

Bone Marrow Involvement in Malignant Lymphoma without Peripheral Lymphadenopathy

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SUMMARY

Twelve cases of non-Hodgkin's lymphoma and a single case of Hodgkin's disease were first diagnosed on bone marrow biopsy. None of the patients had superficially enlarged lymph nodes, and in 3 patients the histological examination of the biopsy specimen showed normal reactive nodes. Eight patients were over the age of 60. The differential diagnosis from benign nodular lymphoid hyperplasia is discussed, with emphasis on the cytology and the paratrabecular position of the lymphoid infiltrate. Ten patients had focal involvement of the bone marrow and 1 of the 3 patients with diffuse involvement had Hodgkin's disease. Lymphoid nodules occur normally in the bone marrow and we conclude that non-Hodgkin's lymphoma and Hodgkin's disease can arise primarily in the bone marrow.

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All patients referred to Tygerberg Hospital for bone marrow examination undergo routine aspiration and trephine biopsy. During the period 1 September 1975-31 November 1976, 606 biopsies were performed and in 13 patients the diagnosis of haematological malignancy was first made on bone marrow biopsy. None of these patients had enlarged lymph nodes but 5 had hepatosplenomegaly.

PATIENTS AND METHODS

In the 13 patients the haematological malignancy was not suspected and the provisional diagnosis was bone marrow failure, anaemia or some other condition. All patients were treated at Tygerberg Hospital and 3 have subsequently died. Postmortem material was available from 1 of the 3 patients who died. The biopsies were performed with both Westerman-Jensen and Jamshidi needles. After an initial decalcifying step, sections were cut and stained with haematoxylin and eosin, Giemsa, and periodic acid-Schiff (PAS) stains. All cases have been classified according to the classification proposed by Dorfman.¹

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The 13 patients (Table I) ranged in age from 18 to 77 years, with a mean age of 66 years. Eight were male and 5 were female. All patients were anaemic, 7 severely so at the onset. Of the latter, 4 had pancytopenia as possible evidence of bone marrow invasion. The other 3 severely anaemic patients had refractory normochromic anaemia, haemolytic anaemia and iron deficiency anaemia respectively. Others presented with loss of weight, upper abdominal pain, haematuria and purpura, and blurring of vision. The 2 youngest patients (18 and 33 years) both presented with pyrexial episodes, initially diagnosed as brucellosis.

None of the patients had superficially enlarged nodes, but in the 3 in whom 'blind' biopsies of nodes were performed the histology revealed reactive changes. In 1 patient (case 5) a second 'blind' biopsy eventually revealed obliteration of the architecture, with commencing infiltration of the capsule. Five patients had hepatosplenomegaly, 1 had a palpable spleen and 1 a palpable liver. In 6 patients neither the spleen nor the liver was enlarged. In 1 patient in whom the histological finding was compatible with a diagnosis of Lennert's lymphoma,² both spleen and liver exhibited lymphomatous infiltration.

RESULTS

Histological examination of the bone marrow specimens revealed focal involvement in 10 patients and diffuse involvement in 3. In 8 of those with focal distribution the infiltrate was paratrabecular (Fig. 1); in 6 the specimen contained atypical lymphocytes and in 2 there were lymphocytes with plasmacytic differentiation and PAS positivity in a proportion of the cells. Of the remaining 2 patients whose specimens showed focal distribution, one had a malignant lymphoma with numerous epithelioid histiocytes (case 9, Lennert's lymphoma, Figs 2 and 3) and the other had a large lymphoid lymphoma (case 13, Fig. 4). Of the 3 patients with diffuse involvement, 1 had an atypical small lymphocytic lymphoma, 1 had a large cell lymphoma (Fig. 5), and 1 had Hodgkin's disease (Fig. 6). Therefore, the cells were atypical small lymphocytes in 7 specimens, 6 with focal involvement and 1 with diffuse involvement. As all the patients had bone marrow involvement they were in stage IV at diagnosis (6 were in stage IVB). Three patients died of opportunistic infections (cases 6, 10 and 13) but consent for postmortem was obtained in only 1 case. This patient (case 6) had presented with pancytopenia and bone marrow failure. Bone marrow biopsy revealed focal involvement and lymphocytes with plasmacytic differentiation and PAS positivity. At autopsy all organs contained focal areas of necrosis without any cellular reaction. Acid and alcohol-fast tubercle bacilli were found in these foci on Ziehl-Neelsen staining.

