

Pachydermatous Eosinophilic Dermatitis

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SUMMARY A case is presented of a female Caucasian patient with chronic peripheral blood eosinophilia and unusual skin manifestations. Within a couple of years, the patient developed multiple hyperkeratotic and hyperpigmented papules and plaques all over the body, palmoplantar keratoderma, pachydermia of acral parts of the body, and generalized pruritus. Generalized lymphadenopathy appeared. Other relevant symptoms were persistent peripheral blood hypereosinophilia and increased level of total IgE. The patient was diagnosed with a very rare condition, pachydermatous eosinophilic dermatitis, and was administered combined therapy with dapsons, oral methylprednisolone and fexofenadine. After one month of treatment, the skin changes markedly improved.

KEY WORDS: hypereosinophilia, hypereosinophilic syndrome, pachydermia, treatment, hypereosinophilic dermatitis, eosinophilic dermatitis

INTRODUCTION

Hypereosinophilia is a frequent symptom that may occur in the course of many underlying diseases. The most common reasons are parasitoses and allergic reactions; however, some less frequently observed disorders should also be taken into consideration on differential diagnosis. The first description of a case with persistent eosinophilia with systemic involvement appeared in 1919 (1). In 1968, the term "hypereosinophilic syndrome" (HES) was proposed for patients with chronic peripheral hypereosinophilia and organ involvement related to eosinophilic infiltration (2). Seven years later, the following diagnostic criteria for idiopathic HES were established: peripheral eosinophilia of unknown origin exceeding $1500/\text{mm}^3$, lasting for longer than 6 months and being the cause of organ dysfunction or damage (3). For patients with chronic hypereosinophilia and skin involvement without any other organ dysfunction,

the diagnosis of hypereosinophilic dermatitis was proposed (4). In 2001, the World Health Organization formulated the criteria that distinguished idiopathic HES from chronic eosinophilic leukemia and T-cell-mediated hypereosinophilia (5). The main criteria were the absence of increased percentage of blasts and the lack of clonality of eosinophils or lymphocytes.

In the light of recent molecular studies that might have had implications for the management of eosinophilic disorders, there was a need to create a new classification of these diseases. The Hypereosinophilic Syndromes Working Group reached a consensus in 2005 and divided the heterogeneous group of chronic eosinophil-mediated disorders into six subgroups (6). This classification considers the possibility of clonality of eosinophils, especially the presence of fusion of two genes on 4q12 (FIP1L1 and PDGFRA).

We present a case of a female Caucasian patient with chronic peripheral blood eosinophilia and unusual skin manifestations that did not suit the criteria of current classifications.

CASE REPORT

Case history and clinical manifestations. A 39-year old female patient has been in care of our department for three years now. When she was 20, she noticed mild palmoplantar hyperkeratosis. The symptoms did not progress and did not bother the patient. More serious problems appeared about four years ago. Palmoplantar hyperkeratosis worsened and started to itch. A couple of months later, pruritus became generalized and multiple papules appeared all over the body, especially on the wrists, neck, chest, lumbosacral region and lower legs. Some lesions were weeping. At that time, lichen planus was diagnosed and the patient was treated with prednisone and acitretin without any clinical effect. Then she was referred to our department.

In the next years, the disease progressed. Generalized lymphadenopathy appeared. Other relevant symptoms were peripheral blood hypereosinophilia (up to 50%) and an increased level of total IgE. Two years ago, the patient started to have symptoms of chronic urticaria.

The skin lesions evolved. Apart from palmoplantar keratoderma, excessive pachydermia appeared on her hands and feet. The skin was markedly thickened, stiff and yellowish. Fingers and toes were stubby and skin markings became very deep (Fig. 1). Multiple hyperkeratotic and hyperpigmented papules, plaques and nodules were present on her elbows, knees,



Figure 1. Severe pachydermia of hands with keratoderma. The skin is thickened, yellowish, with deep skin markings and maceration. Fingers are very stubby. Multiple hyperkeratotic papules are seen around the wrist.

armpit areas, wrists and lower legs. Excessive pachydermia and leukoplakia appeared also in the genital region, especially vulva. White hyperkeratosis was observed on oral mucous membranes, in the angles of the mouth.

In the course of the disease, the patient noticed greater susceptibility to different kinds of infections: recurrent vulval candidiasis, recurrent otitis media, as well as pneumonia.

Laboratory findings. The patient showed persistent peripheral blood hypereosinophilia that ranged between 30% and 50%. Absolute eosinophilia amounted to 2000-4000/mm³. Total IgE level was markedly and persistently elevated up to 13000 IU/mL. The level of β -microglobulin was increased to 2.86 mg/L (normal range: 0.7-1.8 mg/L). Bone marrow biopsy revealed excess of eosinophils at various stages with a predominance of mature forms. The direct immunofluorescence test of skin lesions showed sparse granular deposits of C1q at the dermoepidermal junction.

