Non-Hodgkin's Lymphoma of Bone Marrow - An Unusual Presentation

Pages with reference to book, From 230 To 236

Khalid Hassan (Al-Nasser Polyclinic, Tabuk, Saudi Arabia.)
Abdnl Hannan Nagi (Allama Iqbal Medical College, Lahore.)
Abdul Hayee (K.E. Medical College, Lahore.)

Abstract

A clinico-morphological study of twelve patients of non-Hodgkin's lymphomas, diagnosed on bone marrow biopsy, is presented. They manifested with pyrexia of uncertain origin and/or unexplainable anaemia. These patients did not show any superficial lymphadenopa-thy, mediastinal lymph node enlargement or a specific mass in the abdomen. Eleven patients showed enlargement of the liver, whereas, eleven manifested with splenomegaly. Bone marrow aspirate and trephine biopsy performed as an investigational procedure, lead to a diagnosis of non-Hodgkin's lymphoma. According to the classification by W.H.O. (I978), six of them showed diffuse lymphoblastic lymphosarcoma, whereas, in the remaining six patients, the histological type was diffuse lymphocytic lymphosarcoma (JPMA 32:230, 1982).

Introduction

The commonest early manifestation of malignant lymphomas is the enlargement of a single superficial lymph node or a lymph node group, in an otherwise asymptomatic patient (Rappaport, 1966; Freeman et al., 1972; Jones et al., 1973; Rosen et al., 1977). A variable number of patients show a mediastinal lymph node enlargement (Bharat et al., 1976; Rosen et al., 1977). In some instances, the patients of non-Hodgkin's lymphomas may present with an extranodal involvement (Rappaport, 1966; Hellman et al., 1975). Different primary extranodal sites are skin, testis, pharynx, gastro-intestinal tract, salivary glands, breast, bones and spleen (Abell and Holtz, 1968; Parkhill, 1968; Nobrega and Harrison, 1973; Al-Salecm and Blady, 1970; Hamlin et al., 1972; Kim and Dorfman, 1974; Edelsen and Aftab, 1975; Hellman et al., 1975; Nordqvist and Kinney, 1976; Wolley and Canellas, 1976). In some patients, bone marrow involvement by non-Hodgkin's lymphoma may be encountered in biopsies performed as a part of diagnostic evaluation for abnormal peripheral blood parameters, fever of undetermined aetiology or unexplained organomegaly (Brunning et al., 1975).

Diagnosis of lymphomatous infiltration of the bone marrow cannot be based upon the examination of smears alone. It should be correlated with the findings in bone marrow clot (Liao, 1971) and histological examination of trephine sections (Kaplan, 1968; Jones, 1972; Goffinet, 1973). According to a number of reports (Jones et al., 1972; Jones et al., 1973; Goffinet and Kaplan, 1973; Brunning et al., 1975; Stein et al.,' 1976; Castellani and Rilke, 1977), the bone marrow trephine biopsy is superior to bone marrow smears and sections of the clot.

Poorly differentiated lymphocytic lymphoma has been observed to be the commonest varicty of lymphoma (Jones et ai., 1973; Mckenna et al., 1975; Lotz et al., 1976; Reddy et al., 1977; Stein et al., 1976; Castellani and Rilke, 1977). Well differentiated lymphocytic lymphoma is relatively less common (Stein et al., 1976; Castellani and Rilke, 1977).

Material and Methods

Patients: Twelve patients were included in this study. They presented with pyrexia of uncertain origin

and/or unexplainable anaemia, but did not manifest superficial, mediastinal or palpable abdominal lymph node enlargement.

Investigations: Patients were subjected to the following panel of investigations.

Peripheral Blood Examination

1. Haemoglobin estimation by cyanmetha-emoglobin method.
2. Erythrocyte sedimentation rate by Westergren's method.
3. White cell count.
4. Platelet count.
5. Reticulocyte count.
6. Differential leucocyte count.
7. Direct coomb's test.

Bone Marrow Aspiration

Bone marrow aspirate was obtained from posterior part of iliac crest, using Saleh's bone marrow aspiration needle. The smears were stained with May-Grunwald-Giemsa stain. The remaining aspirate was allowed to clot, and fixed in formal saline for 18-24 hours. The marrow was processed through ascending grades of acetone, cleared in xylene and embedded in molten, paraffin wax. Blocks were made, and 3-4 micron thick sections were cut. They were stained with Haemotoxylin and eosin stains.

Bone Marrow Trephine Biopsy

Bone marrow trephine biopsy was obtained, using Gardner's trephine biopsy needle. It was fixed in formal-saline and decalcified in 8% nitric acid. After processing through acetone, xylene and molten paraffin wax, multiple 3-4 micron thick sections were cut, and stained with Haemotoxylin and eosin stains.

Histological diagnosis of non-Hodgkin's lymphoma was based upon correlation between marrow smears, and sections of clots and trephines. Leukemias were excluded by performing peripheral blood picture. Classification of non-Hodgkin's lymphomas by W.H.O. (1978) was followed for histological purpose.

Results

Age and Sex: Ten patients were between 32 and 65 years of age, whereas, the remaining two were 21 and 22 years. Six of these 12 patients were between 32 and 45 years of age. Ten patients were males and two females, with a male: female ratio of 5:1 (Table I).

Table I

Clinical Features in A. Lymphoblastic Lymphosarcoma, and B. Lymphocytic Lymphosarcoma.

