

HAEMATOLOGICAL ASPECTS OF LYMPHOMAS

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Anaemia, leucopenia and thrombocytopenia in various combinations develop during the course of the various lymphomas either before and almost always after treatment.

Basic haematological investigations viz. full blood count, peripheral blood film and ESR, may provide clues to the extent (spread) of disease in lymphomas. Thus, anaemia would suggest widespread disease, and is rare in the early stages. Thrombocytopenia is even rarer, so is leucopenia. The presence of either or both, at presentation, is bad prognostically, since it suggests bone marrow infiltration and therefore widespread disease. High ESR again suggests active or widespread disease, or the presence of monoclonal proteins which may result in clinical complications. Trephine biopsy is absolutely essential. Some centres require *bilateral* marrow biopsy, usually taken from the posterior iliac spines.¹

Bone marrow involvement is one of the commonest events in early spread of the disease. It is also the most easily detectable. The work of Bloomfield and his colleagues² shows that various haematological parameters serve as indicators of bone marrow involvement to varying degrees of reliability. Table I summarises the work of Bloomfield et al.

It is apparent that more than half of the cases with bone marrow involvement at presentation have anaemia, and nearly half have lymphopenia. Presence of lymphocytes which are suspicious of "lymphosarcoma cells" is noted in half of those with bone marrow involvement. All cases with thrombocytopenia, neutropenia or "lymphosarcoma cells" in the peripheral blood show evidence of bone marrow involvement on trephine biopsy examination.

The implication of this work is far-reaching. It is obvious that an especially vigorous search for bone marrow involvement is indicated in patients with these haematological abnormalities. Brunning and his colleagues¹ suggest that bilateral posterior iliac spine trephine biopsies should be done if lymphoma is not demonstrated on the initial trephine in patients who are initially stage I or II but have these haematological abnormalities.

The presence of haematological abnormalities is not in itself an indicator of bad prognosis. Its presence is merely an indicator of bone marrow involvement, which is synonymous with widespread disease. Bone marrow involvement is, of course, related to survival.

Lymphocytopenia may be given a slightly

TABLE I
HAEMATOLOGICAL PARAMETERS AS INDICATORS OF BONE MARROW INVOLVEMENT IN NON-HODGKIN'S LYMPHOMA²

	B.M. NOT INVOLVED	B.M. IS INVOLVED	% WITH B.M. INVOLVED
TOTAL	80	60	43
WITH ANAEMIA	24%	54%	63
WITH THROMBOCYTOPENIA	0%	22%	100
WITH LEUCOPENIA	6%	18%	69
WITH LEUCOCYTOSIS	9%	17%	
WITH LYMPHOCYTOPENIA	46%	45%	
WITH NEUTROPENIA	0%	14%	100
WITH ? LYMPHOMA CELLS IN BLOOD	0%	52%	100

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different interpretation. Since lymph nodes are the sites of lymphocyte formation, their replacement by lymphoma cells will result in lesser production of normal lymphocytes. The bone marrow is not necessarily involved here, yet the mere presence of lymphocytopenia can be expected to be related to poor survival. This has been shown to be true in the case of Hodgkin's disease,³ and may be expected to hold good for non-Hodgkin's lymphoma as well. Indeed other workers have reported the bad influence of lymphocytopenia on prognosis^{4,5} in non-Hodgkin's lymphoma. However, further analysis of these cases relative to histological subtypes and bone marrow involvement seem to reveal these as the more significant prognostic indicators.⁶

Bone marrow infiltration is quite easily recognised by the trained eye. These is, therefore, no excuse for not doing trephine biopsy in every case of non-Hodgkin's lymphoma, even when clinical indications are that the disease is "early". Many a time what appears to the clinician is only the tip of a large iceberg.

Indeed the sizing of this iceberg is the primary duty of the clinician in dealing with a case of non-Hodgkin's lymphoma. It is by no means an easy task, but the challenge must be taken. The true objective is to assess the total tumour burden. It is this assessment that one aims to make by clinical staging. Although, it must be emphasised, the virtue of clinical staging in non-Hodgkin's lymphoma is not realised by results comparable to those seen in Hodgkin's disease, this is no reason to shy away from this disciplined practice. At least it may be said that treatment policy and results of treatment may be more logically worked out.

