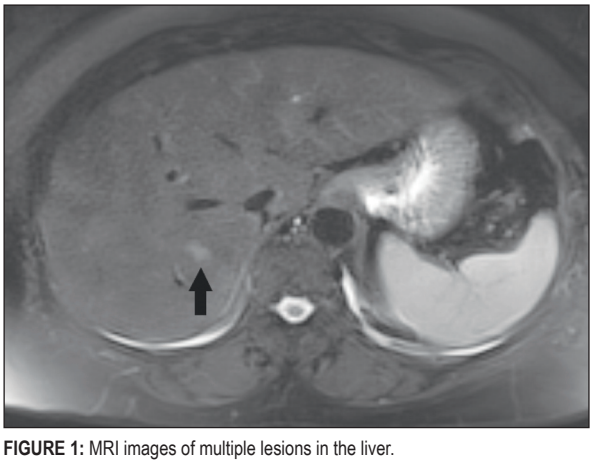

FIGURE 1: MRI images of multiple lesions in the liver.

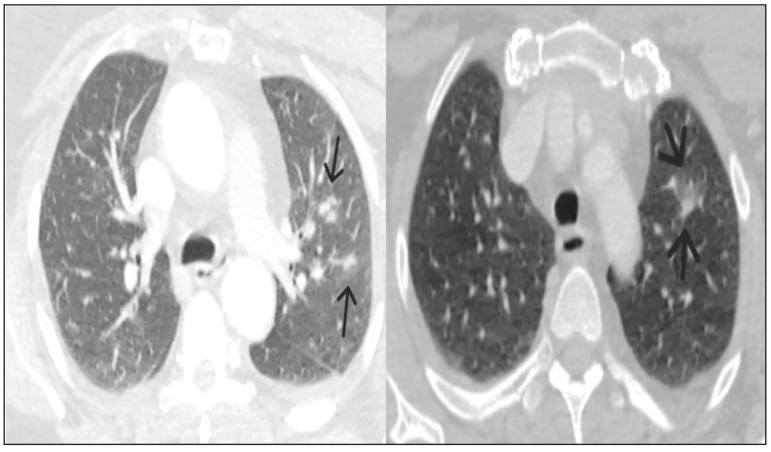

FIGURE 2: Nodular lesions seen on lung CT.

ropathy were within normal limits. Paranasal sinus CT showed mucosal thickening in the left maxillary sinus and sclerosis in the right mastoid cells. Transthoracic echocardiography showed a small pericardial effusion and mildly elevated pro-brain natriuretic peptide and troponin T levels. Proteinase 3 (PR3)-ANCA tests were positive, while myeloperoxidase (MPO)-ANCA and other autoimmune markers were negative.

A liver biopsy confirmed eosinophil infiltration and a bone marrow biopsy showed an increased eosinophil count without evidence of malignancy or granuloma formation. FISH testing for HES-related mutations returned negative results. Given these findings, a diagnosis of EGPA was considered. The patient was started on prednisolone and azathioprine, which led to the normalization of eosinophil levels and improved organ involvement.

Informed consent was obtained from the patient.

DISCUSSION

We described a 59-year-old female with 3200 eosinophils where other causes of hypereosinophilia were excluded, and EGPA was considered based on the patient's anamnesis, physical examination, and examination results. Allergic diseases are more common in the differential diagnosis of hypereosinophilia, but eosinophil counts greater than 1500 are rarely seen. EGPA and HES share overlapping clinical features, particularly in the early disease stages. Alongside blood and tissue eosinophilia, patients commonly exhibit constitutional symptoms, peripheral neuropathies, skin manifestations, interstitial pneumonia, eosinophilic alveolitis, and gastroenteritis. Some individuals may meet the criteria for both diagnoses, leading to overlapping conditions.[3] However, it is noteworthy that there may be a time interval between the onset of peripheral blood eosinophilia or asthma in patients with EGPA and the appearance of vasculitis.[3,4]

Patients with HES should be tested for the Factor interacting with PAPOLA (Fip1)-like 1–platelet-derived growth factor receptor α (FIP1L1-PDGFRA), PDGFRB, fibroblast growth factor receptors 1, and janus kinaz 2 mutations. In EGPA, ANCA positivity is over 40%, and the majority is MPO-ANCA positivity. Our patient had PR-3 ANCA positivity. However, without these features, it isn't easy to distinguish between ANCA-negative EGPA and PDGFR-negative HES. Moreover, although rare, ANCA-positive HES cases have been reported. According to ACR criteria; 1) asthma with history of wheezing or diffuse high-pitched expiratory rhonchi, 2) eosinophilia >10% in differential white blood cell count, 3) mono- or polyneuropathy, 4) migratory or transient lung infiltrates, 5) paranasal sinus abnormality with a history of acute or chronic

paranasal sinus pain, or radiographic opacification of the paranasal sinuses, and 6) detection of extravascular eosinophils on biopsy involving an artery, arteriole, or venue can be used to support a clinical diagnosis of EGPA but may be inadequate to differentiate it from HES.[5] Our patient met 4 of these criteria.

The presence of vasculitis is a prerequisite for diagnosing EGPA. Asthma and nasal polyps are also prevalent clinical features in patients with EGPA. One study showed that PR3-ANCA positive EGPA patients experienced more frequent skin problems like palpable purpuras and petechiae and lung problems like pulmonary infiltrates or alveolar hemorrhage. However, asthma and neurological problems are less common than MPO-ANCA-positive or ANCA-negative patients.[6]

It's noteworthy that our patient did not exhibit asthma or peripheral neuropathy. Moreover, cardiac involvement is more commonly associated with EGPA than Granulomatosis Polyangiitis, rendering it more akin to HES. Mononeuritis multiplex, nasal polyps, skin purpura, glomerulonephritis, gastrointestinal ischemia, and hemorrhages may approach the diagnosis of EGPA.[7] Mediastinal lymphadenopathy has also been described as a manifestation of EGPA-associated systemic inflammation.[3]

Liver involvement is exceedingly uncommon in EGPA. However, there have been reported cases of patients initially presenting with acute cholecystitis and were subsequently diagnosed with EGPA, as documented in several case reports.[8-10] In contrast, focal nodular liver lesions are more commonly associated with HES.[11] Therefore, we did not initially consider EGPA in the patient. Since the suspicion of malignancy was strong, the diagnostic process took a long time.

Corticosteroids remain the first-line treatment for both EGPA and HES. In this case, corticosteroids were started in the patient considering EGPA. For patients with organ involvement such as glomerulonephritis, alveolar hemorrhage, cardiac involvement, central nervous system involvement, intestinal ischemia a combination of high doses of glucocorticoids and cyclophosphamide are recommended.[12] Since there was no severe life-threatening organ involvement in this case, azathioprine was initiated.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Nur Beyza Tükek;* ***Design:*** *Nur Beyza Tükek;* ***Control/Supervision:*** *Nur Beyza Tükek;* ***Data Collection and/or Processing:*** *Nur Beyza Tükek, Seyda Bilgin;* ***Analysis and/or Interpretation:*** *Nur Beyza Tükek, Seyda Bilgin;* ***Literature Review:*** *Nur Beyza Tükek, Seyda Bilgin, Işıl Bavunoğlu;* ***Writing the Article:*** *Nur Beyza Tükek;* ***Critical Review:*** *Işıl Bavunoğlu.*

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