S. No.	Age/ Sex	Duration (Years)	Anorexia	Weight Loss	Fatigue	Fever	Night Sweats	Weakness	Pallor	Lethargy	Hepatomegaly	Splenomegaly
A. Lymphoblastic Lymphosarcoma												
1.	22/ M	8/12	++	++	+++	++	—	++	++	+		—
2.	65/ M	1	++	+++	+++	+	—	++	+++	+	1F	6F
3.	2½/ M	7/12	+	++	—	+++	—	+	+++	—	3F	2½F
4.	32/ M	6/12	++	+	++	+	++	++	++	++	1F	1F
5.	35/ M	6/12	++	++	+	++	++	+	+	+	1F	3F
6.	55/ F	1	++	+	++	++	+	+	+	++	1F	2F
B. Lymphocytic Lymphosarcoma												
1.	45/ M	6/12	—	—	—	+++	—	+	+	—	1F	2F
2.	55/ M	1	++	++	+	—	—	+	+	+	5F	6F
3.	42/ M	2	++	++	+++	++	++	++	++	+	1F	2F
4.	35/ F	6/12	+	+	+	++	+	+	+	—	3F	4F
5.	45/ M	8/12	++	++	+	+	+	+	++	++	4F	6F
6.	65/ M	6/12	+	+	++	+	+	++	++	+	1F	1F

Clinical Features: Majority of the patients (75%), presented with the symptoms of 6-8 months duration. The remaining 25% showed longer duration of symptoms (1-2 years).

Ten patients presented with pyrexia of uncertain origin and symptoms of anaemia, whereas, the remaining two patients mainly showed symptoms of anaemia along with constitutional symptoms other than pyrexia (anorexia, weight loss, fatigue and night sweats). "B symptoms" according to Ann-Arbor staging classification of lymphomas, (fever and/or night sweats and/or weight loss) were observed in all the patients. Pallor, easy fatiguability, and weakness were invariably present. Eleven patients showed a notable degree of weight loss. Other prominent symptoms included exertional dyspnoea (7 patients), and palpitations (6 patients). Pruritus was not observed in any patient.

Superficial lymphadenopathy, even on a very careful examination, was invariably absent.

Hepatomegaly was observed in eleven patients. Nine of them showed enlargement by 1-3 fingers below the subcostal margin. In the remaining two patients, the liver was moderately enlarged (4-5 fingers). Splenomegaly was present in eleven patients; in four of them, it was moderate (4-6 fingers).

Peripheral Blood Picture

Erythrocyte sedimentation rate: ESR ranged from 48-108mm after one hour. In nine of the twelve patients, it was between 60 and 90 mm after one hour.

Haemoglobin: All patients showed anaemia of variable severity. Haemoglobin ranged between 4.0 and

9.8 G/dL. In ten of the twelve patients, haemoglobin was 8.0 G/dL or less.

White cell count: Seven patients showed leucopenia, with total leucocyte count ranging between 2,000 and 4,000/cmm. One patient showed leucocytosis (white cell count-14,700/cmm). In the remaining four patients, leucocyte count was within normal limits.

Differential leucocyte count: Seven patients manifested neutropenia. The remaining five patients showed neutrophil count within normal limits. The lymphocyte count was normal in ten patients, whereas, lymphopenia was observed in two. None of these patients showed leukemic peripheral blood picture (Table II).

Table II

Haematological Parameters in A. 6 Cases of Lymphoblastic Lymphosarcoma, and B. 6 Cases of Lymphocytic Lymphosarcoma.

S. No.	*Haemoglobin G/dL*	*White Cell Count /cmm*	*Differential Leucocyte Count (/cmm)*				*Platelet Count (/cmm)*	*Reticulocyte Count (%)*
			P	*L*	*M*	*E*		
A. Lymphoblastic Lymphosarcoma								
1.	8.0	4,100	2,214	1,722	123	41	90,000	0.6
2	5.0	3,150	1,705	1,382	63	—	70,000	5.0
3.	4.0	3,050	91	2,959	—	—	90,000	0.2
4.	4.3	3,100	930	2,108	62	—	80,000	0.6
5.	8.2	3,750	1,463	2,097	190	—	80,000	0.2
6.	7.8	3,800	950	2,774	38	38	130,000	0.2
B. Lymphocytic Lymphosarcoma								
1.	7.4	4,400	3,080	1,100	220	—	150,000	1.0
2.	8.0	14,700	9,555	4,704	294	147	120,000	0.2
3.	6.4	4,150	3,158	826	166	—	130,000	0.4
4.	9.8	3,250	1,665	1,462	90	33	120,000	0.4
5.	5.7	2,050	245	1,704	72	29	80,000	0.2
6.	7.9	9,200	5,888	3,128	184	—	90,000	2.0

Platelet count: Eleven patients showed thrombocytopenia. Seven of them had a platelet count between 70,000 and 90,000/cmm.

Reticulocyte count: It was between 0.2 and 2% in eleven patients. The count was 5% in one patient.

Direct coomb's test was negative in all the patients.

Bone Marrow Aspiration and Trephine Biopsy. For the purpose of description, we followed the classification of lymphomas by W.H.O. (1978). Six patients were diagnosed to have lymphoblastic lymphosarcoma, whereas, the remaining six showed lymphocytic lymphosarcoma.

Table III

Features of Bone Marrow Smears in A. Lymphoblastic Lymphosarcoma (6 cases), and B. Lymphocytic Lymphosarcoma (6 cases).
N = Normal; D = Depressed; SD = Severely depressed; I = Increased; SI = Severely increased; NB = Normoblastic; MB = Megaloblastic.

