sciendo

The portrait of a stranger: the hypereosinophilic syndrome with cardiac involvement

ANDREEA-CRISTINA IVĂNESCU[1,2*], ALEXANDRU PETRE[2], ANDREI SABIN MARINCAȘ[2], ELISABETA BĂDILĂ[1,2], GHEORGHE-ANDREI DAN[1,2]

[1] "Carol Davila" University of Medicine, Bucharest, Romania
[2] Colentina University Hospital, Bucharest, Romania

Abstract

Introduction: Hypereosinophilic syndrome is a rare clinical condition, and cardiac involvement confers a poor prognosis. Hypereosinophilic myocarditis is a medical emergency and targeted treatment should be started promptly even before a definitive diagnosis could be made.

Case presentation: A 27-year-old female patient is hospitalized for exertional dyspnea, chest pain, and fatigue for the past 2 weeks. She also describes left leg paresthesias. Clinical examination was in normal limits. ECG showed sinus tachycardia, QS pattern in V1–V4, and diffuse flattened T waves. Laboratory tests revealed increased inflammatory markers, hypereosinophilia, elevated cardiac enzymes, high NT-proBNP. Echocardiography revealed LV dysfunction (EF 31%), while cardiac MRI showed diffuse delayed enhancement with predominant subendocardial disposition. The electromyogram was suggestive of left tibial nerve neuropathy.

We interpreted the case as eosinophilic myocarditis with an urgent requirement of therapy and initiated high-dose glucocorticoid therapy and the GDMT 4-pillar heart failure treatment. We excluded common infectious, myeloproliferative syndromes, and frequent associated autoimmune diseases. With prednisone, the eosinophil count rapidly normalized and we gradually tapered the dose by 5 mg per week, however continuing with heart failure therapy. At monthly follow-up visits, there was a significant clinical improvement, with normalization of the eosinophilic count, and a near-normalization of myocardial function. The only symptom that persisted was paresthesias linked to left tibial neuropathy.

Conclusion: The surprisingly rapid and favorable course of the disease offers a high index of suspicion for a toxic or a reactive transitory etiology, however still unidentified. In our case, the cause of eosinophilia remained unknown, although we managed to narrow down the possible etiologies. A surprisingly good clinical response was obtained with non-specific treatment targeting mainly hyperosinophilic myocarditis.

Keywords: hypereosinophilic syndrome, eosinophilic myocarditis, myocarditis, glucocorticoid therapy, tibial neuropathy.

INTRODUCTION

Hypereosinophilic syndromes (HES) encompasses a rare group of heterogeneous disorders with clinical manifestations ranging from non-specific mild symptoms to life-threatening endomyocardial fibrosis and thromboembolic events. A comprehensive approach is needed to identify potentially treatable etiologies and define end-organ manifestations [1]–[3]. Cardiac involvement confers a poor prognosis, with eosinophilic myocarditis being a medical emergency [4]–[7].

PATIENT PRESENTATION

A 27-year-old female patient is hospitalized for exertional dyspnea and fatigue for the past 2 weeks, associated with chest pain that improves when bending forward. She also describes distal lower limb paresthesia. Her medical history is insignificant and she has no chronic medication. The current disease apparently begins two months earlier, with self-limiting scapulohumeral myalgia followed by lower limbs mild myalgia. At that time, she worked in a slaughterhouse without direct contact with raw meat. She initially received symptomatic treatment with NSAIDs (naproxen 250mg bid) with no effect. One month later, an increase in the number of eosinophils (~11,600/mm^3) was noted for the first time during an outpatient evaluation but no specific management plan was recommended. A couple of weeks before the current presentation, eosinophilia (~11,000/mm^3) is confirmed and Dexamethasone 8 mg daily is recommended for 7 days. Apparently, this treatment does not resolve the number of eosinophils as it was unchanged at the end of the treatment period.

 DOI: 10.2478/rjim-2023-0016

We also note that 8 months ago she had an episode of intercurrent respiratory infection manifested with dyspnea and wheezing. The patient received inhaled bronchodilator for a short period.

