Acute necrotising eosinophilic myocarditis

CHARLES A HERZOG, DALE C SNOVER, NANCY A STALEY

From the Departments of Medicine (Cardiovascular Section) and Laboratory Medicine and Pathology, University of Minnesota Hospitals, and the Department of Pathology, Veterans Administration Medical Center, Minneapolis, Minnesota, USA

SUMMARY Löffler's endocarditis is a recognised complication of diseases associated with eosinophilia. Eosinophilic heart disease is usually chronic, but there is a rare acute variety. Three patients with an unusual form of eosinophilic heart disease characterised by acute necrotising eosinophilic myocarditis after a possible initial viral infection and underlying allergic diathesis are reported. In contrast to previously reported cases of acute Löffler's endocarditis there was no notable extracardiac pathology.

The association of eosinophilia and heart disease has been well documented,¹ and cardiac involvement may be a major complication.²⁻⁷ Brockington and Olsen⁸ and Baandrup⁹ have proposed a unitarian hypothesis of eosinophilic heart disease, with the degree of chronicity affecting the clinical manifestations. Davies's endomyocardial fibrosis may be a chronic variety of Löffler's endocarditis.¹⁸⁻¹⁰ A rare "acute necrotic" stage of Löffler's endocarditis characterised by eosinophilic pancarditis, muscle necrosis, and arteritis with a short duration of symptoms of a few weeks has also been reported.^{8,9}

Previous descriptions of acute Löffler's endocarditis have been in the clinical setting of systemic disease with extracardiac involvement, such as the hypereosinophilic syndrome,^{6,7,11} eosinophilic leukaemia,⁸ polyarteritis nodosa,^{12,13} reaction to anti-tuberculous drugs,¹⁴ bronchial asthma,^{9,15,16} and biliary tract carcinoma.¹⁷

We report three patients with fulminant acute necrotising eosinophilic myocarditis occurring without notable extracardiac pathology.

Patients and methods

CASE 1

A previously healthy 34 year old white man developed mid-epigastric pain during the third week of April 1982, and cimetidine was prescribed. One week later

he developed fever, malaise, myalgia, and headache. The leucocyte count was 11.0×10^9 cells/l with 6% eosinophils. Erythromycin was prescribed. He had persistent fatigue and fever and was admitted to a hospital on 5 May 1982 with a diagnosis of viral infection. His medical history included peptic ulcer and seasonal allergic rhinitis, which typically began in April. He had taken antihistamine drugs for three weeks before admission. There was no history of travel outside of Minnesota, pork ingestion, or exposure to animals. The physical examination on admission was remarkable only for right upper quadrant tenderness. Examination of the chest and heart was normal. His previous medications were withdrawn.

The Table shows the laboratory findings. The erythrocyte sedimentation rate (Westergren) was 32 mm in the first hour. The urine analysis was normal, as was the chest radiograph. An electrocardiogram on 8 May 1982 showed sinus tachycardia and slight right axis deviation. Additional laboratory data included serum alanine transaminase (glutamic pyruvic transaminase) 245 U/l (normal 8-30 U/l), lactic dehydrogenase 375 U/l (normal 38-210 U/l), and creatine phosphokinase 261 U/ml (normal 30-170 U/ml). Tuberculin skin (purified protein derivative) test, hepatitis A and B serologies, *Trichinella* serology, fluorescent antinuclear antibody, and Monospot tests were negative. Stool examination for ova and parasites and four sets of blood cultures were negative.

The patient became severely dyspnoeic, and his condition deteriorated rapidly. A diastolic gallop and inspiratory crepitations were new findings. The chest radiograph on 9 May 1982 showed bibasilar infiltrates. The leucocyte count was 20×10^9 /l with

Requests for reprints to Dr Charles A Herzog, University of Minnesota Hospitals, Box 508 Mayo Memorial Building, Minneapolis, Minnesota 55455, USA.

