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Single Case

Hypereosinophilic Syndrome Secondary to Ulcerative Colitis and Primary Sclerosing Cholangitis

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Keywords
Ulcerative colitis · Primary sclerosing cholangitis · Hypereosinophilic syndrome

Abstract
Hypereosinophilic syndrome (HES) is a rare condition characterized by hypereosinophilia in peripheral blood or tissue infiltrate and organ damage. HES has been associated with several diseases, including inflammatory bowel diseases (IBDs), especially ulcerative colitis (UC). In this report, we describe a case of a UC and primary sclerosing cholangitis patient who was diagnosed with HES and severe cardiovascular and neurological injury. During hospitalization, an extensive diagnostic workup was performed and secondary causes of hypereosinophilia were ruled out. The patient was treated with glucocorticoids and full anticoagulation with significant clinical improvement and a marked reduction in the eosinophil count. In the literature, hypereosinophilia in the IBD population has been related to the severity of the disease and worse prognosis. The high index of clinical suspicion and the accurate diagnosis of HES are essential to avoid delay in therapy and prevent complications.

Introduction

Hypereosinophilic syndrome (HES) is a rare hematologic disease with an incidence of 0.018–0.036/100,000 person-years [1, 2]. It is characterized by sustained overproduction of eosinophils and eosinophilic infiltration in several organs with subsequent tissue damage. The diagnosis of HES requires peripheral blood eosinophil count ≥1,500 cells/mm^3 present

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on at least two occasions performed 6 months apart or tissue eosinophilia without clear etiology. The most common clinical presentation includes endocarditis, myocarditis, pneumonitis, hepatosplenomegaly, or gastroenterocolitis [3, 4].

HES has also been related to inflammatory bowel diseases (IBDs), mainly ulcerative colitis (UC) associated or not with primary sclerosing cholangitis (PSC) and autoimmune hepatitis [5, 6]. The presence of hypereosinophilia in patients with UC is considered a marker of disease severity at diagnosis. Additionally, it is associated to severe colitis and higher need for surgery [7].

Although the exact mechanism of the inflammatory response induced by hypereosinophilia is unknown, eosinophils are rich in pro-inflammatory cytokines, cytotoxic proteins, and epithelial growth factors that probably contribute to the exacerbation of IBD [6]. In the present study, the authors report a case of HES with cardiovascular and neurological involvement in a patient with IBD and discuss the clinical features and management of this condition in the UC and PSC setting.

Case Report

A 24-year-old male with UC and PSC admitted to the emergency room with severe holocranial headache and progressive worsening 1 week prior to the admission. He reported persistent pain despite the use of common analgesics. In addition, the patient presented nonspecific malaise, myalgia, and nausea. He denied fever, abdominal pain, vomiting, or worsening of diarrhea.

His past medical history was consistent with the diagnosis of UC and PSC for 10 years in sustained endoscopic remission. He was on regular treatment with mesalamine 4 g/day and ursodeoxycholic acid 1,200 mg/day for the past 3 years. He had never undergone abdominal surgery and never smoked. The family history was negative for IBD or hematological malignancies.

On admission, the patient had stable vital signs with BP 110 × 80 mm Hg, HR of 90 bpm, RR of 18 bpm, and was afebrile. He was in a regular-appearing, dehydrated +/IV+ and pale +/IV+. Cardiovascular and respiratory examinations were otherwise normal. He presented mild diffuse pain on abdominal palpation, without palpable masses or signs of peritonitis. The neurological exam showed mental confusion, reduced visual acuity, and acalculia while muscle strength, coordination, and sensitivity were preserved. Intravenous hydration and analgesia were initiated in the emergency department, without improvement, requiring hospitalization for pain management and etiological investigation.

Laboratory tests showed a total number of white blood cell count of 20,530 cells per microliter and eosinophilic count of 10,758 cells per microliter. The C-reactive protein was elevated 60.1 mg/L (normal range, <5). The alkaline phosphatase level was 394 U/L (normal range, 40–129) and the gamma glutamyl transferase level was 336 U/L (normal range, 8–61). The alanine aminotransferase level was 103.2 U/L (normal range, <41) and the aspartate aminotransferase level was 103.8 U/L (normal range, <37).

In a complementary diagnostic evaluation, infectious and parasitic etiologies were ruled out, with negative ova and stool parasite tests. After neurology evaluation, magnetic resonance imaging (MRI) of the brain was performed, which identified multiple diffuse hyperattenuating foci in the white matter, suggestive of ischemic involvement of cardioembolic origin (Fig. 1).