S. No.	Cellularity	Erythropoiesis		Myelopoiesis (Cellularity)	Number of Megakaryocytes	Lymphocytes	Blast Cells
		Cellularity	Type				
A.	**Lymphoblastic Lymphosarcoma**						
1.	N	N	NB & MB	D	D	I	I
2.	D	D	NB	D	D	SI	I
3.	N	SD	NB	SD	D	I	I
4.	N	D	NB & MB	N	D	I	SI
5.	I	D	NB & MB	N	D	I	I
6.	I	D	NB	D	D	I	SI
B.	**Lymphocytic Lymphosarcoma**						
1.	N	D	NB & MB	N	D	SI	D
2.	N	D	NB & MB	D	D	SI	D
3.	N	D	NB	N	D	SI	D
4.	I	D	NB	D	D	SI	D
5.	D	D	NB	D	D	SI	D
6.	N	D	NB	D	D	SI	D

Lymphoblasts were large cells, round or oval in shape. They contained large, round or oval nuclei, containing open chromatin, and 1-2 nucleoli. Nuclear cleavage and convolutions were not observed (Fig. 1).

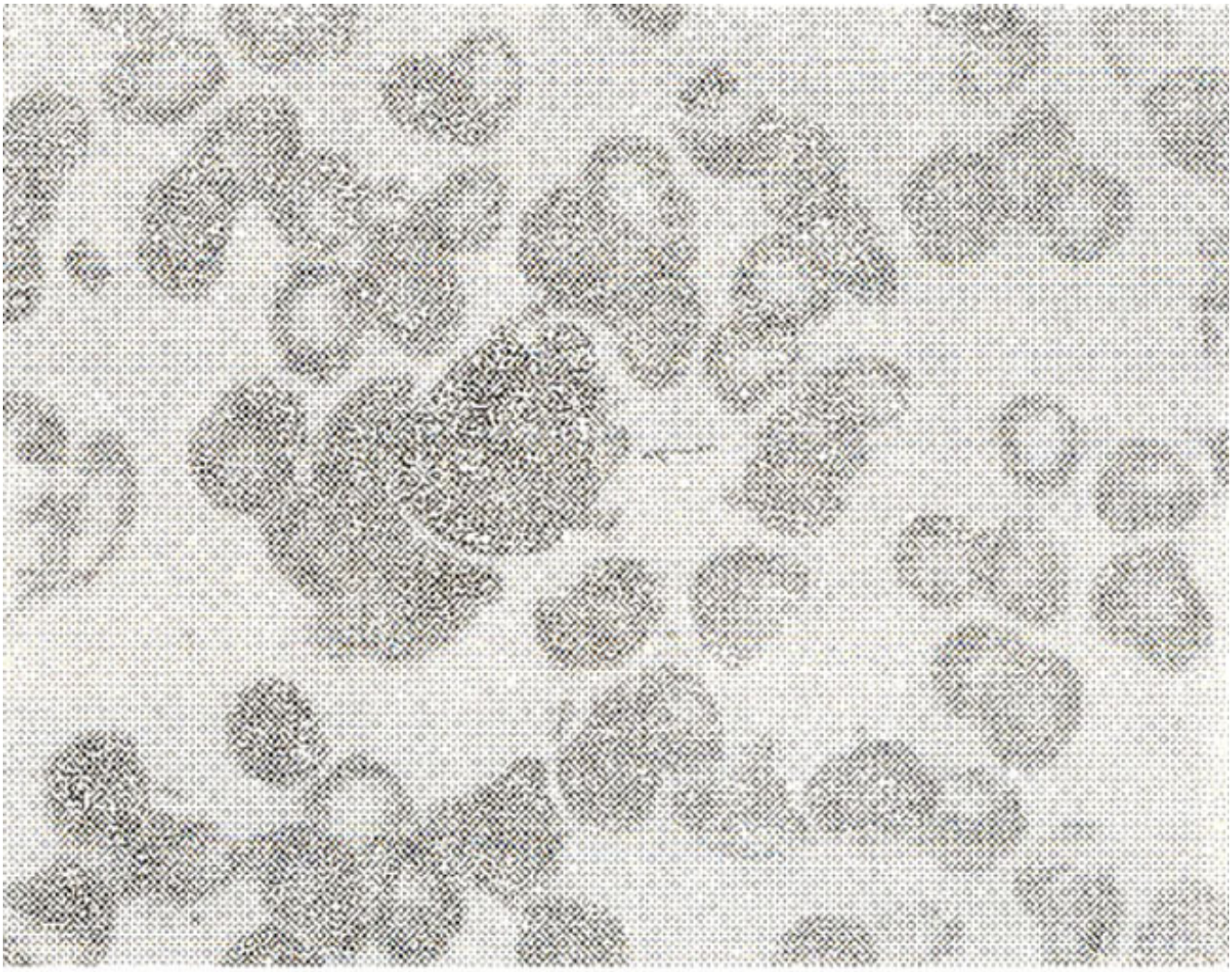

Fig. 1: Photomicrograph in a Case of Lymphoblastic Lymphosarcoma, showing a Blast Cell (arrow) in a Bone Marrow Smear. Giemsa x1250.

Bone Marrow Clot Sections: Bone marrow-clot sections could be prepared in four patients. The marrow sections were slightly hypercellular in three, and markedly hypercellular in one patient. Normal cellular elements were uni-formally depressed in all the patients. Although lymphocytes were slightly increased in number, the main cell type was lymphoblasts (Fig. 2, 3).