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Table Laboratory results for cases 1 and 2

	Case 1		Case 2
	On admission	After 8 days	
Haemoglobin concentration (g/dl)	16.5	15.2	17.6
Leucocyte count ($\times 10^9/l$)	20.1	14.0	20.5
Neutrophils (%)	58	76	70
Band forms (%)	17	5	—
Monocytes (%)	1	2	1
Lymphocytes (%)	5	12	27
Eosinophils (%)	19	4	1
Metamyelocytes (%)	—	1	—
Basophils (%)	—	—	1
Platelet count ($\times 10^9/l$)	—	749	—
Serum concentrations:			
Glucose (mmol/l)	7.5	—	10.6
Sodium (mEq/l)	—	—	129
Potassium (mEq/l)	—	—	5.2
Bicarbonate (mEq/l)	—	—	15
Chloride (mEq/l)	—	—	92
Calcium (μ mol/l)	—	—	2.04
Phosphorus (mmol/l)	—	—	0.77
Bilirubin (μ mol/l)	17.1	—	—
Creatinine (μ mol/l)	123.7	—	—
Albumin (g/l)	33	—	34
Uric acid (mmol/l)	0.36	—	1.07
Total protein (g/l)	63	—	—
Alkaline phosphatase (U/l)	282	—	222
Lactate dehydrogenase	—	—	368
Aspartate aminotransferase (U/l)	282	—	2505
Cholesterol (mmol/l)	4.2	—	—
Total thyroxine (nmol/l)	74.6	—	—
Amylase (IU/l)	58	—	—
Blood urea nitrogen (mmol/l)	—	—	24.2

Conversion: SI to traditional units—glucose: 1 mmol/l $\approx$ 18 mg/dl; calcium: 1 μ mol/l $\approx$ 4.0 mg/dl; creatinine: 1 μ mol/l $\approx$ 0.01 mg/dl; bilirubin: 1 μ mol/l $\approx$ 0.05 mg/dl; uric acid: 1 mmol/l $\approx$ 16.8 mg/dl; cholesterol: 1 mmol/l $\approx$ 38.6 mg/dl; thyroxine: 1 nmol/l $\approx$ 0.07 μ g/dl; phosphorus: 1 mmol/l $\approx$ 3.1 mg/dl; blood urea nitrogen: 1 mmol/l $\approx$ 2.6 mg/dl.

40% eosinophils. Prednisone 60 mg/day, digoxin, and frusemide were given with transient symptomatic improvement. The leucocyte count on 11 May 1982 was $16.3 \times 10^9/l$ with 13% eosinophils, many of which were hypersegmented, and rare eosinophils were partially degranulated. A bone marrow examination showed a normocellular marrow with a pronounced increase in mature eosinophils.

When transferred to the coronary care unit on 14 May 1982 he was gravely ill with severe respiratory distress. His temperature was 37.7°C, pulse 120 beats/min and regular, blood pressure 82/60 mm Hg without pulsus paradoxus, and respiratory rate 32/min. Crepitations were present in both lung fields. A loud diastolic and presystolic gallop were present; there were no murmurs or pericardial rubs. Central venous pressure was estimated at 18 cm of water by neck veins, and hepatojugular reflux was present. The liver was enlarged and there was mild ankle oedema. The pertinent laboratory data are given in the Table. Coagulation tests and serum electrolyte concentra-

tions were normal. The electrocardiogram showed left bundle branch block. M mode echocardiography showed a small posterior pericardial effusion. The left ventricular posterior wall and interventricular septal thicknesses were 18 mm. A cross sectional echocardiogram showed a small posterior pericardial effusion, concentrically increased thickness of the left ventricle, global reduction of systolic performance, and normal chamber size. Shortly after admission he developed ventricular fibrillation and could not be resuscitated.

Necropsy findings

Notable changes were confined to the heart, which weighed 550 g. The right and left ventricular wall thicknesses were 0.6 cm and 1.8 cm respectively. The pericardium was unremarkable. The endocardium was not fibrotic, and no mural thrombi were present. The myocardium showed a diffuse yellow-white discoloration with a mild preponderance for the subendocardial region, although the process was transmural (Fig. 1). The cardiac valves and coronary arteries were normal.

