SYNDROMA HYPEREOSINOPHILICUM -
CASE REPORT AND REVIEW

M. Kadurina, A. Jordanova, S. Tonev
Military Medical Academy, Department of Dermatology and Venereology, Sofia, Bulgaria

ABSTRACT
There are three categories of blood eosinophilia: reactive (non-clonal), clonal and Idiopathic hypereosinophilic syndrome (HES). The empirical diagnostic criteria of HES are: blood eosinophilia exceeding 1.5x10^9/l for more than six consecutive months; absence of an underlying cause of hypereosinophilia despite extensive diagnostic evaluation and organ damage or dysfunction as a result of local release of toxic eosinophil substances. We present a patient who fulfills the diagnostic criteria of HES and demonstrates disseminated, multiple, erythematous, pruritic papules on the trunk and extremities and Raynaud's phenomenon as a rare cutaneous manifestation of the disease. The patient was successfully treated with systemic corticosteroids and no evidence of haematological disorder were found.

Introduction
The eosinophil count in the blood is normally 0.4 x 10^9/1 (0.1-0.6 x 10^9/1), and results from a balance between their bone marrow production, eosinophil apoptosis and cytolytic degradation (1,2). Eosinophils are a minority of peripheral blood leucocytes and, in normal subjects, most are found in the lung tissues and gastro-intestinal tract (3). They leave the circulation when cell surface adhesion molecules are activated. Eosinophil production, maturation and survival are under the control of various cytokines and growth factors, including the interleukins (IL-2, IL-3, IL-5, IL-13) and granulocyte macrophage colony-stimulating factor (GM-CSF)(4). Blood eosinophilia is classified as mild when the blood eosinophil count is between 0.6 and 1.5 x 10^9/l, moderate when 1.5-5x10^9/l and severe when > 5x10^9/l.

There are three categories of blood eosinophilia:
1. Reactive (non-clonal) eosinophilia. Infections, parasitic disorders, asthma and allergies, respiratory diseases, cytokine infusions, vasculites, non-haematological malignant diseases, drug reactions and connective tissue diseases (Table).
2. Clonal disorders of the bone marrow associated with eosinophilia: acute and chronic eosinophilic leukemia, chronic myeloid leukemia, polycythemia rubra vera, essential thrombocythaemia, acute myeloid leukemia, chromosome 16 variants, the 8pl 1 myeloproliferative syndrome (EMS) and T-lymphoblastic lymphoma with eosinophilia, myelodysplastic disorders (MDD) with eosinophilia, systemic mastocytosis, and acute lymphoblastic leukaemia (6)
3. HES (Idiopathic hypereosinophilic syndrome). After exclusion of the above two categories, patients with persistent, unexplained eosinophilia fall into the category of HES.

In 1975, Chusid et al established the empirical diagnostic criteria of the "idiopathic HES" that are still in use today (7):
• Blood eosinophilia exceeding 1.5x10^9/l for more than six consecutive months.
• Absence of an underlying cause of hypereosinophilia despite extensive diagnostic evaluation.
**TABLE**

**Conditions associated with non-clonal eosinophilia (5)**

| Infections | bacterial, mycobacterial, fungal (coccidioidomycosis), rickettsial, HIV, HTLV II, viral (herpes) |
| Parasitic diseases | Visceral larva migrans (VLM), filariasis/tropical pulmonary eosinophilia (TPE), Ancylostoma duodenale, Toxocara canis, Ascariasis, Trichinella spiralis, Nippostrongylus brasiliensis, Fasciola hepatica, Schistosoma mansoni, Echinococcus/ hydatid disease, Trichurus trichura, Capillaria, Gnathostoma, Enterobius vermicularis, Isospora belli, Dientamoeba fragilis, myiasis due to maggots. Toxoplasma is the only protozoan parasite that produces hyper eosinophilia |
| Allergic diseases | asthma, allergic rhinitis, atopic dermatitis, urticaria |
| Respiratory diseases | Churg-Strauss syndrome, Loeffler’s syndrome/pulmonary eosinophilia, bronchiectasis, cystic fibrosis |
| Drug reactions | carbamezapine, IL-2 infusions, maprotiline, Minocycline: usually disappear on stopping drug |
| Malignant disease | Langerhans cell histiocytosis; Kimura-Weil’s disease (angiolymphoid hyperplasia); Hodgkin’s disease; breast, renal and lung tumours; female genital tract neoplasms and vascular tumours; angioimmunoblastic lymphadenopathy with eosinophilia |
| Connective tissue disease | rheumatoid arthritis, pol yerarteritis nodosa, Wegener’s granulomatosis, eosinophilic fasciitis |
| Lung diseases | bronchiectasis, cystic fibrosis, Churg-Strauss syndrome, Loeffler’s syndrome |
| Gastrointestinal diseases | allergic gastroenteritis (young children), eosinophilic, coeliac disease (usually produces tissue eosinophilia) |
| Skin diseases | atopic dermatitis, eczema, bullous pemphigoid |

- Organ damage or dysfunction as a result of local release of toxic eosinophil substances.