INITIAL WORK-UP

Clinical examination is within normal limits, without signs of congestion, BP 106/72 mmHg, HR= 91 bpm, room air oxygen saturation of 97%. Of note, the liver and spleen were not enlarged. ECG shows sinus tachycardia, low voltage in frontal plane leads, QS in leads V1–V4, and diffuse flattened T waves (Fig. 1). Laboratory tests showed an inflammatory syndrome (CRP 38.5 mg/L, ESR 32 mm/h, fibrinogen 482 mg/dl, ferritin 237 ng/ml, LDH 607 UI/L) with leukocytosis and hypereosinophilia (15,360/mm^3), elevated cardiac enzymes (hsTnT=1445 pg/mL), high NT-proBNP (6174 pg/ml) and elevated IgE (1296 UI/ml). Echocardiography reveals LV dysfunction with an EF of 31%, diffuse hypokinesia, mild LV hypertrophy LVMI 109g/m^2), grade II diastolic dysfunction, and circumferential pericardial fluid (max 15 mm). Cardiac MRI showed diffuse delayed enhancement (DE) with predominant subendocardial disposition suggestive of endomyocardial fibrosis. The areas of DE have a dominant distribution at the lateral segments along with transmural areas (Fig. 2). Computed tomography of the chest shows left upper lobe ground glass non-specific interstitial opacities, discrete right lobe apical and basal ground glass interstitial opacities. Spirometry was inconclusive, with an FEV1 at the lower limit of normal and positive bronchodilator response (12% (316ml) increase in FEV1). Chest and sinus radiographies are within normal limits. The electromyogram was suggestive of left tibial nerve neuropathy.

DIAGNOSIS AND MANAGEMENT

We interpreted the case as eosinophilic myocarditis with urgent requirement of therapy (because of cardiac involvement) and initiated corticosteroid therapy with prednisone (1mg/kg/day) and the 4-pillar heart failure treatment (75mg metoprolol, 5mg ramipril, 25 mg spironolactone and 10mg dapagliflozin). A multidisciplinary team consisting of cardiologists, hematologists, rheumatologists, neurologists, and parasitologists is formed and a plan is established. Next, we looked for a cause for hypereosinophilia. We excluded common parasites (negative results for Toxocara canis, Toxoplasma gondii, Trichinella spiralis) and infectious causes (negative for HIV, hepatitis B and C, Treponema palidum). We continued to investigate for myeloproliferative disease; bone marrow aspirate was suggestive of reactive hypereosinophilia, and genetic testing for mutations of FIP1L1-PDGFRA were negative. We also excluded common autoimmune diseases (Systemic lupus erythematosus, mixed connective tissue disease, vasculitis): anti DNA antibodies, anti cANCA antibodies, anti pANCA antibodies, anti-CCP, anti-SM antibodies, anti-uridine Ac 1–70 RNP, were all negative and the complement titer was normal. We also looked for the myeloproliferative variants of HES (M-HES) and the serum vitamin B12 was mildly increased (753 pg/ml). Although eosinophilic granulomatosis with polyangiitis (Churg Strauss syndrome) seems to be the closest plausible diagnosis (after the exclusion of other causes and the combination of eosinophilia, respiratory symptoms, and neuropathy), there was not enough evidence (according to ACR and Lanham criteria) to support a definite positive diagnosis (especially due to the absence of asthma, lung infiltrates, and mononeuritis multiplex).

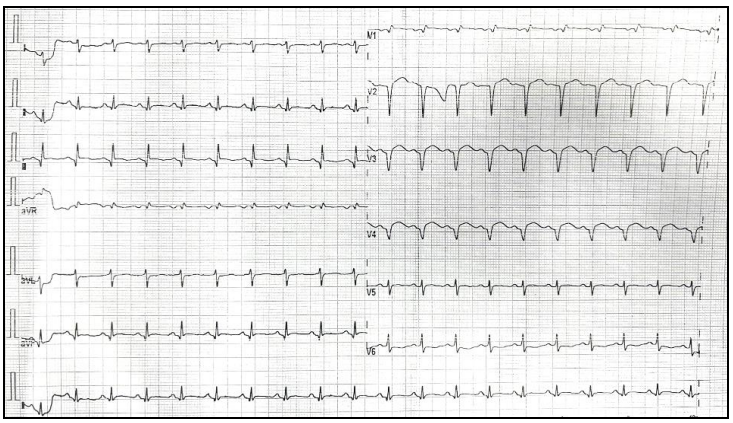


Figure 1. ECG during acute myocarditis episode shows sinus tachycardia, QS in leads V1-V4 and diffuse flattened T waves.