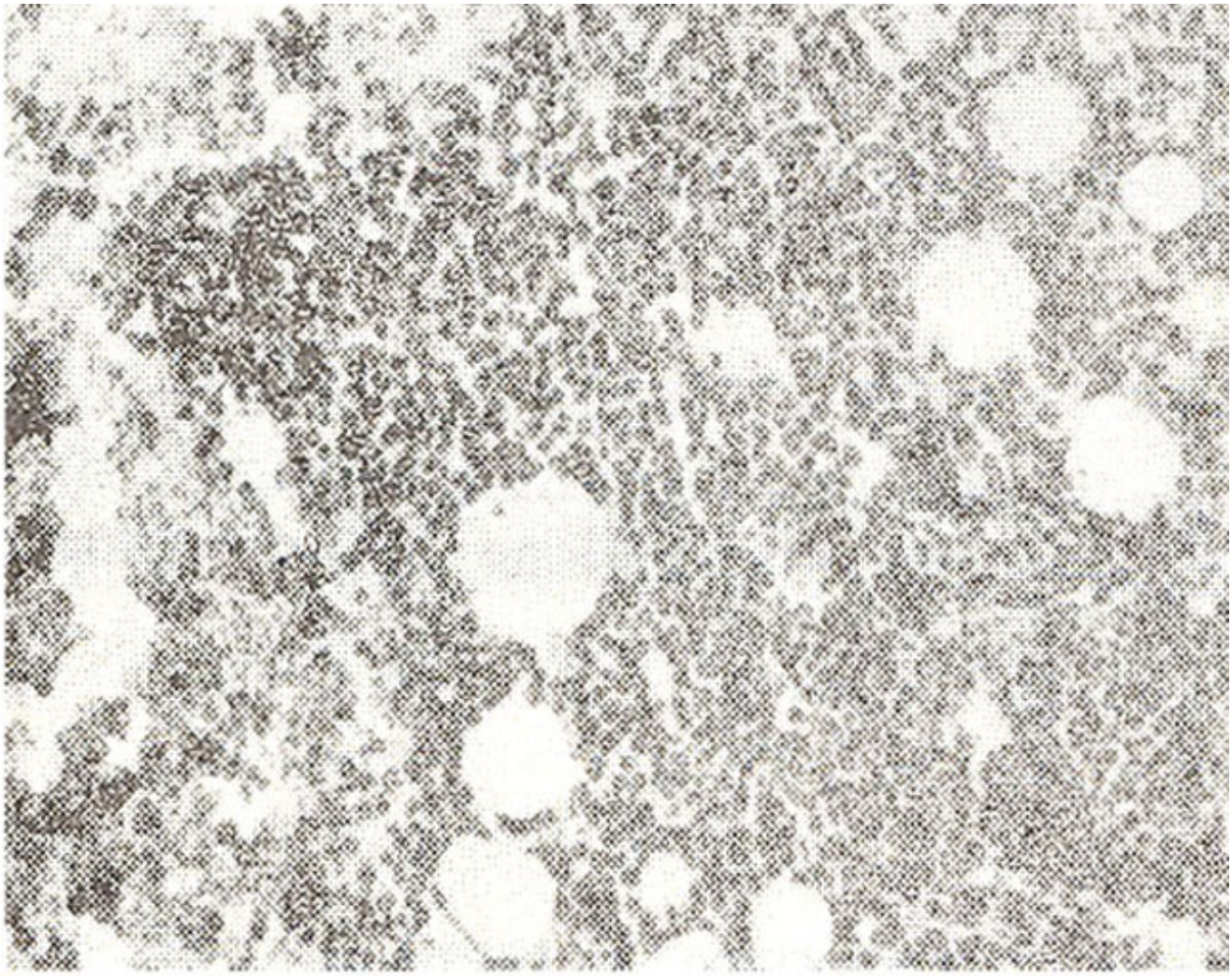

Fig. 2: Photomicrograh of a Bone Marrow Clot Section, showing infiltration by aggregates of Lymphoblasts in a Case of Lymphoblastic Lymphosarcoma. Haematoxylin and Eosin x200.

