

A Case of Hypereosinophilic Syndrome with Cutaneous Lesions as Presenting Sign

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Introduction

Hypereosinophilic syndrome (HES) is a rare disorder that is characterized by elevated eosinophilic counts above $1.5 \times 10^9/l$ for greater than 6 months without any underlying causes [1]. The disease can affect multiple organs with a varied clinical presentation and may also affect the skin [2]. Skin lesions can be the dominating and/or presenting symptom affecting up to 50% of patients with HES [2]. We here present a case of HES with cutaneous involvement as presenting and dominating symptom.

Case Report

A previously healthy 64 year old woman was referred to our outpatient dermatology department with signs of digital cutaneous microthrombi consisting of punctate necrosis and subungval hematoma. At first consultation numerous uniform erythematous papules on the trunk and extremities, and erythema and hyperkeratosis of the soles and palms were noted (Figure 1). The symptoms had debuted five months prior to referral. The dermatitis was complicated by a tendency to develop

micro abscesses scattered around the body, some with cribriform patterns. The patient also had complaints of dysphagia and malaise and had suffered a substantial weight loss. Lymphomatoid papulosis, lymphoma, and paraneoplasia were initially considered because of the type of presenting skin lesions and general symptoms. A short course of systemic prednisolone was given with initial relief of symptoms but with rapid reoccurrence on discontinuation. Low dose systemic prednisolone was resumed because of growing shortness of breath. Despite treatment, a sudden deterioration occurred and the patient was hospitalized with acute respiratory distress with signs of bronchospasm and infiltrates on chest x-ray. At admission, the patient had developed palpable necrotic papules, petechiae and suggilations on large parts of the body in conjunction with the monomorphic papular dermatitis and digital ischemia. During the following days, angioedema and urticaria developed. At time of deterioration, Churg-Strauss syndrome and HES were the main diagnoses considered based on symptoms and results from various tests described below.

The biochemistry tests revealed elevated white cell counts ($25.6 \times 10^9/l$) with marked eosinophilia ($10.34 \times 10^9/l$), elevated IgE levels of 3790 g/l, elevated acute phase reactions, and elevated alkaline phosphatase and amylase, both 3 times the upper limit. Alanine transaminase and bilirubin levels were normal. A slight anemia was present (6.4 mmol/l) but more importantly a marked thrombocytopenia ($1 \times 10^9/l$) was demonstrated.

Biochemistry tests, taken at debut and during a short admission three months prior for cholangitis, revealed a persistently elevated white cell count with maximum levels reached at time of diagnosis. Marked eosinophilia at debut was also present ($3.7 \times 10^9/l$). Elevated alkaline phosphatase levels persisted throughout from debut to diagnosis (3-6 times upper limit). Alanine transaminase and bilirubin was only elevated during the acute episode of cholangitis.

Additional tests identified anti-nuclear antibodies but no anti-neutrophil cytoplasmic antibodies. Stools were negative for ova and parasites. Skin histology was performed from four of the monomorphic papular elements (arm, legs and buttocks), which were the dominating and most representative skin lesions. The histology was dominated by perivascular infiltrates of lymphocytic cells of polyclonal type and without cell atypia starting from the dermoepidermal barrier



Figure 1: Dermatological manifestations in a patient with hypereosinophilic syndrome showing a highly varied morphology.

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reaching into the subcutaneous layer with many eosinophil's and few plasma cells. No signs of vasculitis or thrombosis were present. Polyclonality was determined by staining for CD4, CD8 and CD30. A PET scan was performed because of suspected internal malignancy and revealed multiple enlarged lymph nodes multifocally above and below the diaphragm. Bone marrow and peripheral blood smear showed eosinophilia but was otherwise normal without blast excess or signs of malignant infiltrations. Chromosomal karyotyping and FISH examination did not reveal any cytogenetic abnormalities, PDGFRB or FIP1L1/PDGFRB rearrangements.

The patient was diagnosed with a lymphocytic variant of hypereosinophilic syndrome and treated with high dose systemic prednisolone. Upon treatment, the eosinophil count ($0.12 \times 10^9/l$), alkaline phosphatase levels, blood plate count and acute phase reactions normalized and the skin changes, general malaise, and multifocally enlarged lymph nodes revealed on PET scan, cleared. The white cell count ($12.3 \times 10^9/l$) and IgE levels (1400) decreased.

