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Endomyocardial fibrosis and eosinophilia

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Absolute eosinophil counts were assessed in 15 African patients with proven endomyocardial fibrosis. Though the mean eosinophil count in patients with endomyocardial fibrosis was higher compared with the normals reported from Kampala (1·13 vs 0·72 $\times 10^9$/l), the absolute range was comparable. A high percentage of patients with endomyocardial fibrosis had malarial parasites, high malarial antibody titres, hookworms, or strongyloides, but the correlation of eosinophilia to various parasitic infections was poor. Both eosinophilia and parasitic infections are common in the tropics and they affect patients with endomyocardial fibrosis no more than the population at large. Other aetiological factors, genetic, environmental, and immunological, are felt to be important in the causation of endomyocardial fibrosis in Uganda and evidence for this is reviewed. Though there is a similarity in pathological features, African endomyocardial fibrosis is a distinct entity from Löffler's endocarditis and cardiac lesions seen in eosinophilic leukaemia or reactive eosinophilia. There is no hard evidence to suggest that African endomyocardial fibrosis is a variant of Löffler's endocarditis caused by parasitic infections via eosinophilia.

Considerable knowledge of endomyocardial fibrosis has accumulated since its recognition as a clinicopathological entity by Davies and his co-workers (Ball *et al.*, 1954). While the clinical and haemodynamic features have been well delineated over the past decade (Somers *et al.* 1968a, b; and Connor *et al.* 1967, 1968), the cause of endomyocardial fibrosis remains unknown. Gerbaux and associates (1956) suggested that endocardial fibrosis and Löffler's endocarditis were essentially the same disease. Subsequently Roberts and associates (1969) reported 3 cases of 'eosinophilic leukaemia', without abnormal myelopoiesis but with endomyocardial lesions. They suggested that endomyocardial lesions in 'eosinophilic leukaemia', Löffler's endocarditis, and the endomyocardial fibrosis seen in Africa were the same disease. They further postulated that endomyocardial fibrosis without eosinophilia may be a later or inactive stage of either Löffler's endocarditis or 'eosinophilic leukaemia'. Brockington and Olsen (1973) reviewed 90 cases of cardiac lesions associated with eosinophilia, comparing them with 32 other fibrotic lesions including endomyocardial fibrosis from Uganda, Nigeria, and Brazil. Their conclusion was, 'There are no hard data to contradict the simple hypothesis that Davies' endomyocardial fibrosis is a late form of Löffler's endocarditis due to parasitic infections via eosinophilia'. Meanwhile, Bell *et al.* (1976) have shown that both the haemodynamic and angiographic findings in Löffler's endocarditis can mimic those described in endomyocardial fibrosis (Somers *et al.*, 1968a). Though eosinophilia has been implicated as an important link between Löffler's endocarditis and Davies' endomyocardial fibrosis, no detailed studies on eosinophilia have been reported from Uganda, which is the major focus besides Nigeria and Brazil. The present study was undertaken to: (1) assess absolute eosinophil counts in patients with endomyocardial fibrosis: (2) compare the eosinophil counts with those in normal individuals from the same area: (3) correlate the eosinophil counts to parasitic infections in these patients; and (4) differentiate features typical of African endomyocardial fibrosis from those of Löffler's endocarditis.

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Methods

Fifteen black African patients with endomyocardial fibrosis proven by cardiac catheterisation and cineangiography were studied. They were either inpatients or were attending the cardiology outpatient clinic at Mulago Hospital, Kampala. There were 10 male and 5 female patients, with ages ranging from 7 to 28 years. There were 10 Rwan-

dans, i.e. they had originated from Rwanda or Burundi; 3 Ganda, i.e. indigenous to the Kampala region; and 2 from other tribes (Table 1). The white blood cell count was done according to the method of Dacie and Lewis (1963). The differential counts were all performed, on 200 cells, by a haematologist. A thick blood smear was examined for malarial parasites and microfilaria. Malarial antibody tires were estimated by the fluorescent antibody technique of Voller and Bray (1962) using human films containing *Plasmodium falciparum*. Stool examination was performed by the formol-ether concentration method followed by direct examination under the microscope (King, 1966).

Table 1 *Sex, age, ethnic group, and liver biopsy results in patients with endomyocardial fibrosis*

Case No.	*Sex*	*Age*	*Ethnic group*	*Liver biopsy*
1	M	18	Hangaza	0
2	M	26	Ganda	Normal
3	M	15	Ankole	TSS
4	F	7	Rwanda	Congested
5	M	15	Rwanda	Normal
6	M	28	Rwanda	Congested
7	F	26	Rwanda	Cirrhosis
8	F	16	Rwanda	TSS
9	M	9	Rwanda	TSS
10	F	28	Rwanda	Normal
11	M	20	Ganda	Congested
12	M	17	Rwanda	Normal
13	M	17	Rwanda	Congested
14	F	13	Ganda	Cirrhosis
15	M	10	Rwanda	0

0, not done; TSS, tropical splenomegaly syndrome.