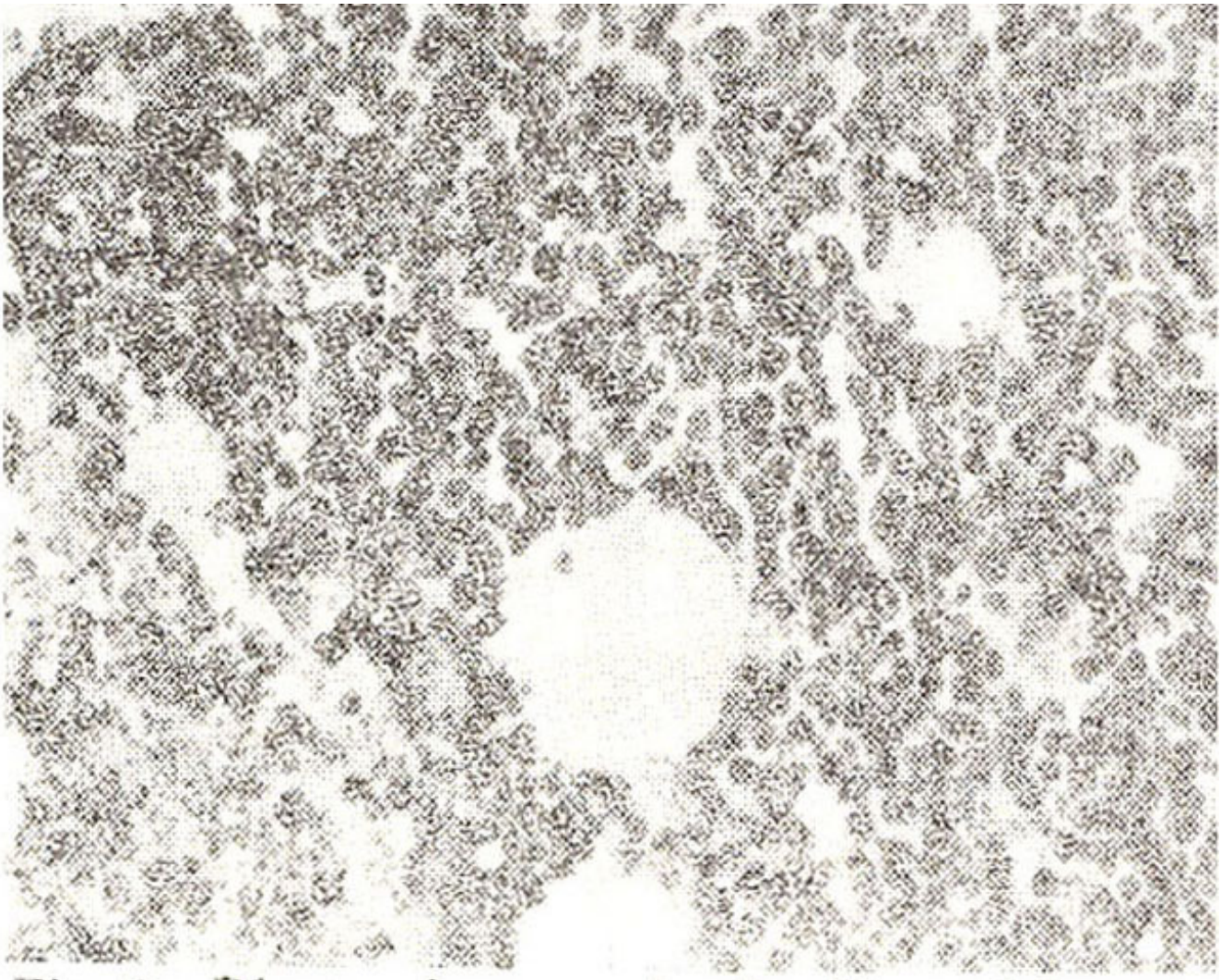

Fig. 3: Photomicrograph of a Bone Marrow Clot Section, showing infiltration by Lymphoblastic Lymphosarcoma. Haematoxylin and Cosin x500.

There was no evidence of nuclear clefting and convolutions. The lymphoblasts were scattered diffusely in the marrow fragments. However, in two of them, they also formed cell aggregates. Follicle formation was not observed.

Bone Marrow Trephine Biopsy: Trephine biopsy was performed in five patients. The marrow fragments were slightly hyperplastic in one, and markedly hyperplastic in four patients. The normal marrow cells were moderately or severely depressed in all the patients. Lymphoblasts constituted 50-75% of all the cells. Lymphoma cells were represented both in aggregates and diffusely scattered forms.

Lymphocytic Lymphosarcoma

Bone Marrow Smears: Erythropoiesis and megakaryopoicsis were depressed in four patients. A gross increase in the number of mature lymphocytes was observed in all patients (Fig. 4).

