

Idiopathic Hypereosinophilic Syndrome Presenting With Embolic Stroke

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Abstract

Hypereosinophilic syndrome is a rare condition characterized by eosinophilia associated with organ damage, most commonly affecting the skin, lung, gastrointestinal, cardiovascular and central nervous system. The idiopathic form is characterized by the absence of other conditions associated with hypereosinophilia such as allergies, infectious, hematological, immunological, endocrine or neoplasm diseases. The authors present a clinical case of a 70-year-old man with no relevant history, who went to the emergency department for neurological deficits and nonspecific chest pain. Laboratory tests revealed marked eosinophilia, elevation of cardiac enzymes with normal electrocardiogram. Computed tomography of the head showed multiple bilateral ischemic lesions. Upon further investigation for the cerebrovascular disease, transesophageal echocardiogram showed a thrombus at the aortic arch, as a probable embolic source. Despite anticoagulant therapy and corticosteroids, the patient's status deteriorated, with multiple successive ischemic strokes and worsening neurological deficits. After a thorough investigation, the diagnosis of idiopathic eosinophilia was established.

Categories: Cardiology, Internal Medicine, Neurology

Keywords: hypereosinophilic syndrome, stroke, thrombosis, aorta, idiopathic

Introduction

Hypereosinophilic syndrome (HES) is a rare entity characterized by eosinophilia associated with organ damage, most frequently affecting the skin, lungs, central nervous systems, gastrointestinal and cardiovascular systems. The idiopathic form is defined by the absence of other entities associated with hypereosinophilia. The clinical spectrum is highly variable and depends on the organs infiltrated by eosinophils, which cause inflammation, fibrosis, vasculitis and thrombosis. It is hypothesized that the neurological symptoms result from direct effects caused by eosinophils, but can also be secondary to thromboembolic phenomena, a serious complication of HES as we reported in the clinical case.

Case Presentation

A 70-year-old man with no relevant past or recent medical history, went to the emergency department due to disorientation, decreased muscle strength in the upper limbs and nonspecific chest pain with three days of evolution. Upon observation, he was afebrile and hemodynamically stable. Cardiopulmonary auscultation and abdominal examination revealed no alterations. In the neurological examination, we highlighted the temporal-spatial disorientation, proximal plegia of the upper limbs, paresis of the lower limbs and extended cutaneous-plantar reflex on the left side. We observed small linear subungual hemorrhages (Figure 1) and a lesion with necrotic background measuring approximately 5 mm in the distal portion of the right lower limb (Figure 2).

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FIGURE 1: Linear subungual hemorrhages (splinter hemorrhage).



FIGURE 2: A lesion with necrotic background measuring approximately 5 mm in the right lower limb.

Laboratory evaluation revealed 18,900 leukocytes/uL with eosinophilia of 9853/uL, and troponin elevation (7.2 ng/ml) with normal electrocardiogram. Cranioencephalic computed tomography (CT scan) showed ischemic lesions in several territories, better defined by brain magnetic resonance which documented multiple bilateral frontoparietal and right occipitotemporal lesions (Figure 3). Transesophageal echocardiography showed a mass measuring 7x14 mm in the arch of the aorta, compatible with a thrombus (Figure 4), confirmed by magnetic resonance imaging. The echocardiogram also showed left ventricular hypertrophy, with preserved systolic function and no restrictive pattern. Holter and echo-Doppler of carotid and vertebral arteries were normal.