  Major tissue targets include the skin, heart, and nervous system. Cutaneous manifestations consist of either angioedematous and urticarial lesions, or erythematous, pruritic papules and nodules. A hallmark of the HES is its great clinical heterogeneity and highly variable prognosis, ranging from paucisymptomatic disease to a rapidly fatal disease, severe heart failure or acute leukemia.

**Case Report**

We describe a 42-year-old woman, who presented with disseminated, multiple, erythematous, pruritic papules on her trunk and extremities with 2-month duration. Physical examination demonstrated also brownish papules and plaques with symmetrical distribution on the lower part of the back and buttocks (Fig. 1, Fig. 2). The lesions showed no tendency to coalesce and were excoriated. She complained of intensive permanent itching and was treated with topical and systemic corticosteroids with temporarily effect.

Laboratory investigations revealed leucocytosis (12.2x10^9/L; 17.7x10^9/L; 19.2x10^9/L) within the range of 28% - 10% eosinophils, anemia-Hg-114g/l-109g/l, Ery 3.74-3.60x10^12/l; serum level of Fe-3.3-3.4 µmol/l; laboratory abnormalities included an elevated erythrocyte sedimentation rate of 48 mm in the first hour. Biochemical and immunological (IgA, IgM, IgE, IgG, ANA, AMA, ASMA, ANCA, anti-DNA-antibody) findings were normal. Electrocardiogram, echocardiogram, chest X-ray, abdominal ultrasonography and computed tomographic scans of the abdomen and pelvis were normal. No evidence of parasitic infestation and underlying malignancies such as eosinophilic leukemia or lymphoma on clinical and laboratory studies were found. Polymerase chain reaction (PCR) for identification of human papillomaviruses (HPVs) was obtained with no pathological findings (35).
Skin biopsy from representative, pruritic lesion showed epidermal hyperkeratosis, irregular acanthosis, and focal parakeratosis. In the upper dermis - edema and perivascular infiltrates of lymphocytes, plasmocytes, and numerous eosinophils along the collagen fibers (Fig. 4). In the deep reticular dermis - massive inflammatory cell infiltrate around and into the vessels, consisting predominantly of eosinophils; some of the vessels are obstructed and with edematous walls.

Immunohistochemical study of tissue specimens for CD4, CD8, CD20, CD43 and CD68 (Dako, Denmark), revealed that the infiltrating lymphocytes were CD4+, CD43+, CD68+ and CD8- and CD20- T-cells. She was treated with prednisolone 60 mg/daily. The dose of corticosteroid was gradually tapered down to 20 mg/day over a month and the patient was discharged from the clinic with improvement. However, after self-withdrawal of medication she developed again disseminated erythematous pruritic lesions involving the hands and feet, especially their distal part. Two months after withdrawal the fingers and toes became painful, cyanotic and swollen, in the beginning after a cold exposure, but later - permanently. Four months later on the periungual zone of her right hand third finger appeared painful necrotic ulceration (Fig. 3).

Doppler sonography showed intact pulsations at the two palmar arteries. Capillaroscopy revealed vasoconstriction on the both hands, capillary loops-Raynaud type. We again started with intramuscularly corticosteroid - 60 mg daily and added pentoxiphylline 400 mg daily to the therapy with good clinical effect. The ulceration showed a tendency to epithelisation and vasoconstriction disappeared. The dose of corticosteroid again was slowly reduced to 15 mg orally daily and in three-month-period of follow up the condition of the patient is under control and no new lesions appeared.

Results and Discussion

The idiopathic hypereosinophilic syndrome by definition excludes all patients with eosinophilia in whom a cause for this blood
abnormality can be found. One possible algorithm for management of the persistent eosinophilia is shown on Fig. 5 (5).

In our case after a meticulous search for a cause for the eosinophilia, such was not found by conventional techniques and we reached to the conclusion of HES.

