Case reports

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Endomyocardial fibrosis associated with daunorubicin therapy

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A case of endomyocardial fibrosis in a patient with acute myeloblastic leukaemia treated by daunorubicin is reported. The pathological findings are indistinguishable from tropical endomyocardial fibrosis.

Endomyocardial fibrosis has a well-defined geographical distribution, most reported cases occurring among the indigenous tribes of East and West Africa (Shaper, 1970). The disease has been described in Europeans living in Africa (Brookington, Olsen, and Goodwin, 1967) but in most of these there was some evidence of filariasis and eosinophilia was usually present. Eosinophilia is also seen in Loeffler's endocarditis, a non-tropical disease which has macroscopical features identical to those seen in tropical endomyocardial fibrosis (Roberts, Liegler, and Carbone, 1969). In eosinophilic leukaemia a cardiac lesion indistinguishable from endomyocardial fibrosis has been described (Odeberg, 1965). We report here the finding of severe endomyocardial fibrosis in a young woman dying from acute myeloblastic leukaemia and who received prolonged therapy with daunorubicin, a powerful cytotoxic agent known to be cardiotoxic.

Case report

In February 1973 a 21-year-old student presented with a two-month history of progressive tiredness, bruising, and upper respiratory tract infections. At the age of 18 months she had developed a hypoplastic anaemia following sulphonamide therapy for upper respiratory tract infection.

On examination she was found to be anaemic with purpura and ecchymoses. There was no lymphadenopathy or hepatosplenomegaly. The heart was normal clinically. The peripheral blood count showed: haemoglobin 6.9 g/dl, white cell count 52 000/mm³, with 75

per cent blasts and platelets 16 000/mm³. The bone-marrow confirmed acute myeloblastic leukaemia.

Clinical and haematological remission was induced with daunorubicin and cytosine arabinoside (M.R.C. Leukaemia Trial, Barts III induction programme). After eight courses she was maintained on a monthly regimen of daunorubicin and cytosine arabinoside alternating with thioguanine and cytosine arabinoside (M.R.C. Leukaemia Trial, Barts III remission programme).

In January 1974, having received a total dose of 880 mg daunorubicin (550 mg/m² body surface area), she complained of increasing dyspnoea and was found to be in heart failure, with clinical evidence of cardiac tamponade. An echocardiogram confirmed the pericardial effusion; the electrocardiogram showed sinus rhythm, low voltage complexes, and flattening of the T waves in the chest leads. She responded well to digoxin and diuretics, and repeat echocardiograms showed progressive reduction in the size of the effusion. She continued to have clinical evidence of heart failure, with a triple rhythm and tachycardia, but was well enough to return to her college. Daunorubicin was withdrawn and she remained in haematological remission on monthly five-day courses of thioguanine, cytosine arabinoside, and prednisolone. After a further five months her leukaemia relapsed and despite an intensive course of cytotherapy with a combination of thioguanine, cytosine arabinoside, methotrexate, prednisolone, cyclophosphamide, and vincristine, remission was never again achieved. In December 1974 she was readmitted with systemic candidiasis and intractable heart failure and died a week later. An echocardiogram was suggestive of a thickened myocardium and there were no new changes on the electrocardiogram.

FIG. 1 Two apical slices of heart demonstrating endocardial fibrosis with superimposed thrombus.

FIG. 2 Photograph of a histological section (stained with elastic van Gieson) of the left ventricular wall. Thrombus (A) is seen overlying the endocardial fibrosis (B), fibrosis. (C) Fibrosis extends into the underlying myocardium.

Necropsy

The body was that of a thin, young woman (weight 59 kg, height 173 cm). The necropsy was limited to an examination of the thoracic and abdominal viscera. All the internal organs were pale, there was a mild hepatosplenomegaly (liver weight 1970 g; spleen weight 280 g) but otherwise no macroscopical abnormality was seen in the abdominal viscera. The significant findings were in the chest, both lungs being oedematous (right lung 950 g; left lung 600 g). 70 ml clear straw-coloured fluid were present in the pericardial cavity and the heart was enlarged, weighing 500 g. Both chambers of the heart were slightly dilated (mitral valve circumference 11 cm, tricuspid valve circumference 13 cm). Fibrous thickening of the endocardium was present in both ventricles. On the right the fibrosis was confined to the apical region producing endocardial thickening of up to 0.1 cm. In the left ventricle the endocardial fibrosis was most obvious at the apex where it reached a thickness of 0.3 cm; however it rapidly diminished away from the apical region, the papillary muscles, chordae tendineae, and valves being uninvolved. A 3 cm mass of thrombus was superimposed on the apical fibrosis in the left ventricle (Fig. 1). Histological sections of the heart showed that the endocardial thickening was a result of the deposition of mature collagen, upon which thrombus was superimposed (Fig. 2). The deeper layers of the thickened endocardium showed a conspicuous vascularity with numerous small capillary blood vessels. This vascular fibrous tissue extended irregularly into the inner third of the underlying myocardium and was associated with a heavy deposition of haemosiderin. In addition to the associated chronic inflammatory infiltrate, occasional primitive cells of the myeloid series were seen. The myocardium away from the scarred areas showed dilated capillary blood vessels and an

increase in interstitial connective tissue but no other significant abnormality. Histological sections of other organs confirmed the macroscopical findings and many organs were infiltrated by leukaemic cells. The bone-marrow was hypercellular and replaced by primitive myeloid cells.

