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Case report

Hypereosinophilia in a boy with asthma and Varicella Zoster Virus infection

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Abstract. Hypereosinophilia is a rare pediatric condition that could be secondary to infections, allergens, immunologic disorders or may be expression of a clonal proliferation. We report the case of an asthmatic boy aged 9 years who presented hypereosinophilia with spontaneous resolution. He had positive serum IgM antibodies to Varicella Zoster Virus while other tests, including genetic ones, gave negative results. Our findings suggest that in children with unexplained hypereosinophilia Varicella Zoster Virus infection should be investigated. (www.actabiomedica.it)

Key words: hypereosinophilia, varicella zoster virus infection, asthma, children, allergy

Hypereosinophilia (HE) consists in a peripheral eosinophilia greater than 1.5 x 10^9/L that is persistent for at least 4 weeks (1). Eosinophilia may be primary due to a malignant clone or included in the familial variant of hypereosinophilia (1). Among secondary causes of eosinophilia, infections (viral, fungal, bacterial and parasitic), allergy to foods, inhalants or drugs, and immunologic disorders, such as vasculitis, autoimmune diseases and primary immunodeficiency must be included (1). Among drug allergic reactions, drug reaction with eosinophilia and systemic symptoms syndrome (DRESS) is characterized, according to criteria of RegiSCAR group (2), by a rash with at least three of four systemic features (fever, lymphadenopathy, internal organ involvement, hematological abnormalities) (3). In addition, neoplastic diseases, including varied adenocarcinomas, some forms of Hodgkin disease, T-cell lymphoma, and mastocytosis, might be associated with paraneoplastic eosinophilia as a result of ectopic prodution of IL-5 (10). Organ-specific eosinophilic disorders might also be associated with blood eosinophilia; these include acute and chronic eosinophilic pneumonias, eosino-philic gastroenteritis, and some skin diseases (1). Finally in the HE of undetermined significance (HEUS) no underlying cause of HE is identified. If clinical manifestations develop in a patient with HEUS the diagnosis should be changed into idiopathic HES (1). We report on a case of a atopic boy aged 9 years with persistent hypereosinophilia, associated with varicella-zoster infection.

Case report

After 5 days fever, sore throat, abdominal pain, headache, pains in the joints and cough a caucasian boy aged 9 years, was admitted at hospital. He received Clarithromicyn at onset of symptoms. At second day of fever, blood exams were performed revealing 16150/mm^3 leucocytes, with 30,5% eosinophils (E), 45.5% neutrophils (N), 17.8% lymphocytes (L), 5.5% monocytes (M), 0.7% basophils (B), 2,74 mg/dL

C Reactive Protein (CRP) (normal values 0,05-0,3 mg/dL). At hospital admission, physical examination revealed fever, pharynx redness, pain at deep palpation of the abdomen, with liver and spleen exceeding the rib cage for 1 cm, enlarged limph nodes (2-3 cm diameter) at the neck and at the groin. Blood smear revealed 54700/mm^3 leucocytes, with 55% E, 27% N, 15% L, 3% M, and 10.07 mg/dL CRP. There was no history of abroad travels. The boy was treated with intravenous fluids and electrolyte. The day after, a diffuse itchy papular rash at trunk appeared. Clarithromycin was stopped and ceftriaxone was administered. He was treated with clorpheniramine maleate i.v. The boy developed wheezing and received nebulized salbutamol, ipratropium bromide and oxygen. After 5 days of hospitalization, the boy recovered from fever and symptoms and the blood smear revealed 17060/mm^3 leucocytes with 71,6% E. A number of investigations were performed to identify the cause of hypereosinophilia (Table 1). Serum IgM antibodies to varicella zoster virus (VZV) were positive but serum IgG antibodies to VZV were negative. After 10 days,

Table 1. Investigations performed in order to assess origin of hypereosinophilia

Cause of hypereosinophilia	Investigations	
	Normal	Abnormal values
Infections	- Serum Antibodies to Toxoplasma, Parvovirus B19, HHV6, CMV, EBV, rubella, HIV, HBV, HCV, Aspergillus, Borrellia, Toxocara canis, Rickettsiae. - Stools cultures for bacteria, virus, fungi and parasites. - Pharynx swab for bacteria virus and fungi. - Quantiferon TB Gold test - Urinalysis. - Chest x-ray	- IgM VZV positive and IgG VZV negative (ten days after also IgG VZV became positive) - Weil Felix reaction: positive 1/512 - Streptokinase 1:2560 (normal value < 1/2560), Antistreptolysin O titer 907 (normal values < 200), Streptozyme 1/2000 (normal value < 1/200)
Allergic reactions	-Serum tryptase	- Positive skin prick tests to grass, lanciuola, dog's epithelium. - Total IgE (982 IU/L) - ECP >200 mm^3/L (normal value < 15)
Immunologic diseases (Autoimmune disorders and Immunodeficiency)	- Immunoglobulins, p-ANCA, c-ANCA, AMA, ASMA, APCA, anti DNA, liver/kidney microsomal antibody, cardiolipin antibody, Thyroglobulin antibody,Thyroid Peroxidase antibody, antibody anti-ENA (Extractable Nuclear Antigen), Beta-2 microglobulin, cryoglobulinemia, C3 C4, complement, capillaroscopy, lupus anti-coagulant test 1.47 (grey zone: 1.2-1.5)	ANA 1:80 fine speckled
Neoplasm	- Red blood cells, hemoglobin, hematocrit, MCV, MCH, MCHC, platelet count. - Medullar blood sample: expansion of the eosinophilic component (60000/mL) without anomalies of the other components), blood sample for genetic test (karyotype 46, XY, normal. No deletion 4q12, therefore no FIP1L1-PDGFRA fusion. No inversion chromosome16), molecular screening for genetic anomalies through RT-PCR: no arrengements. - Neck's limph nodes US	- Vitamin B12 1182 pg/mL (normal values 180-914 pg/mL)

