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Hypereosinophilic Syndrome Complicated by Ischemia of the Lower Limb Clinical Case with Review of the Literature

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Abstract **Case Report**

Hyper eosinophilia is the result of a disorder, which can be of central origin, with an excessive production of polymorphonuclear eosinophils (PNE), or of a peripheral dysfunction with an abundant recruitment of polynuclear neutrophils from the marrow by the tissues. peripheral more frequently the digestive and urogenital respiratory tissue. The diagnostics must be early to avoid complications. Any case of hypereosinophilia requires a very precise etiological investigation, with a balance sheet of visceral repercussions of eosinophilia. Some genetic abnormalities of the eosinophil line or a dysfunction of the lymphoid line, can be discovered, the targeted therapy trials have revolutionized the prognosis, sometimes pejorative of these diseases, we report here the case of hypereosinophilia complicated by ischemia of the lower limbs.

Keywords: Hypereosinophilia, embolia, hypereosinophilic syndrome.

I. INTRODUCTION

Hyper eosinophilia is defined by an increase in the circulating level ≥ 500/µL and is classified as mild (500- 1500/µL), moderate (1500-5000/µL) or severe (>5000/µL) [1]. We speak of hyper eosinophilia from a moderate blood elevation (>1500/µL) found twice 1 month apart or from tissue damage (medullary eosinophils >20% and/or extensive tissue infiltration and/ or tissue deposition of proteins of PNE origin are part of the white blood cells, which are mainly involved in allergic reactions and parasitic diseases. They are the result of the commitment of pluripotent hematopoietic stem cells into granular progenitors. This action is conditioned by various factors, especially interleukins 3 and 5 and GM- CSF (granulocyte-macrophage colonystimulating factor). Any alteration of these phenomena linked to any event will have consequences on the eosinophilic lineage. Granulaire) [1]. Hyper eosinophilia is defined by an increase in the circulating level ≥ 500/µL and is classified as mild (500-1500/µL), moderate (1500-5000/µL) or severe (>5000/µL) [1]. We speak of hyper eosinophilia from a moderate blood elevation (>1500/µL) found twice 1 month apart or from tissue damage (medullary eosinophils >20% and/or extensive tissue infiltration and/ or tissue deposition of proteins of granular origin) [1]. Any discovery of blood or tissue hyper eosinophilia requires a rigorous approach due to the diversity of the circumstances of their discovery. Hyper eosinophilias can be warning signs of serious illnesses (for example, systemic diseases, or cancers) or illnesses causing the development of visceral lesions with pulmonary, cardiac and thromboembolic which are linked to the toxicity of enzyme mediators, free radicals but especially cytotoxic proteins: MBP (major basic protein), ECP (eosinophil cationic protein), EDN (eosinophil derived neurotoxin) and EPX (eosinophil peroxidase) released by activated eosinophils [2].

II. CLINICAL CASE

We report the case of a 15-year-old patient with no particular history. She was referred by a general practitioner for abdominal pain associated with difficulty breathing. The initial assessment carried out showed hyper leukocytosis at 117,435, with hyper eosinophilia at 115,435/mm3, PNN at 1172, Lymphocytes at 729, Hb at 13g/dL and Platelets at 84,000. splenomegaly with a subcapsular hypoechoic area suggestive of a suppurative area (Figure 1).

Physical examination on admission revealed NYHA stage II dyspnoea with bilateral crackles. There was no hepatomegaly or clinical splenomegaly or peripheral adenopathy.

An exhaustive assessment to eliminate another cause: parasitic, drug and autoimmune hypereosinophilia was carried out.

- Myelogram: bone marrow eosinophilia.
- Bone marrow karyotyping: normal.
- The chest X-ray shows a bilateral alveolar-interstitial syndrome.
- CT: alveolo-interstitial syndrome with pleuropericardial effusion, splenic ischemia with hepatosplenomegaly.
- Angio-CT: Focus of predominantly basal pneumopathy, with associated arteriovenous thrombosis.

Short thrombosis of SFA and AFP on the right, repermeabilization of PA and HA on the right. Long thrombosis of the AIP and EIA on the left, with right superficial venous thrombosis.The patient was put on corticosteroids association with hydroxyurea, as well as anticoagulant treatment at a curative dose.