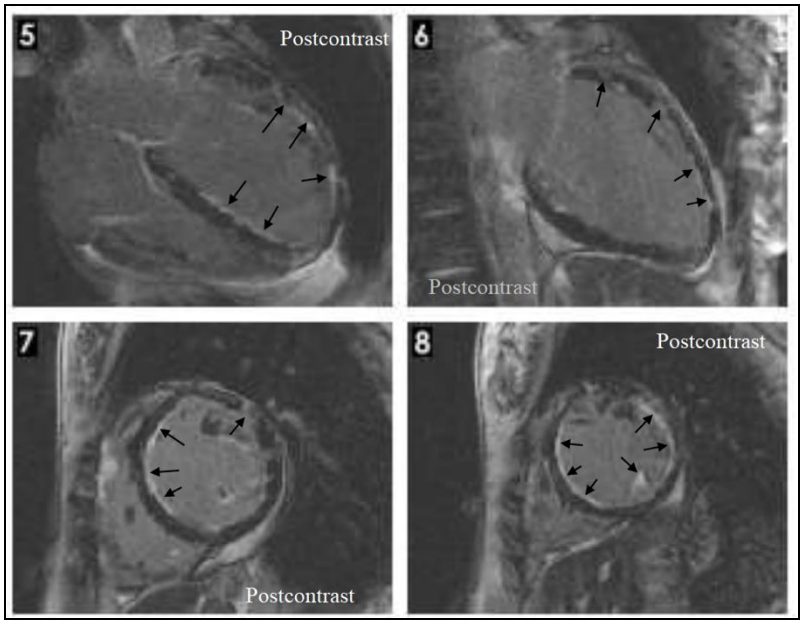


Figure 2. Cardiac MRI showing diffuse delayed enhancement (DE) with subendocardial disposition. The areas of DE have a dominant lateral and transmural distribution.

FOLLOW-UP

With prednisone treatment, the eosinophil count was rapidly normalized (within 3 days). Also, there was a significant decrease of troponin and NT-proBNP accompanied by clinical improvement (chest and muscle pain subside, dyspnea and fatigue are significantly improved but bilateral leg pain and paresthesia persist, more pronounced on the left side). We decided to continue prednisone therapy with a tapering dose of 5 mg per week along with 4-pillar heart failure therapy. At the 1-month follow-up visit, there was a significant clinical improvement with mild pain in the lower left limb that does not affect mobility and complete resolution of fatigue and chest pain. The clinical examination was normal. Laboratory findings show normal eosinophilic count (60/mm^3, 1%), complete resolution of inflammation markers (CRP 0.27 mg/L, ESR 2 mm/h, fibrinogen 226 mg/dl), a significant decrease of NTproBNP (1967 pg/ml) and hsTnT (50.24 pg/ml). The favorable course of the disease was noted also by echocardiography which showed only mild, diffuse LV hypokinesia with an EF of 48%. A timeline showing the evolution of the main laboratory parameters is shown in Table 1.

The surprisingly rapid and favorable course of the disease offers a high index of suspicion for a toxic, reactive transitory etiology that we were unable to identify for the time being.

Our multidisciplinary team decided to repeat the chest computed tomography and spirometry during the 3-month follow-up visit in order to determine the potential lung involvement, and both tests were within normal limits. The eosinophilic count was normal, and we also noticed an almost complete resolution of myocardial dysfunction, with an LVEF of 50% with only mild diffuse hypokinesia.

We recommended the continuation of prednisone dose de-escalation, and after complete cessation of treatment, the patient remained asymptomatic and with normal eosinophilic count. For the next stage, we recommend the eosinophil count be determined monthly, along with a thorough clinical examination and monitoring of myocardial function.

DISCUSSION AND LEARNING POINTS

A comprehensive evaluation of HES requires a highly skilled multidisciplinary team and significant resources.

An Occam's razor approach is desirable, centred on detailed medical history, thorough physical examination, and comprehensive evaluation of possible eosinophil-associated end-organ damage. Work-up often extends over a long period, leading to delayed initiation of specific treatment, with a subsequent negative impact on prognosis and quality of life [1]–[3], [8]. Figure 3 provides a summary algorithm with the main differential diagnoses that must be considered in a patient with eosinophilia.

Table 1

Temporal evolution of the main important laboratory parameters

Parameter	Admission	Discharge	1-month follow-up	3-months follow-up	6-months follow-up
Eosinophils /mcL	15360	130	60	50	240
hs-CRP(mg/L)	38.5	11	0.27	0.3	0.99
ESR	32	19	2	2	4
hs-Troponin T (pg/mL)	1445	121.1	50.24	39.4	18.96
NTproBNP (pg/mL)	6174	3405	1967	1546	762

