Clinical, haemodynamic, and angiographic findings in Löffler's eosinophilic endocarditis

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Detailed haemodynamic and angiographic findings in Löffler's endocarditis are presented for the first time in a report of 3 cases of this rare disease. In 2 of the cases the right ventricular cavity was obliterated; in one of them this was shown by biopsy to be caused by organized thrombus. In the third case, there was progressive mitral regurgitation.

Since Löffler (1936) described 2 cases of fibrous endocarditis there have been occasional reports of this rare condition. Reinbach (1893) anticipated Löffler's findings with a report of a woman with eosinophilia in whom greyish-white mural thrombus was found on the right ventricular endocardium at necropsy. Brockington and Olsen (1973), in a survey of the published reports, found 87 cases with a post-mortem diagnosis of Löffler's endocarditis; they added 3 further cases. Two other cases, proved at necropsy, have been described (Rasche, Kelsch, and Weaver, 1973; Shepherd *et al.*, 1971).

The relation of Löffler's endocarditis to endomyocardial fibrosis is debated. Davies (1961) clearly distinguished the two on the basis of the systemic involvement and greater incidence of embolic phenomena in Löffler's disease. He noted that the cardiac lesions were similar but that in endomyocardial fibrosis they were usually confined to the inflow tract and rarely involved the middle or outer part of the myocardium. Roberts, Liegler, and Carbone (1969) and Brockington and Olsen (1973) suggest that the myocardial lesion in the two diseases cannot be distinguished histologically. The haemodynamic and angiographic findings in endomyocardial fibrosis are clearly defined (Somers *et al.*, 1968; Shillingford and Somers, 1961; Abrahams, 1962; Fowler and Somers, 1968; Cockshott, 1965). Physiological studies have been reported in only a few cases of Löffler's endocarditis (Roberts *et al.*, 1969; Davies, Deuchar, and Missen, 1965; Lennox, 1948; Clark, Valentine, and Blount, 1956; Nagy *et al.*, 1969; Gardner-Thorpe *et al.*, 1971; Van der Hauwaert, Corbeel, and Maldague, 1965). They

suggest that the haemodynamic characteristics of the two diseases are similar.

Though the combination of eosinophilia and unexplained heart failure may suggest the diagnosis, Löffler's endocarditis is rare and is seldom diagnosed before necropsy. We present comprehensive haemodynamic data in 3 cases in which the diagnosis was made in life.

Case reports

Case 1

A 56-year-old white man was seen in 1971 with symptoms of peptic ulceration. He had served in North Africa during the second world war and had had no illness at that time. He reported several attacks of soreness and swelling of the tongue relieved by chlorpheniramine. A routine blood test showed an eosinophilia (white blood cells $17.9 \times 10^9/l$, eosinophils 31%). Stool examination for parasites and serological tests for trichinella and toxocara were negative.

In mid-1972 he noted dyspnoea on exertion and an episodic irritating skin rash. Clinical examination showed a slightly raised jugular venous pressure, ankle oedema, a soft systolic murmur in the mitral area, and an enlarged liver. The spleen was not palpable. Abnormal results of investigations included a white blood cell count of $9.9 \times 10^9/l$ (eosinophils 25%) and the following immunoglobulin levels: IgG 16.30 g/l, IgA 1.06 g/l, and IgM 9.04 g/l. Protein electrophoresis showed a paraprotein band. Cold agglutinins were detected, and were found to be mixed IgG and IgM complexes. The Rose-Waaler titre was positive in a

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TABLE Cardiac catheterization data in 3 cases of Löffler's endocarditis