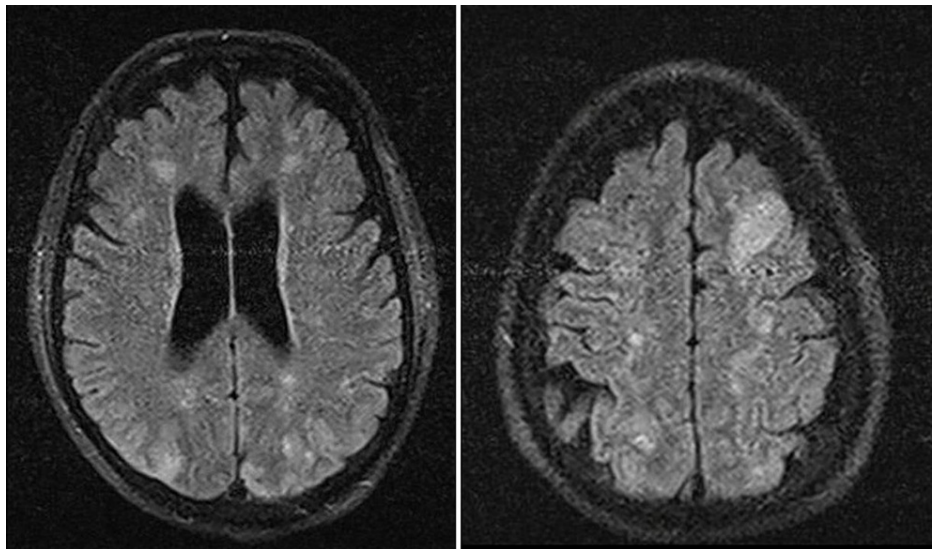


FIGURE 3: Multiple bilateral frontoparietal lesions, predominantly right, observed on brain magnetic resonance.

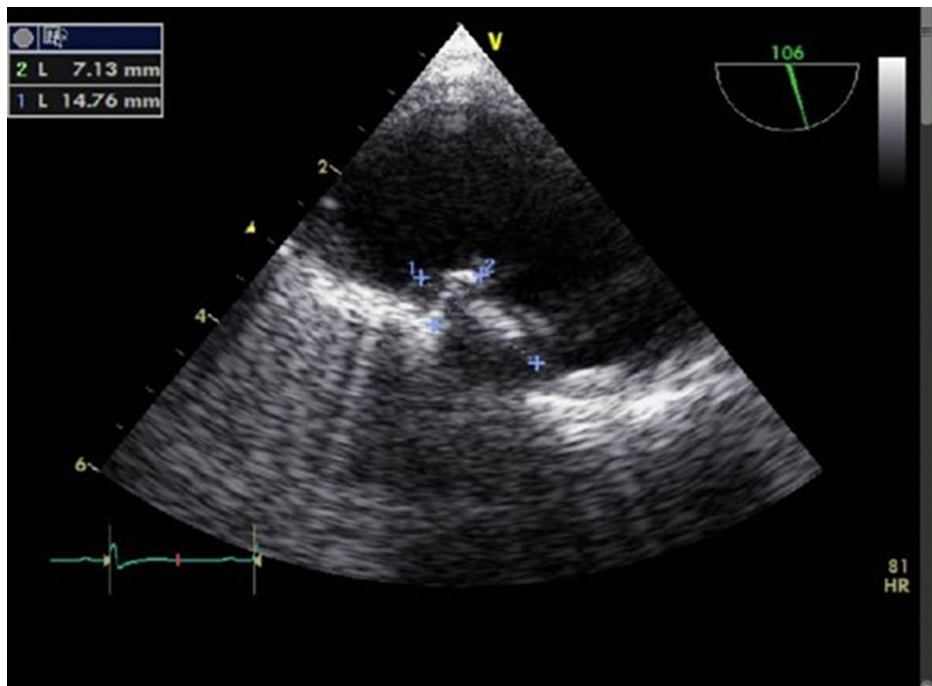


FIGURE 4: Thrombus in the aortic arch seen on transesophageal echocardiography.

In the presence of eosinophilia with organ damage, we started therapy with methylprednisolone 1 g/day for five days (followed by prednisolone 60 mg/day), anticoagulation with enoxaparin 1mg/kg twice daily and antiaggregation with acetylsalicylic acid 100 mg/day. Cardiac enzymes returned to normal levels and a gradual decline in eosinophils (up to 1200/uL after six weeks).

