Afr. J. med. Sci. (1970) **1**, 343–352.

CASE REPORT

The Heart in Eosinophilic Leukaemia

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(*Received* 24 *January* 1970)

Summary. A case of eosinophilic leukaemia, complicated by cardiac ventricular lesions including endomyocardial degeneration, infiltration by eosinophils and primitive cells, and superimposed thrombi is presented. Nineteen other similar cases are reviewed. Eosinophilic leukaemia appears to be frequently associated with a particular type of heart lesion, which may be related to endomyocardial fibrosis.

Résumé. Un cas de laucemie éosinophilique aggravé par des lésions cardiaques ventriculaires qui sont notamment la fibrose endomyocardique, l'infiltration cardiaque par les éosinophiles et les plasmocytes ainsi que des thrombus y surajoutés, est présenté. Dix-neuf d'autres cas semblables sont discutés. Leucemie éosinophilique semble être souvent associeé à une lésion cardiaque particulière qui peut être mise en rélation avec la fibrose endomyocardique.

It has been known for some time that eosinophil leukocytosis is often associated with curious thrombi in the heart (Hay & Evans, 1929; Punch & Close, 1938; Jucker, 1946). They have also been found in eosinophilic leukaemia (Bentley *et al.*, 1961; Thomas, 1963). Eosinophilic leukaemia is a rare disease, and to the best of our knowledge only forty-eight cases have been reported in the literature (all listed in Table I and in the reference section). In this paper, we report a further case with a lesion in the heart.

CASE REPORT

A 60-year-old Yoruba tailor from Ibadan (No. 201,797) presented on 24 August 1968 with 7 days' history of fever, rigors, and chest pains. For a few hours, his sensorium had been clouded. No other history was obtained.

He was a thin, stuporose man with a fever of 103°, deep grunting respirations, and crepitations at both lung bases. The pulse rate was 120/min, the blood pressure 50/40 mm of

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mercury, and the liver was enlarged four fingers' breadth below the costal margin; no abnormality was detected in the heart.

He died shortly after admission, and no investigations were done except an examination of the blood. He had a packed cell volume of 25%, and a white cell count of 510 000/mm^3, with the following differential count: blasts, 9%; neutrophil metamyelocytes, 1%; neutrophil polymorphonuclears, 4%; eosinophil promyelocytes and myelocytes, 7%; eosinophil metamyelocytes, 15%; eosinophil polymorphonuclears, 42%; lymphocytes, 22%.

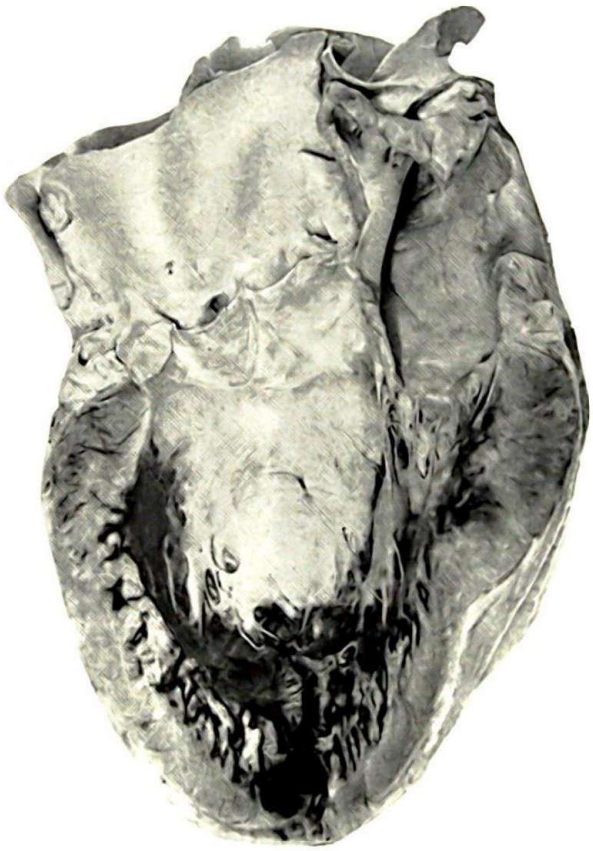

FIG. 1. The left ventricle, showing a slightly dilated chamber lined by thrombus which fills the intertrabecular spaces, and reaches a thickness of a little more than 1 cm.