The evolution was marked by the appearance of a lividity of the lower limbs, with disappearance distal pulses and the presence on CT angiography of deep arteriovenous thrombosis. The patient subsequently died in a clinical picture of pulmonary embolism following this thrombosis (Figure 2).

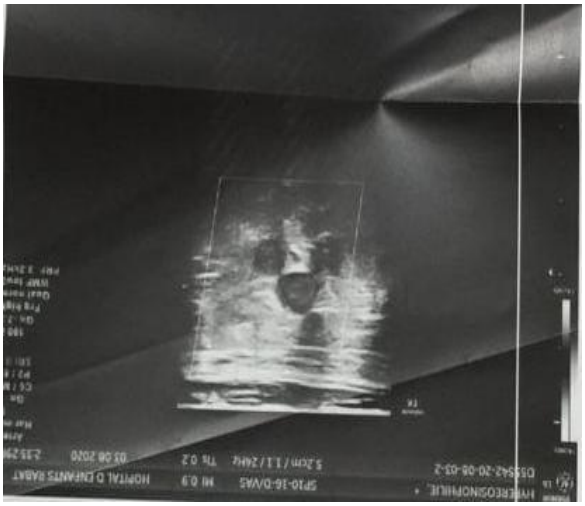

Figure 1: **Suppurative area ultrasound**

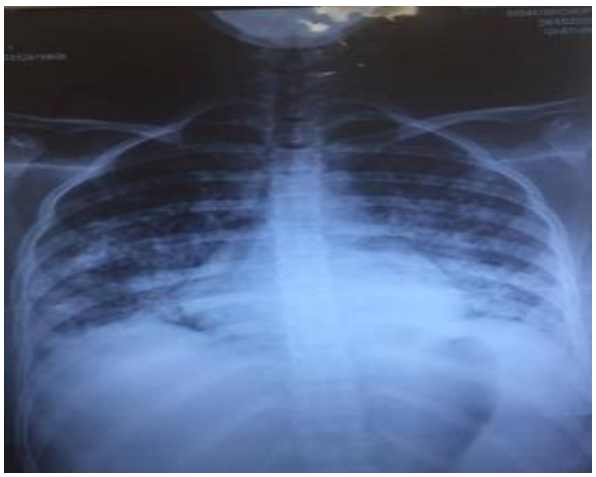

Figure 2: Chest x-ray bilateral alveolar-interstitial image

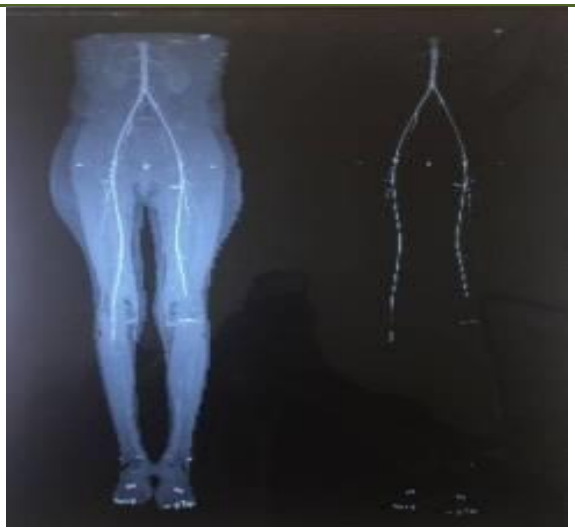

Figure 3: CT angiography with short thrombosis of the superior femoral artery and the posterior femoral artery