The transthoracic echocardiogram showed enlargement of the right heart chambers and the presence of an obliteration in the apical region of both ventricles with a small mobile thrombus in the left ventricle. The echocardiographic findings were confirmed by MRI and

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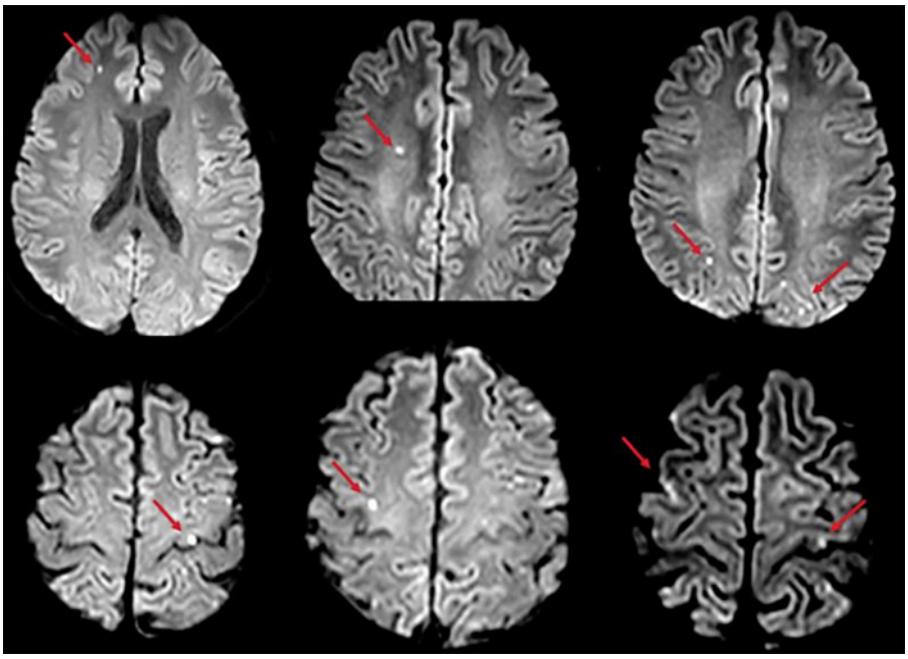

Fig. 1. MRI of the brain exhibiting multiple foci with hypersignal and diffusion restriction, suggestive of acute/subacute ischemia (red arrows).

characteristic of eosinophilic endomyocardial fibrosis, often described in cases of Löeffler's endocarditis (Fig. 2).

The etiological hypotheses of hereditary or acquired thrombophilia, in addition to eosinophilic leukemia, were ruled out through laboratory exams and myelogram, which were all negative (Fig. 3). The fluorescence in situ hybridization exam was negative for the rearrangement of the *PDGFRA* gene. The association of peripheral hypereosinophilia, intracavitary thrombus, and neuroimaging of stroke confirmed the diagnostic hypothesis of HES with endomyocardial fibrosis and subsequent embolization to the central nervous system.

The patient was treated with prednisone 1 mg/kg/day and full anticoagulation initially with low molecular weight heparin 1 mg/kg every 12 h, later changed to apixaban 10 mg/day. During hospitalization, he responded to the established clinical treatment. He showed complete neurological recovery with improvement in headache and absence of focal deficits, in addition to a significant reduction in peripheral eosinophilia after 4 weeks (Fig. 4).

On an outpatient follow-up, the patient remained clinically well, with preserved bowel habits, and was neurologically asymptomatic. Complete weaning from corticosteroid therapy was performed without clinical or laboratory recurrence of the disease.

Discussion

This young man diagnosed with UC and PSC presented with neurological damage secondary to thromboembolic event in the setting of peripheral hypereosinophilia. The patient's symptoms combined with laboratory and imaging tests met the diagnostic criteria for HES. HES is a cause of primary hypereosinophilia and the diagnosis requires the exclusion of secondary causes, such as allergic-mediated, parasitic infections and hematological diseases [3, 7].

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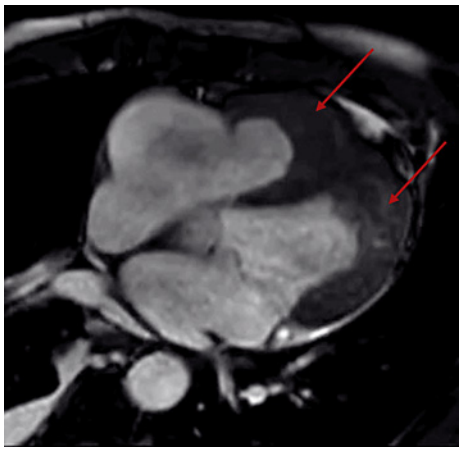

Fig. 2. Cardiac MRI demonstrating thrombus-associated obliteration at the ventricular apices and diffuse subendocardial necrosis/fibrosis of both ventricles (red arrows).

