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Lymphocytic variant of hypereosinophilic syndrome: Diagnostic challenge

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Abstract

T-cell phenotyping by flow cytometry and PCR analysis of TCR gene rearrangement patterns, are necessary to assess the diagnosis of Lymphocytic variant of Hypereosinophilic Syndrome (L-HES). The aim of this study was to evaluate the diagnostic contribution of flow cytometry using a single panel.

This is a retrospective, single-center study, including patients diagnosed as Idiopathic HES (I-HES) or L-HES from 2005 to 2016. Clinical and biological data as well as the steroids-response were collected. The results of CMF and clonality were reviewed by 2 investigators.

Within a ten year period, among 518 investigated patients only 20 patients fulfilled I-HES (n=12) and L-HES criteria (n=8). Comparison of these two groups resulted in two identical profiles without any differences in terms of demographic, clinical, biological data and steroid responses. One patient developed EBV-induced angioimmunoblastic lymphoma and two patients classified as I-HES developed an aberrant phenotype CD3-CD4+ several years later.

Flow cytometry is an important diagnostic tool with some limits such as the use of a single antibody panel or difficulties in analyzing the results. We recommend an extended antibody panel for patients with constitutional symptoms and the choice of antibodies to be tested would be a joint decision taken with the biologists.

Keywords: Lymphocytic variant hypereosinophilic syndrome; Flow cytometry; T-lymphoma.

Introduction

Chusid, et al. defined Hypereosinophilic Syndrome (HES) for the first time in 1975 [1]. Advances in diagnostic approaches and therapeutic options for HES prompted reevaluation of the definition and classification of HESs [2]. The following six classification categories were identified [3]; [1] Myeloproliferative

HES (M-HES), [2] Lymphocytic variant HES (L-HES), in which an aberrant or clonal lymphocyte population drives eosinophilia through the production of soluble mediators; [3] overlap HES or eosinophilic disease restricted to a single organ system; [4] associated HES or HES in the setting of a distinct diagnosis (ie, parasitic helminth infection, drug hypersensitivity and primary immunodeficiency) in which eosinophilia has been described in a subset of affected patients; [5] familial HES, a rare autosomal dominant disorder; and [6] idiopathic HES. Identification of patients with L-HES is challenging, and has important prognostic and therapeutic implications. Among the heterogeneous group of L-HES, the CD3-CD4+ immunophenotype is the most frequently identified, in which overproduction of IL-5 has systematically been confirmed when tested [4], however, there are many others aberrant phenotypes T [4]. Each laboratory uses its own panel composed of approximately 10 anti-differentiation Cluster (anti-CD) antibodies, so there are as many panels as laboratories. Our hypothesis was that the use of a single antibody panel is insufficient to identify all aberrant T cell subsets and therefore some patients with not identified aberrant phenotype are classified as I-HES. The aim of this study was to evaluate the diagnostic contribution of flow cytometry using a single panel.

Materials and Methods

Patients fulfilling Idiopathic Hypereosinophilic Syndrome (I-HES) or L-HES criteria were enrolled in this retrospective, single-center study from 2005 to 2016. All patient's demographic, clinical, laboratory data and steroid responses of treated patients were recorded by the practitioners in charge of these patients, and were reviewed by 1 investigators of this study. Phenotyping was performed on blood within 24 hours by flow cytometry using a Beckman Coulter Navios-2. Flow cytometry results were reviewed by 2 investigators. Fluorochrome-coupled antibodies (CD45, CD3, CD4, CD8, CD10, CD7, CD5, CD16, CD19, CD56) were purchased from Beckman Coulter. Intracytoplasmic CD3ε expression was detected after fixation and permeabilization with the intraprep kit. T-Cell Receptor gamma and delta chain (TCRγδ) rearrangement analysis was performed according BIOMED-2 protocol. Complete clinical remission under Corticosteroids (CS) was defined by the disappearance of symptoms. A partial clinical remission was defined as an improvement without disappearance of symptoms. A Complete Hematologic Response (CHR) was defined by a decrease of AEC under 0.5 G/L, and a Partial Hematologic Response (PHR) by a decrease of AEC of more than 50% within the first month after treatment.

Results

Demographical and clinical findings: Within a ten year period, 518 patients were investigated for eosinophilia in University Hospital Center of Limoges. Only 20 patients fulfilled I-HES (n=12) and L-HES criteria (n=8). The median age at diagnosis was 58.53 years of age. Sex ratio was 1:1. The median delay between inaugural HES-related symptom(s) and detection of CD3-CD4+ T cells leading to diagnosis of L-HES is 1 year (range 1-4 years). Dermatologic involvement (65%) and constitutional symptoms (75%) were the most common subsequent clinical manifestation of HES without statistical significance between I-HES and L-HES. Different cutaneous manifestations could be combined in a single patient included erythema (n:5), eczema lesions (n:3), urticarial plaques (n:3), pruritus (n:2). Other organ involvement included gastro-

intestinal (n:11), rheumatologic (n:4), respiratory (n:7), neurologic (n:4) and cardiac (n:5) manifestations.