Microscopical examination showed diffuse infiltration of the myocardium of both ventricles and atria by eosinophils and fewer lymphocytes, plasma cells, and immunoblasts. The eosinophils were atypical with hypersegmented nuclei and were partially degranulated (Fig. 2). There was diffuse myocardial necrosis. Although giant cells were found in some areas, there were no granulomata. There was no evidence of arteritis. Microscopical examination of the liver, bone marrow, and lymph nodes did not show eosinophilic infiltration. Cultures of serum and heart for viruses were negative.

CASE 2

A 47 year old white male food produce handler in

Fig. 1 Case 1. Morphological appearance of the heart at necropsy (weight 550 g). Showing mottling of the myocardium of both right and left ventricles. The endocardium is unremarkable.

Fig. 2 Case 1. Histological section of the heart showing mixed infiltrate containing lymphocytes, plasma cells, and eosinophils, some of which are hypersegmented (arrow) and partially degranulated. The hypersegmented cells were negative by the chloroacetate esterase stain, confirming that they were not neutrophils (haematoxylin and eosin $\times 1200$).

good health developed a cough and low grade fever on 28 August 1973. His medical history was remarkable only for borderline hypothyroidism, treated with levothyroxine 0.1 mg/day. A chest radiograph on the next day was normal, and his physician prescribed ampicillin and promethazine syrup for bronchitis. The patient developed a generalised erythematous rash and dyspnoea on 10 September 1973. The ampicillin was withdrawn and diphenhydramine was given with a resolution of symptoms. He felt well until 24 September 1973, when he developed exertional fatigue and dyspnoea. Two days later, he became rapidly progressively dyspnoeic and orthopnoeic with nausea and vomiting and was admitted to hospital the following day. There was no history of recent travel, pork ingestion, or exposure to ill persons or animals.

On physical examination on admission he was acutely ill and cyanosed with respiratory distress. His temperature was 38°C, pulse 128 beats/min and regular, blood pressure 110/60 mm Hg with a paradoxical pulse of 20 mm Hg. The chest was clear, and heart sounds were indistinct. The liver was tender and enlarged. There was no oedema.

Laboratory findings on admission are shown in the Table. The urine analysis showed 1+ proteinuria. Blood and urine cultures were negative. The electrocardiogram was normal apart from sinus tachycardia. The chest radiograph showed cardiomegaly and Kerley B lines.

An emergency pericardiocentesis yielded 150 ml of amber fluid, and there was immediate relief of symptoms. Analysis of the fluid showed a leucocyte count

of 10.5×10^9 cells/l (differential cell count not performed) and 9.9×10^9 /l red blood cells with 57 g/l of protein. Cultures for bacteria, fungi, and acid fast bacilli were negative. Tetracycline, digoxin, and frusemide were given. On 28 September 1973 right bundle branch block was noted on the electrocardiogram. A repeat leucocyte count was 15.2×10^9 cells/l (81% neutrophils, 10% lymphocytes, 1% monocytes, 1% basophils, and 7% eosinophils). The patient's condition rapidly deteriorated. The next day an emergency anterior pericardiectomy was performed since pericardiocentesis failed to produce haemodynamic improvement. The patient sustained a cardiac arrest during the procedure and could not be resuscitated.

Necropsy findings

The heart weighed 550 g. The myocardium was flabby with large irregular tannish areas involving the full thickness of walls of all four cardiac chambers. There was no evidence of endocardial fibrosis and mural thrombi were absent. The valves and coronary arteries were normal. Microscopical examination showed a diffuse infiltrate of the myocardium with associated cardiac necrosis. The infiltrate was composed largely of normal eosinophils, but there were some lymphocytes and plasma cells (Fig. 3). In focal areas there were micro abscesses composed of eosinophils, polymorphonuclear cells, and occasional giant cells. There were no granulomata and no arteritis. Other necropsy findings included small aggregates of eosinophils in a peribronchial location in the lung and scattered eosinophils in the spleen. There was also extramedullary haematopoiesis in the spleen. The liver showed passive congestion and centrilobular fatty change but no eosinophilic infiltrate.