The following investigations were performed and were within the normal ranges: blood cell count, basic serum biochemistry, serum lactate dehydrogenase, levels of immunoglobulin subtypes, protein electrophoresis, serum level of vitamin B12, serologic tests for human immunodeficiency virus, patch tests and prick tests with basic allergens, x-rays of the chest, hands and head, electrocardiograms and echocardiograms, abdominal sonography, spirometry, karyogram, and immunophenotyping of lymphocytes. The clonality of eosinophils was not demonstrated in the test for FIP1L1-PDGFRA fusion. Repeat stool examination for parasites was negative.

Histopathologic findings. Three skin biopsies were obtained: two were taken from the skin lesions and one from vulva. Sections were stained with hematoxylin and eosin. In addition, immunohistochemistry was performed on paraffin embedded section for T cells (CD3, CD43, CD45RO), B cells (CD20), macrophages (CD68, MAC-387), Langerhans cells (CD1a, S-100 protein, langerine) and dermal dendrocytes (factor XIIIa-related antigen). Skin biopsies showed hyperkeratotic and acanthotic changes of the epidermis. There was no spongiosis. All biopsies showed polymorphous infiltrates with lymphocytes, neutrophils, plasma cells and a large eosinophilic component (predominantly perivascular). In some areas of the specimens, the infiltrate was focal and perivascular, whereas in others it was more diffuse and interstitial (Fig.2). All biopsies showed small vessel proliferation and ectasia. Vessel thrombosis was not seen and flame figures were absent. The stains for mucins and

amyloid deposits were negative. In vulval biopsies, interstitial and perivascular infiltrates showed an important number of plasma cells. In addition, in vulval biopsies fibrosis was particularly marked.

Immunohistochemistry demonstrated the presence of T cells, whereas B cells were absent. There were a moderate number of dermal macrophages and a small number of dermal dendrocytes and dermal Langerhans cells.

Additional findings. Serologic tests for toxocarasis did not exclude the possibility of active disease and the patient underwent appropriate therapy. However, this treatment was not relevant for the course of hypereosinophilia and skin changes.

In the course of the disease, the patient underwent thorough endocrinological diagnosis, mainly due to the suspected acromegaly. There was a transient increase in the plasma prolactin level, which was treated with bromocriptine. According to the endocrinologists' opinion, this symptom had a reactive character and was not relevant for the clinical picture. Pituitary gland dysfunction including acromegaly was excluded. Magnetic resonance of the head was normal. There were no other hormonal disturbances.

TREATMENT AND FOLLOW UP

The patient was treated with acitretin, cyclosporine A, oral prednisolone, methylprednisolone in intramuscular depot injections and antihistaminics with partial, transient or no clinical effect. The disease progressed in spite of treatment. Then we diagnosed pachydermatous eosinophilic dermatitis and the patient was administered combined therapy with dapsone 100 mg daily, oral methylprednisolone 24 mg daily and fexofenadine 180 mg twice daily. After

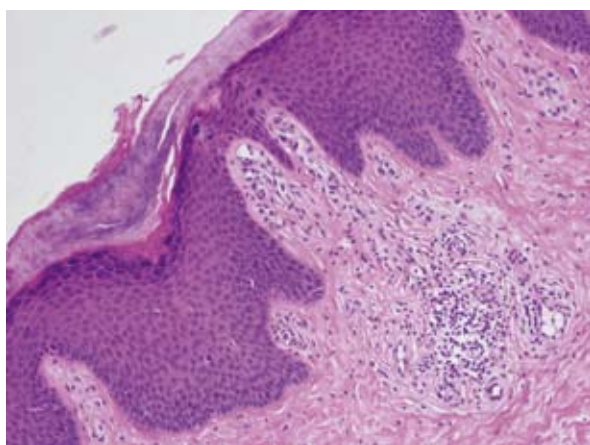


Figure 2. Hyperkeratosis and acanthosis of the epidermis. Mixed diffuse infiltrates, more dense in the perivascular areas. (HE; x 400)

one month of treatment, the skin changes markedly improved with diminution of pruritus and flattening of skin lesions. The pachydermic changes were not as severe as before the triple treatment (Fig 3). The clinical improvement was accompanied by normalization of eosinophilia. The serum level of total IgE was still elevated but the values were lower than at the beginning of the disease.

Four months after the introduction of combined treatment, we observed further improvement of skin lesions. However, we had to stop further dapsone therapy because of skin changes of erythrodermic type that might have been caused by dapsone. At present, the patient is still on methylprednisolone-fexofenadine therapy and remains in the care of our department.