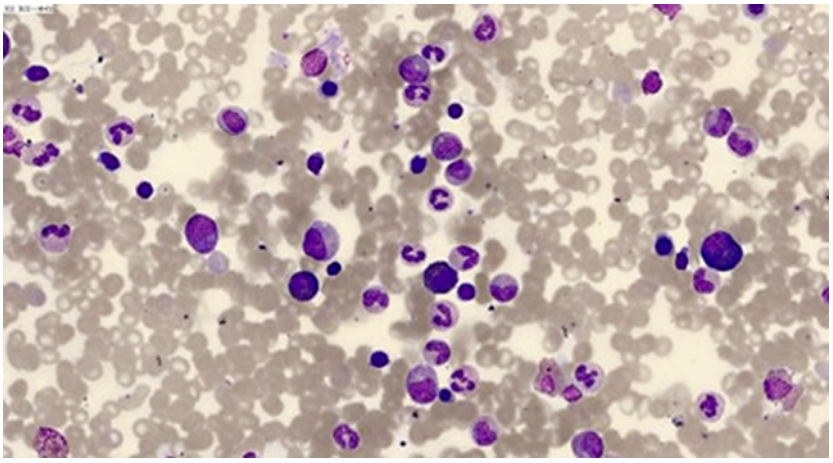

Fig. 3. Myelogram showing normocellular bone marrow, with hypercellularity of the eosinophilic cell line (Wright-Giemsa stain, magnification, ×50).

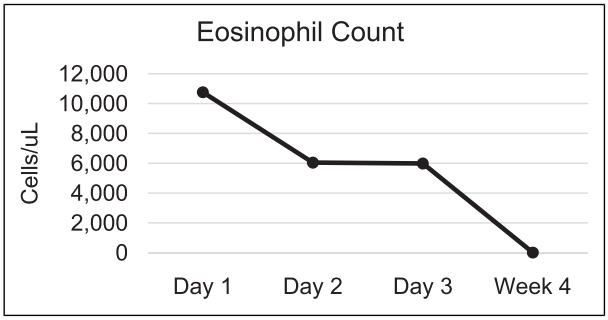

Fig. 4. Eosinophil count during hospitalization and treatment

The HES involvement is broad and includes dermatological (37%), pulmonary (25%), gastrointestinal (14%), and rarely cardiac (5%) symptoms. In some cases, serious complications can occur, such as endomyocardial fibrosis and neurological injuries [8, 9].

The cardiac injury mediated by eosinophils progresses in three stages. The early necrotic form is usually silent and can be diagnosed by MRI. In the intermediate phase, which is characterized by endocardial damage, there is overt thrombosis and increased risk of

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embolization. Finally, a fibrotic stage, with fibroinflammatory remodeling of valve structures and chordae tendineae, ultimately leads to ventricular heart failure [10].

In patients with Löeffler's endocarditis, intracardiac thrombi generate cerebral emboli that can manifest as transient ischemic attacks or strokes. The diagnosis is established by MRI of the brain that reveals multiple areas of infarcts [11].

Barrie et al. [5] have identified 1176 IBD patients who developed eosinophilia in a tertiary referral center and performed a case-control study with patients with no history of eosinophilia. The authors found that eosinophilia was more prevalent in UC than Crohn's disease patients (22.2% vs. 12.7%) and that recurrent eosinophilia was predominantly present in male with higher rates of colectomy for either refractory disease or dysplasia and cancer than control UC patients. PSC occurred in 37.5% of UC patients with recurrent eosinophilia compared to only 3.1% in the UC controls [5].

Previously, Click et al. [12] have reported that absolute eosinophil level and duration of hypereosinophilia did not correlate with risk of adverse events or disease severity. However, the finding of hypereosinophilia was associated with more complex forms and extensive disease, in addition to negative clinical outcomes when compared to the control group [12].

In IBD patients, eosinophil-predominant infiltration in the lamina propria has been associated with reduced risk of disease flares and hospitalization. The degree of eosinophilic inflammation appears to stratify disease severity and to be a poor predictor of disease outcome. In the present case report, no eosinophilic cryptitis was observed in the histological results from a previous colonoscopy [13].

Once the diagnosis of HES is stablished, the therapeutic goals are to minimize symptoms and decrease eosinophil count to values under 1,500 cells/mm^3 to prevent organ damage. Patients with positive myeloid variants for the *PDGFRA* gene are initially treated with imatinib mesylate, while those who are negative are treated with glucocorticoids. The treatment should be immediate in the presence of cardiac damage and thromboembolic events [14].

The mechanism of action of glucocorticoids in HES is not fully understood. They are believed to mediate eosinophilopoiesis, accelerate apoptosis, and eosinophil sequestration. The literature recommends initial dose between 1 mg/kg of prednisone to 1 g/day of methylprednisolone. Anticoagulation is often instituted in the presence of an embolic event. Finally, thrombectomy can be indicated in patients with valve involvement, thrombosis, or endomyocardial fibrosis [15].