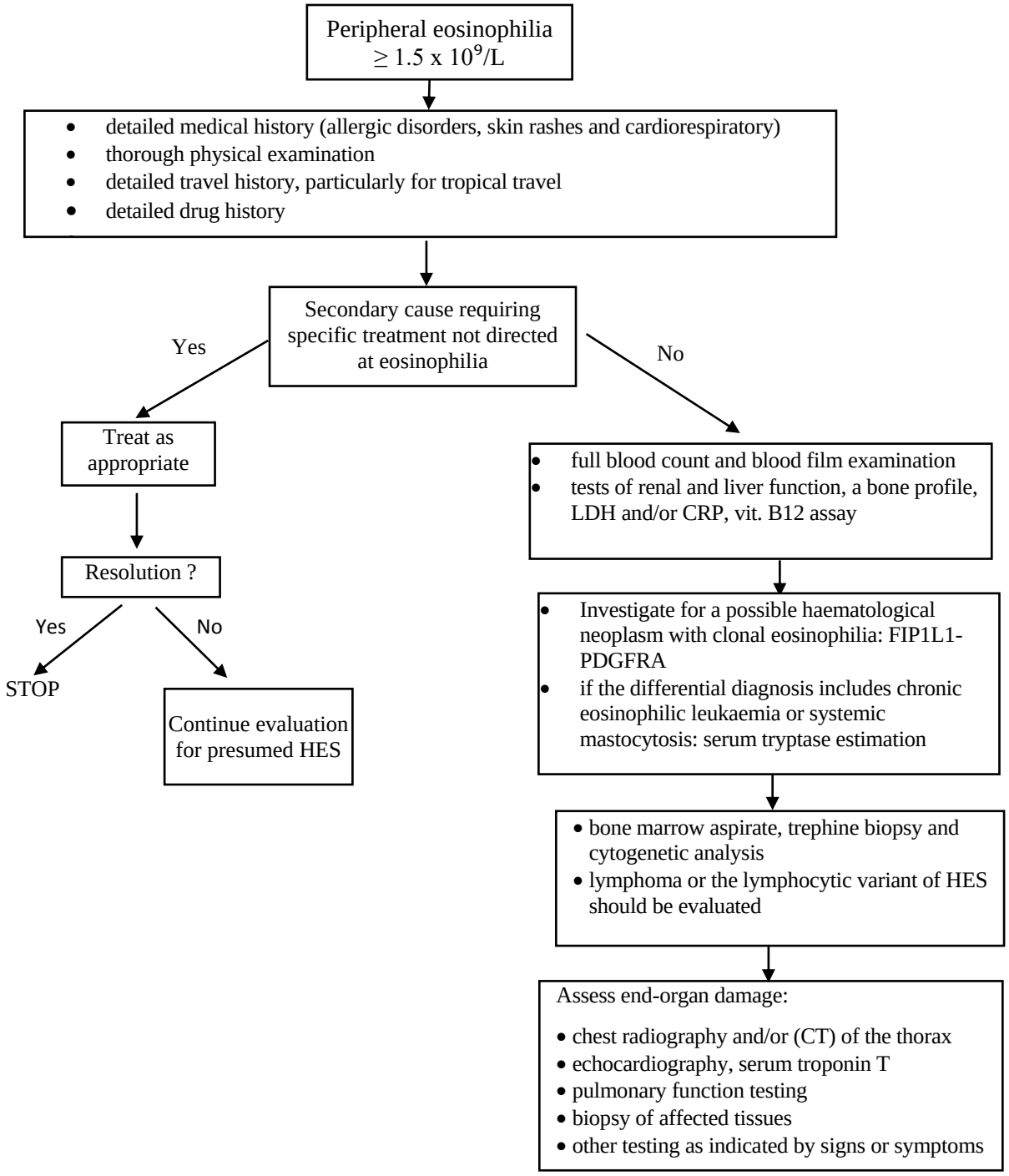


Figure 3. Algorithm for differential diagnosis in eosinophilia.
(Adapted from Klion, Blood, 2009 and Nauman M. Butt, Br J Haematol 2017)

Myocardial involvement makes HES a life-threatening medical emergency with a poor prognosis. Therefore, the therapy needs to be instituted urgently, even before a definitive diagnosis. The severity of cardiac injury does not always clearly correlate with the degree of peripheral eosinophilia. Long-term outcome is influenced by the risk of evolving to restrictive cardiomyopathy, severity of ventricular dysfunction, and development of pulmonary hypertension. In the absence of these, the prognosis is usually favorable [5]–[7].

A favourable response to corticosteroid therapy and nonspecific heart failure treatment should not put the continuous search for aetiology in the background.