	Case 1	Case 2	Case 3
Body surface area (m ²)	1.84	1.77	1.56
Pressures (mmHg above sternal angle)			
RA	12/5 (mean 10)	a 13; x 4; v 11; y 4 (mean 8)	a 13; x 1; v 8; y 0 (mean 5)
RV	12/5	10/2	60/2-15
PA	12/5 (mean 10)	10/3 (mean 6)	60/30 (mean 37)
LA	a 6; x 2; v 5; y 3 (mean 5)	a 4; x 0; v 8; y 1 (mean 4)	a 18; x 17; v 48; y 17 (mean 26)
LV	95/7-12	95/0	105/0-18
Ao	95/75	95/60	105/74
Telco micromanometer data			
Sinus beat: max dP/dt (mmHg s ⁻¹)	1122	1620	1353
KVmax (s ⁻¹)	65	130	84
Post-ectopic beat: max dP/dt (mmHg s ⁻¹)	1440	2280	1535
KVmax (s ⁻¹)	100	380	93
Cardiac index (l/min per m ²)	2.2	2.2	2.8
Angiographic volumes (ml per m ²)			
EDV	59	98	173
ESV	26	42	87
SV	33	56	86
Ejection fraction (EDV s ⁻¹)	0.55	0.57	0.50
Normalized ejection rate (EDV s ⁻¹)	3.0	2.2	2.2
Angiography			
Left ventricular angiogram	Slightly thick-walled LV with smooth deformed apex; grade 1/4 early systolic mitral regurgitation	Normal	Slightly enlarged LV contracts well; grade 3/4 mitral regurgitation with left atrial systolic expansion
Aortogram	—	—	Grade 1/4 aortic regurgitation
Right ventricular angiogram	Gross tricuspid and pulmonary regurgitation with almost complete obliteration of RV apex and body, leaving only infundibulum opacified	Similar to Case 1	—
Coronary angiogram	Normal	Normal	50% narrowing of left anterior descending artery distal to first diagonal

Conversion factors from Traditional to SI Units: 1mmHg≈0.133 kPa.

dilution of 1:256. The latex titre was less than 1:20. No antinuclear antibodies were present. The serum complement level was normal. Chest x-ray examination, electrocardiogram, liver and lung scans, peripheral phlebograms, and 24-hour urinary 5-hydroxyindole-acetic acid (5-HIAA) excretion were normal. An echocardiogram showed a normal mitral valve but paradoxical septal motion; neither the right ventricle nor the tricuspid valve was identified. A bone marrow aspirate contained an increased number of eosinophils and their precursors. A needle liver biopsy specimen was infiltrated with histiocytes, lymphocytes, and eosinophils. A definite diagnosis was not made.

Over the next two years increasing breathlessness, fatigue, and ankle swelling developed. Despite increasing doses of diuretics, the heart increased in

size and there was a progressive rise in jugular venous pressure, with prominent v wave. The eosinophilia persisted and nodal rhythm developed. In January 1974 cardiac catheterization (Table and Fig. 1) showed identical pressures throughout the right heart chambers. Right ventricular angiography confirmed free tricuspid and pulmonary regurgitation with extensive obliteration of the right ventricular cavity (Fig. 2). Left ventricular endomyocardial biopsy showed focal areas of fibrosis in the myocardium, appearing in one area to extend to the endocardial surface; no eosinophils were seen. A diagnosis of Löffler's endocarditis was made and treatment started with corticosteroids, azathioprine, and anticoagulants. At the most recent follow up the patient was improved subjectively but the physical signs remained unchanged.

Case 2

The patient, a 48-year-old white man, had spent the first 34 years of his life in India. At the age of 24 he had malaria. He remained well until January 1974 when he noted ankle swelling and breathlessness. He was not orthopnoeic. Findings at another hospital were a raised jugular venous pressure, peripheral oedema, and hepatosplenomegaly. The eosinophil count was high (white blood cells $21.7 \times 10^9/l$, eosinophils 74%), and a bone marrow aspirate showed an excess of eosinophils and their precursors. He was treated with diuretics and transferred to this hospital with a provisional diagnosis of lymphoma or eosinophilic leukaemia.

On admission the jugular venous pressure was raised 15 cm, with equal a and v waves. The right ventricular impulse was palpable and in the tricuspid area there was a pansystolic murmur, a loud third sound, and a short diastolic murmur. Stool examination for ova and parasites was negative and serological tests were also negative. Chest x-ray film, electrocardiogram, lung scan, and 24-hour urinary 5-HIAA excretion were normal. An echocardiogram showed a normal mitral valve but paradoxical septal motion; the tricuspid valve was not

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FIG. 1 Right heart pressures: withdrawal record (Case 1)

(A)

(B)

FIG. 2 (A) Right ventricular cineangiogram: right anterior oblique projection (Case 1). (B) Line drawing of same frame

FIG. 3 *Right heart pressures: withdrawal record (Case 2)*

seen. Needle liver biopsy showed infiltration of some portal tracts with neutrophils and eosinophils.

