Severe Multi-Organ Failure and Hypereosinophilia: When to Call It "Idiopathic"?

Severe multi organ failure and hypereosinophilia: when to call it "idiopathic"?

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ABSTRACT

The hypereosinophilic syndrome (HES) is a rare disease characterized by the association between high absolute eosinophil count and eosinophil-mediated organ damage. We described a case of a 70-years-old man with an absolute eosinophil count of 2130 cells/μl. Clinical symptoms and signs included: severe asthenia, axonal sensitive motor neuropathy, basal pleural effusion with signs of hypoventilation on chest radiography and gastrointestinal symptoms as severe diarrhea, weight loss (-10 kg in 6 months), abdominal pain and vomiting. On physical examination he had an urticarial dermatitis on his back, abdomen and lower limbs.

An extensive instrumental and laboratory diagnostic work-up was performed. When all causes of primary and secondary HES were excluded, treatment with solumedrol infusion and oral prednisone was started, with a rapid recover of clinical symptoms and normalization of laboratory parameters. A complete remission of the laboratory and clinical findings was achieved after two months and maintained over one year follow-up.

BACKGROUND

Hypereosinophilia (HE) is defined in the peripheral blood as an absolute eosinophil count >1500 cells/μl, confirmed on two examinations and/or pathological confirmation of HE on tissue[1]. The hypereosinophilic syndrome (HES) is a rare disease characterized by the association between HE and eosinophil-mediated organ infiltration and damage or dysfunction. Clinical presentation of patients might be very heterogeneous since is strictly correlated to organ damage mediated by eosinophils. Symptoms can be insidious, and HES might be overlooked, however in some patients the evolution of cardiovascular or neurological complication might be swift and life-threatening.

In idiopathic hypereosinofilic syndrome (IHES), the underlying cause of HE remains unknown despite the investigations and the complete etiological work-up[2]. When all causes of primary and secondary HES are excluded, treatment is generally warranted[3].

CASE PRESENTATION

A 70-years-old man, with history of rheumatic pericarditis in childhood and no family history of lymphoproliferative and autoimmune diseases, was taken to the emergency department for neuralgic pain in both feet and in the lumbosacral region. Electromyography showed axonal sensitive motor neuropathy. He also complained a persistent non productive cough over the previous month before the admission. On physical examination he had an urticarial dermatitis on his back, abdomen and lower limbs, more marked on the left side

(Figure 1). After a preliminary workout, he was referred to our Center. When he came to our attention, after six months since the onset of the first clinical manifestation, the sensitive motor neuropathy had worsened, especially in the left leg, compromising the deambulation of the patient. Furthermore, he reported severe asthenia and a further deterioration in his gastrointestinal symptoms including severe diarrhea, weight loss (over 10 kg), abdominal pain and vomiting. On physical examination the urticarial dermatitis had spontaneously resolved. At admission in our Center, he was not receiving any treatment.

INVESTIGATIONS

When the patient came to our attention initial blood count highlighted an absolute eosinophil count of 2130 cells/µl with 7900 white blood cells/µl (relative eosinophil count 27%) with normal differential. Liver and renal function tests, vitamin B12 level, complement, prothrombin time, serum protein electrophoresis, angiotensin-converting-enzyme, and serum tryptase were all within normal range.

Indirect parameters of inflammations were elevated: ESR 87mm, CRP 2 mg/dl and LDH 289 UI/l. Autoimmunity (ANA screening, ANCA and cryoglobulins) and JAK2 V617F mutation were negative. EMG showed a considerable deterioration of the axonal sensitive motor neuropathy compared on the EMG of 6 months before. Table 1 summarized the performed investigations and Figure 2 resumes the histological images showing significant multi organ eosinophilic infiltrates.

Since both secondary and clonal eosinophilia have been ruled out as possible diagnoses, a probable diagnosis of IHES was made.

DIFFERENTIAL DIAGNOSIS

Categories of HES are subclassified according to the pathogenic mechanisms resulting in eosinophil expansion: primary, secondary, or idiopathic (when the underlying cause of HE remains unknown).

In primary HES, the eosinophilic expansion is due to an underlying clonal stem cell neoplasm (myeloid, or eosinophilic). On the other hand, in the case of secondary HES, the eosinophilic expansion is driven by overproduction of eosinophilopoietic cytokines by other cell types and is polyclonal. This is the case in parasitic infections, certain solid tumors, and T cell lymphoma, and the HE, when severe, can cause organ damage and dysfunction.

Furthermore, one should bear in mind that there are specific syndromes associated with HE, in which the role of eosinophils to the clinical presentation of the disease is still unknown, such as eosinophilic granulomatosis and polyangiitis (EGPA) and certain immunodeficiencies.

Table 2 summarize the clinical and laboratory features of HE syndrome variants.

TREATMENT

The patient was treated with three infusions of 1g of methylprednisolone in three consecutive days. Oral prednisone was introduced with a dose of 50 mg, followed by a slow tapering with a maintenance dose of 10 mg for 8 weeks. The patient showed a complete remission of the laboratory parameters after the first infusion of methylprednisolone, with an absolute eosinophil count of 50 cells/µl with 9240 white blood cells/µl (relative eosinophil count 0.005%) (Graphic 1).

