Malignant Lymphomas

Dr SAFRAZ ALI MBBS, D. Path.
DEPARTMENT OF PATHOLOGY, S.L.H.

RONNIE BORG
MEDICAL STUDENT

Malignant lymphomas is a generic term given to the tumours of lymphoreticular system that includes lymphocytes of T, B and Null type, histiocytes-monocytes and Reticular cells. This term is reserved for those neoplastic processes that initially present as localized lesions and are characterized by formation of gross tumour nodules. Neoplastic lesions that are systemic and diffuse from their inception are called Leukaemias or Malignant histocytosis, depending upon their presumed cell of origin: Malignant lymphomas have also been defined as tumours of the Immune System.

The term lymphoma was first proposed by Billroth in 1871. Based upon differences in histology and mode of spread, Dreschfield in 1891 delineated. these tumours into two distinct entities namely lymphosarcoma and Hodgkins disease. Roulet in 1930, suggested that in addition to the previously described lymphosarcoma and Hodgkins disease there was a third type of tumour that was cytologically related to the reticular cells and thus different from lymphomas which expressed lymphoid differentiation. He proposed the term Retothelsarcoma (Reticulum cell sarcoma) for this third type of tumour. The fourth major type of lymphoma was the so called giant follicular lymphoma. This category was originally reported by Ghon & Roman (1916) who reported follicle like structures as part of malignant proliferation. Brill et al and Symmers believed this to be a benign process due to massive hyperplasia of germinal centres. Gall and Mallory in 1942 established detailed criteria by which this neoplastic follicular proliferation could be distinguished from benign follicular hyperplasia. In 1957 Rappaport and Gall proposed the term nodular instead of follicular lymphoma.

Numerous classifications of malignancies of the lympho-reticular system have been proposed. Of these the Rye classification of Hodgkins disease has gained universal acceptance. Difference of opinion still prevails with regards to classification of Non Hodgkins lymphomas. Six different classifications namely: working classification of Non Hodgkins lymphomas, (Dorfman classification), British National

Lymphoma Investigation classification, Keil classification, Lukes and Collins classification, Rappaport classification and W.H.O. classifications, are being widely applied presently. The proponents of each system have advanced arguments for the superiority of their system over others. As a result, clinical studies which utilize one classification cannot be properly evaluated and compared to others which utilize another system. Clinicians, often relatively uninformed about the various systems, have become confused and cannot adequately assess recent publications concerning Non Hodgkins lymphomas. In an attempt to resolve these issues objectively, a unique multi-institutional study was planned and sponsored by the National Cancer Institute and National Institues of Health, Bethesda, Maryland.

The resultant classification is called *A working formulation for Non Hodgkins Lymphomas for clinical usage.* This working formulation has been welcomed, albeit with reservations, by proponents of all other systems. It is not intended as a new classification but rather as means of *translation* among all other systems. The success of the working formulation as an alternative classification remains to be seen, but it is certainly worth while to familiarise oneself with it.

Working Formulation of Non Hodgkins Lymphomas for clinical usage:

1. Low Grade
   - a Malignant lymphoma small lymphocytic.
   - b Malignant lymphoma, follicular, predominantly small cleaved cell.
   - c Malignant lymphoma, follicular, mixed small cleaved and large cell.
2. Intermediate Grade
   - a Malignant lymphoma, follicular, predominantly large cell.
   - b Malignant lymphoma, diffuse small cleaved cell.
   - c Malignant lymphoma, diffuse, mixed small and large cell.
   - d Malignant lymphoma, diffuse large cell.
3. High Grade
   - a Malignant lymphoma, large cell, immunoblastic.
   - b Malignant lymphoma, lymphoblastic.
   - c Malignant lymphoma, small non cleaved cell.
4. Miscellaneous
   - a Mycosis fungoides
   - b Composite lymphoma
   - c Plasma cytoma
   - d Unclassified

In Malta ever since it was proposed, W.H.O. classification has been used.

