Hypereosinophilic syndrome associated with multiple thromboses requiring ICU admission: A case report

Syndrome hyperéosinophilique associé à des thromboses multiples nécessitant l'admission en réanimation: A propos d'un cas

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Abstract

Hypereosinophilic syndrome (HES) is a leucoproliferative disorder, characterized by marked blood eosinophilia and organ damage due to tissue eosinophilia. Pulmonary involvement may lead to life-threatening acute respiratory failure and intensive care unit (ICU) admission. Association between eosinophilia and thromboembolism has been previously described. However simultaneous venous and arterial thromboses are less reported. We report a case of a 25-year-old man, admitted to the ICU and developed acute respiratory failure, laboratory tests revealed hyperleukocytosis (39,700 /µL) with high eosinophil count (27393 /µl), Computed tomographic (CT) pulmonary angiography on admission showed a right pulmonary embolism and foci of splenic infarctions. Echocardiography showed a thrombus in the ascending aorta. On day 3, the patient presented worsening polypnea with increase of oxygen requirements. Chest CT scan showed pulmonary parenchymal involvement with bilateral condensations surrounded by "tree-in-bud" micronodules. The diagnosis of eosinophilic pneumonia was established. Bone marrow biopsy showed hyperplasia of the 3 lineages, predominant on the granulocyte lineage made mostly of eosinophilic polynuclear mature cells, suggesting myeloproliferative syndrome. The patient was treated with corticosteroids and anticoagulation. Physicians should consider HES diagnosis in case of hypereosinophilia and evolving life threatening organ damage to avoid therapy delay and complications.

Key words: Hypereosinophilic syndrome, myeloproliferative syndrome, Thrombosis, Intensive care unit

Résumé

Le syndrome hyperéosinophilique (SHE) est un trouble leucoprolifératif caractérisé par une éosinophilie sanguine marquée associée à des dommages d'organes dus à l'éosinophilie tissulaire. L'atteinte pulmonaire peut entraîner une insuffisance respiratoire aiguë potentiellement mortelle et une admission en réanimation peut être requise. L'association entre l'hyperéosinophilie et la maladie thromboembolique a été décrite. Cependant, les thromboses veineuses et artérielles simultanées sont moins rapportées. Nous rapportons le cas d'un homme de 25 ans, admis en réanimation et ayant développé une insuffisance respiratoire aiguë, les examens biologiques ont révélé une hyperleucocytose (39 700 /µL) avec un taux d'éosinophiles élevé (27393 /µl), un angioscanner thoracique a montré une embolie pulmonaire droite et des foyers d'infarctus spléniques. L'échocardiographie a montré un thrombus dans l'aorte ascendante. Au troisième jour, le patient a développé une aggravation de la polypnée avec augmentation des besoins en oxygène. Le scanner thoracique a montré une atteinte parenchymateuse pulmonaire avec des condensations bilatérales entourées de micronodules de type « arbre en bourgeon ». Le diagnostic de pneumonie à éosinophiles a été posé. La biopsie de la moelle osseuse a montré une hyperplasie des 3 lignées, prédominante sur la lignée granulocytaire constituée majoritairement de cellules matures polynucléaires éosinophiles, évoquant un syndrome myéloprolifératif. Le patient a été traité par corticoïdes et anticoagulation. Le diagnostic de SHE doit être envisagé en cas d'hyperéosinophilie et des lésions d'organes afin d'éviter le retard du traitement et les complications.

Mots clés: Syndrome hyperéosinophilique, Syndrome myéloprolifératif, Thrombose, Réanimation

INTRODUCTION

Hypereosinophilic syndrome (HES) is a leucoproliferative disorder, characterized by marked blood eosinophilia (peripheral blood eosinophil count greater than 1.5 x 109 /L) and organ damage due to tissue eosinophilia (1), this syndrome may be due to several diseases (2-4) or be idiopathic (5). Pulmonary involvement in this situation may lead to life-threatening acute respiratory failure requiring intensive care unit (ICU) admission (6). Association between eosinophilia and thromboembolism has been previously described (7, 8) and it could be explained by promotion of hypercoagulable state favouring thrombosis (9-11), arterial and cardiac thromboses are less reported in this setting (7, 12, 13), moreover simultaneous association with pulmonary embolism is unusual. Here, we describe a case report of a patient admitted to intensive care unit (ICU) for acute respiratory failure due to hypereosinophilic

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syndrome associated with multiple thromboses; the patient was successfully treated with corticosteroids and anticoagulation.