Other exams like abdominal ultrasound and body CT scan did not reveal abnormalities; skeletal radiography showed no calcified or lytic lesions; microbiological and parasitological tests were negative; viral serologies were negative; bone marrow analysis showed 18.6% eosinophils and no atypical cells; study of genetic mutations associated with clonal forms of eosinophilia was negative; the study of vasculitis and thrombophilia was negative (Table 1). As the investigation did not result in an etiology for eosinophilia, we admitted that it was an idiopathic form.

Laboratory tests	Admission	Discharge	Reference values
Hemoglobin (g/dl)	13.1	11.6	13-17
Leukocytes /uL	18,900	7700	4000-11,000
Neutrophils /uL	7400	4900	2100-7500
Eosinophils /uL	9853	1200	0-500
Lymphocytes /uL	960	1100	1000-4000
Monocytes /uL	450	500	100-1000
Basophils /uL	220	0	0-200
Platelets /uL	179,000	272,000	150,000-400,000
International Normalized Ratio	1.1		0.8-1.2
D-dimers (ug/L)	1811		<500
Creatinine (mg/dl)	1.15		0.7-1.3
Urea (mg/dl)	53		<50
Sodium (mEq/L)	140		135-147
Potassium (mEq/L)	4.3		3.7-5.1
Troponin T (ng/ml)	7.2	0.02	<0.03
Creatinine kinases (U/L)	281		32-294
Creatinine kinases - myocardial band (ng/ml)	48		<5
Natriuretic peptide (pg/ml)	928		<100
Aspartate aminotransferase (U/L)	29		<34
Alanine aminotransferase (U/L)	25		<35
gamma-glutamyl transpeptidase (U/L)	20		12-64
Reactive C protein (mg/dl)	10.5		<0.5
Thyroid Stimulating Hormone (mU/L)	1.87		0.4-4.5
Free T4 (ng/dl)	1.4		0.7-1.8
Vitamin B12 (pg/ml)	430		300-900
Protein C, protein S and antithrombin III	Normal		
Lupus anticoagulant, anti-cardiolipin and anti-beta2 glycoprotein antibodies	Normal		
ANA, ANCA	Negative		
Peripheral blood smear	eosinophilia, without atypical cells		
Myelogram	18.6% eosinophils (16.6% mature), no myelodysplasia or atypical cells		
Genetic study	No mutations: PDGFRa, PDGFRb, BCR-ABL, CBFb, JAK2		
Protein Electrophoresis	No monoclonal pattern		
Total IgE (UI/ml)	433		<100
HIV, Hepatitis B and C	Negative		
Antibodies for Treponema pallidum	Negative		
Antibodies for CMV, EBV and herpes simplex	Negative		
Antibodies for Leptospira and Borrelia	Negative		

Feces	Microbiological exam	Negative
	Parasitological exam	No protozoan cysts or Helminth eggs were observed
Blood cultures		Negative
Urine culture		Negative

TABLE 1: Laboratory tests

ANA - antinuclear antibodies; ANCA - antineutrophil cytoplasmic antibodies; BCR-ABL - breakpoint cluster region-abelson gene; CFBF - core-binding factor beta; CMV - cytomegalovirus; EBV - Epstein-Barr virus; HIV - human immunodeficiency virus; IgE - Immunoglobulin E; JAK2 - Janus kinase 2; PDGFRa - platelet-derived growth factor receptor, alpha polypeptide; PDGFRb - platelet-derived growth factor receptor, beta polypeptide.

Despite corticosteroids therapy, anticoagulation and antiaggregation, the patient deteriorated with generalized hypertonia, new focal deficits - left central facial paresis, dysphagia and dysarthria, with evidence of new lesions on brain CT scan.