**Pathogenesis of HES**

Eosinophils are derived from myeloid progenitors in bone marrow through the action of three hematopoietic cytokines: interleukin (IL)-3, IL-5, and granulocyte-macrophage colony-stimulating factor (GM-CSF) (10). IL-5 is specifically involved in differentia-
**MANAGEMENT OF PERSISTENT EOSINOPHILIA**

- **Look for reactive cause**
  - **Cause identified**
  - **TREAT**
  - **Myeloid or lymphoid clone**
    - **Treat clonal disorder: Chemotherapy +/- bone marrow transplantation**
  - **No clone**

- **No cause identified**
  - **? Treatment for parasites if appropriate**
  - **Look for a clone bone marrow disorder**
    - **Myeloid or lymphoid clone**
    - **Treat clonal disorder: Chemotherapy +/- bone marrow transplantation**
    - **No clone**

- **No evidence of eosinophilic end-organ damage**
  - **Look for evidence of eosinophilic end-organ damage**
  - **TREAT**
    - **End-organ damage**
      - **Eosinophilia > 1.5x10^9/L for 6 months with evidence of end-organ damage**
      - **HES**
      - **Responsive to steroids**
        - **YES**
          - **Benign disease. Steroids, HU α-IFN**
        - **NO**
          - **Aggressive and progressive disease**
            - **Chemotherapy +/- bone marrow transplantation**

- **Serial follow up (6 monthly)**
  1) Watch trend in eosinophilia count
  2) Look for rarer reactive causes
  3) Measure cytokine pattern
  4) Look for clonality
  5) Look for end organ damage

---

**Fig. 5.** Diagram of steps to be taken in diagnosing and treating a patient with persistent unexplained eosinophilia.

The proliferation of eosinophil precursors, whereas IL-3 and GM-CSF also favor maturation of other myeloid precursors. Mature eosinophils released into the bloodstream and rapidly migrate to peripheral tissues, namely bronchial, gastro-intestinal mucosa...
and skin. These eosinophils soon undergo apoptosis and are cleared by the macrophages. This process is controlled by survival factors such as IL-3, IL-5, and/or GM-CSF. The overproduction of one or more of these cytokines is sufficient to induce blood and tissue eosinophilia by stimulating bone marrow generation and inhibiting peripheral destruction. Hence, malignant cells producing GM-CSF, IL-3, and IL-5 are responsible for hypereosinophilia in patients with non-Hodgkin's lymphoma and Sezary syndrome (9,12). In allergic disorders and parasitosis, the role of IL-5 in induction of hypereosinophilia is now well established (11). Although several cellular sources of IL-5 have been identified (including mastocytes, basophils, and eosinophils), T-helper (CD4+) cells that display a type 2 cytokine profile appear to be primarily involved in these disorders (13). These so-called Th2 cells produce a variety of cytokines in addition to IL-5, including IL-4 and IL-13, which induce IgE synthesis. In clinical practice, Th2-mediated immune responses are characterized by the association of hypereosinophilia and high serum IgE levels. Whatever its cause, eosinophil accumulation may in itself have pathological consequences as a result of local release of toxic substances, including eosinophil cationic protein (ECP), eosinophil major basic protein, enzymes, reactive oxygen species, pro-inflammatory cytokines, and arachidonic acid-derived factors (10). There are evidences for a correlation between the high levels of ECP and eosinophil major basic protein in the serum of patients with HES and the stage of tissue damage (14).

**Variants of the HES**

The striking clinical heterogeneity of patients with the idiopathic HES and the occasional development of malignancy involving either the myeloid or lymphoid lineage (9) strongly suggest pathogenic diversity.

**The Myeloproliferative (MP) variant**

The clinical and laboratory features include increased serum vitamin B12, an abnormal leukocyte alkaline phosphatase score, chromosomal abnormalities, anemia and/or thrombocytopenia, hepatomegaly, splenomegaly, and circulating leukocyte precursors. MP is more aggressive variant of HES with poor prognosis because of the frequent occurrence of severe cardiac complications, resistance to glucocorticoid therapy, and the increased risk of developing myeloid malignancy.

For some patients who show eosinophilic clonality, clonal cytogenetic abnormalities within cells of the eosinophilic lineage, and/or increased blasts, the diagnosis HES is debatable. The more appropriate diagnosis - (chronic) eosinophil leukemia has been recommended (15,16).