Statement of Ethics

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. Ethical approval was not required for this study in accordance with local and national guidelines.

Conflict of Interest Statement

The authors of this manuscript do not have any conflict of interest to declare.

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Author Contributions

Davi Viana Ramos and Diogo Delgado Dotta contributed to this paper's conception and literature review. Luísa Leite Barros contributed to critical revision and approval of the final version.

Data Availability Statement

All data that support the findings of this study are included in this article. Further inquiries can be directed to the corresponding author.

References

1 Terrier B, Fontaine H, Schmitz J, Perdu J, Hermine O, Varet B, et al. Coexistence and parallel evolution of hypereosinophilic syndrome, autoimmune hepatitis, and ulcerative colitis suggest common pathogenic features. Am J Gastroenterol. 2007 May;102(5):1132–4.
2 Koneru S, Koshy G, Sharp C, Khalafallah AA. Hypereosinophilic syndrome associated with ulcerative colitis presenting with recurrent Loeffler's endocarditis and left ventricular thrombus treated successfully with immune suppressive therapy and anticoagulation. BMJ Case Rep. 2013 Sep;2013:bcr2013200919.
3 Awano N, Ryu T, Yoshimura N, Takazoe M, Kitamura S, Tanaka M. Successful treatment of ulcerative colitis associated with hypereosinophilic syndrome/chronic eosinophilic leukemia. Intern Med. 2011;50(16):1741–5.
4 Patel B, Butterfield JH, Weiler CR, Kane SV. Tolerance and efficacy with simultaneous use of two monoclonal antibodies for a patient with hypereosinophilic syndrome and ulcerative colitis. Monoclon Antib Immunodiagn Immunother. 2016 Dec;35(6):300–3.
5 Barrie A, Mourabet ME, Weyant K, Clarke K, Gajendran M, Rivers C, et al. Recurrent blood eosinophilia in ulcerative colitis is associated with severe disease and primary sclerosing cholangitis. Dig Dis Sci. 2013 Jan;58(1):222–8.
6 Neubauer K, Matusiewicz M, Bednarz-Misa I, Gorska S, Gamian A, Krzystek-Korpacka M. Diagnostic potential of systemic eosinophil-associated cytokines and growth factors in IBD. Gastroenterol Res Pract. 2018;2018:1–10.
7 Zabrowski D, Abraham D, Rosenthal G, Kader H. Development of peripheral eosinophilia in inflammatory bowel disease patients on infliximab treated at a tertiary pediatric inflammatory bowel disease center is associated with clinically active disease but does not result in loss of efficacy or adverse outcomes. JGH Open. 2020 Aug;4(4):636–41.
8 Parrillo JE, Borer JS, Henry WL, Wolff SM, Fauci AS. The cardiovascular manifestations of the hypereosinophilic syndrome. Am J Med. 1979 Oct;67(4):572–82.
9 Ogbogu PU, Rosing DR, Horne MK 3rd. Cardiovascular manifestations of hypereosinophilic syndromes. Immunol Allergy Clin North Am. 2007 Aug;27(3):457–75.
10 Plastiras SC, Economopoulos N, Kelekis NL, Tzelepis GE. Magnetic resonance imaging of the heart in a patient with hypereosinophilic syndrome. Am J Med. 2006 Feb;119(2):130–2.
11 Aida L, Parkhutik V, Tembl JI, Martin N, Frasquet M, Bataller L. Embolism and impaired washout: a possible explanation of border zone strokes in hypereosinophilic syndrome. J Neurol Sci. 2013 Feb 15;325(1–2):162–4.
12 Click B, Anderson AM, Koutroubakis IE, Rivers CR, Babichenko D, Machicado JD, et al. Peripheral eosinophilia in patients with inflammatory bowel disease defines an aggressive disease phenotype. Am J Gastroenterol. 2017 Dec;112(12):1849–58.
13 Leoncini G, Villanacci V, Marin MG, Crisafulli V, Cadei M, Antonelli E, et al. Colonic hypereosinophilia in ulcerative colitis may help to predict the failure of steroid therapy. Tech Coloproctol. 2018 Dec;22(12):941–6.
14 McMillan HJ, Johnston DL, Doja A. Watershed infarction due to acute hypereosinophilia. Neurology. 2008 Jan 1;70(1):80–2.
15 Kariyanna PT, Hossain NA, Onkaramurthy NJ, Jayarangaiah A, Hossain NA, Jayarangaiah A, et al. Hypereosinophilia and Loffler's endocarditis: a systematic review. Am J Med Case Rep. 2021;9(4):241–8.