Cardiac catheterization (Table and Fig. 3) showed severe tricuspid regurgitation and mild tricuspid stenosis, and the right ventricular cavity was almost totally obliterated (Fig. 4). Right ventricular endomyocardial biopsy showed only organized thrombus. A focal area of fibrosis was found in the left ventricular myocardium; the myofibrils appeared normal apart from myocytolysis in the fibrotic area; no eosinophils were seen.

A clinical diagnosis of Löffler's endocarditis was made and treatment with corticosteroids, azathioprine, and anticoagulants started.

The patient died from cardiac failure after eight months. Necropsy confirmed obliteration of the right ventricular cavity. There were firm adhesions between the tricuspid valve cusps and the right

ventricular endocardium; the valve itself was narrowed to a 2-cm orifice. There were a few small vegetations on the opposing surfaces of the mitral valve leaflets.

Case 3

The patient, a 47-year-old white man, presented in 1969 with a three-week history of abdominal pain. The only time he had spent abroad was during the second world war, when he served in the Middle East. He had splenomegaly and a high eosinophil count (white blood cells $17.4 \times 10^9/l$, eosinophils 64%). Investigations for parasites were negative, bone marrow aspirate showed an increase of neutrophil and eosinophil myelocytes and promyelocytes, and a needle liver biopsy showed infiltration of occasional portal tracts by lymphocytes and a few eosinophils. Atypical chronic myeloid or eosinophil

FIG. 4 Right ventricular angiogram: right anterior oblique (Case 2). This shows obliteration of most of body and apex of right ventricle

leukaemia was diagnosed and treatment with busulphan and prednisone begun.

A few months later, when he was readmitted with further splenic pain, an apical pansystolic murmur was noted for the first time. The heart was of normal size on chest x-ray examination and an electrocardiogram showed sinus rhythm with a mean frontal QRS vector of 0° . The eosinophilia was less. Treatment was started with azathioprine, chlorpheniramine, and diuretics in addition to corticosteroids. During the next two years the patient was admitted with pneumonia on one occasion and a retinal artery branch embolus on another. In mid-1971 he was readmitted in heart failure with signs of severe mitral regurgitation. There was clinical and radiographic evidence of an enlarged heart and pulmonary venous congestion. The electrocardiogram now showed a mean frontal QRS vector of -60° , left atrial hypertrophy, and a T-wave abnormality. An echocardiogram showed an enlarged left atrial dimension (4.9 cm) and a normal mitral valve.

Initially he responded to conventional treatment of heart failure, but in August 1973, after a progressive worsening of his symptoms, cardiac catheterization was performed. Severe mitral regurgitation, mild aortic regurgitation, a 50 per cent stenosis of the left anterior descending coronary artery, and moderate impairment of left ventricular function was found (Table). Endomyocardial biopsy was unsuccessful.

Mitral annuloplasty and a left anterior descending bypass graft procedure were performed at the National Heart Hospital (Mr. Donald Ross). The operation was technically difficult because of excessive friability of all the tissues. The mitral valve leaflets were floppy, with attenuated chordae, and the mitral ring was dilated. The histology of the rectus abdominis muscle, aorta, and internal mammary artery was normal. Myocardial biopsy was not done. The diagnosis of Löffler's endocarditis was thus not proved, but seemed the most likely.

Six months after operation the patient had an increased exercise tolerance and no orthopnoea.

Discussion

Cases with similar clinical findings to those of Löffler's endocarditis (Brockington and Olsen, 1973; Rasche *et al.*, 1973) have been reported as cases of eosinophilic leukaemia (Bentley *et al.*, 1961), disseminated eosinophilic collagen disease (Engfeldt and Zetterström, 1956), fibroma of the right ventricle (Van der Hauwaert *et al.*, 1965), Löffler's eosinophilic endocarditis (Gardner-Thorpe *et al.*, 1971), and endocarditis parietalis fibroplastica (Nagy *et al.*, 1969; Jennings and Pengelly, 1968). Löffler's endocarditis is one of the rarest cardiomyopathies and over the decade 1960 to 1970 only one case was seen at the clinical cardiology unit at the Royal Postgraduate Medical School, London. During that period 246 cases of hypertrophic and congestive cardiomyopathies were seen (Oakley, 1973).

In the face of the semantic problems diagnostic criteria are difficult to establish. An eosinophilia, often intense, with counts as high as $126 \times 10^9/l$ (Rasche *et al.*, 1973), is an essential feature. The cause of the eosinophilia may not be apparent but the characteristic cardiac findings are described in association with the eosinophilia of parasitic infestation and other allergies, malignant disease, and polyarteritis. Odeberg (1965) and Bousser (1957) have doubted the existence of true eosinophil leukaemia and comment on the maturity of the eosinophils in the bone marrow.