**The Lymphocytic variant**

Some authors suggest that T cells were involved in the pathogenesis of the HES through the release of soluble factors (17). More recently, elaboration of the Th1/Th2 paradigm has rekindled interest in the pathogenetical role of T cells in the setting of the HES, since the association of hypereosinophilia with increased IgE levels in some patients (8, 9) suggests the possibility of a Th2-mediated disorder. It is characterized by clonal expansion of a T cell population able to produce IL-5 and IL-4 and by a unique CD3-, CD4+ (CD2+TCRα/β) surface phenotype (18).

IL-5-producing T cell subsets have been identified in the blood of the most of the patients with HES (19-24). The pathogenic T cells, usually CD3-CD4+ cells, display an aberrant surface phenotype in all re-
ported cases. Whatever their surface phenotype, the aberrant lymphocyte subsets generally display an activated (HLA-DR+ and/or CD25+) memory (CD45RO+) phenotype. Extensive analysis of the cytokine profile of the aberrant T cells has led to their identification as Th2-subtype cells, depending on their capability of simultaneous production of IL-5, IL-4, and IL-13 and their inability to produce interferon (IFN)-γ (25).

Clinical presentation of the lymphocytic variant of the HES: Clinical features of patients with HES are heterogeneous, but those in whom aberrant IL-5-producing T cells have been detected exhibit a strikingly homogenous clinical and biological profile. According to the available data, some authors consider that the lymphocytic variant of HES is a primitive lymphoid disorder characterized by nonmalignant expansion of an IL-5-producing T cell population.

Cutaneous manifestations, including pruritus, eczema, erythroderma, urticaria, and angioedema, are observed in all patients reported in the literature (25). Biologically, in accordance with the type 2 cytokine profile of the aberrant T cells, serum IgE levels are often increased and polyclonal hypergammaglobulinemia is observed in some cases (25). Approximately one quarter of HES patients have the lymphocytic variant, based on the frequency of phenotypically aberrant circulating T cell subsets, detected in a large retrospective series of 60 patients with chronic idiopathic hypereosinophilia (22).

Raynaud’s phenomenon is a rare cutaneous manifestation of HES. In the anglo-saxon language literature, only six cases of HES with Raynaud’s phenomenon and digital necrosis of the fingers have been reported (26,27). A case of HES with multiple cutaneous microthrombi was reported (28). Major basic protein and eosinophil cationic protein located within the eosinophil granule matrix were supposed to be involved in the formation of microthrombi. This theory could explain the development of Raynaud’s phenomenon and digital gangrene in the patients with HES.

Prognosis

Distinguishing HES patients with lymphocytic variant has important prognostic implications. In some cases identification of phenotypically aberrant T cells in peripheral blood of patients with HES may be followed by protracted development of peripheral T cell lymphoma (19,21,22,29).

Recent observations indicate that the two variants of HES are two distinct hematological disorders, involving the myeloid and lymphoid lineages respectively, account for hypereosinophilia in patients who meet the diagnostic criteria of the HES. It can be hoped that further refinements in cytogenetic and molecular genetic analysis will extend the possibilities of identifying HES patients with an underlying hematologic disorders.

Therapeutic approaches

Therapeutic strategies to control eosinophil levels in HES patients have changed little since they were defined in 1975(8,9). Prednisolone is the drug of choice and can reduce eosinophil infiltration and deposition of ECP (30,31). Steroids reduce the effects of release of eosinophil granule contents, reduce blood eosinophilia and suppress inflammation. The treatment usually starts with doses 1 mg/kg/d after accurate identification of end-organ damage. HES often respond well to treatment with agents that decrease T cell - production such as steroids and cyclosporine (32). As both cyclosporine and steroids inhibit
the IL-2 gene transcription factors and IL-5 production by peripheral lymphocytes and are useful in cases of HES in which T cell eosinophilia is present (32). Hydroxyurea can be used for steroid-resistant patients at a dose of 1-2 g/d. IFN-\( \alpha \) has induced clinical, biological and even cytogenetic remission in some patients with HES, whose case histories are generally highly suggestive of the MP variant (9,33). Another potential therapeutic approach for patients with the lymphocytic variant is extracorporeal photochemotherapy. Its suppressive effects on the pathogenetic T cell clones are the result of several distinct mechanisms, including induction of T cell apoptosis and modulation of cytokine profiles in favor of type 1 responses (38).

In conclusion, the myeloproliferative and lymphocytic variants of the HES are each characterized by specific clinical and biological presentations and are associated with increased risk for development of specific hematological malignancies. Future progress in unveiling variants of the syndrome is likely to consign to history the term "idiopathic" hypereosinophilic syndrome, replacing it with an array of well-defined hematological disorders.

REFERENCES