Necropsy (301/68) showed an emaciated elderly man, weighing 52·5 kg. There was no jaundice, oedema or serous effusions. The tongue, pharynx, oesophagus, stomach, intestines, gall bladder, pancreas, pituitary, adrenals and thyroid were normal macroscopically. The lungs showed mild generalized oedema, patchy consolidation in all lobes, and linear depressed scars in the apices. The kidneys were pale and firm, weighing 125 g each; the corticomedullary junction was slightly blurred, and the capsules stripped with some difficulty revealing generally smooth pale cortical surfaces with many depressed scars. The bladder showed increased trabeculation, and the prostate was slightly enlarged. The brain and cerebral vessels showed no lesions except for slight leptomeningeal thickening.

The liver was markedly enlarged weighing 2430 g. Its capsular surface was smooth and on section there was evidence of fatty change and centrilobular congestion; there was generalized portal infiltration by greyish tissue. The spleen was also enlarged, weighing 685 g. It was firm, and the cut surfaces showed small whitish nodules and loss of normal markings. There were many subcapsular infarcts. There was no enlargement of lymph nodes.

The heart weighed 455 g. The pericardial surface showed abundant fat, diffuse mild thickening of the epicardium, and a few focal areas of dark red deposits. The right atrium was slightly dilated; the appendage contained a small adherent ante-mortem thrombus;