Table 2 *White blood cell, neutrophil, and eosinophil counts in patients with endomyocardial fibrosis*

Case No.	*Hb g/l*	*WBC ×10⁹/l Total*	*Neutrophils %*	*Neutrophils Absolute*	*Eosinophils %*	*Eosinophils Absolute*	*Others %*	*Others Absolute*
1	134	5	23	1·15	52	2·60	25	1·25
2	158	4	37	1·48	35	1·40	28	1·12
3	130	5	53	2·65	9	0·45	38	1·90
4	120	10	45	4·50	13	1·30	42	4·20
5	122	4	16	0·64	31	1·24	53	2·12
6	100	8	60	4·80	4	0·32	36	2·88
7	112	7	37	2·59	24	1·68	39	2·73
8	130	5	28	1·40	33	1·65	39	1·95
9	112	4·5	27	1·22	15	0·68	58	2·61
10	128	6	42	2·52	30	1·80	28	1·68
11	122	3	62	1·86	11	0·33	27	0·81
12	152	3	61	1·83	11	0·33	28	0·84
13	70	4	44	1·76	1	0·04	55	2·20
14	128	5	13	0·65	30	1·50	57	2·85
15	93	5	24	1·20	31	1·65	45	2·25
Mean		5·23		2·01		1·13		
Range		3–10		0·64–4·80		0·04–2·60		
% mean			38		22			
Mean		5·10		1·96		0·72		Shaper (1972)
Range		1·90–8·30		0·32–3·60		0–2·26		(African,
% mean			39		12			Kampala)
Mean		7·00		3·65		0·15		Wintrobe
Range		4·30–10·00		1·83–2·25		0–0·70		(1974)
% mean			53		3·2			

These values are compared with the normals reported by Shaper in healthy African subjects from Kampala and Wintrobe from U.S.A. Shaper and Wintrobe figures give 95 per cent confidence limits: endomyocardial fibrosis figures give full range.

Results

WHITE BLOOD CELL COUNTS

Table 2 summarizes detailed white cell count in 15 patients with endomyocardial fibrosis. These values are compared with normals from the Kampala area (Shaper, 1972), and from values quoted by Wintrobe (1974). The total white blood cell and neutrophil counts were lower, and the eosinophil counts higher in both the normals and patients with endomyocardial fibrosis from Kampala, compared with values reported by Wintrobe. Though the average eosinophil percentage was higher in the patients with endomyocardial fibrosis, the absolute range was comparable.

MALARIAL PARASITES, MALARIAL ANTIBODY TITRES, MICROFILARIA, AND INTESTINAL PARASITES

Table 3 summarises various parasites found in patients with endomyocardial fibrosis. Three patients had malarial parasites in their blood stream, and 9 patients had malarial antibody titres of 1 in 800 or greater. Microfilaria *Dipetalonema perstans* was found in 4 patients. Various intestinal parasites were detected in 10 patients, the commonest one being hookworms and the species *Necator americanus*. The correlation between

Table 3 *Malarial parasites, malarial antibody titres, microfilaria, and stool parasites in patients with endomyocardial fibrosis*

Patient No.	*BS for MP*	*MABT*	*Microfilaria*	*Stool parasite*
1	0	1:1600	DP	HW, Tr
2	0	1: 100	0	0
3	+	1:1600	DP	HW
4	0	1: 200	0	HW
5	0	1: 800	0	HW
6	0	1: 200	0	HW
7	0	1:1600	0	HW
8	0	1: 100	0	0
9	+	1:1600	DP	0
10	0	1: 800	0	HW, St
11	0	1: 100	0	0
12	0	1: 200	DP	St
13	0	1:1600	0	HW
14	+	1:1600	0	0
15	0	1:1600	0	HW

BS, blood slide; MP, malarial parasites; MABT, malarial antibody titres; DP, *Dipetalonema perstans*; HW, hookworms; Tr, *trichuris*; St, *strongyloides*; 0, none; +, positive.

eosinophilia and the presence of hookworm was poor. Of 9 patients with hookworm, 6 had an absolute eosinophil count over $0{\cdot}80 \times 10^9/1$, while 3 out of 6 patients without hookworm had an eosinophil count in the same range.

LIVER BIOPSY

Liver biopsies were done in 13 patients to assess tissue oesinophilia or changes consistent with tropical splenomegaly syndrome. Eight patients had normal liver architecture and/or changes secondary to liver congestion from heart failure. Two patients had cirrhosis. Three patients had sinusoidal infiltration with lymphocytes consistent with tropical splenomegaly syndrome attributed to chronic malarial infection (Hutt and Hamilton, 1972).