W.H.O. Classification:

1 Hodgkins Lymphoma 2 Non Hodgkins Lymphoma.

Hodgkins Lymphomas

1 Lymphocytic predominance type.
2 Nodular sclerosing type.
3 Lymphocytic depletion type.
4 Mixed cellularity type.

Non-Hodgkins Lymphomas

1 Nodular lymphosarcoma. Prolymphocytic
2 Nodular lymphosarcoma. Prolymphocytic -lymphoblastic
3 Diffuse lymphosarcoma, lymphocytic
4 Diffuse lymphosarcoma, lymphoplasmacytic
5 Diffuse lymphosarcoma, prolymphocytic
6 Diffuse lymphosarcoma, lymphoblastic
7 Diffuse lymphosarcoma, immunoblastic
8 Burkitt's tumour
9 Mycosis fungoides
10 Plasmacytoma
11 Reticulosarcoma (Histiocytic)
12 Malignant lymphoma unclassified
13 Composite lymphoma.

Nodular Lymphomas

These tumours originate from altered B lymphocytes and are characterized by a nodular pattern of growth. In Malta nodular lymphosarcomas comprise 10% of all Non Hodgkins lymphomas whereas in United States Nodular lymphomas comprise about 50% of all the Non Hodgkins lymphomas. Sex incidence in Malta is predominantly Male, Male:Female ratio being 5:1. In United States the incidence is almost equal in both sexes. Histologically the tumour is characterized by a nodular pattern of growth. Neoplastic cells proliferate in nodular aggregates throughout the lymph nodes and compress the intervening parenchyma. Unlike the germinal centres in reactive follicular hyperplasia, these nodules are usually of a more uniform size and lack a well defined lymphoid cuff. The neoplastic cells within the nodules are more monotonous than those in the normal germinal centres and do not exhibit evidence of cellular polarization. Based upon the characteristics of the neoplastic cells the nodular lymphosarcomas may be divided into small cell type, large cell type and mixed cell type. The cells are usually prolymphocytes of a mixture of prolymphocytes and lymphoblasts. The division of nodular lymphosarcomas into subtypes has prognostic significance. Prognosis is best in the mixed cell type and worst in the large cell type. Involvement of liver and bone marrow is common in small cell type. During the natural history of disease, progression from small cell type to large cell type and progression from nodular pattern to diffuse pattern may occur. A small percentage of cases with nodular lymphosarcoma develop blastic transformation with corresponding leukaemic picture. In such patients survival after development of leukaemic phase is very brief.

Diffuse Lymphomas.

Diffuse lymphomas are a group of heterogenous tumours representing neoplastic proliferations of various cell types.

1. Diffuse lymphocytic lymphosarcoma.

This is the most common type of Non Hodgkins lymphoma in Malta. It represents 34% of all the Non Hodgkins lymphoma. Median age of patients suffering from diffuse lymphocytic lymphoma in Malta is 54.6 years, Male to Female ratio being 2:1. These patients usually have minimal symptomatology and despite the frequent presence of disseminated disease at the time of diagnosis have an indolent clinical course and prolonged survival. Clinically the patients present with localized or generalized lymphadenopathy. Bone marrow involvement is a late feature in the natural history of disease. Histologically in the lymph node there is diffuse effacement of normal architecture by a monotonous population of small round lymphocytes with clumped chromatin, scanty cytoplasm and inconspicious nucleoli. A vast majority of these tumours arise from B cells. They bear monoclonal immunoglobulin on their surface, usually IgM. Occasionally the tumour may undergo progression to blastic or histiocytic cell type.

2. Diffuse lymphoplasmacytic lymphosarcoma.

This is a rare tumour which usually occurs in older people. The tumour is composed of lymphocytes and plasma cells. These cells usually secrete IgM. If the tumour secretes significant amounts of IgM into the serum the disease is usually refered to as Waldenstorm's Macroglobulinaemia.

3. Diffuse Prolymphocytic lymphosarcoma.

This is a disease of middle aged people, median age of incidence in Malta being 52 years. This is a rather uncommon variant of Non Hodgkins lymphomas. In Malta it represents 5% of all the Non Hodgkins lymphomas. All cases studied in Malta occurred in Male population. The disease follows an indolent course and carries relatively better prognosis than lymphoblastic type. Histologically there is usually diffuse effacement of lymph node architecture. The tumour is composed of a mixture of cells with small rounded nuclei and with cleaved nuclei. The tumour arises from B lymphocytes and the cells usually bear IgM on their surface.