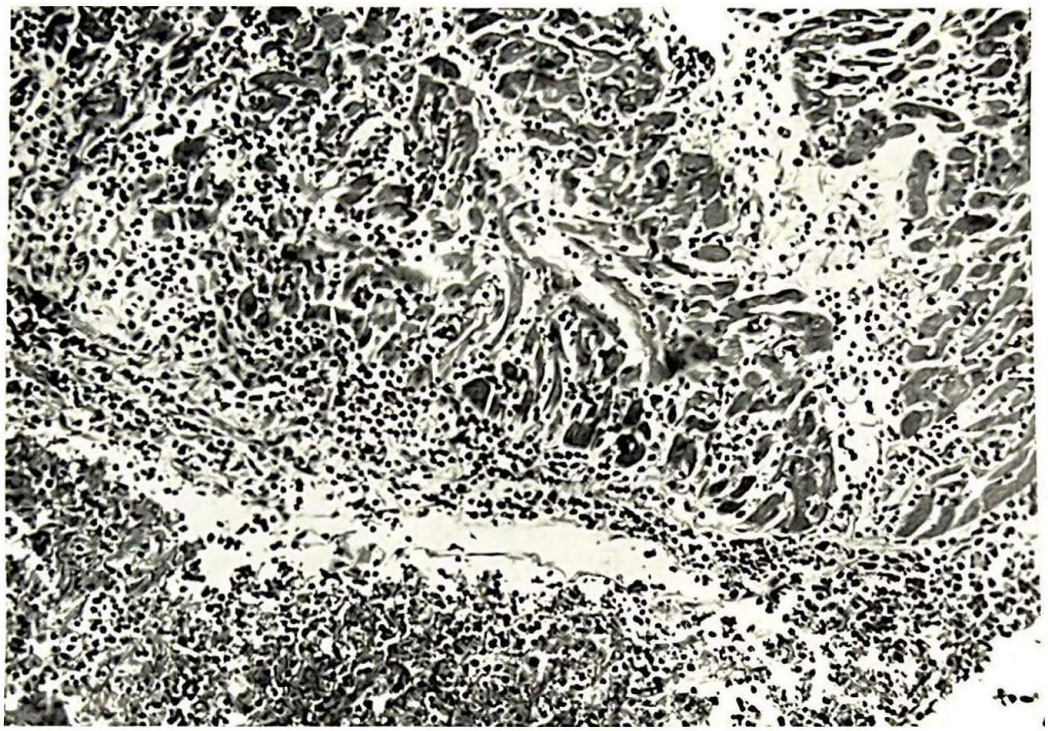

FIG. 2. Photomicrograph of the junction between thrombus (below) and myocardium (above). The myocardium is oedematous, with some fibres undergoing necrosis and with some fibroblastic and cellular infiltration; the endocardial zone is heavily infiltrated by primitive cells and mature eosinophils, and merges with the organizing thrombus.

there was whitish discoloration of the subendocardial myocardium. The tricuspid leaflets were thin, translucent and elastic; the chordae tendineae were normal. There was moderate dilatation of the right ventricular cavity with numerous mural thrombi at the apex; the wall measured 8 mm at the outflow tract; there was whitish discoloration of the subendocardial myocardium, particularly of the outflow tract and apex. The pulmonary valve and pulmonary artery were normal. The left atrium was slightly dilated and showed endocardial thickening. The appendage contained no thrombus. The mitral valve leaflets were slightly thickened but normal. The left ventricular cavity was slightly dilated (Fig. 1). The apex of the cavity was obliterated by mural thrombi, completely inseparable from the myocardium and of a consistency firmer than the myocardium itself; the maximum thickness of the

thrombus was over 1 cm; it extended up the inflow tract, burying the trabeculae carneae and partly burying the papillary muscles. On section, it was separated from the myocardium by a thin reddish-brown line. There was diffuse whitish discoloration of the endocardium uninvolved by the thrombus, i.e. parts of the inflow tract and the outflow tract up to the base of the aortic valve. The aortic cusps were normal. The coronary arteries were patent. There was mild atheroma of the ascending aorta.

Microscopic findings

Histology of the heart showed that the pericardium contained small focal leukaemic deposits, some of which were associated with small haemorrhages. The myocardium was extensively infiltrated by leukaemic cells. Generally the infiltration was sparse and lay between individual muscle fibres, but it increased in severity towards the subendocardial zone where there was interstitial oedema with wide splitting of the muscle fibres, necrosis and replacement by proliferating fibroblasts and capillaries. Some medium sized arteries were occluded by organized thrombus. Underlying the mural thrombus (Fig. 2), no endocardial tissue was recognizable; in that region there was heavy infiltration by eosinophils and primitive cells. The mural thrombus consisted of amorphous eosinophilic masses of fibrin and leucocytes, and merged imperceptibly with the endocardial cellular proliferation. The endocardium not overlain by thrombus was infiltrated by primitive cells.

In the spleen, there was almost complete destruction of the architecture by diffusely infiltrating leukaemic cells, mainly eosinophils, and there were also nodular foci of haemopoietic elements, predominantly of primitive cells with granular cytoplasm. The bone marrow was highly cellular, with overwhelming preponderance of mature and immature eosinophilic elements. There was infiltration by leukaemic cells in the portal tracts and sinusoids of the liver, the renal medulla and the perirenal tissues. There was a mild chronic pyelonephritis. In the adrenals there was, in addition to leukaemic infiltration, coagulation necrosis of the cortices, and thromboses of a few medullary vessels. The lungs showed interstitial and perivascular fibrosis, with chronic inflammatory cell infiltration, heavy deposits of anthracotic granules, and focal granulomata consisting of epithelioid cells and lymphocytes, surrounding caseation necrosis. No acid-fast bacilli were seen.