CASE REPORT

A 25-year-old man with no medical history, admitted to the ICU and developed acute respiratory failure, history of the disease was marked by asthenia since 2 months with pain in the left hypochondrium a few days before admission. On physical examination, he was conscious well oriented and neurologic examination was normal, with a temperature at 38.8°C, blood pressure at 140/90, heart rate at 103 BPM, respiratory rate at 22 c/min and a SpO2 at 94 at room air, lung auscultation revealed bilateral basal crackles. Body mass index was at 39.2 kg/m2.

Laboratory tests revealed a biological inflammatory syndrome with a C reactive protein level at 315 mg/l with hyperleukocytosis (39,700 /µL) and especially high eosinophil count (27393 /µl), D-dimers at 5191 ng/ml, creatinine at 56.1 µmol/l, Sodium at 137 mEq/l, potassium at 4.1 mEq/l, high sensitive troponin I at 27.9 ng/l, procalcitonin at 0.2 ng/ml and BNP at 60 pg/ml. Computed tomographic (CT) pulmonary angiography on admission showed a right pulmonary embolism (Figure 1) and right basal infarction focus and foci of splenic infarctions. Doppler of lower limbs showed no ultrasound sign of thrombophlebitis. Transthoracic and transesophageal echocardiographies showed a thrombus in the ascending aorta, a preserved systolic function (LVEF= 70%), no dilation of the right ventricle, absence of valve adenoids or valve disease, no interatrial or interventricular communication and no patent foramen ovale.

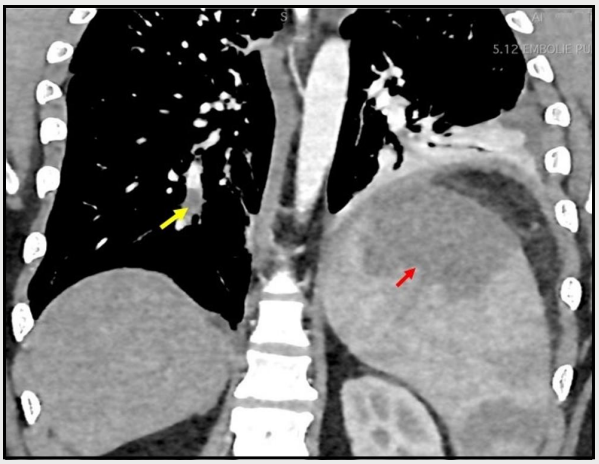

Figure 1. Computed tomographic pulmonary angiography on admission showing a right pulmonary embolism (yellow arrow) and foci of splenic infarctions (red arrow).

The patient was treated by curative anticoagulation (Enoxaparine 1 ml twice daily), on day 2 he developed acute respiratory failure with polypnea. Oxygen at 2-3 l / min and empirical antibiotic therapy was started. On day 3, the patient presented with worsening of his polypnea with an increase of oxygen requirements up to 10 l/min with high concentration mask, high flow nasal oxygen (HFNO) sessions were started (oxygen flow = 30 l / min, FiO2 = 70%) alternating with noninvasive ventilation (NIV) with awake prone positioning. Chest CT scan showed pulmonary parenchymal involvement with the appearance of bulky bilateral condensations predominant in the upper areas surrounded by “tree-in-bud” micronodules (Figure 2A). Eosinophilic pneumonia in its acute form was the diagnosis established and corticosteroid therapy was started with methylprednisolone 1 g daily for 3 days and prednisolone 60 mg daily after. The outcome was favorable with substantial decrease of eosinophil counts and C reactive protein levels (Table 1). Respiratory state improved and oxygen needs decreased, patient transferred medical ward on day 8 with oxygen therapy at 2 l/min with a CT scan control (Figure 2B) showing marked improvement with regression of lung damage.

