CASE REPORT

Fulminant idiopathic hypereosinophilic syndrome

FH Ng, HL Kong, WF Ng, KY Lam, CC Chan, CM Chang

We report a patient with rapidly fatal idiopathic hypereosinophilic syndrome presenting with tetraparesis and acute congestive heart failure. Post-mortem examination showed extensive myocardial necrosis but no pathology in the brain. The possible mechanisms leading to organ damage and the treatment of this condition are discussed.

HKMJ 1995;1:150-152

Key words: Eosinophilia; General paralysis; Congestive heart failure; Myocarditis

Introduction

Mild peripheral blood eosinophilia is not an uncommon laboratory finding. In most cases, it is asymptomatic and an underlying parasitic infestation, drug allergy, or systemic allergic disease can be found. Severe hypereosinophilia on the other hand is uncommon, one of the causes being the idiopathic hypereosinophilic syndrome (HES). This usually has an insidious onset and follows a chronic course.[1] Rapidly fatal presentation is a rare event.

Case report

A 44-year-old Chinese woman was admitted with weakness of the left upper and right lower limbs and repeated vomiting of one day's duration. The patient had had a generalised skin rash for the previous three years and was receiving topical corticosteroid treatment. A blood test was not performed. There was no history of allergy and she was not taking any oral medication. Prior health had been otherwise unremarkable.

Ruttonjee Hospital, 266 Queen's Road East, Hong Kong
Department of Medicine
FH Ng, MB, BS, MRCP
HL Kong, MB, BS, MRCP
CC Chan, MB, BS, MRCP
CM Chang, MB, BS, FRCPE
Department of Pathology
WF Ng, MB, BS, MRCPath
Department of Pathology, Queen Mary Hospital, Pokfulam, Hong Kong
KY Lam, MB, BS
Correspondence to: Dr CM Chang

Examination revealed satisfactory general condition, a generalised erythematous maculopapular rash, tachycardia with a heart rate of 100 beats per minute, moderate weakness of the left upper and right lower limbs, and bilateral Babinski sign. The rest of the examination was normal. Blood haemoglobin was 12.4 g/dL, WBC 51 x 10^9/L (neutrophils 38%, lymphocytes 8%, eosinophils 48%, monocytes 6%), platelets 159 x 10^9/L, and an ESR of 84 mm. A peripheral blood smear showed mature-looking eosinophils. Serum electrolytes were normal, however, the serum urea (22.5 mmol/L), creatinine (770 mmol/L), creatine phosphokinase (1494 mmol/L), and lactate dehydrogenase (1317 mmol/L) levels were markedly elevated. Routine liver biochemistry was normal apart from mildly

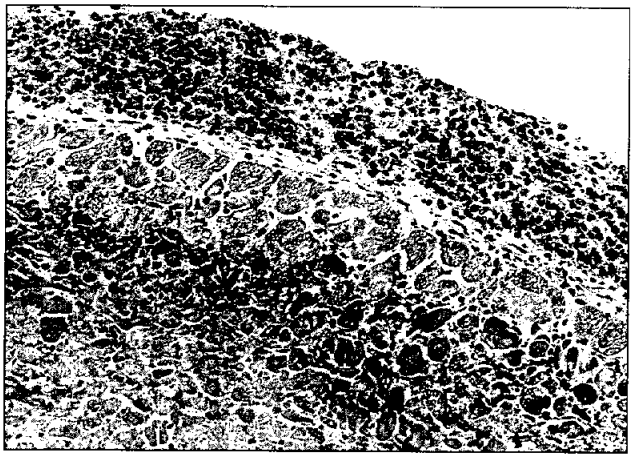

Fig 1. Infiltration of the endocardium by a large number of eosinophils and polymorphonuclear leukocytes. Myocardial necrosis is evident (x 50).

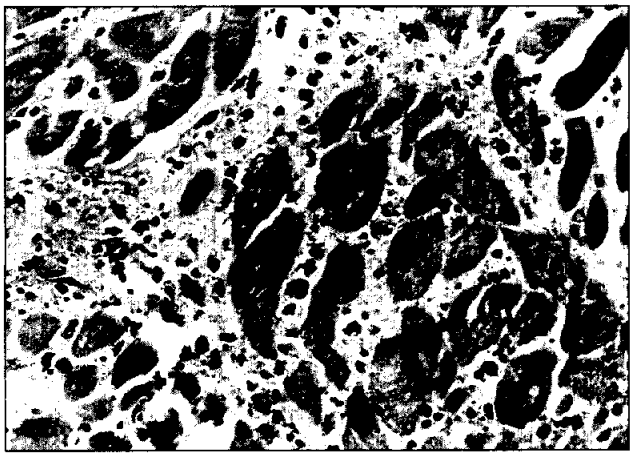

Fig 2. Infiltration of the myocardium by eosinophils and polymorphonuclear leukocytes. Myocardial necrosis is evident (x 250).

elevated alanine aminotransferase levels. Various serum autoantibodies (antinuclear factor, anti-double-stranded-DNA, anti-neutrophil cytoplasmic antibody) were negative and C3, C4 levels were within normal limits. Chest radiography was unremarkable but electrocardiography showed poor R wave progression over V2 and V3 leads.

