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Marco CUSINI, alessio PIZZATI, Giovanni GENOVESE, Simona MURATORI, giuseppina SCHINCO, Emilio BERTI

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Lymphocytic variant of hypereosinophilic syndrome presenting with polymorphic cutaneous manifestations and nonspecific histopathological findings

Marco Cusini[1], Alessio Pizzati[1], Giovanni Genovese[1], Simona Muratori[1], Giuseppina Schinco[2], Emilio Berti[1]

[1] Department of Physiopathology and Transplantation, Dermatology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy
[2] Department of Internal Medicine, University of Milan, IRCCS Ospedale Maggiore di Milano, Italy.

Corresponding author:
Marco Cusini
Department of Dermatology, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Via Pace 9, Milan, Italy
Telephone: +390255035236
Fax: +390255035236
Email: marco.cusini@policlinico.mi.it

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Dear Editor,

Hypereosinophilic syndrome (HES) is a heterogeneous group of disorders defined by persistent peripheral blood hypereosinophilia (HE) > 1.5 g/L on 2 examinations and/or tissue HE, HE-attributable organ damage and/or dysfunction, and exclusion of other explanations for organ dysfunction[1]. Different variants of HES have been distinguished, including idiopathic, primary, and secondary. Among the latter group, L-HES is due to the presence of an aberrant T cell clone determining an over-production of T helper-2 (Th2) cytokines, i.e. interleukin (IL)-5, IL-4, and IL-13, that leads to reactive expansion and activation of eosinophils[1].

An 80-year-old woman presented with a 3-year history of widespread pruritic erythemato-papular rash. This condition had been diagnosed as prurigo-like eczema and treated with systemic steroid, with good response but relapsing to discontinuation. Her medical history revealed multiple superficial thrombophlebitides, a thrombosis of the external jugular vein and a 10-year history of hypereosinophilia. Hypereosinophilia and itch started briefly after hip joint replacement. The patient was not taking any drug. Dermatological examination showed erythematous maculo-papular and nodular lesions involving the trunk, (Fig.1a) gluteal area, lower and upper limbs (Fig.1b), dyshidrosiform vesicobullous lesions on the palmo-plantar areas (Fig.1c), facial flushing, and diffuse excoriated lesions (Fig.1a,b,c). Histopathological examination resulted nonspecific, showing acanthosis with spongiosis, focal parakeratosis with neutrophils, and dermal infiltrate consisting of lymphocytes, histiocytes and numerous eosinophils. Full blood count was normal except for a high eosinophil count ($5 \cdot 10^3$/mmc, 30% of total white blood cells). A blood film confirmed eosinophilia, without atypical cells. Serum immunoglobulin E (IgE) levels were 244 kUA/L. Tryptase levels were within normal ranges. Erythrocyte sedimentation rate was mildly increased (35 mm). Serology testing for parasites, human T-cell lymphotropic virus, and hepatitis B and C gave negative results. Autoimmunity panel was also negative. Plasma levels of tissue factor were high. Memory Lymphocyte Immuno Stimulation Assay (MELISA) for cobalt was positive, with an increase of blasts proliferation of 40%, at a cobalt concentration of 5 mg/ml. Bone marrow aspirate and biopsy exhibited normal findings except for marked eosinophilic hyperplasia. Medullary blood karyotype was normal. Molecular analysis on peripheral blood was negative for BCR/ABL t(9;22)-p210, JAK2 V617F, and FIP1L1/PDGFRA. Flow cytometry immunophenotyping of peripheral blood found an aberrant population of T cells, which showed a CD4-positive, CD7-negative immunophenotype. The same T-cell clone was identified by T-cell gene rearrangement studies on two skin biopsies and peripheral blood. Computed tomography imaging of the entire body found no abnormalities. Lymphocytic variant of hypereosinophilic syndrome (L-HES) was diagnosed. During hospitalization, the patient was administered oral prednisone 25 mg/day, at progressively tapering doses, and intramuscular chlorpheniramine maleate 10 mg/day. At a 2-month follow-up, with a maintenance corticosteroid dose of 10 mg/day, the rash was almost cleared and itch was partially controlled.

In the current case, our patient met the criteria of HES, and given the presence of clonal T-cell populations and cells with aberrant immunophenotype in the skin and peripheral blood, was classified as L-HES. L-HES is characterized by eosinophilia and eosinophil-infiltrating lesions, especially of the skin, subcutaneous tissue, and – less often – internal organs[1]. Lefèvre and co-workers demonstrated in a study involving 21 patients with L-HES that dermatologic manifestations were the most common, being observed in 81% of the patients.[1] L-HES is responsible for a wide spectrum of protean mucocutaneous manifestations that could also be combined in a single patient[1] (as observed in our case) and include diffused isolated pruritus[1], recurrent attacks of facial angioedema[1,2],diffuse eczematous lesions[1], macular and maculopapular rash[1], urticarial plaques[1], papular lesions[1], ulcerated plaques[3], necrosis of the oral cavity[4], subcutaneous nodules[5] and widespread papulo-nodular lesions[1,6]. Besides, cutaneous manifestations are usually the presenting sign of the disease[1]. To date, little is known about the molecular mechanisms underlying L-HES pathogenesis. The immunophenotype of the T-cell clone is most frequently represented by CD3+CD4-CD8- or CD3-CD4+ subsets of lymphocytes. Other immunophenotypic abnormalities consist of elevated CD5 expression on CD3-CD4+ cells, loss of surface CD7 (as in our patient) and/or expression of CD27[1]. L-HES usually has an indolent course, even though the prognosis is variable and rare cases of malignant evolution towards T-cell lymphoma or Sézary syndrome have been described, usually after several years of stable disease[1]. The aim of treatment is to inhibit eosinophilopoietic cytokine production (IL-5 and IL-3, GM-CSF) by aberrant T cells and to control their expansion and prevent end-organ damage, thromboembolic events and malignant transformation. Cugno *et al.* reported an increased risk of thrombosis due to a higher tissue factor (TF) expression in eosinophil-mediated disorders. In fact, eosinophils have been described as source of TF, the main initiator of blood coagulation[7]. As proof of this, our patient's medical history comprised a thrombophilic diathesis. First-line treatment in patients affected by L-HES is represented by systemic steroids, which are characterized by high response rates but need to be maintained at low dosages for long periods.[1] Considering the possible side effected of prolonged corticosteroid therapies, the use of mepolizumab, a monoclonal antibody that acts blocking IL-5[8], cyclosporine[1] or interferon-α[1] as corticosteroid-sparing agents may have also a rationale.

In conclusion, an important point of discussion is the possible role of the prosthetic material in the induction of the T-cell aberrant clone. Indeed, in our patient there is a temporal link between the eosinophilia and prosthetic surgery. Moreover, by means of MELISA we demonstrated a type IV hypersensitivity to cobalt that was contained in the prosthesis of our patient.

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