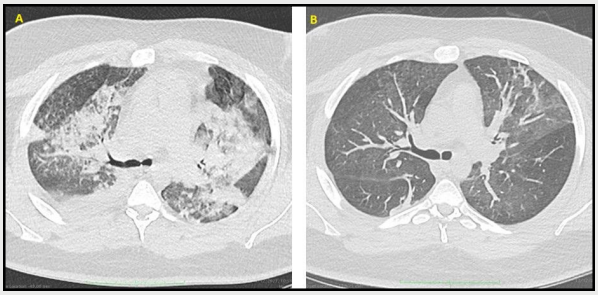

Figure 2. (A) CT scan at day 6 showing diffuse condensations and “tree-in-bud” micronodules. (B): CT scan after corticosteroids boluses showing marked improvement with regression of lung damage.

Table 1. Evolution of blood count and C-reactive protein

	Admission	Day 2	Day 4	Day 6	Reference values
Hemoglobin (g/dl)	13.1	12.1	10.7	11.6	13-18
Leukocytes /µl	39,700	30,900	21,300	6,300	4,000-10,000
Neutrophils / µl (%)	10322 (26)	(84.7)	(85.2)	(87)	40-75
Eosinophils / µl (%)	27393 (69)	(8.6)	(4.4)	(0.4)	1-5
Lymphocytes /µl (%)	1985 (5)	(4.9)	(6.6)	(7.7)	20-45
Monocytes / µl (%)	-	(1.6)	(3.5)	(4.6)	4-8
Basophils / µl (%)	-	(0.2)	(0.3)	(0.3)	<1
Platelets /µl	203,000	217,000	232,000	210,000	150,000-400,000
C reactive protein mg/l	315	-	250	74	<7

Etiological investigations performed (table 2) were negative, including search for inherited and acquired thrombophilia, C3 and C4 fraction of serum complement, antinuclear and antineutrophil cytoplasmic antibodies, hydatid cyst and larva migrans serologies, parasitological stool examination and detection of Schistosoma haematobium eggs in urine.

Table 2. Etiological and other tests

Test	Result	Reference values
Protein C (%)	100	60-130
Protein S (%)	80	80-130
Antithrombin III (%)	90	80-120
Anti-cardiolipine antibodies (GPL/ml)		
IgG	10	<15: Negative
IgM	8	<10: Negative
Anti-beta 2 glycoprotein antibodies (GPL/ml)		
IgG	4	<10: Negative
IgM	3	<10: Negative
C3 complement fraction (g/l)	1.34	0.9-1.80
C4 complement fraction (g/l)	0.51	0.09-0.36
Antinuclear Antibodies (ANA)	<1/100	Negative
Antineutrophil Cytoplasmic Antibodies (pANCA) (GPL/ml)	Negative	<20
Hydatid cyst serology	Negative	-
Larva Migrans serology	Negative	-
Parasitological stool examination	Negative	-
Detection of Schistosoma haematobium eggs in urine	Negative	-

Bone marrow biopsy showed hyperplasia of the 3 lineages, predominant on the granulocyte lineage which is made mostly of eosinophilic polynuclear mature cells, making a histological aspect of myeloproliferative syndrome. Search for JAK2 and BCR-ABL mutations was negative but FIP1L1- PDGFR was not available. The patient was finally discharged on day 13 with prednisolone and acenocoumarol and he was doing well at 3 months of follow-up.

DISCUSSION

This case describes a rare association of clonal HES (myeloproliferative variant) and multiple thrombosis affecting both venous and arterial vessels leading to a life threating condition and ICU admission, rapid diagnosis and treatment were needed to reverse severity situation.

Hypereosinophilia is observed in several conditions such as allergic condition, various inflammatory diseases and diverse hematologic malignancies, Idiopathic HES corresponds to the majority of cases (14) and applies to all clinical presentations in which blood hypereosinophilia can be documented and directly linked to organ damage after ruling out other causes.

HES could be considered as a risk factor of thromboembolism (11), venous thrombosis is one of the most commonly described in hypereosinophilia (15) but arterial thrombosis remain rarely described (5) and it may influence short and long term prognosis and management of these patients, the link between HES and thrombosis is not fully understood, first eosinophils can form aggregates that obstruct blood vessels, causing tissue ischemia and micro-infarction, we observed in our case foci of splenic infarction that may be due to this mechanism. Second hypercoagulability can be promoted through hypercoagulable and platelet-activating effects of eosinophil granule proteins (9, 16-18). Another explanation maybe a higher tissue factor expression in patients with hypereosinophilic disordes leading to thrombotic risk increase (10). Moreover, more explanations could be genetic, a recent study (19) noted that thrombosis was common in patients with genetic alteration and with HES and it was significantly associated with increased risk of death.