Discussion

The cardiotoxic effects of daunorubicin have been known since the first clinical trials (Tan *et al.*, 1967; Macrez *et al.*, 1967). The usual clinical features are tachycardia, hypotension, and intractable heart failure. These effects appear to be dose-related in children but not in adults, where they may be quite abrupt in onset, with few specific warning signs. Serial electrocardiograms during therapy may show arrhythmias, depression of the ST segments, and T wave inversion, which are more frequent in the elderly (Toghill *et al.*, 1971). Cardiotoxicity usually appears after at least three months of therapy and within one hundred days of the last dose (Halazun *et al.*, 1974). Malpas and Scott (1969) warned against using daunorubicin in continuous high dosage and reported three patients who developed cardiotoxicity after having received less than 300 mg of the drug. It has been estimated that approximately 10 per cent of patients receiving daunorubicin die as a result of cardiotoxicity (*British Medical Journal*, 1967). The other two maintenance drugs used in this patient, cytosine arabinoside and thioguanine, have not been described as being cardiotoxic, either administered alone or in combination (D. A. G. Galton, 1975, personal communication).

The structural changes induced in the heart by daunorubicin were first reported by Ripault, Weil, and Jacquillat (1967) and included patchy myocardial degeneration and fibrosis and intraventricular thrombosis. More recent studies by Buja *et al.* (1973) have confirmed these findings and related the severity of damage to the total dose of daunorubicin received. In our patient the heart showed all these features, with extensive myocardial fibrosis extending through the inner third. The distribution of the cardiac damage and the presence of haemosiderin are difficult to explain. There was no infiltration by eosinophils.

Endomyocardial fibrosis is endemic in several tropical countries affecting the indigenous population (Davies, 1948) as well as Europeans who have lived there for some time (Brockington *et al.*, 1967). It usually begins as a non-specific febrile illness merging eventually into congestive cardiac failure. Morphologically there is fibrosis of the inflow tract and at the apex of one or both ventricles. This reduces the elasticity of the heart and, if the

chordae tendineae are involved, causes regurgitation of the atrioventricular valves. There is commonly a pericarditis without constriction. In early cases the endocardial lesions are covered by thrombus but in chronic cases thrombus is rarely seen. The cause is unknown but studies have focused on an immunological disorder, and hypersensitivity reactions to streptococcus (Abrahams, 1959), filaria (Ive *et al.*, 1967), and malaria (Shaper *et al.*, 1967) have been suggested. A similar condition was described by Löffler (1936) in two Europeans with non-tropical endomyocardial fibrosis and striking eosinophilia. Morphologically and histologically tropical endomyocardial fibrosis and Loeffler's fibroplastic endocarditis are indistinguishable, apart from the comparative lack of superficial thrombus in the former (Brockington and Olsen, 1972). Eosinophilia is pronounced in Loeffler's endocarditis (average 32 000/mm³), compared with endomyocardial fibrosis in Europeans resident in Africa (average 7000/mm³) and tropical endomyocardial fibrosis (average 685/mm³). Furthermore, some 40 per cent of patients with eosinophilic leukaemia are said to develop endomyocardial fibrosis indistinguishable from the types mentioned above (Odeberg, 1965).

It is possible, therefore, that endomyocardial fibrosis may be the end result of a variety of initiating factors linked in some way by an altered reaction to various toxins or allergens. In West Africa and in Europeans living in the tropics this factor may be parasitic or bacterial. In other instances the presence of eosinophilia suggests a hypersensitivity state. Indeed, the possibility of eosinophils themselves being cardiopathic cannot be ignored (Brockington, Luzzato, and Osunkoya, 1970). As far as daunorubicin cardiotoxicity is concerned eosinophilia has not been reported and it was not seen in our patient, whereas the morphology and histology of the heart was identical with endomyocardial fibrosis. The absence of cardiotoxicity with anti-leukaemic treatment regimens not incorporating daunorubicin suggests that this drug has a direct toxic effect upon the heart (Smith, 1969) and we believe that the findings in this present case support such an effect.

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