CASE 3

This patient was briefly described in an earlier report.¹⁸ A 7 year old white girl in good health developed a sore throat, headache, and fever in early February 1974 with resolution of her symptoms in three days. Her medical history was unremarkable. Her mother and nephew had asthma. Her maternal uncle and a brother had allergic rhinitis. Her father died of a probable myocardial infarction aged 49 years. Her maternal grandmother died of tetanus aged 49 years. On 26 February 1974 she experienced anorexia, fatigue, and fever. Antibiotics were prescribed for presumed bronchitis. Two days later she complained of chest pain. On 2 March 1974 she felt much worse with dyspnoea, fatigue, cough, and headache. The following morning she awoke from sleep with acute dyspnoea and suffered a cardiopulmonary arrest. Attempts at resuscitation were unsuccessful.

Fig. 3 Case 2. Histological section of the heart showing diffuse infiltrate of the myocardium with relatively diffuse necrosis (haematoxylin and eosin $\times 100$). Insert: The infiltrate consists of a mixture of eosinophils, lymphocytes, and plasma cells with eosinophils predominating (haematoxylin and eosin $\times 480$).

Necropsy findings

Findings at necropsy were predominantly confined to the heart. The heart weighed 150 g (normal 100 g). The epicardium was translucent. The endocardium was smooth with slightly raised underlying whitish plaques, but there were no mural thrombi. The myocardium showed a diffuse whitish mottling with focal accentuation resulting in plaque like areas measuring 2–15 mm in diameter. The valves and coronary arteries were normal. Microscopically, the heart showed a diffuse mixed inflammatory infiltrate composed of eosinophils and lymphocytes and sparse polymorphonuclear cells. The eosinophils were morphologically unremarkable. There was myocardial necrosis associated with this infiltrate, and occasional myocardial giant cells were identified. There was no vasculitis nor granulomata.

Additional findings included a mild interstitial pneumonitis and focal peribronchiolar aggregates of eosinophils. The marrow was mildly hypercellular but with a normal number of eosinophils. There was no eosinophilic infiltration of any other organ. Postmortem viral cultures of the heart and serum were negative. Serum titres for mumps, herpes virus, psittacosis, mycoplasma, and influenza A and B were negative; adenovirus complement fixation titre was 1/32.

Discussion

These cases do not fall into the conventional spectrum of eosinophilic heart disease. They appear to share several important features which set them apart from

previously reported examples of the “acute necrotic” stage of Löffler’s endocarditis. Clinically, all three patients were previously healthy and had clinical evidence suggesting an initial viral infection, although there were no objective laboratory data confirming this. The illness was short, ranging from 18 to 32 days from the onset of symptoms of presumed viral infection. Cardiac decompensation was fulminant with death occurring 5–7 days after the onset of dyspnoea (in cases 1 and 2) or reappearance of fatigue (in case 3). These patients shared an allergic diathesis: active allergic rhinitis (case 1), development of a rash while taking ampicillin (case 2), and a family history of allergic rhinitis and asthma (case 3). Serum IgE concentrations would have been of interest but were unfortunately not measured, and postmortem serum is unavailable for all three patients. Interestingly, two of the patients stopped taking antihistamines before they developed cardiac dysfunction. Significantly, the predominant pathological process was limited to the heart, and the degree of peripheral eosinophilia did not necessarily correlate with the degree of cardiac damage, as illustrated by case 2.