Discussion

HES is characterized by elevated eosinophilic counts $>1.5 \times 10^9/l$ for more than 6 months without any underlying causes and presence of symptoms of organ dysfunction attributable to eosinophil infiltration [1]. This case had marked eosinophilia above $1.5 \times 10^9/l$ for more than six months, and besides skin lesions presented with symptoms from the lung with respiratory distress, from the vascular system with microthrombosis, from the gastrointestinal tract with signs of cholangitis and signs of persistent pancreatitis in the biochemistry tests. Even though rare, cases of sclerosing cholangitis associated with HES have been reported [3]. Other causes of eosinophilia must be ruled out before a diagnosis of HES can be made. Common causes of secondary elevated blood eosinophilia include helminthic parasite infections, atopic and allergic diseases and adverse drug reactions [4]. Stools examination ruled out parasitic infestation, prescribed drugs were discontinued at debut and no history of allergic or atopic diseases were present. Several other causes of eosinophilia exist including systemic rheumatic diseases e.g. Churg-Strauss syndrome (CSS), eosinophilic pneumonias, lymphoid malignancies and solid tumor neoplasia, systemic mastocytosis and primary immunodeficiency diseases, eosinophilic gastrointestinal diseases and non-helminthic infections e.g. scabies, fungi and tuberculosis [4]. Primary skin diseases associated with blood eosinophilia include atopic disease, autoimmune blistering diseases such as bullous pemphigoid, cutaneous T-cell lymphoma, angiolymphoid hyperplasia and Kimura disease, eosinophilic cellulitis, panniculitis and vasculitis, and eosinophilic postural folliculitis [4,5]. Evidence of these disorders was ruled out by an extensive investigation programme. Further, conventional allergic diseases including atopic dermatitis only result in low-grade eosinophilia and cannot explain blood eosinophil's counts $>1.5 \times 10^9/l$. The distinction between HES and CSS is difficult. However, key symptoms characteristic of CSS were not present: No necrotizing vasculitis, extravascular granulomas or giant cells were evident in the skin biopsy and ANCA screening was negative. Respiratory symptoms e.g. sinusitis, rhinitis and asthma were not dominating signs and most importantly first developed at a late phase in the course of disease. CSS is almost invariably associated with asthma, the onset which often by years precedes other clinical manifestations [6]. On the contrary, eosinophilic infiltrates in the histology without signs of vasculitis, eosinophilic bone marrow infiltration, hypereosinophilia above $1.5 \times 10^9/l$ for greater than 6 months without any other underlying causes and multi-organ involvement were diagnostic of HES.

HES are a potentially lethal disorder. Most organ systems can be involved e.g. heart, vascular system, skin, central and peripheral nervous system, gastrointestinal tract, and eyes [2]. The symptoms are variable related to the organs involved and to the nature and severity of organ damage either caused by eosinophilic infiltration or thrombo-embolic events. The pleomorphic picture is also characteristic for the dermatological manifestations which include vesicles, petechiae, papules and papulonodules, angio-oedema, livedo reticularis, erythematous lesions, necrosis, gangrene, Raynaud's phenomenon, eosinophilic cellulitis and vasculitis, urticaria, mucosal ulcerations and pruritus [5]. This case was referred to a hospital dermatology department because of signs of cutaneous micro-thrombi. They were, however, not the only or the debuting symptoms. During a course of six months, the patient presented with papules, papulonodules, petechiae, angio-oedema, urticaria and micro abscesses; the dominating symptoms changing over time. Development of symmetrical hyperkeratosis of the soles and palms, general malaise and weight loss and the polymorphic presentation resulted in an extensive investigation programme to rule out various differential diagnoses including underlying malignancies.

The pathology of skin lesions in HES is in general non-specific with variable eosinophilic infiltration and cutaneous microthrombi. In this instance marked infiltration of eosinophil's was noted.

Two subtypes of HES exist: the myeloproliferative and the lymphocytic variant [7]. This case was diagnosed with the lymphocytic variant that is characterized by a non-malignant clonal T-cell expansion producing eosinophilopoietic cytokines [6]. Patients with the lymphocytic variant often have increased serum IgE, frequently have cutaneous involvement, rarely cardiac involvement, and show a good response to glucocorticoids, as did this case [6]. In contrast, the myeloproliferative variant is characterized by presence of chromosomal abnormalities leading to a clonal expansion of the myeloid lineage, dysplastic eosinophil's on peripheral blood smear, and normal IgE levels. Skin manifestations are less common but mucosal ulcerations are suggestive of the myeloproliferative variant [7].

Dermatologists should be aware of the hypereosinophilic syndrome and the possibility of a very pleomorphic clinical presentation. Skin lesions may be the dominating and/or presenting symptoms affecting up to 50% of patients with HES [2]. A marked eosinophilia for a prolonged period of time should be appreciated and prompt further investigation.

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