TABLE I. CLINICAL INFORMATION, HAEMATOLOGICAL FINDINGS AND HISTOPATHOLOGY

Case	Age	Sex	Presenting symptoms	Haematology			Clinical data		Bone marrow histology
				Hb (g/100 ml)	WBC (/ μ l)	Platelets ($\times 10^3$ / μ l)	Liver enlarged (cm)	Spleen enlarged (cm)	
1	64	F	Tiredness, symptoms of anaemia	9,1	5 900	220	0	0	Focal paratrabeular — atypical small lymphocytic lymphoma
2	62	M	Upper abdominal pain, dyspnoea	12,9	6 500	200	5	5	Focal paratrabeular — atypical small lymphocytic lymphoma
3	43	M	Abdominal pain, loss of appetite and weight	11,5	1 700	155	8	8	Focal paratrabeular — atypical small lymphocytic lymphoma
4	62	M	Shortness of breath, palpitations	4,6	7 700	290	0	0	Focal paratrabeular — atypical small lymphocytic lymphoma
5	68	M	Haematuria, purpura, ischaemic heart disease	12,6	7 300	126	0	0	Focal paratrabeular — atypical small lymphocytic lymphoma
6	44	M	Skin rash, fever	11,6	1 700	97	0	±	Focal paratrabeular — lymphocytic lymphoma with plasmacytic differentiation
7	69	F	Weight loss, pruritus	11,5	4 900		2	3	Focal paratrabeular — atypical small lymphocytic lymphoma
8	67	F	Blurred vision left eye	10,8	6 600	495	0	0	Focal paratrabeular — lymphocytic lymphoma with plasmacytic differentiation
9	69	F	Massive splenomegaly, symptoms of anaemia	7,4	3 300	29	14	18 (1 200 g)	Focal — lymphoma with numerous epithelioid histiocytes
10	50	F	Haematemesis, epistaxis, melaena, tiredness	6,3	1 900	21	3	0	Focal — large lymphoid pyroninophilic lymphoma
11	33	M	Fever, night sweats, loss of weight	8,4	4 000	164	0	2	Mixed cell Hodgkin's disease
12	18	M	Polyarthralgia, pyrexia, night sweats	7,5	4 700	150	0	0	Diffuse — atypical small lymphocytic lymphoma with marrow replacement
13	77	M	Pyrexia, malaise	8,6	1 800	40	4	10	Diffuse — large lymphoid lymphoma

DISCUSSION

Lymphomas, including Hodgkin's lymphoma, usually present as localized malignant tumours, originating in lymph nodes, spleen, or extranodal lymphoid tissue. Localized disease is more common in Hodgkin's disease and in the large-cell lymphomas. Young patients with Hodgkin's disease usually present with well-defined local

tumours, whereas in older patients the disease is often multifocal from the start.³

There is a high incidence of bone marrow involvement at the outset in the nodular, small lymphoid cell group — up to 85% in some series.⁴ This accounts for almost one-third of all patients with non-Hodgkin's lymphomas.⁵ Of the patients with large-cell lymphomas, less than 10% have bone marrow involvement, even with widespread

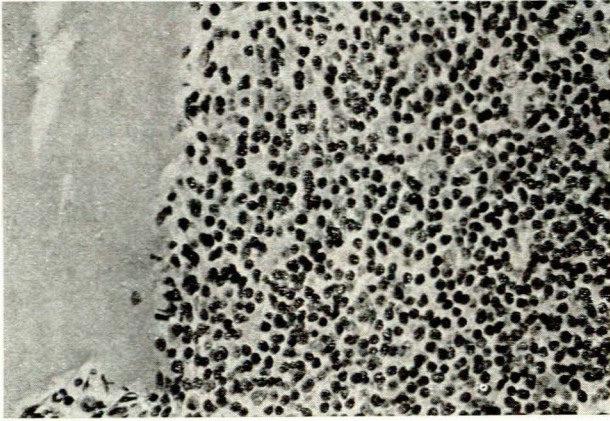


Fig. 1. Trephine biopsy specimen from patient with atypical small lymphocytic lymphoma illustrating the paratrabeular position of the cells (H and E $\times 250$).