The patient's weakness progressed rapidly to involve all four limbs over the next day but there was no level to sensory loss. Computerised tomography of the brain was not performed because the patient developed acute pulmonary oedema. Echocardiographic examination showed severe global hypokinesia with a left ventricular ejection fraction of 26% only. There was no evidence of mural thrombus or abnormal echo intensity. Lumbar puncture yielded clear cerebrospinal fluid with opening pressure of 15 cm water, normal cell count, protein, and glucose levels, and negative culture for organisms. Skin biopsy histology results were normal with no abnormal cellular infiltration or vasculitis seen. Intravenous hydrocortisone (100 mg every six hours), frusemide, nitroglycerin, and dopamine infusions were given. The absolute eosinophil count fell from 24.5 to 1.8 x 10^9/L one day after the hydrocortisone was commenced. Despite the institution of peritoneal dialysis and artificial ventilation, the patient's conditon continued to deteriorate and she died three days after admission.

Post-mortem examination revealed a very active eosinophilopoeisis in the bone marrow, with no increase in blast cells. The myeloid to erythroid ratio was 15:1. Eosinophils in various stages of maturation comprised 50% of the white cell series; the remainder consisted of promyelocytes (3%), myelocytes (9%), metamyelocytes (8%), neutrophils (25%), and lymphocytes (5%). The erythroid and megakaryocyte series were normal. In the left ventricle of the heart, numerous small yellowish-white necrotic areas were found. In these areas, both the endocardium (Fig 1) and the myocardium (Fig 2) were infiltrated with large numbers of eosinophils and polymorphonuclear neutrophil leukocytes. Necrosis of myofibrils and thrombosis of small blood vessels were visible. Coronary arteries showed mild atherosclerosis only. There was no vasculitis, mural thrombus, or myocardial fibrosis evident. The lungs and spleen were similarly heavily infiltrated with eosinophils. Despite a very careful search, no gross or histological abnormality could be found in the brain. The kidneys showed no eosinophil infiltration but did show changes of chronic pyelonephritis and benign nephrosclerosis. No parasitic infestation was observed in any of the organs examined.

Discussion

The diagnosis of HES requires a sustained blood eosinophilia of greater than 1.5 x 10^9/L for longer than six months, and the exclusion of all known causes of eosinophilia. Because of the very short history, application of the six-month criteria was not possible with our patient. Although allergic and connective tissue diseases can be excluded based on the history and negative serology, other important differential diagnoses were only excluded after the post-mortem examination. Since there was no evidence of either helminthic parasitic infestation, necrotising vasculitis, extravascular granuloma (Churg-Strauss syndrome), lymphoma, leukaemia, or carcinoma, the most likely diagnosis is HES. The only other possibile diagnosis is that of an early eosinophilic malignancy. In the absence of chromosome studies, this question cannot be properly addressed.

Cardiac involvement is seen in 58% of patients with HES[1] and was the direct cause of death in our patient. It is the most important factor associated with morbidity and mortality. The earliest pathological change is thought to occur in the endocardium, however, the exact mechanism causing it is unknown. A specific eosinophil granule protein (major basic protein) has been held responsible because it can inhibit the growth of aortic endothelial cells.[2] The changes usually evolve over several months, going through stages of endocardial damage, myocardial necrosis, mural thrombi formation, and finally, endomyocardial fibrosis.[3] Acute myocardial necrosis resulting in early death is rare.[4] However, a very high absolute eosinophil

count—as was seen in our patient—may be associated with a particularly poor outcome.[5]

While eosinophilia from diverse aetiologies may result in the same cardiac disease, not all patients with sustained eosinophilia have cardiac involvement. Therefore, some as yet undefined local factor is probably necessary for eosinophil recruitment and activation to commence.[1] The same is probably true for the other organs and may explain why the kidneys were not infiltrated by eosinophils in this patient. Although chronic pyelonephritis could account for her uraemia, we believe it was incidental and not caused by her HES.