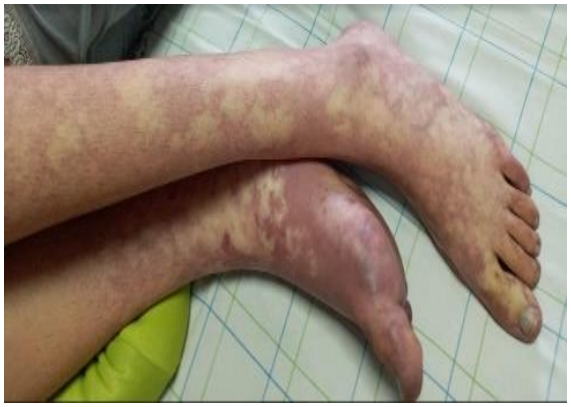

Figure 4: **Image of lesion progressions of the lower limbs**

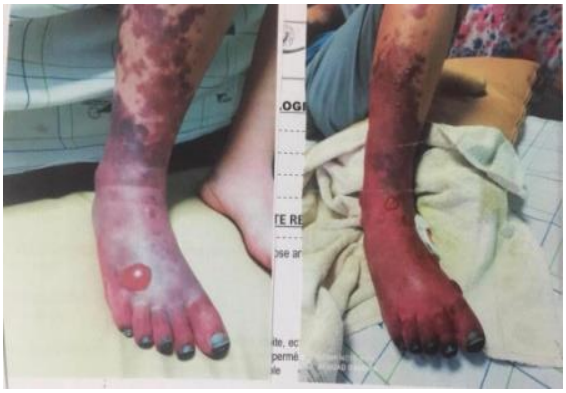

Figure 5: **Image of ischemia of the lower limbs and necroses**

III. DISCUSSION

i. Physiopathology and Classification

Hypereosinophilias are important indicators of various neoplastic and non-neoplastic conditions. Depending on the underlying mechanisms, eosinophil infiltration can lead to dysfunction of organs, systems, or both [3]. Hypereosinophilia is classified into three groups:

- Primary or clonal HE, which is linked to recurrent molecular abnormalities or neoplastic proliferations of cells of the myeloid lineage. These forms represent less than 20% of hypereosinophilia [1, 2].
- HE Secondaires, qui sont secondaires a une production importante des facteurs de croissance ou des cytokines actives sur la lignée des éosinophiles [5-8]. Secondary HE, which is secondary to a significant production of growth factors or active cytokines on the eosinophil line [5-8].
- Reactive hypereosinophilia of the lymphoid type, defined by the existence of a circulating and T tissue population with an abnormal phenotype, producing IL-5, the main pro-eosinophil cytokine [3, 4].

- **Lymphoid Hemopathies:** Like Hodgkin's lymphoma, NHL T, in particular LAI – Myeloma – Leukemia/lymphoma linked to HTLV1 (if endemic zone: Japan, Caribbean, Central America and Black Africa.
- **Myeloid Hemopathies:** LMC, Vaquez, TE, Myelofibrose, Myelodysplasias.
- **Parasitic Hyper Eosinophilia:** Helminthiasis only: Indigenous: toxocariasis, Tænia, oxyuriasis, distomatosis, trichinosis – Endemic: anguillulosis, bilharziasis, filariasis.

Systemic Damage:

- Eosinophilic vasculitis and eosinophilic granulomatosis with polyangiitis [4].
- **Allergic hypereosinophilia:** asthma, chronic rhino sinusitis, dermatitis, allergic bronchopneumopathy.
- **Cardiac and vascular disorders:** Valve disease of the mitral insufficiency type Eosinophilic myocarditis, VG thrombosis (embolism ++), Coronary aneurysms, necrotizing endocarditis and myocarditis progressing to the formation of intravascular thrombicavities then finally towards fibrosis [10].
- **Lung damage:** eosinophilic asthma, eosinophilic bronchitis and chronic eosinophilic pneumonia.
- **Neurological damage:** meningitis, encephalopathy, cerebral vasculitis, damage to the cranial nerves, cerebrovascular accidents and peripheral neuropathies.
- **Rheumatological damage:** predominant in lymphoid damage, it is manifested by arthritis and Raynaud's phenomena [4, 7].
- **Adrenal damage:** Which is manifested by hypocorticism, whether primary or secondary.
- **Digestive disorders:** manifested by eosinophilic oesophagitis, abdominal pain, diarrhea, sub-occlusive syndromes and eosinophilic ascites.
- **Cutaneous lesions:** episodic angioedema, Gleich syndrome and fixed angioedema.
- **Eosinophilic cystitis.**
- **Eosinophilic mastitis.**

Among the primary etiologies we find graft-versus-host disease (GVHD) in a transplanted patient [2-5].

Drug-induced hyper eosinophilia: often occurs during hospitalizations, certain therapeutic classes are more at risk, such as antibiotics. But potentially any drug can be incriminated. DRESS (Drug rash eosinophilia and systemic symptoms) is a form with specific organ involvement. It usually begins within 3 months after taking the causative drug [5-11].

Neoplasia of myeloid origin, during which HE is frequently observed. They are well characterized at the molecular level, falling within the WHO classification: chronic myeloid leukemia (CML) BCR-ABL, myeloproliferative disorders associated with the V617F mutation of JAK2, chromosomal abnormalities in 8p11 (involving FRGR1), certain systemic mastocytosis with D816V mutation of KIT. HE is often present but ultimately epi phenomenal in these pictures where other hematological abnormalities will make it possible to make a molecular diagnosis [14].