Discussion

Indigenous African people have a white blood cell count pattern which differs from that usually described in the standard textbooks of haematology. The total leucocyte counts and neutrophils are lower than in Caucasians and the eosinophil counts are higher. Any haematological study in Africans must be compared with normals from that particular area. The total white cell count and neutrophil counts in the patients with endomyocardial fibrosis are comparable to the values reported from 250 normal individuals from the Kampala area by Shaper (1972). Of the normal Africans, 49 per cent showed an eosinophilia of $0{\cdot}50 \times 10^9/1$, 18 per cent were over $1{\cdot}00 \times 10^9/1$, and 5 per cent were over $2{\cdot}00 \times 10^9/1$. The majority (39%) of normal Africans showing an eosinophilia were Rwandans. Though the average eosinophil percentage was higher in the patients with endomyocardial fibrosis, in the present study the absolute range was comparable to the normal Africans. A high eosinophil count is common in the tropics, and though various intestinal and blood parasites have been incriminated as a cause, its genesis remains unexplained. Intestinal parasitism is less regularly associated with eosinophilia than is parasitism in which tissue invasion is prominent. A high incidence of hookworms was found in patients with endomyocardial fibrosis, but the relation between eosinophilia and the presence of hookworms was poor. In another study reported from the tropics, no correlation was observed between the oesinophil levels and parasitic infection (Ashcroft *et al.*, 1969).

Ive and associates (1967) found evidence of exposure to one or the other form of filariasis in patients with endomyocardial fibrosis from West Africa. In Kampala most of the patients with endomyocardial fibrosis come from areas free of onchocerciasis (Shaper and Coles, 1966). None of the 15 patients in the study had any past history or clinical features consistent with onchocerciasis. *Dipetalonema perstans* is a common non-pathogenetic filariasis found in up to 50 per cent of blood donors in the Kampala area (Shaper, 1972). A high frequency of heart antibodies and autoimmunity against the heart in endomyocardial fibrosis has been shown by van der Geld and his Ugandan associates (1966). Shaper *et al.* (1968) described an immunological syndrome in Rwandans characterised by high titres of malarial antibody and a high incidence of heart, thyroid, and parietal cell antibodies. While this syndrome affects predominantly the people originating from Rwanda and Burundi, areas relatively free of malaria, it does affect the Ganda people indigenous to the highly malarious area. Nine patients in this study had evidence of malaria either on direct blood smear or by high malarial antibody titres. Three patients had histological changes of tropical splenomegaly syndrome. It is probable that the presence of tissue antibodies associated with an unusual host response to malarial infection may play a critical role in the pathogenesis of endomyocardial fibrosis (Patel *et al.*, 1971).

The degree of eosinophilia varies considerably among patients with Löffler's endocarditis, eosinophilic leukaemia, or reactive eosinophilia, and endomyocardial fibrosis. Counts of 2 to $5 \times 10^9/1$ are not unusual in the former entities. The absolute eosinophil count in patients with endomyocardial fibrosis has been relatively low. Though it has been postulated that eosinophilia may be intense only in the acute stage (Roberts *et al.*, 1969), from observations by cardiologists and pathologists in Kampala, where endomyocardial fibrosis accounts for 12 per cent of all heart disease (Somers *et al.*, 1972), no such progression has been observed. At necropsy, where acute cases are recognised by endocardial lesions with a spongy, grey-green layer of thrombus, detailed histopathological studies by Connor and associates (1967, 1968) failed to show tissue eosinophilia in early or well-established lesions. Among the few patients in the present study who had endomyocardial biopsies in life (Somers *et al.*, 1971), or who came to necropsy, none showed tissue eosinophilia. Liver biopsies also failed to reveal any tissue eosinophilia.

There are important differences in the clinical presentation of endomyocardial fibrosis seen in the tropics and Löffler's endocarditis. The former is a disease of children and young adults. In Uganda there is a striking predilection for the immigrants from Rwanda and Burundi. The natural history of the disease has been difficult to study, since the

earlier stages of the disease are not recognised. The disease is only recognised when the haemodynamic disturbance secondary to endocardial restriction and valvular regurgitation produces overt symptoms. Pericardial effusion with a high protein content but low cell count is common on first presentation, disappears during the follow-up, and recurs again terminally. Embolic manifestations may be present in 16 per cent of the patients. They involve the large arteries, often occluding the aorta completely. This clinical presentation is in sharp contrast to Löffler's endocarditis and endomyocardial involvement in eosinophilic leukaemia or reactive eosinophilia. The evidence linking eosinophilia and parasitic infections to endomyocardial fibrosis cases seen in Uganda is lacking. Both eosinophilia and parasitic infections are common in the tropics, but they affect patients with endomyocardial fibrosis no more than the population at large. Other aetiological factors, genetic (Patel *et al.*, 1971), and/or environmental and immunological, may be much more important in the causation of endomyocardial fibrosis in Uganda. Bell and his associates (1976) have suggested that the similarity of the pathogenetic mechanisms in Löffler's endocarditis and endomyocardial fibrosis perhaps reflects a restricted spectrum of endocardial response to disease. While not in dispute with this hypothesis, we are in agreement that there is no basis for regarding Löffler's endocarditis and endomyocardial fibrosis as variants of a single entity.

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