Diagnostic confirmation of HES requires evidence of elevation of absolute eosinophil count to 1.5×109/L or above for a period of at least 6 months or on two examinations (interval ≥1 month), and organ damage due to tissue eosinophilia (1), but in the case of a life-threatening condition and organ damage such as pulmonary embolism and cerebrovascular thromboembolism, the diagnosis can be made immediately to avoid therapy delay and complications (20). Physicians should consider HES diagnosis in case of hypereosinophilia and evolving life threatening organ damage. Cardiovascular complications may occur in 40 to 60% of cases (21) with respiratory involvement (pulmonary damage and pulmonary embolism) are both the major causes of morbidity and mortality (5, 7, 12, 13, 22, 23). Digestive and neurological involvement are also reported as important organ damage in this setting (5, 24-26).

Two main subtypes of hypereosinophilic syndrome described in clonal HES are myeloproliferative and lymphoproliferative variant, in our case severe hypereosinophila observed was probably clonal due to myeloproliferative variant that which is often associated with small chromosomal deletion, known as thrombosis predictive factor (1, 27).

Corticosteroids are often proposed as immediate treatment of organ damage. Imatinib benefits in FIP1L1-PDGFRA-positive myeloid neoplasms has been confirmed in numerous studies. There is no fixed eosinophilia cutoff at which organ damage occurs or at which treatment should be started, but most experts recommend an absolute eosinophil count 1.5 to 2 × 109/L. For very severe eosinophilia, corticosteroids should be administered as soon as possible. Once the eosinophil count is controlled, additional medications can be started. Patients without symptoms or organic damage are followed for at least 6 months for these complications (1). Other management in ICU for pulmonary damage includes oxygen therapy HFNO, NIV (28) and mechanical ventilation when needed, prone position may be also beneficial (29).

REFERENCES

1. Shomali W, Gotlib J. World Health Organization-defined eosinophilic disorders: 2022 update on diagnosis, risk stratification, and management. American journal of hematology. 2022;97(1):129-48.
2. Roufosse FE, Goldman M, Cogan E. Hypereosinophilic syndromes. Orphanet journal of rare diseases. 2007;2:37.
3. Maino A, Rossio R, Cugno M, Marzano AV, Tedeschi A. Hypereosinophilic syndrome, Churg-Strauss syndrome and parasitic diseases: possible links between eosinophilia and thrombosis. Current vascular pharmacology. 2012;10(5):670-5.
4. Ames PR, Aloj G, Gentile F. Eosinophilia and thrombosis in parasitic diseases: an overview. Clinical and applied thrombosis/hemostasis : official journal of the International Academy of Clinical and Applied Thrombosis/Hemostasis. 2011;17(1):33-8.
5. Silva MS, Ramalho C, Ferreira F, Maia I, Joosten A. Idiopathic Hypereosinophilic Syndrome Presenting With Embolic Stroke. Cureus. 2021;13(11):e19307.
6. Gaillet A, Bay P, Péju E, Ait-Oufella H, Azoulay E, Benchabane N, et al. Epidemiology, clinical presentation, and outcomes of 620 patients with eosinophilia in the intensive care unit. Intensive care medicine. 2023;49(3):291-301.
7. Sato Y, Fukunaga T, Hayashi T, Asada Y. Hypereosinophilic syndrome associated with occlusive coronary thrombosis and right ventricular thrombus. Pathology international. 2008;58(2):138-41.
8. Liu Y, Meng X, Feng J, Zhou X, Zhu H. Hypereosinophilia with Concurrent Venous Thromboembolism: Clinical Features, Potential Risk Factors, and Short-term Outcomes in a Chinese Cohort. Scientific reports. 2020;10(1):8359.
9. Lippi G, Montagnana M, Salvagno GL, Franchini M, Targher G, Guidi GC. Eosinophilia and first-line coagulation testing. Journal of thrombosis and thrombolysis. 2009;28(1):90-3.
10. Cugno M, Marzano AV, Lorini M, Carbonelli V, Tedeschi A. Enhanced tissue factor expression by blood eosinophils from patients with hypereosinophilia: a possible link with thrombosis. PloS one. 2014;9(11):e111862.
11. Aukstuolis K, Cooper JJ, Altman K, Lang A, Ayars AG. Hypereosinophilic syndrome presenting as coagulopathy. Allergy, asthma, and clinical immunology : official journal of the Canadian Society of Allergy and Clinical Immunology. 2022;18(1):25.
12. Bondue A, Carpentier C, Roufosse F. Hypereosinophilic syndrome: considerations for the cardiologist. Heart (British Cardiac Society). 2022;108(3):164-71.
13. Grolla E, Dalla Vestra M, Bonanni L, Cutolo A, Rigo F. A Rare Case of Aortic Valve Thrombosis in Patient with Idiopathic Hypereosinophilic Syndrome. Case reports in cardiology. 2015;2015:607107.
14. Ogbogu PU, Bochner BS, Butterfield JH, Gleich GJ, Huss-Marp J, Kahn JE, et al. Hypereosinophilic syndrome: a multicenter, retrospective analysis of clinical characteristics and response to therapy. The Journal of allergy and clinical immunology. 2009;124(6):1319-25.e3.
15. Li D, Xu L, Lin D, Jiang S, Feng S, Zhu L. Acute pulmonary embolism and deep vein thrombosis secondary to idiopathic hypereosinophilic syndrome. Respiratory medicine case reports. 2018;25:213-5.
16. Mukai HY, Ninomiya H, Ohtani K, Nagasawa T, Abe T. Major basic protein binding to thrombomodulin potentially contributes to the thrombosis in patients with eosinophilia. British journal of haematology. 1995;90(4):892-9.
17. Torrent M, Nogués MV, Boix E. Eosinophil cationic protein (ECP) can bind heparin and other glycosaminoglycans through its RNase active site. Journal of molecular recognition : JMR. 2011;24(1):90-100.
18. Di Micco P, Scudiero O. Idiopathic Hypereosinophilia and Venous Thromboembolism: Is There a Pathophysiological or Clinical Link? Description of an Intriguing Clinical Case. Journal of blood medicine. 2020;11:73-6.