Anatomical summary

(1) Leukaemic infiltration of spleen, liver, heart, kidneys and adrenals. (2) Biventricular mural thrombi; endomyocardial degeneration and infiltration by eosinophils, primitive cells and fibroblasts; right ventricular dilatation and hypertrophy. (3) Renal and splenic infarcts. (4) Chronic pyelonephritis. (5) Pulmonary granulomata, probably tuberculous. (6) Adrenal cortical necrosis.

DISCUSSION

According to a widely accepted definition (Wintrobe, 1967) leukaemia is a 'widespread proliferation of the leukocyte and its precursors in the tissues of the body . . . usually also associated with qualitative and quantitative changes in the circulating blood'. Our patient had a leucocytosis of 510 000 per cubic millimetre and proliferation of the leucocytes and their precursors in the bone marrow, spleen, liver, kidney, adrenals and heart; so there can be no doubt that he had a leukaemia. There has been some debate about eosinophilic

TABLE 1. Eosinophilic leukaemia with ventricular mural lesions

Authors	Sex, age, origin	Eosinophil count	Main basis for the diagnosis of leukaemia	Pathological findings in the heart
Shapiro (1919)	F 17 U.S.A.	84% of 236,000	Moderate infiltration of lung, spleen, liver and splenomegaly 1268 g	'In the lower part of the R.V. there was a conical thrombus fitting into the cavity like a mould . . . The greatest thickness of the thrombus was 2·5 cm.' Histology showed organization of the base of the thrombus.
Hay & Evans (1929)	F 54 England	50% of 46,375	Di Guglielmo's syndrome, infiltration of organs	'The L.V. was nearly half-filled with a tough, rather shaggy, wedge-shaped ante-mortem clot adherent to the apex.' Histology showed reorganization of the clot.
Harrison (1930)	M 23 U.S.A.	60% of 16,000	'Frequent myeloblasts' in marrow; infiltration of lung and spleen	'A thrombus, 0·5–1 cm in thickness, lines practically the entire cavity of the L.V.' Histology showed adherence of the thrombus to the wall, and myocardial scars.
Stephens (1935)	F 17 U.S.A.	69% of 130,000	98·6% myeloblasts in marrow, infiltration of organs	'The inner two-thirds of the heart wall was yellowish-red, dull and opaque and demarcated from normal muscle by a well-defined red line. There were firmly attached mural thrombi in the L.V.' Histology showed that 'the inner half of the L.V. wall showed extensive inflammatory changes' with necrosis, haemorrhage, infiltration by polymorphs, and invasion by bacteria.
Thomas & Plum (1939)	M 11 Denmark	90% of 65,000	Terminal stem cell crisis	In R.V., the endocardium was thickened throughout, especially towards the apex, and in the conus; in L.V. similar areas of fibrosis and thrombi on the septum, anterior and posterior walls.
Engbaek, Heerup & Thomsen (1942)	M 7 Denmark	140,000	Eosinophils grossly abnormal and heterogeneous; infiltration of lung	A large part of both ventricles was filled with a mass of fibrin (photograph in text); endocardium and white fibrous layer at the junction of myocardium and thrombus; flame-shaped scars in myocardium. Histology showed myocardial fibrosis, chronic inflammation of the endocardium, and intimal thickening of myocardial vessels.
Sposito & Nava (1950)	M 44 Italy	80% of 210,000	Terminal stem cell crisis, infiltration of organs	Parietal thrombus at apex of L.V.
Weber (1952)	F 43 Germany	84% of 80,800	Infiltration of spleen, liver and colon	On the endocardium of both ventricles, a firm greyish-red deposit, filling the spaces between the trabeculae. Histology showed this to be a thrombus with chronic inflammation of the underlying myocardium.
Hoffmann & Themel (1953), case 5	M 26 Germany	26% of 355,200	Chronic myeloid leukaemia infiltration of liver, spleen and kidneys	Dilated ventricles; L.V. mural thrombus which histology showed to be attached to oedematous connective containing dilated capillaries and eosinophils

TABLE I (*continued*)