DISCUSSION

Disorders with hypereosinophilia are a heterogeneous group of diseases. First step in the diagnosis is excluding the reactive causes of high eosinophil level, such as parasitic infections, atopy or other allergic disorders and malignancies (7,8). The current classification of nonreactive hypereosinophilic disorders divide these conditions into subgroups, taking into consideration different presentations and pathogenic variants (5,8). The classification concerns fulfilling the diagnostic criteria of HES:

- FIP1L1-PDGFR α -positive HES, which is more appropriately classified as FIP1L1-PDGFR α -positive chronic eosinophilic leukemia;
- chronic eosinophilic leukemia with clonality of eosinophils or increased percentage of blasts;
- lymphocytic-mediated HES with chronic polyclonal hypereosinophilia secondary to IL-5 overproduction by T cells;



Figure 3. Improvement after therapy; the pachydermic changes are visibly diminished.

- myeloproliferative HES with features suggesting the possibility of underlying myeloproliferative disorder (hepatomegaly, splenomegaly, anemia, increased serum level of vitamin B12, bone marrow hypercellularity with left shift in maturation);
- idiopathic HES of unknown pathogenesis; and
- organ-restricted eosinophilic disease in which there is eosinophilic infiltration and damage of specific organ, e.g., eosinophilic pneumonia, eosinophilic dermatitis, eosinophilic fasciitis.

The patient described in this paper does not fulfill any of the above-mentioned criteria. There was no evidence for parasitic or allergic disease. The episodes of chronic urticaria appeared in the course of the disease, probably secondary to persistent hypereosinophilia. The diagnosis of HES was taken in consideration, mainly due to the degree of peripheral blood eosinophilia. However, thorough diagnostic work-up, biochemical and imaging, did not reveal any organ dysfunction or damage. Systemic changes are one of the symptoms of HES (7-9). One of other possible diagnoses could be eosinophilic dermatitis, a hypereosinophilia with only skin involvement. However, the skin symptoms described in this condition differed from the skin manifestations observed in our patient (4,10-12). Erythemas, maculae, pruritic papules and urticarial changes are usually present. There are no reports describing hypertrophy, pachydermic changes or genital involvement.

We diagnosed pachydermatous eosinophilic dermatitis in the patient presented. This condition was first described in 1996 by Jacyk *et al.* (13). The authors presented three cases of South African black teenage girls with pruritic papules and nodules on thickened and pachydermatous skin with coexistence of lymphadenopathy. All patients had very similar clinical appearance. The lesions were particularly extensive on the extremities and in the genital region. The hands and fingers were stubby and stiff. There were no systemic changes. All patients showed persistent peripheral eosinophilia, leukocytosis and elevated serum IgE level. Bone marrow biopsies revealed an excess of mature eosinophils with no increase in blast cells. Other disturbances included increased IgG, IgA and IgM levels, elevated levels of circulating immune complexes and raised activity of serum lactate dehydrogenase, which were not present in our patient. Histologic picture showed similar findings as in biopsies taken from our patient: perivascular and/or diffuse infiltrates consisting mainly of mononuclear cells and eosinophils, small vessel proliferation and ectasia, and fibrosis in the dermis. Two patients described by Jacyk *et al.* (13) benefited from dapsone therapy, administered in a dose of 100 mg/day. The third patient

developed the signs of hemolysis, so the dose of dapsone was diminished to up to 50 mg/day and additionally prednisolone 20 mg/day and cetirizine 10 mg/day were introduced. This therapy resulted in significant improvement. Being inspired by the good clinical effects of combined therapy with dapsone, steroids and antihistaminics, we also tried triple treatment in our patient. This treatment brought significant improvement of the skin changes and decrease of itch.

To the best of our knowledge, there are no other reports of similar conditions, suggesting that this may be an extremely rare disorder.

Several other conditions might be taken in consideration on differential diagnosis in our patient. A similar clinical picture may be present in the course of T-cell lymphoma. Moraillon *et al.* describe a case of a male patient with papulonodular changes and pachydermia with peripheral eosinophilia and elevated IgE level (14). More detailed examination allowed them to diagnose a T-cell pleomorphic lymphoma. Sometimes peripheral eosinophilia is present in patients with benign clonal T-cell population that produce high levels of IL-5 (15,16). Our patient did not present clonality of circulating lymphocytes. The clonal type of hypereosinophilia was also ruled out by the negative test for FIP1L1-PDGFR α fusion. This kind of abnormality may have implications for the treatment and is an indication for imatinib therapy (7,8,17).

Other conditions considered on differential diagnosis included hyperimmunoglobulin E syndrome, Kimura's disease, angiolymphoid hyperplasia with eosinophilia (ALHE) and conditions with distal pachydermia or hyperkeratosis such as acropachyderma, Bureau-Barrière-Thomas syndrome or palmoplantar keratodermas. However, the clinical picture of these disorders differed from the features observed in our patient (18-21).

CONCLUSION

We would like to emphasize that the case presented in this paper is the first example of this rare condition in a Caucasian patient and the first case reported in Europe.

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