Pathology of the heart and conduction system in lymphoma and leukaemia

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The clinical and pathological findings in two patients with non-Hodgkin's lymphoma and two patients with T helper cell prolymphocytic leukaemia affecting the heart are described. All four patients had extensive malignant disease, with infiltration of multiple organs. Cardiac infiltration varied from microscopic foci in one case, to grossly identifiable tumour deposits destroying and replacing normal heart structures in three cases. Two patients with infiltration of the conduction system had abnormal electrocardiograms and cardiac dysfunction: one died suddenly, and the other died in heart failure. A third patient with widespread cardiac lymphoma did not show any electrocardiographic abnormalities or dysfunction. Clinicians should be aware of the possibility of cardiac and conduction system disease, particularly in the light of the evolution of specific antitumour chemotherapeutic agents.

There is growing awareness of both the pathological appearances and the clinical effects of infiltration of the heart in diseases affecting several organs. Diminished myocardial function and the production of conduction defects have been reported in systemic amyloidosis,¹⁻⁶ Wegener's granulomatosis,⁷⁻⁹ systemic lupus erythematosus,¹⁰ rheumatoid disease,¹¹ polyarteritis nodosa,^{12 13} and scleroderma.¹⁴ Metastases occur more frequently than primary tumours in the heart; bronchogenic carcinoma, malignant lymphoma, and leukaemia share a particular tendency to cardiac infiltration.¹⁵ This study illustrates the clinical and pathological findings in four patients with lymphoma and leukaemia, resulting in cardiac disease.

Patients and methods

After full necropsies and careful examination of the hearts in four patients the conduction system tissues were dissected. The sinus and atrioventricular nodal areas were identified and serial blocks taken. Multiple sections were stained with haematoxylin and eosin and van Gieson's solution.

The table shows the clinical and pathological

findings. All four patients had widespread lymphomatous or leukaemic dissemination, with grossly identifiable cardiac disease in cases 1, 2, and 3. Cases 1 and 2 had associated electrocardiographic and dysfunctional abnormalities. Case 1 showed extensive interatrial septal deposits (fig 1), sinus and atrioventricular nodal replacement, and infiltration of the His bundle, with degeneration of the conducting myofibrils (fig 2); the proximal bundle branches were also affected (fig 3). Case 2 showed leukaemic cells in the epicardium, and in the autonomic nerves and

Fig 1 Case 1: opened right atrium and ventricle show pale, nodular tumour deposits elevating endocardium of interatrial septum and thickening atrial walls.

Table Clinical and pathological findings in four patients with cardiac lymphoma and leukaemia

Case No	Age and Sex	Diagnosis	Clinical course	ECG	Cardiac disease	
					General	Conducting tissues
1	63 Female	Non-Hodgkin's lymphoma	Sudden death	Atrial flutter atrioventricular dissociation; incomplete right bundle branch block	Nodular tumour deposits atrial walls and interatrial septum	Tumour replacement SA node, AV node, His bundle and proximal bundle branches
2	81 Male	T helper cell prolymphocytic leukaemia ¹⁶	Initial response to deoxycoformycin; refractory cardiac failure	Atrial fibrillation, left anterior hemiblock, wide QRS complexes, ST/T wave changes	Pale tumour deposits in pericardium, atrial, and ventricular myocardium	Tumour superficially in SA node, superficial to AV node; origin, proximal mid-course left bundle branch
3	74 Female	Non-Hodgkin's lymphoma	Died—chest infection	Sinus rhythm, atrial ectopics	Diffuse tumour pericardium, myocardium, both ventricles	Tumour superficially in SA node, upper bundle branches
4	74 Female	T helper cell prolymphocytic leukaemia	Initial response to deoxycoformycin; deteriorating renal function	Sinus tachycardia	Focal infiltration epicardium of atrioventricular sulci	

SA = sinoatrial (sinus) node; AV = atrioventricular node.

ganglia overlying, and associated with, the superficial aspects of the sinus node (fig 4).¹⁶ The left bundle branch was also diseased (fig 5).