serum IgG antibodies to VZV became positive. In order to evaluate an organ involvement, serum troponins, electrocardiography (ECG), echocardiography, chest x-ray, capillaroscopy, urine 24 hours collection, urinalysis, creatinine, bilirubin, and liver enzymes were performed with negative results (Table 1). The abdomen US revealed splenomegaly and some reactive limph nodes (diameter 2 cm). The neck US showed several enlarged limph nodes (maximum 3.2 cm). Three weeks after discharge, a diffuse and itchy papular rash appeared and was treated with Hydroxyzine. One month after hospitalization, hypereosinophilia persisted, VZV DNA in lymphocytes by quantitative PCR assay resulted negative. After three months, blood smear revealed 17360/mm^3 leucocytes with 2950/mm^3 E. At the fourth month, E count was normal. During follow-up, the boy suffered from recurrent wheezing. In agreement with skin prick test results (Table 1), he was diagnosed with allergic asthma and oculorhinitis and long-term treatment with inhaled corticosteroids, long-acting-beta2 agonist and desloratadine was prescribed. After eight months from hospitalization, blood E were 760/mm^3 and after 10 months 600/mm^3.

Discussion

We have described a boy with persistent hypereosinophilia associated to VZV infection and allergic respiratory diseases. Persistent reactive eosinophilia is frequently found in patients with chronic infections (viral, fungal, bacterial, parasitic). To our knowledge, this is the first case in which hypereosinophilia is associated with VZV infection. In our case report, the pathogenic role of VZV infection is supported by the hypereosinophilia appearance during an acute infectious status associated with positive serum IgM antibodies to VZV and negative serum IgG to VZV indicating an acute or subacute infection. The mechanisms by which viruses may induce hyperoeosinophilia are unknown. We may hypothesize that they activate T cell response (4). The resulting release of citokines such as interleukine 5 (IL-5) stimulates the proliferation of eosinophils. Along this line, an hypereosinophilia secondary to immune dysregulation may be present in patients affected by HIV infection (5). Our data confirm that asthma and allergic rhinitis may contribute to the increase of eosinophils. Nevertheless, eosinophilia greater than 1.5 x 10 9/L is uncommon in most subjects with asthma (6). In selected cases it would be helpful to perform spirometry and to measure exhaled biomarkers to clarify the diagnosis (7, 8). Eosinophilia in association with asthma may occur in Churg-Strauss syndrome, or in allergic bronchopulmonary aspergillosis. However, the patient did not show abnormalities at chest X-ray, capillaroscopy was normal and autoantibodies were negative. The clinical history, physical examination and investigations performed excluded other causes of hypereosinophilia such as different infections, immunologic disorders, hematopoietic neoplasm's or syndromes associated with peripheral eosinophilia: eosinophilia-myalgia syndrome, Omenn syndrome or Hyper-IgE syndrome. A DRESS syndrome caused by clarithromycin was excluded on the basis of RegiSCAR criteria and because the range time between drug intake and onset of symptoms was shorter than that commonly reported (9). Familial hypereosinophilia is characterized by a family history of documented persistent eosinophilia of unknown cause. In our case no other parents were found to be affected by hypereosinophilia. In primary eosinophilic diseases clonal eosinophils tipically derived from progenitors containing mutations in oncogenic tyrosine kinase receptors (PDGRFA, PDGFRB, FGFR1) or other acquired cytogenetic lesions (1). In our case report a blood sample was collected for genetic tests with negative results (Table 1). We did not find eosinophil-related organ damage at heart, lungs, skin, spleen, GI tract and central nervous system. Therefore, no treatment (corticosteroid, hydroxyurea IFN-a and vincristina mepolizumab, Imatinib mesylate, acyclovir (10)) was administered. In conclusion, our findings suggest that VZV may elicit an hypereosinophilia with spontaneous resolution. Our patient had symptoms at presentation that were similar to those found in idiopathic hypereosinophilia (11). Therefore, in these cases the search for possible agents should include the detection of serum antibodies to VZV.

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