The hypereosinophilic syndrome—a diagnostic enigma

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Summary

The hypereosinophilic syndrome groups together a number of conditions in which eosinophilia occurs for no apparently identifiable cause. Initial reports indicated a uniformly grave prognosis but recent observations suggest a more favourable outcome in certain cases. Two patients with hypereosinophilic syndrome are described whose course of disease and outcome have been completely different.

Introduction

A century ago Paul Ehrlich first used the term eosinophil to describe this polymorphonuclear leucocyte. Its existence had first been hinted at by Wharton Jones in 1846. The association of eosinophilia with metazoan parasitic infection has become well established since it was first recorded in ancylostomiasis in 1891 by Müller and Rieder. Eosinophilia occurring with allergies and atopic conditions has been noted since the earliest identification of this cell. Recently interest has become increasingly focused on a number of disorders in which eosinophilia occurs for no apparently identifiable cause and which have been grouped together as the hypereosinophilic syndrome (Hardy and Anderson, 1968).

Two patients with this syndrome are described whose outcomes have been totally different.

Case reports

Case 1

A 26-year-old policeman was first seen in 1976 with an 18-month history of sudden attacks of marked swelling of eyes and lips, unsuccessfully treated with various antihistaminic preparations. Other complaints included frequent episodes of dry cough, at times severe enough to wake him up, bouts of severe abdominal pain localized mainly in the right iliac fossa, vague headaches and what he described as short periods of 'misty' vision.

Full clinical, biochemical and radiological investigation at the surgical department had failed to reveal a cause for his abdominal complaint. Clinical examination at the time of his first visit was thought to be normal except for a barely palpable spleen. There was no family history of atopy. A complete biochemical investigation showed normal hepatic and renal function. Repeated examinations of blood and stools failed to detect any ova, cysts or parasites. A pre- and post-exercise ECG and chest X-ray were all normal. Echocardiography and a full skeletal survey revealed nothing of note. A detailed ophthalmological examination failed to detect any abnormality. Skin testing with a wide variety of allergens was negative. There was no evidence of drug hypersensitivity. Pulmonary function tests were all within normal limits. Haematological investigation showed that the ESR was 3 mm in one hr; haemoglobin concentration 15.3 g/dl; total leucocyte count $19 \times 10^9/l$; absolute eosinophil count $8.17 \times 10^9/l$. A biopsy of the bone marrow showed hypercellularity with large numbers of eosinophils. No primitive white cells were visible in either the marrow or in the peripheral blood. The patient refused to undergo a liver biopsy. Regular haematological examinations have shown a persistent leucocytosis ranging from $15 \times 10^9/l$ to $24.5 \times 10^9/l$ with an eosinophilia of 38 to 66%. Anaemia has never been present and the ESR continued to be normal. Serum immunoglobulin levels were normal. Repeated chest X-rays, biochemical investigations and a further bone marrow biopsy have failed to reveal any abnormalities. An absolute eosinophil count performed in August 1979 showed an eosinophilia of $4 \times 10^9/l$; this has been the lowest count recorded. He has continued to keep clinically well with occasional attacks of peri-orbital oedema. The patient has not received any treatment during these 3 years as there has been no evidence of significant progressive organ system involvement and dysfunction.

Case 2

A 16-year-old boy was first seen at the Allergy Clinic in April 1976 with one year's history of episodic attacks of wheezing and breathlessness. Clinical examination at the time revealed marked scattered bilateral expiratory rhonchi but was otherwise normal. Pulmonary function studies showed a moderate degree of airway obstruction. His leucocyte count was $11.6 \times 10^9/l$ with an eosinophilia of 14%. Skin testing with a wide variety of allergens was negative, as was repeated examination of blood and faeces for ova, cysts or parasites. A chest X-ray was normal. There was no family history of atopic disease and no evidence of drug hypersensitivity. He attended the Allergy Clinic irregularly for a period of about 2 years where his condition, diagnosed as bronchial asthma, was fairly well controlled with salbutamol and beclomethasone dipropionate inhalers and aminophylline suppositories. During this time, various short courses of oral corticosteroids had to be added to his therapeutic regimen because of attacks of acute breathlessness. The patient underwent an appendectomy at another hospital in May 1978. Nine months later he was admitted as a medical emergency to Al Sabah Hospital with a diagnosis of status asthmaticus. On this occasion he also complained of a 3-week history of recurring bouts of low grade pyrexia and multiple flitting joint pains involving mainly wrists, fingers and ankles. Clinical examination showed marked bilateral inspiratory and expiratory wheezing and tender and swollen wrists and ankle joints but was otherwise normal. His temperature was 37°C , BP 120/80 mmHg, pulse 120/min regular. Haematological examination showed an ESR of 50 mm/hr (Westergren); a leucocyte count of $17.1 \times 10^9/l$ with an eosinophilia of 48%. His serum immunoglobulin levels were normal. A chest X-ray and an ECG were both normal. A full laboratory investigation of his joint pains was carried out but no identifiable cause could be found. His wrist and ankle joints remained tender and swollen and, after one week, in spite of corticosteroid treatment, his knees were similarly affected. Treatment with intravenous hydrocortisone, high doses of oral prednisolone, salbutamol and aminophylline had in the meantime relieved his acute breathlessness but the patient still had some impairment of his pulmonary function and audible wheezing. At this time he started to complain of diffuse, vague abdominal pain which he claimed to be of similar nature to that present before his appendectomy. No cause could be found to explain his abdominal symptoms in spite of repeated laboratory and radiological investigations. His ESR remained high (42 mm/hr) and so did his eosinophil count (WBC $15.7 \times 10^9/l$ with an eosinophilia of 38%). Biopsy of his bone marrow