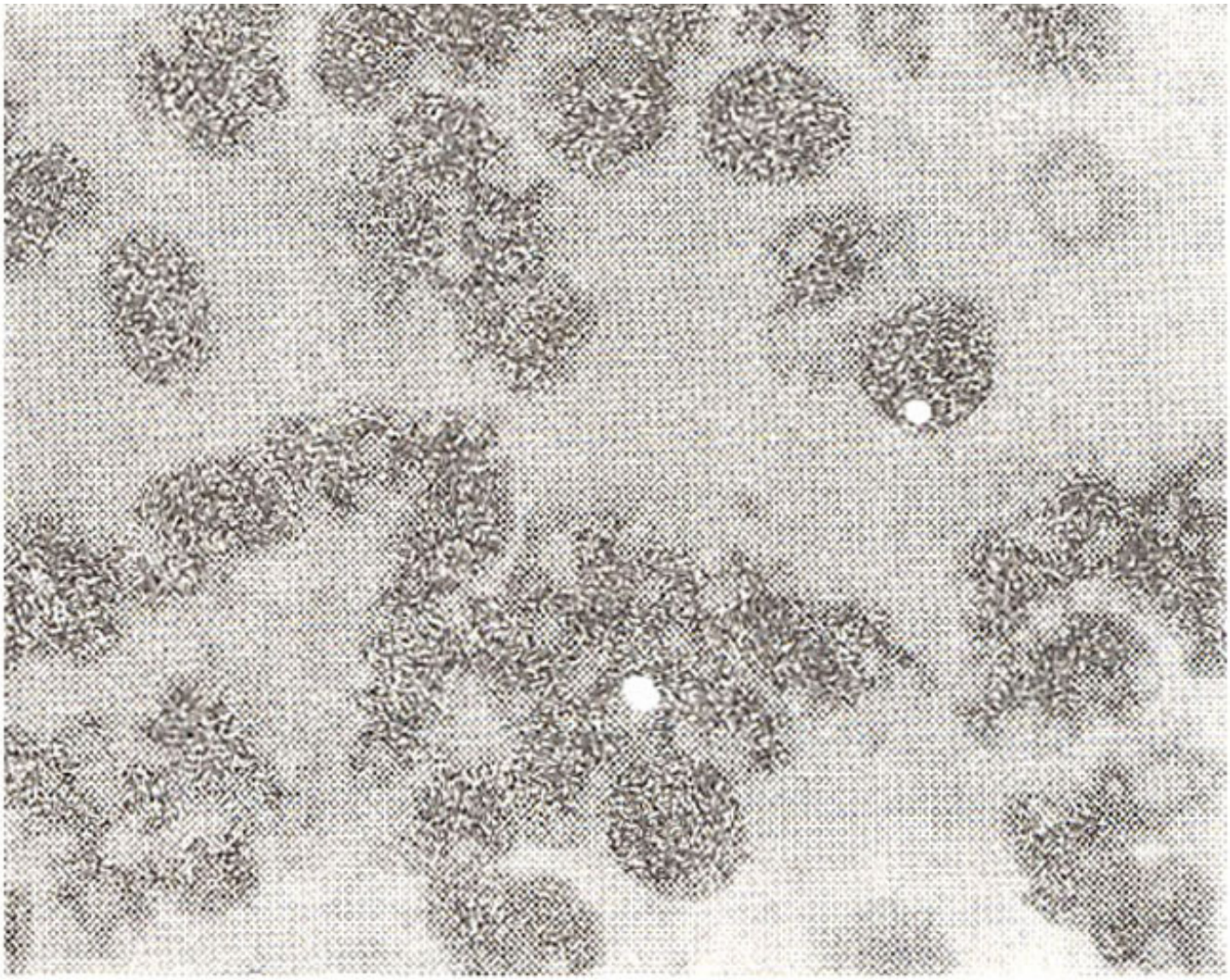

Fig. 4: Photomicrograph in a Case of Lymphocytic Lymphosarcoma, showing Mature Lymphocytes in Bone Marrow Smears. Giemsa x1250.

These cells constituted 50-70% of the nucleated cells of the marrow.

Bone Marrow Clot Sections: The clot sections could be made available in four patients. Cellularity of the marrow fragments was remarkably increased in three, and slightly in one patient. Normal marrow cells were invariably depressed. Lymphocytes constituted 50-70% of nucleated cells of the marrow. They showed the features of normal lymphocytes. These cells were present both diffusely scattered amongst the remaining normal cell, as well as in aggregates (Fig. 5).

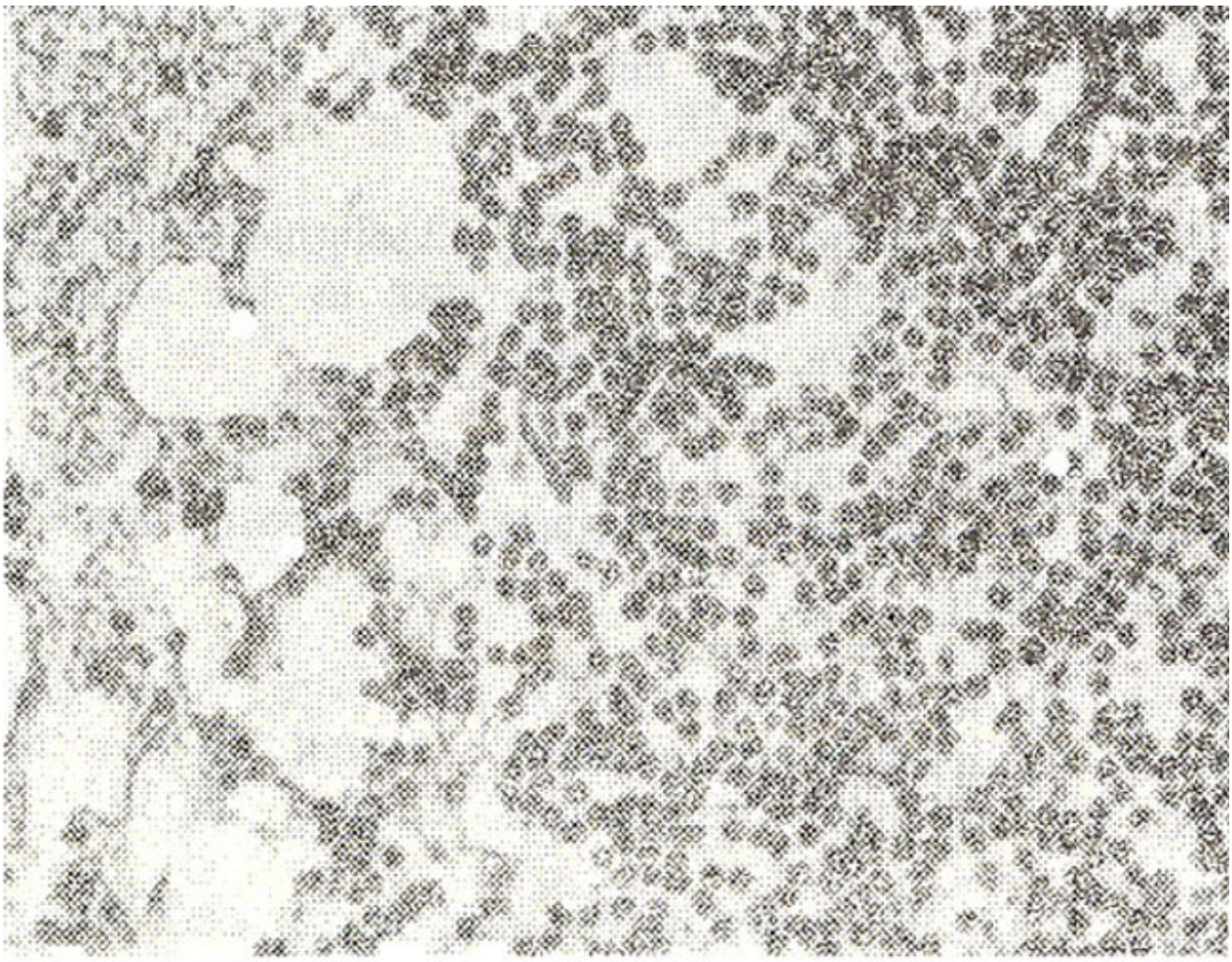

Fig. 5: Photograph of a Bone Marrow Clot Section, showing aggregate of Lymphocytes in a Case of Lymphocytic Lymphosarcoma. Haematoxylin and Eosin x500.

Bone Marrow Trephine Sections: Trephine biopsy was performed in all the patients. The marrow fragments were very hypercellular. Normal cells were grossly depressed. The main cell type was mature lymphocytes, which constituted 80-90% of the nucleated cells (Fig. 6).