Laboratory findings

The median recorded Absolute Eosinophil Count (AEC) was 4.37G/L (range 2.5-17.1 G/L). The median of highest AEC recorded during the follow-up was 10.5 G/L (range 5.8-20.8 G/L). Serum IgE level was performed for 19 patients and was increased in 14 cases (73.6%). Flow cytometry was performed for all 20 patients and identified 4 aberrant phenotypes (CD3+CD4+CD7-; coexistence CD3+CD4-CD5+CD7+ with CD3-CD4+CD5+CD7-; CD3-CD4+CD5+CD7 low; CD3+CD5+CD7-). A clonal TCRγδ rearrangement was performed in 15 patients and was detected in 6 patients (75%) including 2 with an aberrant phenotype. Fourteen patients (70%) had myelogram: A high eosinophil count was reported in one half and other half was normal. Bone biopsy marrow was performed in 7 cases (35%) and was normal in 4 cases, eosinophil infiltration was noted for 3 other patients.

Therapeutic response

Sixteen patients were treated (80%). The first line treatment were corticosteroids. Were treated symptomatic patients (cardiac manifestations, high hyper eosinophilia with organ involvement, cough, constitutional symptoms, dermatologic local treatment refractory manifestations). Complete clinical and biological response was observed in 15 cases (75%).

Table 1: Demographic, clinical and biological features of two populations.

	I-HES N=12		L-HES N=8		Total N=20		p-value
	Number (%)						
Gender							**0.9999**
Male	6	50.0%	4	50.0%	10	50.0%	
Constitutional symptoms	7	58.3%	8	100.0%	15	75.0%	**0.0547**
Dermatologic symptoms	9	75.0%	4	50.0%	13	65.0%	**0.3563**
Rheumatological symptoms	3	25.0%	1	12.5%	4	20.0%	**0.6186**
Digestive symptoms	5	41.7%	6	75.0%	11	55.0%	**0.1968**
Respiratory symptoms	5	41.7%	2	25.0%	7	35.0%	**0.6424**
Neurological symptoms	2	16.7%	2	25.0%	4	20.0%	**0.9999**
Cardiological symptoms	4	33.3%	1	12.5%	5	25.0%	**0.6027**
Abnormal blood count	3	25.0%	3	37.5%	6	30.0%	**0.6424**
Inflammatory syndrome	7	58.3%	5	62.5%	12	60.0%	**0.9999**
Increased serum IgE	8	66.7%	6	85.7%	14	73.7%	**0.6027**
Increased serum tryptase	0	0.0%	2	40.0%	2	18.2%	**0.1818**
Hypergammaglobulinemia	4	33.3%	3	37.5%	7	35.0%	**0.9999**
Autoimmunity	5	41.7%	3	37.5%	8	40.0%	**0.9999**

Table 2: Comparison of therapeutic response in two groups.

	I-HES n=9		L-HES n=7		P-value
	Average +/- Standard deviation or Median				
Cortico-dependency threshold (mg/day)	4,0	1,0- 10,0	9,5	4,5- 22,0	0,0814
Clinical response					0,4375
Complete	9	100%	6	85,7%	
Partial	0	0%	1	14,3%	
Biologic response					0,4375
Complete	9	100%	6	85,7%	
Partial	0	0%	1	14,3%	
Cortico-dependancy	6	66,7%	2	28,6%	0,9999

Discussion

In our study, only 20 patients fulfilled I-HES (n=12) and L-HES criteria (n=8). Comparison of these two groups resulted in two identical profiles without any difference in terms of demographic, clinical, biological data (Table 1) and steroid responses (Table 2). Clinical manifestations are varied and non specific [5-7]. Currently, there is no recommended antibody cocktail able to distinguish L-HES from I-HES at baseline or during follow-up. Our antibody panel was able to detect the most frequently aberrant T phenotypes (CD3-CD4+; CD3+CD4+CD7-), however some antiCD such as CD2, CD25, CD95 described in literature were missing [5,6]. In two cases, CD3-CD4+ phenotype was found a posteriori for patients classified in I-HES. In fact, one of them was revealed after proofreading seven years after eosinophilia appearance. Another one appeared seven years later. It is likely that a single antibody panel is not sufficient to diagnose all aberrant T cell phenotypes. Moreover, analyzing flow cytometry results is not always easy and collaboration between clinicians and biologists appears therefore essential. Indeed, one patient presented an insufficient percentage (25%) of T cells with an aberrant phenotype and it was very difficult to classify him as L-HES. Thus, L-HES may be misdiagnosed because of inadequacy of the target CD molecules or difficulties in interpreting the results.

To our knowledge, patients with L-HES are at risk of developing T cell lymphoma, generally after many years of indolent pre-malignant disease [7]. One patient developed EBV-induced angioimmunoblastic lymphoma and two patients classified as I-HES developed an aberrant phenotype several years later. These findings may suggest some continuity between I-HES and L-HES and secondarily developing T cell lymphoma and implies an extended follow-up and repeated flow cytometry.

Finally, Roufosse et al. [8], highlights the importance of cytometry compared to increased serum immunoglobulin levels or clonal TCR gene rearrangements insufficiently sensitive or specific for L-HES diagnostic.

According to the literature and our study, invasive investigations (bone marrow cytology or histology) do not seem to provide diagnostic benefit.

Conclusion

Identification of patients with L-HES has an important prognostic and therapeutic implications. Flow cytometry is an important diagnostic tool with some limits such as the use of a single antibody panel or difficulties in analyzing the results. To improve these points, we recommend an extended antibody panel for patients with constitutional symptoms and the choice of antibodies to be tested would be a joint decision taken with the biologists. Moreover, based our experience we recommend to repeat the tests.

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