A high eosinophil count was a feature of all the

cases described here. No cause for the eosinophilia was found in our Cases 2 and 3. In Case 1 angioneurotic oedema and the rash suggest an allergy. The raised plasma IgM, the positive Rose-Waaler test, and the presence of cold agglutinins supported this, but the allergen remains unidentified.

Löffler's disease predominantly affects men. Though the clinical presentation is variable, progressive heart failure, a febrile course, and multiple systemic emboli are said to be characteristic (Davies, 1960). The cardiac lesion at the onset may be occult but later dominates the clinical picture and determines the outcome. Non-specific or incidental symptoms may lead to the discovery of eosinophilia as in Cases 1 and 3. Apical systolic murmurs, common in reported cases of Löffler's endocarditis, were present in 20 of the 40 cases reviewed by Brink and Weber (1963). Conduction disturbances were seen in 19 of the 65 cases reviewed by Raizner, Silverman, and Waters (1972). Bundle-branch block and intraventricular conduction delays were most frequent, not surprisingly in view of the subendocardial pathological lesion. Systemic emboli occur commonly and are probably responsible for the frequent association with neurological disease (Gardner-Thorpe *et al.*, 1971). Embolism may be the basis for the renal impairment reported in some cases.

Pathologically, hyalinized fibrous endocarditis, subendocardial necrosis or fibrosis or both, plus the presence of mural thrombi are described (Brockington and Olsen, 1973). Extensive thrombosis, eosinophilic infiltration, periarteritis, and endarteritis of small vessels, as well as involvement of the whole thickness of the ventricular wall are reported as important distinctive features of Löffler's endocarditis (Davies, 1960). In the 90 cases reviewed by Brockington and Olsen (1973), 46 had biventricular endomyocardial lesions, 35 left ventricular lesions, and 9 only right ventricular lesion. The left ventricular endomyocardial biopsy specimens in Cases 1 and 2 were difficult to assess because of their small size and difficulty in orientation. Nevertheless, they were unequivocally abnormal and the histological features were compatible with a diagnosis of Löffler's endocarditis. Several attempts had to be made in each case to obtain biopsy material, and the failure to obtain a specimen showing hyaline thickening of the endocardium may be a result of the nature of the lesion. Endomyocardial biopsy may also be difficult in endomyocardial fibrosis as the bioprobe tends to slide over the smooth fibrous endocardium (Somers *et al.*, 1971). Right ventricular biopsies in Case 2 showed organized thrombus. No biopsy specimen was obtained in Case 3, but the excessive myocardial friability noted at operation

suggests myocardial involvement. Valvular lesions are described in more than 20 per cent of the published cases: the tricuspid and mitral valves are most commonly affected. Postmortem studies indicate two main reasons for mitral regurgitation. There may be warty deposits or friable vegetations on the mitral valve leaflets (Brockington and Olsen, 1973) or, more commonly, one of the mitral valve leaflets, usually the posterior, is tethered by the fibrous endocardium (Rasche *et al.*, 1973; Roberts *et al.*, 1969). Eosinophilic and lymphocytic infiltration of liver and spleen have been described in necropsy material in most cases and were present in liver tissue in our cases.

The cardiac lesions in Löffler's endocarditis have many histological features in common with endomyocardial fibrosis. The relative incidence of left and right ventricular lesions in Löffler's endocarditis is the same as in endomyocardial fibrosis (Shaper, Hutt, and Coles, 1968), which often presents with severe right heart failure. It is characteristic of severe right-sided endomyocardial fibrosis that identical pressures are recorded throughout the right heart, and the value of the intracardiac electrocardiogram in locating the tricuspid and pulmonary valves in this disease has been reported (Emslie-Smith and Somers, 1968). Our cases show for the first time that both the haemodynamic and angiographic findings in Löffler's endocarditis can mimic those described in endomyocardial fibrosis (Somers *et al.*, 1968; Cockshott, 1965). A variant of endomyocardial fibrosis presenting as mitral regurgitation of varying severity has been described (Fowler and Somers, 1968). Shillingford and Somers (1961) made haemodynamic observations in 15 cases and found mitral regurgitation in 12, which was severe in 7; the cardiac lesion in our Case 3 is very like that seen in this type of endomyocardial fibrosis. Löffler's endocarditis is an uncommon multisystem disease which has been reported from various parts of the world whereas endomyocardial fibrosis primarily affects the heart and has a very well-defined geographical distribution. While the pathogenetic mechanisms which lead to the cardiac lesions may have features in common, perhaps reflecting a restricted spectrum of endocardial responses to disease, the two diseases should not be regarded as variants of a single entity.