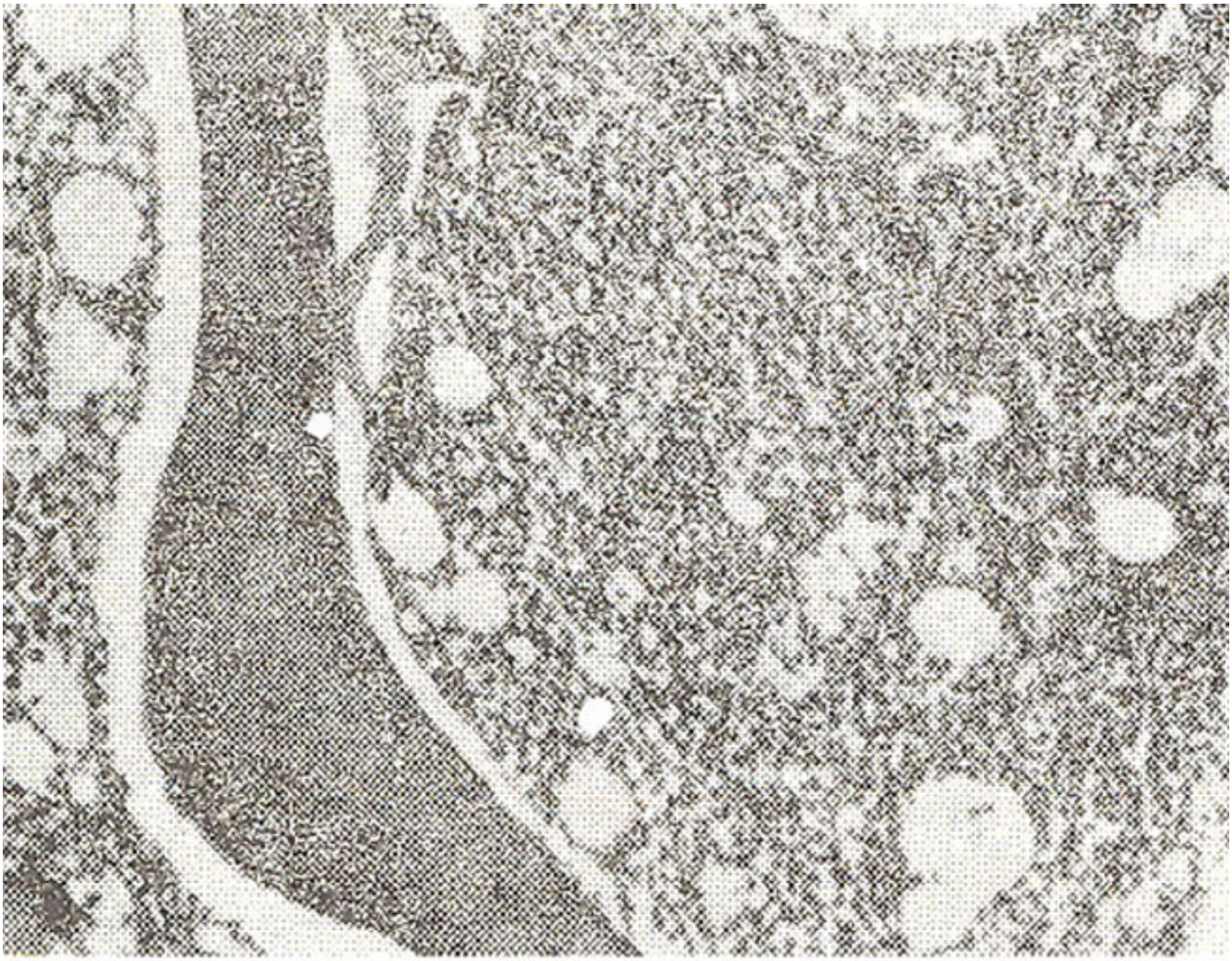

Fig. 6: Bone Marrow Trephine Section in a Case of Lymphocytic Lymphosarcoma. Haematoxylin and Eosin x200.

Discussion

The commonest presenting feature of non-Hodgkin's lymphomas is a superficial lymph node enlargement (Lotz et al., 1976). A few patients may present with mediastinal (Bharat et al., 1976) or abdominal lymphadenopathy. Primary extranodal lymphomas, which usually arise from pharynx, skin, testis and gastrointestinal tract, (Al-Saleem and Blady,' 1970; Hellman et al., 1975; Nordqvist and Kinney, 1976; Wolley and Canellas, 1976), may occasionally originate from the bones (Jones et al., 1973).

In the present series, we have documented an unusual presentation of non-Hodgkin's lymphomas in 12 patients. These patients presented with pyrexia of uncertain origin and/or unexplainable anaemia, along with constitutional symptoms. They did not manifest superficial, mediastinal or palpable abdominrl lymph nodeenlargement. However, they showed a high incidence of hepatomegaly (91.7%), which is

very high as compared to the previous reports of 9.9% to 20% (Olumide et al., 1971; Hanks et al., 1972; Muggiaand Ultmann, 1972). Splenomegaly was also observed in 91.7% of patients, whereas, Liao (1971), Jones et al. (1972) and Goffinet and Kaplan (1973) observed a palpably enlarged spleen in 10-54% of patients.

Haematological parameters, which are usually within normal limits in non-Hodgkin's lymphomas (Bloomfield et al., 1976; Stein et al., 1976), were grossly abnormal in this series. Anaemia was invariably present in 83% of patients, haemoglobin level was between 4.0 and 8.0 grams/dL. Leucopenia was observed in 58% of patients; it was mainly due to neutropenia. One patient manifested leucocytosis. Thrombocytopenia was present in 91.7% of patients. Erythrocyte sedimentation rate was increased invariably.