Neurologic involvement is also common, occurring in 54% of patients.[1] Three patterns of involvement are recognised.[6] One comprises primary central nervous system (CNS) involvement which presents with changes in behaviour, confusion, ataxia, memory loss, and upper motor neuron signs. As the disease was so rapidly fatal in our patient, there was probably no time to develop this full-blown picture. Moreover, any encephalopathy could have been overshadowed by the acute pulmonary oedema. As with our post-mortem finding, autopsies in four other patients failed to identify any pathology in the brain.[7] It is possible that an intact blood-brain barrier prevented direct infiltration by eosinophils, but could not prevent the diffusion of eosinophil-derived toxins. Two specific eosinophil granule proteins (eosinophil-derived neurotoxin, eosinophil cationic protein) have been shown to be neurotoxic in experimental animals,[8] but their relationship with human CNS damage is still unclear.[1] Apart from primary CNS involvement, patients may also present with embolic transient ischaemic attack or stroke, secondary to the formation of cardiac mural thrombi. A diffuse polyneuropathy or mononeuritis multiplex may also be encountered.

High dose corticosteroid was given,[1] as recommended for HES patients with organ involvement. The rapid fall in the eosinophil count was consistent with previous reports and suggests a redistribution of circulating eosinophils into the spleen or lymph nodes.[9] Interference with eosinophilopoeisis or eosinophil death probably occurs at a later stage. With the use of corticosteroids, short term improvement in myocardial function has been reported,[10] however, progressive cardiomegaly and endomyocardial fibrosis may not be prevented in all cases.[11] Judging from the recent, but extensive, degree of myocardial necrosis found in this patient, any other forms of treatment including hydroxyurea, vincristine, alkylating agents, alpha interferon, cyclosporin, leukapheresis, or even cardiac surgery would not be expected to have altered the outcome. The normal skin biopsy was unexpected, but could be due to previous topical corticosteroid treatment. It is unfortunate that a further skin biopsy was not taken during the post-mortem examination. However, we believe that the chronic skin rash was almost certainly a manifestation of the HES. The survival of HES patients has improved significantly in recent years, due primarily to earlier diagnosis, intensive monitoring, the prompt introduction of chemotherapeutic agents, and timely cardiac surgery.[1] Cardiac transplantation may be another alternative but we are not yet aware of any reports in the literature. In this context, the outcome for our patient might have been different, had she been referred to us sooner.

References

1. Weller PF, Bubley GJ. The idiopathic hypereosinophilic syndrome. Blood 1994;83:2759-79.
2. Wassom DL, Loegering DA, Solley GO, et al. Elevated serum levels of the eosinophil granule major basic protein in patients with eosinophilia. J Clin Invest 1981;67:651-61.
3. Brockington IF, Olsen EG. Loffler's endocarditis and Davies' endomyocardial fibrosis. Am Heart J 1973;85:308-22.
4. Davies J, Spry CJ, Sapsford R, et al. Cardiovascular features of 11 patients with eosinophilic endomyocardial disease. Q J Med 1983;52:23-39.
5. Parrillo JE, Fauci AS, Wolff SM. Therapy of the hypereosinophilic syndrome. Ann Intern Med 1978;89: 167-72.
6. Patricia MM, Harley JB, Fauci AS. Neurologic dysfunction in the idiopathic hypereosinophilic syndrome. Ann Intern Med 1985;102:109-14.
7. Spry CJ. Eosinophils: a comprehensive review and guide to the scientific and medical literature. 1st ed. Oxford: Oxford University Press, 1988.
8. Gleich GJ, Loegering DA, Bell MP, Checkel JL, Ackerman SJ, McKean DJ. Biochemical and functional similarities between eosinophil-derived neurotoxin and eosinophil cationic protein: homology with ribonuclease. Proc Natl Acad Sci USA 1986;83:3146-50.
9. Sabag N, Castrillon MA, Tchernitchin A. Cortisol-induced migration of eosinophil leukocytes to lymphoid organs. Experientia 1978;34:666-7.
10. Uetsuka Y, Kasahara S, Tanaka N, et al. Hemodynamic and scintigraphic improvement after steroid therapy in a case with acute eosinophilic heart disease. Heart Vessels 1990; Suppl 5:8-12.
11. Christen R, Morant R, Schneider J, Jenni R, Fehr J. Progressive dilated cardiomyopathy in a patient with longstanding and complete prednisone-induced hematological remission of idiopathic hypereosinophilic syndrome. Wien Klin Wochenschr 1989;67:358-65.