OUTCOME AND FOLLOW-UP

Oral prednisone was slowly tapered down to 5 mg in two months' period. The patient was closely monitored with weekly blood counts.

The absolute eosinophil count remained under 140 cells/µl over year of follow up. After the two infusions of methylprednisolone the patient had a prompt resolution of the asthenia and nausea. After one month, the chest radiography showed a resolution of the basal pleural effusion and showed no signs of hypoventilation of the surrounding parenchyma. The patient gained the weight that he had lost in the past, with resolution of diarrhea and abdominal pain.

The deambulation of the patient was improved, however episodes of neuralgia in the left leg persisted. After two months' period, the oral prednisone was tapered down to 5 mg and deambulation of the patient was improved. After 4 months, EMG showed a net improvement of the axonal sensitive motor neuropathy with a resolution of the clinical symptoms.

DISCUSSION

IHES is a rare disorder, characterized by sustained HE, where the underlying cause of HE is unclear despite thorough etiologic investigations. When organ damage, mediated by eosinophilic infiltration and mediators, is associated to IHES, therapeutic intervention is warranted.

Prospective studies investigating IHES are still lacking and, to date, only single retrospective studies on a natural history of HE have been performed [4,5]. Furthermore, the vast majority of reported patients with HE in these retrospective studies had well-defined causes of HE after appropriate etiologic work-up, and only a small minority of cases was actually idiopathic. An appropriate diagnostic work-up is crucial for a tailored management, as patients with IHES benefit from steroids, as shown in a retrospective cohort responded to by Ang and colleagues [4].

Recent research in cellular and molecular biology is leading to further characterization of distinct underlying hematological disorders in some patients with IHES. In fact, there have been a small number of reports documenting clonal populations of mature eosinophils in patients with IHES [6,7], but there they represent a limited minority of cases in the vast spectrum of this disease.

There is still an unmet need for future prospective studies involving this patient population, especially in regard to long-term follow up and further clinical and laboratory

characterization. The lack of studies is the main reason of no clear consensus regarding therapy introduction and gold standard therapeutic intervention for these patients. The risk of IHES relapse after initial treatment in a long follow up observation remains also unknown. Similarly, while the use of other immusuppressants could be considered as steroid sparing agents, their use in this setting still needs further investigation. Besides, in our case the lack of new clinical or laboratory sign of relapse after oral tapering down to 5 mg in two months' period, did not supported in our opinion the use of any further therapy.

Our patient is still laboratory and clinically monitored on a monthly based, with an oral dose of prednisone tapered down to 5 mg. All organ involvement had completely resolved, with the exception of the sensitive motor neuropathy which, at one year follow-up, is currently in remission.

REFERENCES

1 Valent P, Klion AD, Horny H-P, *et al.* Contemporary consensus proposal on criteria and classification of eosinophilic disorders and related syndromes. *J Allergy Clin Immunol* 2012;**130**:607–612.e9. doi:10.1016/j.jaci.2012.02.019

2 Curtis C, Ogbogu P. Hypereosinophilic Syndrome. *Clin Rev Allergy Immunol* 2016;**50**:240–51. doi:10.1007/s12016-015-8506-7

3 Klion AD, Bochner BS, Gleich GJ, *et al.* Approaches to the treatment of hypereosinophilic syndromes: a workshop summary report. *J Allergy Clin Immunol* 2006;**117**:1292–302. doi:10.1016/j.jaci.2006.02.042

4 Ang AL, Wong RX, Zhuang QY, *et al.* Natural history of severe eosinophilia with uncertain aetiology and proposals on a practical approach to its management. *Intern Med J* 2012;**42**:928–33. doi:10.1111/j.1445-5994.2011.02648.x

5 Sade K, Mysels A, Levo Y, *et al.* Eosinophilia: A study of 100 hospitalized patients. *Eur J Intern Med* 2007;**18**:196–201. doi:10.1016/j.ejim.2006.09.031

6 Luppi M, Marasca R, Morselli M, *et al.*Clonal nature of

hypereosinophilic syndrome. *Blood* 1994;**84**:349–50.http://www.ncbi.nlm.nih.gov/pubmed/8018930 (accessed 16 Feb2017).

7 Chang HW, Leong KH, Koh DR, *et al.* Clonality of isolated eosinophils in the hypereosinophilic syndrome. *Blood* 1999;**93**:1651–7.http://www.ncbi.nlm.nih.gov/pubmed/10029594 (accessed 16 Feb2017).

Legend of Tables and Figures

Figure 1. Urticarial dermatitis on back and abdomen, left side.

Figure 2. Histological images showing significant eosinophilic infiltrates (arrows) at multiple sites: perivascular and interstitial in skin derma (A: H&E 40X), bone marrow (B: Dominici 40X), gastric antrum (C: H&E 40X) and sigmoid colon (D: H&E 40X).

Graphic 1. Absolute eosinophils count during time

Table 1. Previous investigations undergone by the patient

Table 2. Clinical and laboratory features of hypereosinophilic syndrome variants