Discussion

Roberts *et al*¹⁷ carried out a necropsy study of 196 patients with malignant lymphoma and found cardiac disease in 48 cases. Of the lymphoma subtypes, cardiac infiltration was seen in 16% of the patients with Hodgkin's disease, 25% of the patients with non-Hodgkin's lymphoma, and 33% of the patients with mycosis fungoides. Of these 48 patients, lymphoma was identified grossly in the heart in 27 cases and found on microscopical examination alone in 21. The most common disease sites were the pericardium and epicardial fat, particularly in the atrioventricular sulci. Nodular deposits within the cardiac chambers were also found. There were electrocardiographic abnormalities in 66%, and these were mainly sinus tachycardia and ST-T wave changes. When they compared these patients with a control group, they found that in only few cases were the electrocardiographic changes attributable to lymphoma. In five patients the degree of tumour infiltration was sufficient to cause either congestive heart failure due to myocardial lymphoma, or electrocardiographic abnormalities because of right atrial and interatrial septal tumour deposits. Two cases of mycosis fungoides had several abnormalities as a result of right atrial disease, including atrial flutter, fibrillation, right bundle branch block, and atrioventricular dissociation. They concluded that there was a noticeable discrepancy

Fig 2 Case 1: triangular shaped His bundle, sitting in surrounding central fibrous body, shows diffuse lymphomatous infiltration and degenerate conducting myofibrils.

Fig 3 Case 1: proximal bundle branch tumour infiltration. Endocardium (right), interventricular septal muscle (left).

between the incidence of cardiac lymphoma and the lack of dysfunction it produced.

This is reflected in case 3 of the present study, where despite extensive cardiac lymphoma—even seen on gross examination of the myocardium—and focal sinus node and bundle branch disease, there was no clinically important cardiac dysfunction. This contrasts with case 1, which shows many of the typical features of cardiac lymphoma. The pericardium and epicardium were thickened by tumour, and the atria contained pale, nodular deposits, particularly in the interatrial septum. These sites showed partially necrotic tumour, which obliterated and replaced the sinus and atrioventricular nodes, and diffuse lymphomatous infiltration of the common His bundle and proximal bundle branches. This resulted in atrial flutter, incomplete right bundle branch block, and atrioventricular dissociation. Nodular epicardial, right atrial, and interatrial septal tumour masses have been noted in Hodgkin's disease,¹⁸ non-Hodgkin's lymphoma,^{15, 19, 20} and Burkitt's lymphoma.²¹ These produced symptomatic Stokes Adams attacks with

atrioventricular block,¹⁸ and complete heart block was seen on electrocardiography.^{15, 20, 21} Infiltration and destruction of conducting myofibres were found in the atrioventricular node^{20, 21} and the common His bundle,^{18, 20} but these findings were not illustrated. Sudden death has been described in patients with cardiac lymphoma, due to rupture of the infiltrated myocardium, resulting in haemopericardium.¹⁹ Case 1 died unexpectedly perioperatively, and no doubt conduction system disease contributed to this; as similarly, in sudden death this occurred in other diseases such as amyloidosis^{4, 5, 6} or sarcoidosis.²²

Leukaemic infiltration of the atrioventricular septa, with resultant atrioventricular dissociation was described in 1949;²³ in 1950 Mahaim and Rossier reported infiltration of the sinus node and His bundle by myeloid leukaemia in a patient with progressive atrioventricular block.²⁴ Complete heart block in an 8 year old leukaemic patient has also been reported.²⁵ Widespread prolymphocytic leukaemia with variable

Fig 4 Case 2: heavy infiltration by prolymphocytic leukaemic cells of epicardial fat (top) and nerves (N) lying superficial to periphery of sinus node. Nodal substance (NS) shows light, focal infiltration around sinus nodal artery (SA).

Fig 5 Case 2: tumour infiltration of proximal left bundle branch (BB). Subendocardium (right of field), interventricular myocardium (left).

degrees of cardiac infiltration occurred in two cases (2 and 4). Case 2 had extensive cardiac disease in the myocardium and conduction system, resulting in refractory cardiac failure and an abnormal electrocardiogram. Heavy infiltration of the epicardial fat and nerves overlying the sinus node, as well as direct nodal disease, suggests that local nerve damage may have caused rhythm disturbance.^{9 26} An awareness of the possibility of cardiac dysfunction induced by tumour is of considerable practical importance, and is emphasised by case 2. Deoxycoformycin should not be given if the glomerular filtration rate is less than 60 ml/minute, but as the leukaemia affected cardiac function, and thus renal function, a case could be made for the use of deoxycoformycin in a reduced dose as a genuine attempt to improve cardiac function and minimise conduction abnormalities. This principle may be applied to other chemotherapeutic agents in cardiac lymphoma or diseases such as Wegener's granulomatosis, in which complete heart block regressed to right bundle branch block, following successful treatment of the clinical exacerbation

with temporary pacing and cyclophosphamide.⁷

In conclusion, the clinician should be aware of the existence and possibility of treating cardiac disease in malignant lymphoma and leukaemia. The electrocardiogram is not a sensitive indicator of cardiac infiltration; nevertheless, electrocardiographic abnormalities in patients with these diseases may sometimes be an indication for further invasive investigation, including possibly, myocardial biopsy, to establish a definitive diagnosis with a view to administering specific treatment.

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