Authors	Sex, age, origin	Eosinophil count	Main basis for the diagnosis of leukaemia	Pathological findings in the heart
Pedich (1954)	F 18 Poland	48% of 23,000	53% paramyeloblasts in marrow	L.V. endocardium 9 mm thick; histology showed layered thickening of the endocardium. Small infiltrates of eosinophils in the myocardium.
Engfeldt & Zetterström (1956)	M 18 Sweden	70% of 113,000	60% immature cells in marrow infiltration of organs	Old parietal thrombi in both ventricles; histology showed highly vascular granulation tissue beneath ventricular thrombi; widespread myocardial inflammatory changes, with necrosis, oedema and infiltration by eosinophils.
Knorr & Scheppe (1958)	F 7 Germany	30,500	Infiltration of spleen, liver, lungs, ovary and perirenal fat	L.V. endocardial fibrosis (photograph of cross-section in text); anterior cusp of M.V. thickened. The posterior cusp had almost disappeared into a region of endocardial ulceration and fibrosis.
Mallarme *et al.* (1959)	M 56 France	67% of 37,600	16% myeloblasts in marrow infiltration of organs	Acute pericarditis. Histology showed numerous foci of myocardial necrosis and a dense infiltrate of eosinophils.
Boccato & Marin (1960)	F 83 Italy	52% of 94,600	14% myeloblasts in marrow infiltration of organs	'In the L.V., there was a diffuse, tenaciously adherent mural thrombus.' Histology showed infiltration of the myocardium with eosinophils.
Bentley *et al.* (1961)	M 5 U.S.A.	85% of 185,000	Terminal stem cell crisis	'Several tiny areas of scarring in the substance of the myocardium of L.V.' Histology (photomicrograph in text) showed a mural thrombus and areas of scarring with numerous macrophages and fibroblastic proliferation.
Thomas (1963)	M 27 U.S.A.	120,000	Di Guglielmo's syndrome infiltration of organs	'The entire apical portion and septal aspect of L.V. contained a firmly adherent, well organized mural thrombus blending with the scarred myocardium.'
Kauer & Engle (1964)	M 45 U.S.A.	79% of 256,000	Anaemia, splenomegaly, Ph1 chromosome	Rheumatic mitral valve disease; firm organized mural thrombi in the apices of both ventricles (3 × 2 × 1 cm). 'There was partial obliteration of R.V. with compensatory dilatation of the conus. The endocardium was markedly thickened by fibrous tissue, and the wall measured 8 mm in thickness.'
Mallarme *et al.* (1964)	M 72 France	85% of 295,000	Anaemia and rise of WBC to 395,000 of which only 45% were eosinophils; infiltration of organs	Haemorrhagic pericardial effusion; dilated heart; vegetations on aortic and pulmonary valves; between the papillary muscles, large parietal thrombi foci of myocardial fibrosis, particularly in the subendocardial region, and diffuse endocardial fibrosis.
Lohr & Jahnecke (1965)	M 37 Germany	94% of 304,000	Terminal stem cell crisis	Endocardial fibrosis of R.V., whose apex was distorted by a scar (photograph in text). Similar, lesser changes in L.V. Histology showed hyaline fibrosis of the endocardium, extending in marrow septa into the myocardium, which was the seat of interstitial scarring.
Our patient	M 60 Nigeria	64% of 510,000	9% blasts in peripheral blood infiltration of organs	Biventricular mural thrombi. Histology showed endomyocardial necrosis, and infiltration by eosinophils, primitive cells and fibroblasts.

Key: R.A., right atrium; R.V., right ventricle; L.V., left ventricle; M.V., mitral valve.

leukaemia—whether it should be considered as a separate entity among myeloid leukaemias, and whether it is truly neoplastic. These are subtle problems which are outside the scope of this paper. Our case had a predominance of the eosinophil series (64% of the white cell count), and is in this sense, an 'eosinophilic leukaemia'.