Discussion

HES has an estimated prevalence between 0.36 to 6.3 per 100,000 and is more common in men in the proportion of 9:1 [1,2]. It is defined by persistent eosinophilia (peripheral blood eosinophil count greater than 1500/uL in at least two determinations [3,4]) and organ damage. It can be classified as: primary (clonal) relating to myeloid/lymphoid hematologic neoplasms and leukemias, with the proliferation of eosinophils and associating with mutations PDGFRa, PDGFRb, FGFR1, JAK2 or CFBF [5]; secondary (or reactive) that relates with allergic diseases, drug hypersensitivity reactions, infections, lymphomas, some solid tumors, connective tissue diseases, sarcoidosis, ulcerative colitis and vasculitis [5,6]; idiopathic - diagnosis of exclusion that corresponds to about 80% of cases [7]. Clinical presentation, as well as prognosis, is highly variable and depends on the underlying etiology and on the affected organs (most often the skin, heart, lungs, gastrointestinal tract and central nervous system [8]).

Eosinophils are granulocytic cells that contain active substances that directly exert their toxic effect, as well as cytokines that promote the activation of other cells and the inflammatory cascade. In the presence of hypereosinophilia, there is an unregulated release of these substances that cause damage by phenomena of inflammation, fibrosis, vasculitis and thrombosis [5].

Cardiovascular complications occur in 40 to 60% of cases [9] and are the major cause of morbidity and mortality [10]. A classic presentation of eosinophilic infiltration is Loeffler's endocarditis, in which there is thickening and fibrosis of the endocardium and consequent restrictive cardiomyopathy [11]. Cardiac involvement usually occurs in three phases: necrotic (acute, in which there is myocardial infiltration by eosinophils), thrombotic and fibrotic [10]. The clinical presentation can vary from heart failure, angor, arrhythmias, pericarditis and thrombotic phenomena (as we observed in this clinical case). Cardiac involvement can lead to the appearance of characteristic skin lesions named linear subungual hemorrhages (splinter hemorrhages), nail bed infarctions and ulcers, which usually occur in the necrotic phase [9,10]. Lab tests may show an increase in cardiac enzymes, d-dimers and type B natriuretic peptide. The electrocardiogram may be normal or show alterations in ventricular repolarization. The echocardiogram may reveal thrombi and alterations in cardiac function with a restrictive pattern [12,13]. Definitive diagnosis can be made by biopsy, but cardiac magnetic resonance is sensitive and non-invasive [10,14].

Neurological involvement is another important complication with an estimated incidence of stroke of 12% [15]. There are several mechanisms involved, the most important being embolization from a cardiac source [9]. Clinical presentation includes transient ischemic attacks and multifocal ischemic strokes (with additive deficits and high recurrence rates, even under anticoagulation and antiaggregation [9-12]), behavioral changes and confusional states (in the presence of encephalopathy caused by eosinophilic infiltration) and, more rarely, seizures and peripheral neuropathy [9].

The finding of potentially fatal HES complications is an indication for early treatment. Corticosteroids are one of the pillars of therapy [5]. Other therapeutic options, especially for patients refractory to corticosteroids, include hydroxyurea, interferon alpha and anti-interleukin 5. In the presence of cardiac thrombi, anticoagulation is indicated.

In this patient, despite the reduction in the number of eosinophils with therapy, there was a clinical worsening conditioned by thromboembolic phenomena, typically associated with a worse prognosis.

Conclusions

This clinical case illustrates the complexity of this disease and its diagnostic process in an attempt to

identify its etiology. The wide spectrum of presentations makes the diagnosis of HES a challenging one, and it must be remembered whenever eosinophilia and organ damage present in a patient. This pathology involves multidisciplinary, with the internist being the patient's manager and articulating with other specialties such as Immunology, Infectiology, Cardiology and Neurology.

Additional Information

Disclosures

Human subjects: Consent was obtained or waived by all participants in this study. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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