RECURRENT ANGIOEDEMA IN A PATIENT WITH HYPEREOSINOPHILIA

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An online version of this case, can be found at:
http://www.eaaci.net/site/content.php?l1=17&sel=668
A 29-year-old man referred to our unit for a 6-year history of recurrent angioedema of the head, trunk and limbs, without apparent correlation with food or drug intake.

**MEDICAL HISTORY:**
Episodes of angioedema had begun in 2001 and were characterized by oliguria and weight gain (2-3 Kg), with polyuria and recovery to usual body weight after every episode. He also complained about myalgias during attacks, while he denied arthralgias, dyspnea, fever or other relevant symptoms.

Since 2002 his blood tests documented eosinophilia (4600/mm³, 39% of WBC) and increase of ECP (40 mcg/L, normal value < 12 mcg/L), with total IgE within normal range. C1-esterase-inhibitor levels and functional activity were normal too.

No diagnosis was made at that time and angioedema attacks recurred every 1 or 2 weeks, sometimes associated with urticarial rash. By 2004 his eosinophils had risen up to 18100/mm³ (69% of WBC) and the ECP to >200 mcg/L.

A bone marrow biopsy showed “chronic myeloproliferative pattern compatible with hypereosinophilic syndrome”. During these years, he had been treated with oral corticosteroids (6-methyl-prednisolone 32 mg/day), with significant improvement but incomplete resolution of angioedema attacks. Other therapies, as part of a steroid-sparing strategy, were tried but resulted in no efficacy. These included hydroxy-urea and imatinib mesilate (a therapeutic course was started, despite the absence of genetic abnormalities usually related to hypereosinophilic syndromes, but soon interrupted because of no result).

**CLINICAL EXAMINATION**
When the patient referred to our unit for the first time in 2008, physical examination was unremarkable. Unexpectedly, despite high circulating eosinophil levels, no sign of skin or visceral involvement could be detected at physical examination between attacks.

**WHAT IMMUNOLOGIC TESTS WOULD YOU PERFORM IN THIS PATIENT?**

1) **Search for autoantibodies**
Search for antinuclear antibodies (ANA), anti-dsDNA and anti-neutrophil cytoplasm antibodies (ANCA) were performed in this patient and proved negative. These tests are of fundamental importance whenever an autoimmune disease or a vasculitis is suspected.

2) **Flow-cytometric lymphocyte analysis**
In our patient fluorocytometric analysis of circulating lymphocytes documented the presence of an aberrant CD3-CD4+ lymphocyte population. These cells express CD5 and therefore belong to the lymphocyte lineage, as other monocytic populations (e.g. monocytes, macrophages, etc.) do not express CD5. This kind of aberrant lymphocyte population has been already documented in patients affected by hypereosinophilic syndromes; in these previously reported cases, intracytoplasmic expression of CD3 has been demonstrated.

**WHAT IS YOUR DIFFERENTIAL DIAGNOSIS TO THIS PATIENT?**
DIFFERENTIAL DIAGNOSIS HYPOTHESES

1) Hypereosinophilic Syndrome
The hypereosinophilic syndromes (HES) encompass a spectrum of diseases that have increased blood eosinophils and tissue damage in common. The clinical manifestations are protean and may involve any organ system, but especially the skin (1).

HES was defined by Chusid et al (1975) who proposed three diagnostic criteria (1):
- Persistent eosinophilia (>=10^9 eosinophils/l of blood) for longer than 6 months
- Lack of evidence for parasitic, allergic or other known causes of eosinophilia
- Presumptive signs and symptoms of organ involvement, including hepatosplenomegaly, organic heart murmur, congestive heart failure, diffuse or focal nervous system abnormalities, pulmonary fibrosis, weight loss and anaemia

In our patient just 2 criteria out of 3 were fulfilled, as no organ involvement could be detected. Despite this, the presence of a CD3-CD4+ lymphocyte population was highly suggestive of a lymphocytic variant of HES.

2) Churg-Strauss Syndrome
Churg-Strauss syndrome (CSS) is a systemic vasculitis characterized by eosinophilia and airways involvement. In our patient ACR classification criteria for CSS were not fulfilled. Moreover, ANCA – which are present in about one third of CSS patients – were not present.

EVOLUTION
In the following weeks, a new angioedema attack occurred. As in his usual attacks, oliguria and weight gain occurred in the initial phase, followed by polyuria and return to usual body weight after corticosteroid therapy was increased.

Following the same time course, a rapid increase of blood eosinophils was observed, with return to baseline levels while angioedema was resolving.

SYNTHESIS & CONCLUSION
According to classification criteria a diagnosis of episodic angioedema with eosinophilia (EAE) was made. EAE was first described by Gleich in 1984 and although several hypotheses have been proposed, the exact etiology remains unclear. It is now considered to be one of the several variants of the hypereosinophilic syndrome (1).

Further flow-cytometric analysis showed an increased secretion of Th2 cytokines by lymphocytes, mostly IL-5 (Fig.1).

PCR-analysis documented a small monoclonal lymphocyte population. A therapeutic regimen with cyclosporine-A (CsA) as a steroid-sparing agent was started, reducing the dose of 6-MP to 8 mg/day, but this therapy failed to control disease, with eosinophils rising up to 7300/mm3 (61% of WBC) within a few weeks. CsA was then discontinued and 6-MP dose increased back to 16 mg/day, which continues to maintain acceptable eosinophil levels despite mild side effects. Compassionate use of anti-IL-5 monoclonal antibody (mepolizumab) is currently being evaluated.

Fig.1 Flow-cytometric cytokine production assays (gate on CD4+ lymphocytes).
**DISCUSSION**

EAE is characterized by recurrent episodes of angioedema, urticaria, pruritus, fever, weight gain, elevated serum IgM, and oliguria (2), which were all present in our patient. Angioedema attacks usually occur every few weeks to months with complete resolution of symptoms between episodes, and blood eosinophils levels parallel disease activity (2). It is now considered to be one of the several variants of the hypereosinophilic syndrome (1). Establishing the absence of atopic, parasitic, malignant, or collagen vascular diseases is critical to making a diagnosis of EAE. Awareness of this syndrome and differentiation from other forms of HES is critical because, in contrast to other forms of HES, patients with episodic angioedema with eosinophilia usually have a favorable prognosis with no organ involvement and good response to treatment (1).

Low-dose oral steroids are felt to be the best initial treatment for EAE. There is usually a dramatic fall in eosinophil counts to normal levels following corticosteroid therapy and symptoms of EAE resolve quickly. To date, no successful prophylactic regimens other than systemic corticosteroids have been reported. Patients can be asymptomatic for weeks to months or even years in between flares of EAE (2).

**References:**


**SUMMARY**

A 29-year-old man referred to our unit for a 6-year history of recurrent angioedema of the head, trunk and limbs, without evident cause. His blood test also showed a rise in peripheral eosinophils (up to 18k/mm3, 69% of WBC) and ECP, without any evidence of visceral involvement.

Are these two manifestations expression of the same disease, or are they two separate entities? We describe the clinical and immunologic workup that led to the diagnosis.

**KEY WORDS**

hypereosinophilia, episodic angioedema