Chronic eosinophilic leukemia: it is linked to an interstitial deletion in 4q12, and is currently the best characterized form of LCE. This FIP1L1-PDGFRA fusion gene, not detectable on a conventional karyotype, has definitively allowed establish the concept of ECL, which has been debated up to now [13]. Idiopathic EHS affect more than half of hypereosinophilias. They remain unexplained to this day, but many indirect arguments suggest that they are probably a reaction to an increased secretion of eosinophilopoietins (IL-5).

IV. CLINICAL PRESENTATION

The most common damage to organs and systems in the context of hypereosinophilia are represented by respiratory damage such as hypereosinophilic asthma, Churg Strauss disease, pulmonary embolism, pleural effusions and mediastinal damage [7]. cutaneous represented by eczema, atopic dermatitis and bullous pemphigus. Digestive disorders represented by episodes of diarrhoea, abdominal cramps, gastroenteritis, colitis, chronic hepatitis and cholengitis [12].

V. DIAGNOSTIC

The first step in the diagnostic approach is to eliminate a secondary cause through a rigorous anamnesis, with a good analysis of the symptoms, a

search for lifestyle, dietary habits, occupational exposures, drug consumption as well as the history. personal and family.

A very meticulous clinical examination must look for the points of calls of the affected system or organs. Paraclinical explorations, biology (a blood count, kidney and liver function, a blood ionogram, a dosage of vitamin B12, a protein electrophoresis, a troponin, an autoimmune assessment (antinuclear antibodies, ANCA), a hemo-leukocyte formula, blood smear, parasitic and viral serologies, lymphocyte immunophenotyping), a stool culture, a cardiac assessment (ECG and especially transthoracic ultrasound) [15], respiratory function tests and a thoracoabdominal scanner.If these paraclinical explorations do not objectivate a secondary cause of the hypereosinophilia, a myelogram must be performed with immunohistochemistry, immunophenotyping and karyotyping [16, 17].

VI. TREATMENT

The treatment of hypereosinophilia uses several molecules including antimetabolites that inhibit the DNA synthesis of metabolites, glucocorticoids, imatinib, l'interféron α, Cyclosporines and chemotherapy, especially in a situation of therapeutic failure. Chemical molecules can be used such as vincristine, mercaptopurine, chlorambucil, the combination of these molecules should be reserved for severe situations [17]. Corticosteroids are the most used treatment because of their anti-inflammatory and immunosuppressive effects. Their mechanism of action is a control and neutralization of growth factors, chemokines and cytokines. In addition, they block the tissue deposits of eosinophils and block the release of certain mediators from the granulocytes contained in the eosinophils.

Corticosteroids are used as an attack treatment, especially during respiratory symptoms and allergic forms [20]. Imatinib was first used in the treatment of hypereosinophilia in 2001, it is a protein kinase inhibitor. This treatment would allow a rapid clinical evolution of symptoms, especially in cardiac and neurological disorders as well as myeloproliferative symptoms n attack treatment followed by a maintenance treatment is often effective. Interferon, which has a receptor on the surface of eosinophils to recruit certain eosinophils, has a cytotoxic effect on eosinophils. It also allows the inhibition of the production of interleukins 5 by CD4. Interferon is indicated in case of corticosteroid resistance.

Hydroxyurea allows inhibition of granulopoiesis, as well as inhibition of DNA synthesis. It is most often prescribed in combination with interferon or in combination with corticosteroid therapy.

Finally, cyclosporins block the action of cytokines (IL-3, IL-4, IFNγ, etc.) Allowing a transcription of the IL-2 gene. The efficacy of this molecule is linked to the presence of a circulating T lymphocyte clone [19].

VII. CONCLUSION

Hypereosinophilic syndromes (HES) are very rare pathologies. Their diagnosis is based on a range of arguments. They require an exhaustive etiological investigation.There are several variants of SHE, classified according to the type of molecular abnormality (ies). The most targeted organs are the lungs, the skin, the digestive tract and the central and peripheral nervous system.

A new treatment based on such as anti-IL-5 antibodies has reduced complications and thus improved the quality of life of patients. Corticosteroids, interferon α and hydroxyurea remain the molecules of first choice**.**

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