Cases 1 and 2 are clearly Löffler's endocarditis and Case 3 almost certainly so on the grounds of the systemic disease with obvious eosinophilia together with a compatible cardiac lesion. Cases 1 and 2 show remarkable similarities: one presented with and the other developed severe right heart failure and tricuspid incompetence; in neither was there clinical

evidence of left heart involvement. Cardiac catheterization in both cases showed normal left heart pressures. In both, right ventricular contraction produced no measurable effect on the right-sided pressures and hence right heart work, though normal cardiac outputs were maintained. The right ventricular angiograms were similar to those reported by Gardner-Thorpe *et al.* (1971), and Van der Hauwaert *et al.* (1965). In Case 1 the deformed left ventricular apex and the early systolic mitral regurgitation suggest left-sided involvement. In Case 2, though the right ventricle was equally affected, left ventricular function was normal. The dominant picture in both cases was a severe right-sided obliterative cardiomyopathy. We should have paid more attention to the echocardiogram in these two cases. Paradoxical septal motion in right heart failure implies right ventricular volume overload, and in such patients there should be no difficulty in identifying both the right ventricle and the tricuspid valve (Popp *et al.*, 1969). Neither could be identified and the extensive obliteration of the right ventricular cavity in both cases provides a ready explanation for this.

The haemodynamic findings in Case 3 were very different from those in the other two. Clinically there was mitral regurgitation of increasing severity. A rheumatic aetiology seemed unlikely in view of the normal mitral echocardiogram. Though ischaemic heart disease could not be excluded, a cardiomyopathy was thought to be the most likely cause. Cardiac catheterization confirmed severe mitral regurgitation. Coronary arteriography showed only moderate stenosis of the left anterior descending coronary artery. An ejection fraction of 0.5 and a low KVmax with impaired postectopic response indicated poor left ventricular function. There was no angiographic evidence of endocardial thickening or mural thrombus in the left ventricle. The mitral regurgitation was more akin to that seen in congestive cardiomyopathies with a dilated mitral ring, but in addition the mitral leaflets were found at operation to contain redundant tissue ('floppy valve'). Right ventricular angiography was not done. The raised right-sided pressures were probably secondary to the raised left atrial pressure, rather than the result of a constrictive process.

There is little information on left ventricular function in Löffler's endocarditis. It is not certain whether the two patients described by Davies *et al.* (1965) had endomyocardial fibrosis or Löffler's endocarditis. Both had raised left atrial pressures secondary to endocardial restriction and resembled mitral stenosis. Others have noted raised pulmonary artery wedge pressures (Roberts *et al.*, 1969; Clark *et al.*, 1956), but mitral regurgitation was present in

these patients. Undoubtedly left ventricular disease is common without clinical evidence of impaired filling. The left ventricular biopsies in Cases 1 and 2 both showed fibrosis and it is possible that in some cases high left-sided filling pressures are the result of a restriction of left ventricular filling resulting from fibrosis. Despite considerable pathological evidence of left ventricular disease (Brockington and Olsen, 1973), the lack of clinical evidence for this in most cases remains unexplained. In Case 1 left ventricular dysfunction was seen at cardiac catheterization. The predominant haemodynamic involvement of the right ventricle in this disease may protect the left ventricle to the extent that its dysfunction does not become clinically detectable.

There is no established specific therapy. Congestive heart failure is treated conventionally with digoxin and diuretics. Our patients were given anticoagulants in view of the high incidence of systemic emboli in previously reported cases. Azathioprine and prednisone were given in all three cases. There was a progressive reduction in the size of the spleen and in the eosinophil count, but there was no evidence of improvement or reduced rate of progression of the cardiac lesion. One patient died within a year of the development of cardiac symptoms. A single case of Löffler's endocarditis has been reported in which corticosteroids produced temporary beneficial results but no improvement was noted in others (Nagy *et al.*, 1969; Jennings and Pengelly, 1968).

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