4. Diffuse Lymphoblastic lymphosarcoma.

This type represents 13% of Non Hodgkins lymphomas. All the cases studied occurred in Male population. Median age of incidence is 40 years in Malta. The tumour has two distinct age related patterns. Majority of cases occured in older children and young adults. In elderly people the tumour usually occurs after the age of 60 years. The tumour is very commonly associated with a mediastinal mass, especially in the younger age group. Lymphoblastic lymphosarcoma is closely related to acute lymphoblastic leukaemis and when both haematogenous and extra medullary stages of the disease are present the distinction between the two is impossible and insignificant. The tumour cells, like acute lymphoblastic leukaemia, possess surface markers which show characteristics of either T cells, B cells common type and Null cells. Histologically there is diffuse effacement of the lymph node architecture. The tumour is mainly composed of cells with large round nuclei and convoluted nuclei. Convoluted pattern is more commonly associated with younger age group. The prognosis of diffuse lymphoblastic lymphosarcoma is uniformly grim.

Immunoblastic lymphosarcoma.

This is a rare variant of lymphomas. Only one case was observed during the five years of study. In larger series (N-HLPC project) it constitutes about 8% of all the Non Hodgkins lymphomas with median age of 51.3 years. The tumour can have T cell or B cell markers. Histologically the tumour is composed of diffusely arranged large lymphoid cells with large vesicular nuclei having prominent nucleoli. The cytoplasm is basophilic and vacuolated plasma cells are also seen. Scarcity of reticulin fibres helps to distinguish the tumour from reticulum cell sarcoma. The tumour carries poor prognosis.

Burkitt's Lymphoma.

This is a rare tumour in Malta. Only one case was observed during the last 5 years. This tumour occurs most commonly in children but may also be seen in adults. The tumour in children is endemic in Africa where it occurs in younger age. Median age is 7 years. In these regions the maxillo-mandibular region is the commonest site involved. Sporadic occurence in America and elsewhere has been reported. Median age in sporadic cases was 11 years and abdominal tumours were more common than in the Maxillo-Mandibular region. Ileocaecal region was the most common site. Epstein Barr virus has been isolated from the majority of the tumours in African children. The tumour arises from B lymphocytes. The cells bear monoclonal surface immunoglobin with IgM being the predominant heavy chain class. Histologically the tumour is composed of lymphoid cells with intensely basophilic cytoplasm and many cytoplasmic inclusions. The nuclei have two to three nucleoli. Macrophages are abundantly interspersed throughout the tumour cells forming so called starry sky pattern. Extensive bone marrow involvement and meningeal infiltration may occur. The tumour carries a poor prognosis.

Reticulum cell Sarcoma (Histiocytic lymphomas).

This is the second most common Non Hodgkins lymphoma in Malta. (17% of all Non Hodgkins lymphomas). Ironically this relatively common type of lymphoma is a disputed entity. Immunologic studies performed on this group of tumours have shown a remarkable heterogeneity. About 50-60% of histiocytic lymphomas have B cell markers, 5-15% have T cell markers, 25 to 30% have no cell markers at all and only less than 5% have features consistent with true histiocytes. These findings suggest that probably

histiocytic lymphoma is not a specific entity but rather a common denominator for highly anaplastic or blastic lymphomas. However world wide application of the term seems to have justified this misnomer. Median age of incidence in Malta is 53 years (14-71). Sex incidence is almost equal. Histiocytic lymphoma occurs both in children and adults but is more common in the latter. The tumour has great tendency for being localized at the time of presentation and for extra-nodal sites. Involvement of bone marrow and liver are less common. Sometimes the tumour develops during the course of Chronic Lymphocytic Leukaemia (CLL). This is called Ritcher's syndrome. Histologically the tumour is composed of large cells with abundant cytoplasm, vesicular nuclei and prominent nucleoli. The nuclei may be oval or indented. There is production of intercellular argyrophilic fibres which take-up reticulin stain. The tumour carries a relatively poor prognosis.

Plasma Cytoma.