CONCLUSIONS

Hypereosinophilic syndrome is rare, and cardiac involvement confers a poor prognosis [1], [2]. Eosinophilic myocarditis is a medical emergency, and treatment must be started early. The prognosis of myocarditis varies among clinicopathologic types, but the most important predictors of adverse outcomes include severity of LV/biventricular dysfunction, development of secondary pulmonary hypertension and of restrictive cardiomyopathy as well as the presence of fulminant myocarditis. In the absence of these factors, prognosis is usually favorable [5]–[7].

In many cases, the etiology remains unknown but timely follow-up is essential for proper management. For our patient, although the cause of eosinophilia is still unknown, we managed to narrow down the possible etiologies and achieve a good clinical response with non-specific treatment.

Introducere: Sindromul hipereozinofilic este rar, iar afectarea cardiacă conferă un prognostic nefavorabil. Miocardita eozinofilică este o urgență medicală, astfel că tratamentul trebuie inițiat precoce.

Prezentarea cazului: O pacientă de 27 ani este internată pentru dispnee de efort, fatigabilitate și durere toracică, debutate de 2 săptămâni. Descrie și parestezii ale membrelor inferioare, distal. Examenul clinic este normal. Electrocardiograma are tahicardie sinusală, QS V1-V4, unde T aplatizate difuz. Analizele de laborator indică sindrom inflamator, hipereozinofilie, valori crescute ale enzimelor de necroză miocardică și ale peptidelor natriuretice. Ecocardiografic observăm disfuncție sistolică (FE 31%) iar IRM cardiac obiectivează priză tardivă de contrast, predominant subendocardic. Electromiograma este sugestivă pentru neuropatie tibială stângă.

Am interpretat cazul ca miocardită eozinofilă cu indicație de tratament în urgență (din cauza afectării cardiace). Am inițiat corticoterapie și tratament specific pentru insuficiență cardiacă. Am exclus bolile comune infecțioase, mieloproliferative și autoimune. Sub tratament cu prednison, numărul de eozinofile s-a normalizat rapid și am continuat terapia cu doză descrescătoare cu 5 mg pe săptămână, asociat terapiei insuficienței cardiace. La vizitele de control s-a observat o ameliorare semnificativă, cu normalizarea numărului de eozinofile, și cu funcție miocardică aproape normală. Singurul simptom persistent fiind neuropatia tibială.

Concluzii: Evoluția surprinzător de rapidă și favorabilă oferă un indice ridicat de suspiciune pentru o etiologie tranzitorie toxică, reactivă, încă neidentificată. Prognosticul variază între tipurile clinicopatologice, dar este de obicei favorabil. Pentru pacienta noastră, deși cauza eozinofiliei este încă necunoscută, am reușit să restrângem posibilele etiologii și să obținem un răspuns clinic bun cu tratament nespecific.

Correspondence to: Andreea-Cristina Ivănescu, M.D, Ph.D,
Address: Ștefan cel Mare No.19-21 Street, Sector 2, Bucharest, Romania, zip code 020125
E-mail: andreea.cardio@gmail.com

Declaration of interest: The authors declare that there are no conflicts of interest.

REFERENCES

1. BUTT NM *et al. Guideline for the investigation and management of eosinophilia*. Br J Haematol 2017;176(4):553–572.
2. GOTLIB J. *World Health Organization-defined eosinophilic disorders: 2014 update on diagnosis, risk stratification, and management*. Am J Hematol 2014;89(3):325–327.

3. LERU PM. *Eosinophilia and Hypereosinophilic Disorders - Update on Etiopathogeny, Classification and Clinical Approach*. Rom J Intern Med 2015;53 (4):289–295.
4. BONDUE A, CARPENTIER C, ROUFOSSE F. *Hypereosinophilic syndrome: considerations for the cardiologist*. Heart 2022;108(3):164-171.
5. CAFORIO ALP, *et al. Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases.* Eur Heart J 2013;34(33):2636-2648
6. BRACAMONTE-BARAN W, ČIHÁKOVÁ D. *Cardiac Autoimmunity: Myocarditis.* Adv Exp Med Biol 2017;1003: 187–221
7. BRAMBATTI, M, MATASSINI V, ADLER ED, KLINGEL K, CAMICI PG, AMMIRATI E. Eosinophilic Myocarditis: Characteristics, Treatment, and Outcomes. J Am Coll Cardiol, 2017;70(19):2363–2375.
8. AHKEE S, RAMIREZ J. *Approach to the patient with suspected hypereosinophilic syndrome*. Hematology Am Soc Hematol Educ Program 2022;1:89–92

Received 1st July 2023