A note of caution must be made here. Many a clinician has fooled himself by the satisfaction of seeing a report of a bone marrow aspirate from the laboratory which says, "there is no evidence of bone marrow infiltration by lymphoma cells". The pathologist (or haematologist) who issues this report and does not state that a trephine biopsy is required to confirm the finding is either insincere or ignorant. It should be common knowledge that the technique of cytological examination of smears from marrow aspirates is highly inadequate for documentation of the presence or absence of marrow infiltration. Histopathological examina-

tion of clot sections prepared from marrow aspirates may be better, but the material obtained by biopsy using a suitable needle (e.g. the Jamshidi needle) is far superior for histologic evaluation. Cytologic examination of marrow aspirates is no substitute for histologic examination of biopsy material in the clinical staging of patients with lymphoma.

PROBLEMS RELATED TO TREATMENT

Many problems arise as a result of treatment of the lymphomas. Haemorrhage or infectious complications would perhaps be the commonest and the most serious. Table II indicates some of the major side effects of the drugs commonly used in the management of these disorders.

The side effects of irradiation are by no means less troublesome. Whole body irradiation is especially toxic because of the large field of coverage. Humoral antibody production is much more sensitive than cell-mediated immunity to radiation damage, but both are affected in high dose irradiation. One very important effect of irradiation is the loss of the ability to process antigens for the immune response by macrophages; the ability to phagocytose is not compromised, but phagocytosed organisms are not killed. Also detrimental to the immune response mechanism is the reduction in number of macrophages which occurs following irradiation therapy.

The effect of a high dose of either irradiation (whole body irradiation) or drugs such as cyclophosphamide on blood cells depends on storage pools of the individual elements, as well as their survival peripherally. Fig. 1 indicates the changes that take place after such massive marrow onslaught.

It should be remembered that the disease process itself and its complications (e.g. infection) cause increased utilisation of these cells so that the onset of cytopenia may be earlier than depicted in Figure 1.

Immuno-lymphoproliferative disorders, of which the group "non-Hodgkin's lymphoma" is a large class, are notorious for being associated with defects in host defence as a result of the disease. Table III summarises the common intrinsic causes of reduced host defences in these disorders.

TABLE II
 MAJOR SIDE EFFECTS OF DRUGS USED IN THE TREATMENT
 OF NON-HODGKIN'S LYMPHOMA

"G. I.T." symptoms (nausea and vomiting) are commonest and may be extremely troublesome in some cases. Note that except for a few drugs, in particular vincristine and bleomycin, all these drugs cause marrow suppression and immunosuppression.

MAJOR SIDE EFFECTS

DRUGS	Marrow suppression	Immuno-suppression	Neurological	Others
Cyclophosphamide	++	+		G.I.T. UROLOGICAL SKIN
Vincristine			++	SKIN
Mustine	++	+		G.I.T.
Procarbazine	++	+	+	G.I.T.
Prednisolone		+		BONE G.I.T. PSYCHOSIS
Adriamycin	++	+		HEART G.I.T.
Cytosine arabinoside	++	+		G.I.T. SKIN (LIVER)
Bleomycin				FEVER LUNGS SKIN G.I.T.
CCNU	++	+		G.I.T.
Methotrexate	++	+		G.I.T. LIVER LUNGS/SKIN BONE
Chlorambucil	++	+		G.I.T.

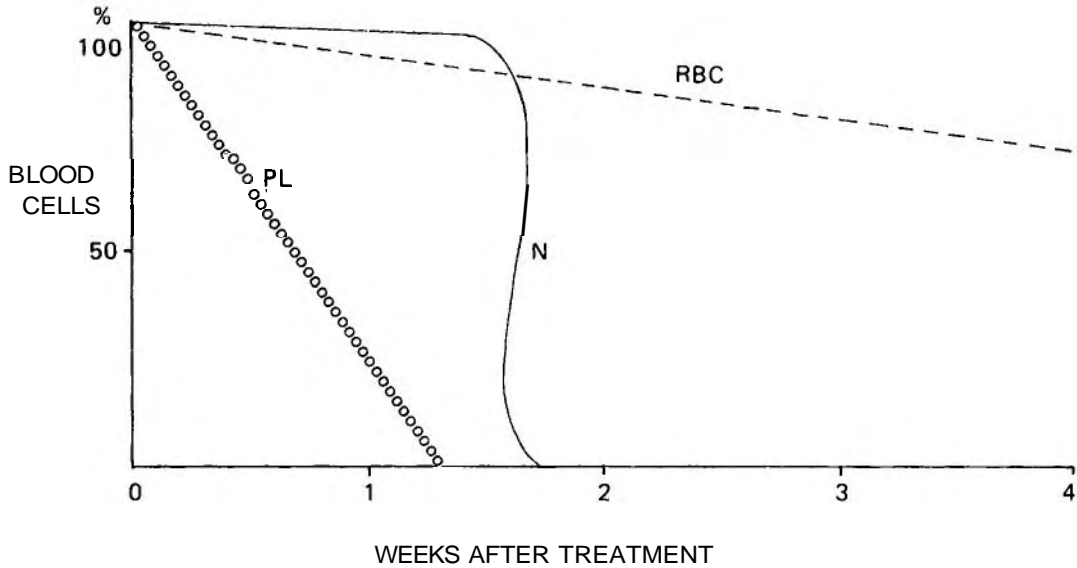


FIGURE 1: The effect of massive marrow onslaught (e.g. high-dose cyclophosphamide or whole body irradiation) on the blood counts.