19. Leiva O, Baker O, Jenkins A, Brunner AM, Al-Samkari H, Leaf RK, et al. Association of Thrombosis With Hypereosinophilic Syndrome in Patients With Genetic Alterations. JAMA network open. 2021;4(8):e2119812.
20. Akuthota P, Weller PF. Spectrum of Eosinophilic End-Organ Manifestations. Immunology and allergy clinics of North America. 2015;35(3):403-11.
21. Roufosse F, Weller PF. Practical approach to the patient with hypereosinophilia. The Journal of allergy and clinical immunology. 2010;126(1):39-44.
22. Ogbogu PU, Rosing DR, Horne MK, 3rd. Cardiovascular manifestations of hypereosinophilic syndromes. Immunology and allergy clinics of North America. 2007;27(3):457-75.
23. Gao M, Zhang W, Zhao W, Qin L, Pei F, Zheng Y. Loeffler endocarditis as a rare cause of heart failure with preserved ejection fraction: A case report and review of literature. Medicine. 2018;97(11):e0079.
24. Lin J, Huang X, Zhou W, Zhang S, Sun W, Wang Y, et al. Thrombosis in the portal venous system caused by hypereosinophilic syndrome: A case report. Medicine. 2018;97(48):e13425.
25. Song XH, Xu T, Zhao GH. Hypereosinophilia with cerebral venous sinus thrombosis and intracerebral hemorrhage: A case report and review of the literature. Heart (British Cardiac Society). 2021;9(28):8571-8.
26. Hinkle L, Gandhi N, Neal R, Narcisse V, 3rd. Hypereosinophilic syndrome presenting with gastrointestinal manifestations. BMJ case reports. 2023;16(4).
27. Mahjoub S, Baccouche H, Sahnoun M, Kaabi H, Manai Z, Slama H, et al. [The JAK2 mutation in myeloproliferative disorders: A predictive factor of thrombosis]. La Tunisie medicale. 2015;93(7):474-7.
28. Grieco DL, Munshi L, Piquilloud L. Personalized noninvasive respiratory support for acute hypoxemic respiratory failure. Intensive care medicine. 2023:1-4.
29. Fujishima S. Guideline-based management of acute respiratory failure and acute respiratory distress syndrome. Journal of intensive care. 2023;11(1):10.