showed this to be hypercellular with moderate eosinophilia but there was no evidence of a neoplastic process. In spite of high doses of oral corticosteroids (80 mg/day) his condition failed to improve. On 15 February 1979 he developed an itchy maculopapular, bluish-red, tender rash over the flexor aspect of both lower limbs and over the palms. This diffuse involvement of the skin later evolved into a petechial eruption over the legs. Biopsy of skin and underlying muscle of one of these areas showed no evidence of periarteritis nodosa. Over the next 2 weeks there was slow deterioration of the patient's condition with clinical evidence of a multiplex mononeuropathy. The patient first complained of numbness and later complete anaesthesia of the left foot, weakness of both upper and lower limbs and loss of sensation in his hands. Clinical examination confirmed the loss of sensation; the wrist and ankle jerks were also completely absent. Repeated ESR estimations and eosinophil counts showed these to be consistently elevated in spite of high oral and parenteral corticosteroid therapy. A series of ECGs taken at this time showed widening of the QRS complex and slurring of the downstroke of the R wave mainly in leads I, II and AVF, changes which were absent before and consistent with cardiac involvement. A number of chest X-rays taken during his last stay in hospital showed flitting soft shadows appearing first in the right upper zone, then in the left lower zone and again in the right lower and left middle and lower zones. These shadows had disappeared by the time chest X-rays were taken on 24 February and 6 March 1979. These showed clear lung fields and a heart shadow which was not enlarged. There was never any evidence of renal or hepatic dysfunction. His blood pressure remained normal throughout. His leucocyte count on 6 March 1979 was $36 \times 10^9/l$ with an eosinophilia of 41%; his ESR was 66 mm/hr. The following day he developed fast atrial fibrillation with multiple ventricular ectopic beats and died suddenly. Permission to perform a post-mortem was refused.

Discussion

The hypereosinophilic syndrome affects predominantly young adults and middle-aged men (20–45 years). As is the case with other syndromes of undetermined aetiology, the hypereosinophilic syndrome has boundaries which are still blurred and largely indistinct. Owing to its apparent heterogenous nature involving a number of different organs and systems, the syndrome had previously been given various names, each indicating a specific characteristic of the condition. When the term was first introduced by Hardy and Anderson in 1968 it included a whole list of diseases ranging from the benign self-limiting Löffler syndrome to conditions

of longer duration, more widespread involvement and more serious prognosis including Löffler's endomyocarditis, disseminated eosinophilic collagen disease and eosinophilic leukaemia. Subsequently Löffler's syndrome has been omitted by various authors. It has been suggested that one should look upon the hypereosinophilic syndrome as some form of 'diagnostic catchall' (Beeson and Bass, 1977).

In 1975 Chusid and his colleagues established criteria in an attempt to define this syndrome. These criteria include a persistent eosinophilia of $1.5 \times 10^9/l$ for longer than 6 months, or death before 6 months associated with signs and symptoms of hypereosinophilic disease, lack of evidence of known causes of eosinophilia, and multiple organ involvement. Both the present patients satisfied these criteria. The heart and bone marrow are most frequently involved but the CNS, skin and muscle, the gastrointestinal tract including liver, lungs, kidneys and the lymphatic system have all been commonly reported to be affected. Initial observations indicated a uniformly grave prognosis (Benvenisti and Ultmann, 1969; Roberts, Liegler and Carbone, 1969; Chusid *et al.*, 1975). Recent reports however suggest a more variable course, with a more favourable outcome in certain cases (Resnick and Myerson, 1971; Parillo, Fauci and Wolff, 1978; Bush *et al.*, 1978). Grave prognostic signs are said to include a total white cell count greater than $100 \times 10^9/l$, eosinophil myeloblasts in the peripheral blood, the presence of leukaemic markers and the appearance of congestive heart failure (Parillo *et al.*, 1978). Cardiac disease has been implicated as the major cause of death in this syndrome.

The first patient seems to fit in the small group of patients who have been reported as having a relatively benign form of the disease compatible with a mild prolonged course. As he had no evidence of significant progressive organ involvement he received no treatment, but is being carefully and regularly followed-up. Parillo has reported following-up 5 similar cases, for a period of 1-9 years, who all did well clinically without being treated. High doses of corticosteroids have been used to treat cases with severe multi-organ involvement, resulting in variable responses. In general, the following characteristics have been found useful in predicting good responses to corticosteroid therapy: the presence of angioedema; elevated serum IgE levels; and a prolonged eosinopenic response to single-dose challenge with prednisolone (Parillo *et al.*, 1978). Busulphan, chlorambucil, 6-mercaptopurine and methotrexate have all been tried and found to have no significant effect. It has been claimed that hydroxyurea has

achieved good results in treating patients unresponsive to corticosteroid (Parillo *et al.*, 1978). The present authors had no opportunity to try using hydroxyurea in their second case. Dramatic improvement has also been reported in a single case by using a continuous-flow cell separator to remove circulating eosinophils (Ellmann, Miller and Rapoport, 1974).

It appears that the hypereosinophilic syndrome embraces a spectrum of disease entities. It is perhaps best regarded as a clinical and pathological continuum of conditions reflecting a hypersensitivity or autoimmune process and which seem to range from the benign to the rapidly fatal forms, having as their common denominator infiltrative eosinophilia (Parillo *et al.*, 1979). The causative mechanisms underlying this syndrome, in particular the role of the eosinophil and the nature of the cause or effect relationships of this cell, are still largely unknown and remain to be determined.

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