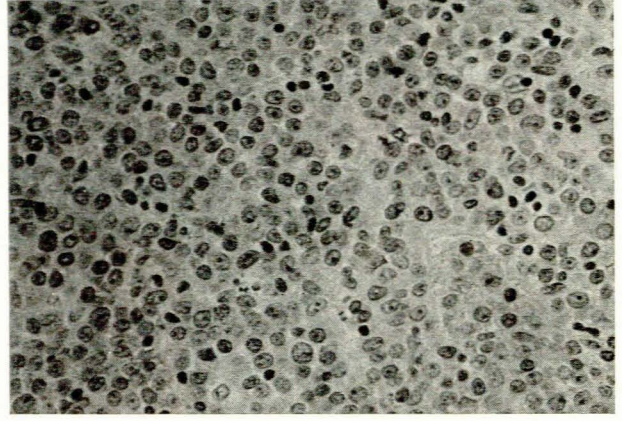


Fig. 4. Trephine section showing a focus involved with a large lymphoid malignancy. The cells have thin rims of cytoplasm, vesicular nuclei and fairly prominent nucleoli (H and E $\times 400$).

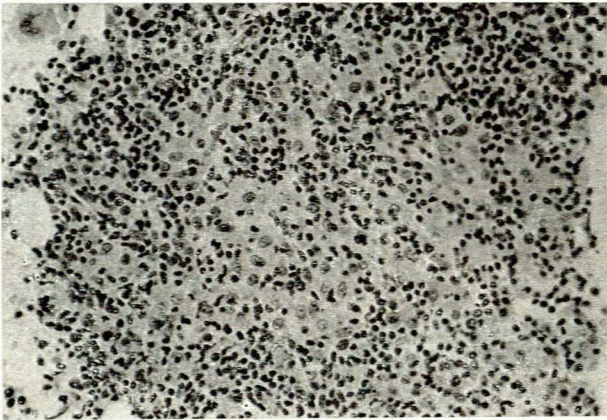


Fig. 2. Trephine biopsy specimen from patient with Lennert's lymphoma exhibiting a focus of atypical lymphocytes and epithelioid histiocytes (H and E $\times 100$).

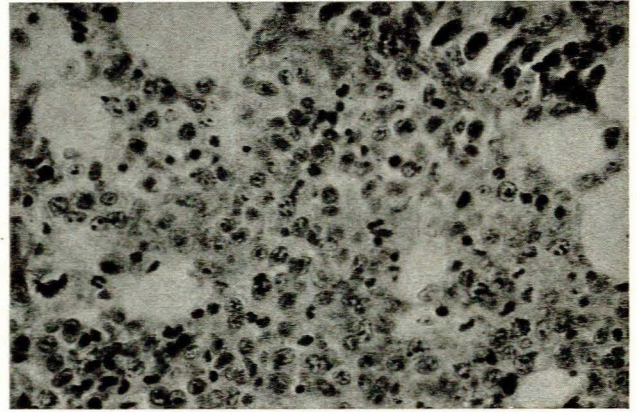


Fig. 5. Trephine section illustrating diffuse infiltration of bone marrow with large lymphoid cells. The cells have inconspicuous cytoplasm, vesicular nuclei and prominent nucleoli (H and E $\times 400$).

