Pleural effusions in an overlap syndrome of idiopathic hypereosinophilic syndrome and erythema elevatum diutinum

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The idiopathic hypereosinophilic syndrome (HES) is defined by the following three criteria: persistent eosinophilia over 1,500·mm⁻³ for at least 6 months; lack of evidence of parasitic, allergic, or other recognized causes of eosinophilia despite careful evaluation; and signs and symptoms of organ involvement or dysfunction either directly related to eosinophilia or unexplained in the given clinical setting [1]. Pulmonary involvement in patients with HES can have various manifestations, the most common of which are pulmonary infiltrates. Pleural effusion (without congestive heart failure) is less common [1]. Skin lesions in HES are generally of two types: erythematous pruritic papules and nodules, or urticaria and angio-oedema [2].

Erythema elevatum diutinum (EED) is a rare, chronic skin disease characterized by persistent red, purple, and yellowish papules, plaques and nodules that are usually distributed acrally and symmetrically over extensor surfaces; histologically, all lesions show a leucocytoclastic angiitis with neutrophilic dermal infiltrates [3, 4]. EED is included among the vasculitides [5].

We report a patient presenting with eosinophilic pleural effusions and overlap of HES and vasculitis of the EED type.

Case report

In 1981, a 28 yr old, previously healthy man developed arthralgia of the knees, wrists, and shoulders, oedema of the legs and feet, and skin lesions. These persisted and by 1984 he also had bilateral pleural effusion. Blood eosinophilia was noted in 1983 (1,638·mm⁻³, then 3,230·mm⁻³) and in 1984 (5,640·mm⁻³). In 1985, his condition deteriorated. In July, his blood eosinophil count was 9,900·m⁻³, and in August he was admitted to hospital with breathlessness. The prednisone 40 mg that he had been taking daily for 10 days was stopped.

Fig. 1. — Pleural effusions on admittance to hospital.

He was subfebrile and, apart from pleural and skin signs, physical examination was normal. He had a large left and a small right pleural effusion (fig. 1) with mild oedema of the arms, legs, feet and face. The skin lesions were clinically and histologically characteristic of EED, being distributed symmetrically over the extensor sur-
faces and especially over the joints of the hands, wrists, elbows, knees, and ankles and the buttocks. They consisted of firm, red and purple papules (1–3 mm diameter), and small plaques or nodules (1–2 mm diameter). Atrophic scars on the elbows were also noted, but the face, ears and trunk were spared, as were the mucous membranes. Haematoxylin-eosin sections of skin biopsies revealed a leucocytotrophic vasculitis with endothelial swelling of most upper and mid-dermal vessels, neutrophilic fragments in and around skin walls, dense perivascular infiltration by neutrophils and eosinophils and dermal deposits of eosinophilic substance between collagen bundles.

The white blood cell count at admittance was 15,300·mm$^{-3}$ with 80% neutrophils and 3% eosinophils. The platelet count was 275,000·mm$^{-3}$. Haemoglobin was 125 g·l$^{-1}$. The blood eosinophil count rose rapidly thereafter, until corticosteroid treatment was resumed (fig. 2). The blood level of vitamin $B_12$ was normal. Leucocyte alkaline phosphatase score was normal.

The patient had a positive rheumatoid factor (1:2560) and anti-nuclear antibodies (1:4096) but no antideoxy ribonucleic acid (anti-DNA) antibodies. Circulating immune-complexes (C1q binding assay) were strongly positive (50%: normal less than 4.7%). The lupus erythematosus cell test was negative and immunoglobulin G, A, M, and E levels were normal. A bone marrow aspiration showed 38% eosinophils. Serological tests and stool examination for parasitic diseases were negative (filariasis, ascariasis, distomatosis, trichinosis, strongyloidiasis and schistosomiasis). The patient's pleural fluid contained 43 g·l$^{-1}$ of protein with 20% eosinophils. Thoracocopy and biopsy showed mild pleurisy consisting histologically of inflammatory lesions with many vessels and lympho-plasmacytic infiltrates but few eosinophils. Two bronchoalveolar lavages showed increased lymphocytes (29 and 26%) and only 3 and 4% eosinophils.