Bone marrow aspiration and trephine biopsies were performed in an attempt to find out the cause of unexplainable anaemia or pyrexia of uncertain origin. After examination of bone marrow smears, marrow clot sections and sections of trephine biopsies, a diagnosis of non-Hodgkin's lymphomas was established.

References

1. Abell, M.R. and Holtz, F. (1968) Testicular and paratesticular neoplasms in patients 60 years of age and older. Cancer, 21:852.
2. Al-Saleem, T., Blady, J.B. (1970) Malignant lymphoma of the pharynx. Cancer, 26:1383.
3. Bharat, N., Kim, H. and Rappaport, H. (1976) Malignant lymphoma, lymphoblastic. Cancer, 38:961.
4. Bloomfield, C.D., Mckenna, R.W. and Brunning, R.D. (1976) Significance of haematological parameters in the non-Hodgkin's malignant lymphomas. Br. J. Haematol., 32:41.
5. Brunning, R.D., Bloomfield, C.D., Mckenna, R.W. and Petersen (1975) Bilateral trephine biopsy in lymphoma and other neoplastic diseases. Ann. Intern. Med., 82:365.
6. Castellani, R., Rilke, F. (1977) Sequential pathologic-staging of untreated non-Hodgkin's lymphomas by laparoscopy and laparotomy combined with marrow biopsy. Cancer, 40:2322.
7. Edelsen, R., Aftab Ahmad. (1975) Cutaneous T cell lymphomas. The Sezary's syndrome, mycosis fungoides and related disorders. Ann Intern. Med., 83:534.
8. Freeman, C, Berg, J.W. and Cutler, S.J. (1972) Occurrence and prognosis of extranodal lymphomas. Cancer, 29:252.
9. Goffinet, D.R. and Kaplan, H.S. (1973) Staging laparotomy in unselected, previously untreated patients with non-Hodgkin's lymphomas. Cancer, 32:672.
10. Hamlin, J.A., Kagan, A.R. and Friedman, N.B. (1972) Lymphoma of the testicle. Cancer, 29:1352.
11. Hanks, G.E., Terry, L.N. Jr., Bryanm, J.A., Newsome, J.F. (1972) Contribution of diagnostic laparotomy to staging of non-Hodgkin's lymphomas. Cancer, 29:41.
12. Hellman, S., Rosenthal, D.S., Moloney, W.C. and Chaffey, J.T. (1975) Treatment of non-Hodgkin's lymphomas. Cancer, 36:804.
13. Jones, S.E., Rosenberg, S.A. and Kaplan, H.S. (1972) Non-Hodgkin's lymphomas. I. Bone marrow involvement. Cancer, 29:954.
14. Jones, S.E., Dorfman, R.F., Kaplan, H.S. and Kim, H. (1973) Non-Hodgkin's lymphoma. IV. Clinico-pathologic correlation in 405 cases. Cancer, 31:806.
15. Kaplan, H.S. (1968) Clinical evaluation and radio-therapeutic management of Hodgkin's disease and the malignant lymphomas. N. Engl. J. Med., 278:892.
16. Kim, H. and Dorfman, R.F. (1974) Morphologic studies of 84 untreated patients subjected to laparotomy for the staging of non-Hodgkin's lymphomas. Cancer, 33:657.
17. Liao, K.T. (1971) The superiority histologic sections of aspirated in bone marrow malignant lymphomas. A review of 1, 124 examinations. Cancer, 27:618.

18. Lotz, M.J., Chabner, B., Devita, V.T. J.R. and Berard, C.W. (1976) Pathologic staging of 100 consecutive untreated patients with non-Hodgkin's lymphomas; extramedullary sites of disease. Cancer, 37:266.
19. Mckenna, R.W., Bloomfield, C.D. and Brunnig, R.D. (1975) Nodular lymphoma; bone marrow and blood manifestations. Cancer, 36:428.
20. Muggia, F.M. and Ultmann, J.A. (1972) Exploratory laparotomy in reticulum cell sarcoma; a retrospective analysis. Cancer, 30:454.
21. Nobrega, F.T., Harrison, E.G. (1973) Malignant lymphomas including Hodgkin's disease occurring in the vicinity of a large medical centre. Cancer, 2:295.
22. Nordqvist, B.C. and Kinney, J.P. (1976) T and B cells, and cell-mediated immunity in mycosis fungoides. Cancer, 37:714.
23. Olumide, A.A., Osunkoya, B.O. and Ngu, V.A. (1971) Superior mediastinal compression; report of five cases caused by malignant lymphoma. Cancer, 27:193.
24. Parkhill, E.M. Tumours of the oral cavity and pharynx. In atlas of tumour pathology, Section IV. Fasc. 10b: 252-258, 1968.
25. Rappaport, H. Tumours of haemopoietic system, Washington, D.C., Atlas of tumour pathology, Armed forces institute of pathology, 1966.
26. Reddy, S., Saxena, V.S., Pellettiere, E.V. and Hendrickson, F.R. (1977) Early nodal and extranodal non-Hodgkin's lymphomas. Cancer, 40:98.
27. Rosen, P.J., Tindle, B.H. and Lukes, R.J. (1977) Convoluted lymphocytic lymphoma in adults. A clini-copathologicai entity. Ann. Intern. Med., 89:313.
28. Stein, R.S., Ultmann, J.E., Byrne, G.E. Jr. and Oetzel, N. (1976) Bone marrow involvement in non-Hodgkin's lymphomas; implications for staging and therapy. Cancer, 37:629.
29. Wolley, P. and Canellos, G.P. (1976) Extranodal presentation of non-Hodgkin's lymphomas . in the testis. Cancer, 38:1026.