In the literature, we have been able to find nineteen cases of eosinophilic leukaemia with heart lesions similar to our own. These are summarized in Table 1. All these cases had, as evidence of leukaemia, either a very high proportion of stem cells at some stage in the disease, or infiltration of non-haemopoietic organs; the exception is the case of Kauer & Engle (1964) who had, however, the Ph^1 chromosome. All had a predominance of eosinophils in the differential count, except the case of Hoffman & Themel (1953) who had, however, an absolute count of 92 000 per cubic millimetre.

In addition to the cases tabulated, there were two (Alexander, 1924; Drennan & Biggart, 1930) in which the descriptions of the heart were equivocal, two (Gerhard & Henschel, 1958; Marchal *et al.*, 1963) with vegetations on the valves, and two (Giffin, 1919; Piso, 1956) with heart lesions probably unrelated to the leukaemia (constrictive pericarditis and hypertensive heart failure). There were also some twenty-three cases without heart disease at necropsy.

It seems clear that eosinophilic leukaemia is associated with a remarkable heart lesion which runs true to type. It is present in about 40% of cases. As an explanation of this association, some remote possibilities can be imagined, for example that some agent is responsible independently for the heart disease and the leukaemia. There are two explanations, however, which seem plausible. The first is that the endomyocardial necrosis found in the earliest lesions is the result of leukaemic infiltration. Certainly large numbers of eosinophils have been found in these lesions. But this complication has not been observed in other kinds of leukaemia (Roberts, Bodey & Wertlake, 1968). An identical lesion has also been found, associated with eosinophil leucocytosis, in polyarteritis nodosa (Smith, 1948; Langer, 1954; Oehlert, 1956), malignant tumours (Paviot, Levrat & Guichard, 1935), asthma (Boyer, 1955; Bosman & Perri, 1963); drug sensitivity (Edge, 1946; Gardiol & Picht, 1957; Remmele & Sessner, 1959) and parasitic infections (Morenas, 1929; Gray, 1951; Sternon *et al.*, 1962).

The other possibility, which we think more likely, is that the presence of an eosinophil leucocytosis, in susceptible persons, by some unknown mechanism, causes endo- and myocardial damage.

In the present case, the lesion seems to have been at a very early stage. The presence of a few fibroblasts suggests that the lesion was between 4 and 14 days old. The cases reported by Stephens (1935), Hoffman & Themel (1953), Engfeldt & Zetterström (1956) and Mallarme *et al.* (1964) are other examples of this early lesion. It is worth considering what would have happened if time had allowed the normal process of repair. It is a fair assumption that the mural thrombi and inflamed endocardium would have become organized into an enormous endocardial scar. A similar lesion has in fact been reported by several authors (Thomsen & Plum, 1939; Pedich, 1954; Knorr & Scheppe, 1958; Bentley *et al.*, 1961; Löhr & Jahnecke, 1965). It is difficult to appreciate how this fibrotic lesion differs in any way from the 'endocarditis' described by Löffler (1936) or African endomyocardial fibrosis (Davies, 1948). Recently Roberts, Liegler & Carbone (1969) pointed out the close similarity between the cardiac lesions seen in Löffler's endocarditis and those in eosinophilic leukaemia. They also suggested that such lesions might represent an early stage of endomyocardial fibrosis.

ACKNOWLEDGMENTS

We wish to thank Dr Carlisle, Professor Edington, the late Professor A. Brown, and also Mr Nwachukwu-Jarrett. We are grateful to Dr Woloszynski for translating the article by Pedich (1954), Dr Hanne Rost for translating the article by Engbaek, Heerup & Thomsen (1942), Professor R. Terry for sending the necropsy protocol of the case published by Stephens (1935), Dr C. L. Kauer and Dr J. W. C. Hagstrom for sending the necropsy protocol of the case published by Kauer & Engle (1964), and Mr Enyogai for the photographs.

Dr Brockington was supported by a grant from the Wellcome Trust.

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