TABLE III
INTRINSIC CAUSES OF REDUCED HOST DEFENCES IN THE
IMMUNOLYMPHOPROLIFERATIVE DISORDERS

DISEASE	DEFECT IN HOST DEFENCE		
	NEUTROPENIA	REDUCED CIRCULATING ANTIBODIES	IMPAIRED C.M.I.
C.L.L.	Uncommon	Common	Common
Myeloma	Uncommon	Common	Rare
H.D.	Rare	Rare	Common
N.H. L. - "lymphocytic"	Uncommon	Common	Common
N.H. L. - "histiocytic"	Rare	Uncommon	Uncommon

- (Note: (i) "lymphocytic" lymphoma refers to the histologically benign types (small lymphocyte lymphoma, small cleaved follicular centre cell lymphoma, nodular)
(ii) "histiocytic" lymphoma refers to the more malignant histological types (non-cleaved follicular centre cell lymphoma).

All these side effects of therapy coupled with the disease process itself result in a very susceptible state. The patient is uniquely prone to infections (Figure 2).

The type of infection that occurs depends

on the attendant defect(s) in the host defence (Table IV). In general, neutropenia and deficiency in humoral immunity predisposes to infection by the Gram-positive cocci, *H. influenzae* and *Salmonella*. Neutropenia per se is a

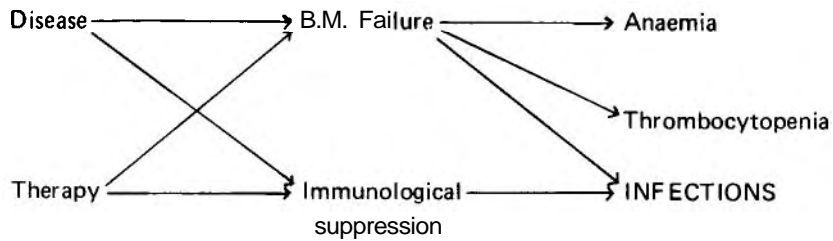


FIGURE 2: Both the disease itself and its therapy predispose the patient with non-Hodgkin's lymphoma to infections.

TABLE IV
TYPES OF INFECTION SEEN IN PATIENTS WITH VARIOUS DEFECTS IN THE HOST DEFENCE

DEFECT IN HOST DEFENCE		
DEFICIENT HUMORAL IMMUNITY	NEUTROPENIA	IMPAIRED C.M.I.
I N F E C T I O N	<i>Pneumococci</i>	T.B.
	<i>Staphylococci</i>	Fungi :
	<i>Meningococci</i>	<i>Candida</i>
	<i>H. influenzae</i>	<i>Aspergillus</i>
	<i>Streptococci</i>	<i>Torula</i>
	<i>Salmonella</i>	Virus :
		<i>Herpes</i>
		<i>Varicella-zoster</i>
		<i>CMV</i>
		Parasitic :
	<i>Pneumocystis</i>	
	<i>Toxoplasma</i>	
	Gram - Neg bacilli :	
	<i>E. coli</i>	
	<i>Pseudomonas</i>	
	<i>Klebsiella</i>	
	<i>Proteus</i>	

predisposition to infection by the Gram-negative bacilli and *Pseudomonas* which often result in septicaemia. Impaired cell-mediated immunity encourages development of tuberculosis, fungal infections (including opportunistic fungi), viral and parasitic infections of which *Pneumocystis pneumonia* is a common type.

There are a few very important points about infections in the immunologically compromised

patients that must be remembered in their management. Septicaemia is exceptionally common. Any fever of unexplained origin must be investigated fully for evidence of infection, which must include blood culture. Any degree of fever that is worrying for any reason requires to be treated as being due to septicaemia unless proven otherwise, and systemic antibiotics to cover the Gram-positive cocci and Gram-

negative bacilli (including penicillin-resistant organisms) are required.

In summary, therefore, we have seen that in the investigation of lymphomas, the bone marrow examination provides many clues to the extent of disease and this in turn reflects on the prognosis. We have also seen that hemopoietic failure and lowering of the host defences as a result of treatment of these diseases is a major if not the prime problem in the management of lymphomas.

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