Although all three patients had taken oral antibiotics, their illness does not meet the usual criteria of drug induced hypersensitivity myocarditis. In their analysis of 24 cases of hypersensitivity myocarditis, Fenoglio *et al* reported that none of their patients were critically ill at the time of their unexpected deaths.¹⁹ Moreover, frank cellular necrosis was an uncommon pathological finding at postmortem examination. In contrast, the patients in cases 1 and 2 died with severe myocardial dysfunction, and all three had myocardial

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necrosis. Finally, no evidence of vasculitis or vascular involvement was seen in these patients in contradistinction to cases of drug hypersensitivity. This contrasts with the case report of Lie and Hunt, whose patient was taking methyldopa,²⁰ an agent strongly implicated as a cause of hypersensitivity myocarditis.^{19, 21} Eight of 24 patients in the series of Fenoglio *et al* were taking methyldopa.¹⁹ Half of their patients had an inflammatory eosinophilic hepatitis, but the others had only cardiac pathology. Lie and Hunt's patient had fibrinoid necrosis of small blood vessels, an intense inflammatory infiltrate, and focal myocardial necrosis—all consistent with hypersensitivity myocarditis—contrasting with the diffuse myocardial necrosis and absence of vasculitis found in our patients with acute necrotising eosinophilic myocarditis.

The initial phase of the illness in our patients may have started with a relatively mild viral infection, yet the type of intense necrotic eosinophilic myocarditis seen has not been previously reported in viral myocarditis, which has a predominantly mononuclear cell infiltrate.²² It also differs strikingly from the benign course of the patient reported by Inoh *et al* with clinically diagnosed perimyocarditis and peripheral eosinophilia.²³ The pathophysiology is obscure but is perhaps related to the selective deposition of viral antigen–host antibody complex in the heart and release of vasoactive materials (such as histamine) with chemotaxis and subsequent activation of eosinophils.²⁴ The persistent presence of large numbers of degranulated eosinophils in the blood may be an important hallmark of Löffler's endomyocardial disease, and the release of eosinophil granule contents may cause cardiac disease.^{25, 26} Spry *et al* reported that 12 of their 15 patients with hypereosinophilic syndrome had large numbers of degranulated blood eosinophils, and in all patients they detected some abnormally degranulated cells.⁶ Abnormally degranulated eosinophils in the myocardium were seen only in case 1, but the transient presence of degranulated blood eosinophils could have been missed in the other two patients. (Furthermore, pathological material for examination by electron microscopy was unavailable for any of our patients, thus we may have failed to identify degranulated tissue eosinophils.)⁷ Once activated, the eosinophil is biochemically well equipped to cause tissue necrosis²⁷; eosinophil major basic protein may play an important role in cell death.²⁸ A similar mechanism may explain the pathophysiology in the interesting report of Popper *et al*, who described a case of IgA₂ alveolitis and eosinophilic pneumonia with systemic eosinophilic involvement, including coronary arteritis and myocarditis.²⁹

A more thorough understanding of our patients' illness is hindered by the retrospective nature of our

study. Spry *et al* and Davies *et al* described serial studies in 15 patients with hypereosinophilic syndrome, of whom five had histologically confirmed "acute necrotic" Löffler's endocarditis.^{6, 7} The duration of illness of these five patients ranged from 0.8 to 11.5 years, contrasting with the fulminant clinical deterioration of our previously healthy patients. Nine patients were studied by echocardiography, and Davies *et al* concluded that amplitude processed cross sectional echocardiography was useful in assessing the extent, severity, and evolution of eosinophilic endomyocardial disease.³⁰ Only one of our patients was evaluated by cross sectional echocardiography, and the findings were consistent with a diffuse infiltrative cardiomyopathy. The rapid fatal progression of disease in our patients would not have allowed serial antemortem diagnostic studies. Finally, steroids, anticoagulants, and antiplatelet drugs have been advocated in the treatment of acute necrotic eosinophilic endomyocardial disease.⁷ One of our patients was treated empirically with prednisone but without any apparent benefit.

In summary, our patients had an unusual variant of Löffler's endocarditis characterised by acute necrotising eosinophilic myocarditis after a possible initial viral illness and underlying allergic diathesis.

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