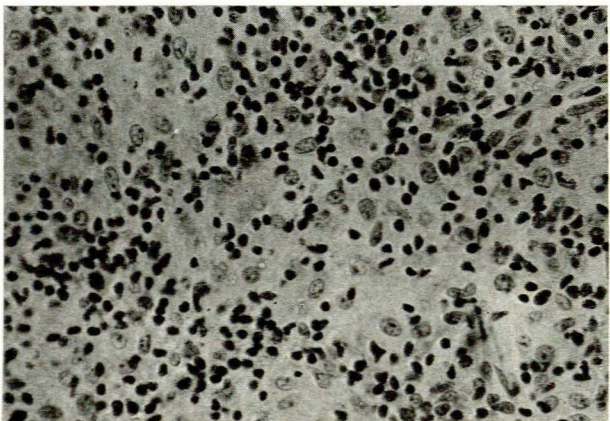


Fig. 3. Higher magnification of Fig. 2, demonstrating the open vesicular nuclei, inconspicuous nucleoli and abundant cytoplasm of the epithelioid histiocytes. Scattered among them are atypical lymphocytes (H and E $\times 400$).

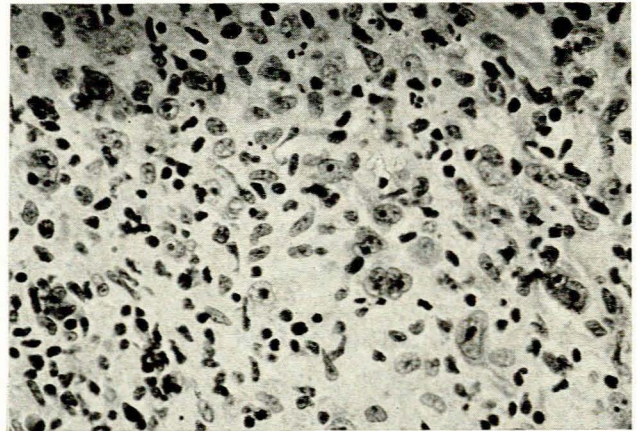


Fig. 6. Trephine biopsy specimen from patient with Hodgkin's disease, showing Reed-Sternberg cells surrounded by atypical lymphocytes, Hodgkin's mononuclear cells and some bland histiocytes.

clinical disease.⁴ In spite of this the prognosis is better with the small lymphoid cell group.⁴ Focal bone marrow involvement usually appears in a distinct paratrabeular position.⁸ Malignancies often show a predilection for the paratrabeular areas, and this is a good means of differentiation from the entity of nodular lymphoid hyperplasia.⁷

It has long been recognized that lymphoid nodules commonly occur in the bone marrow.⁸⁻¹² As such they constitute a normal finding without any clinical significance. Sometimes in the elderly it is difficult to decide whether infiltrates of lymphoid tissue are malignant or whether they constitute the entity of nodular lymphoid hyperplasia. Cytologically the normal lymphocyte can be differentiated from the atypical lymphocyte whose nucleus is oval, elongated and sometimes cleft. The appearance of prolymphocytes and lymphoblasts is said to favour a malignancy,⁷ but they can occur in normal proliferation centres.

As a result of our practice of doing trephine biopsies on all patients in whom bone marrow examinations are requested,¹³ we have found 13 patients with lymphomatous infiltrates of the bone marrow. The atypical small lymphocyte was the commonest type encountered (7 cases), but 2 patients showed small lymphocytes with plasmacytoid differentiation, 1 patient had a Lennert's lymphoma, 2 had large lymphoid lymphomas, and 1 had Hodgkin's disease. In none of the patients were the superficial lymph nodes palpable, and in 3 patients biopsy revealed no lesion. In 1

patient, however, a subsequent biopsy of one node revealed lymphomatous infiltration. In only 1 of the 6 patients with hepatosplenomegaly was tissue obtained to document lymphomatous infiltration (case 9); in this patient both liver and spleen were characteristically infiltrated, with atypical lymphocytes and epithelioid histiocytes.

The bone marrow is a lymphoid organ and a lymphoma can therefore arise in this situation just as it can at any other extranodal site. We therefore perform bilateral trephine biopsy in all suspected cases of malignancy, even if there is no obvious lymphadenopathy. In none of these patients did the aspiration assist in the diagnosis.

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