An echocardiogram was normal apart from a small pericardial effusion. Urinalysis and a renal arteriogram were normal. Blood eosinophils were neither vacuolated (more than 50% of cells with more than ten distinct cytoplasmic vacuoles) nor hypogranular (more than 30% of cells with more than 50% of the visible cytoplasm devoid of granules) [6], and were normal and granular ultrastructurally. Electroneurography showed reduced motor and sensory nerve conduction, consistent with axonal nerve loss, which returned to normal after 15 days of corticosteroid treatment.

The patient was given prednisone 20 mg for five days, then methylprednisolone 60 mg daily, reducing to 40 mg after ten days. The pleural effusions and most skin lesions disappeared within a few days (fig. 3). Blood eosinophil count, which had risen after stopping corticosteroids on admittance to hospital, dropped rapidly (fig. 2). The dosage was gradually reduced over six months to 25 mg prednisone, with some relapses when the reduction was too rapid. No relapse of pleurisy, skin lesions, or eosinophilia had occurred while taking 5 mg prednisone per day, when seen in August 1988.
Discussion

Our patient clearly fulfilled the criteria for HES with, in addition, prominent pleural effusions and characteristic skin lesions. About 20% of patients with HES have pleural effusions [7]. These are generally secondary to congestive heart failure due to cardiac dysfunction, the main cause of morbidity and mortality in HES [8, 9]. Eosinophilic cardiomyopathy is characterized by endocardial fibrosis leading to a restrictive endomyocardiopathy. The echocardiogram is a sensitive and perhaps early indicator of cardiac involvement [8]. In our patient, it revealed only a small pericardial effusion and he had no heart failure. Blood eosinophils are also usually vacuolated or hypogranular only in patients with HES and cardiovascular disease [6]. In our patient they appeared normal.

The patient’s pleural fluid was an exudate with 20% eosinophils. Although the findings on pleural biopsy were nonspecific, the pleural fluid eosinophilia and the rapid disappearance of the effusions with corticosteroids indicate that the pleural involvement was part of HES. Pulmonary infiltrates, transient or otherwise and with or without bronchospasm have been reported in HES but have not been characterized. The lack of parenchymal involvement on chest X-ray in this patient is consistent with the minimal eosinophilia at bronchoalveolar lavage. Little or nothing is known about bronchoalveolar lavage in HES. The distribution of eosinophils in the blood and tissues is thought to be mediated by chemotactic factors. The absence or inactivation of such factors in the alveolar structures could explain the paucity of eosinophils in the alveolar lumen in our patient.

The skin lesions were characteristic of EED although eosinophils in such lesions are uncommon [4]. Moreover, skin lesions, although not diagnostic, are often found in HES [2].

Corticosteroids are often effective in HES, especially in patients with angio-oedema [10] whereas they are not effective in typical EED. In our patient, the eosinophilia and then the symptoms disappeared with corticosteroids within a few days.

The pathophysiology of both HES and EED is unknown but an immune complex basis for both diseases has been suggested. C1q binding activity has been found in 32% of patients with HES [11] and also in patients with EDD [3]. The lesions of EED have been attributed to damage by neutrophils, and those in HES to damage by eosinophils which accumulate in response to immune complexes, which they phagocyte. The coexistence of HES and EED suggests that they have similar pathogenetic mechanisms, whatever these might be. Overlap syndrome of HES and EED may give rise to pleural eosinophilic effusions responding dramatically to corticosteroids.

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References


RÉSUMÉ: Nous rapportons l'observation d'un patient porteur de syndrome hypereosinophilique idiopathique avec épan-
chemement pleural bilateral a eosinophiles. Il etait egalement porteur d'erythema elevatum diutinum, une maladie cutanee rare de type vascularite. L'epanchement pleural, les lésions cutanees, et l'eosinophilie sanguine disparurent sous traitement corticoide prolongé.

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