This is a localized tumour of neoplastic plasma cells. The tumour is rare. This may be a manifestation of already disseminated multiple myeloma or an initial manifestation of plasma cytic tumour which may become generalized after periods of unpredictable duration of time. A few plasma cytomas however may remain localized. These probably represent the benign counterpart of myeloma.

Mycosis Fungoides.

This is a relatively rare type of lymphoma representing about 5% of total Non Hodgkins lymphomas in Malta. The lesion usually afflicts elderly people. Median age incidence in Malta is 60 years. It is a T cell lymphoma arising in the skin. Classic mycosis fungoides is clinically characterized by a scaly eruption that progresses through a plaque stage and eventually forms grossly evident tumours in the skin. In about 50-70% of cases visceral and lymph node involvement is observed. Cutaneous biopsy shows a hand like dermal infiltrate of atypical lymphoid cells. These neoplastic cells infiltrate the epidermis to form aggregates known as Darier Pautier abcesses. In about 20% of cases, skin lesions are accompanied by presence of atypical lymphoid cells in the peripheral blood. These cells have been shown to be helper T cells. This entity is known as *Sezary syndrome*. Sezary syndrome is most likely a leukaemic variant of mycosis fungoides.

Composite Lymphoma.

This is a rare tumour. It is composed of two distinct types of lymphomas within a single lymph node or organ.

Malignant Lymphoma unclassified.

Some malignant tumours of lymphoid tissue or histiocytoid tissue cannot be classified histologically. Incidence of such lymphomas in Malta is 11% of all the Non Hodgkins lymphomas. Technical imperfections and presence of more than one cell type contribute to the difficulty in typing. A routine application of immunologic methods to identify the cells should diminish this category.

HODGKINS LYMPHOMAS.

Unlike Non Hodgkins lymphomas, Hodgkins disease has not been subjected to as many conflicts and controversies. Ever since the original description by Sternberg (1898) and Reed (1902), Hodgkins disease has been recognised as a form of lympho-reticular malignancy with distinctive clinical and pathological features. The first clinically useful classification of Hodgkins disease was provided by Jackson and Parker in 1947. This was improved by Lukes and Butler in 1966, and was further modified at the Rye conference. Rye classification is widely accepted by pathologists and clinicians alike and almost enjoys a universal concensus. According to this classification Hodgkins lymphoma is sub-divided into 4 main categories.

1. Hodgkins disease with lymphocytic predominance.
2. Hodgkins disease nodular sclerosing type.
3. Hodgkins disease with mixed cellularity.
4. Hodgkins disease with lymphocytic depletion.

Hodgkins disease with lymphocytic predominance.

This is the second most common type of Hodgkins lymphoma in Malta. It represents 28% of all the Hodgkins lymphomas. Median age of incidence in Malta is 35 years (15-65) which is in conformity with the median age of incidence elsewhere. The disease is common in Males (62%). This type of Hodgkins lymphoma carries the best prognosis of all the sub-types of Hodgkins lymphoma. Histologically the lymph node architecture may be completely or partially effaced. The cellular proliferation may be diffuse or vaguely nodular and is composed predominantly of mature lymphocytes. Reed Sternberg cells, eosinophils and plasma cells are few.

Nodular Sclerosing Type.

This is the commonest type of Hodgkins lymphoma in Malta and elsewhere. It constitutes 36% of all the Hodgkins disease in Malta, median age of incidence in Malta being 44.3 years. This is slightly higher than the median age in the United States. Also unlike other places, Nodular Sclerosing type of Hodgkins lymphoma is commoner in Males in Malta (60% in Males). The disease carries good prognosis and usually presents with enlarged lymph nodes in the neck and/or mediastinum. Histologically the lymph node shows bands of collagen tissue sub-dividing it into nodules composed of lymphocytes, eosinophils, plasma cells, histiocytes, Reed Sternberg cells and Lacunar cells. Lacunar cells with abundant pale and retracted cytoplasm and multiple nuclei are a characteristic finding. For those who are interested in hair-splitting, Nodular Sclerosing type of Hodgkins lymphoma can be further subdivided in three sub-

divisions - namely Nodular Sclerosing with lymphocytic predominance, Nodular Sclerosing with mixed cellularity and Nodular Sclerosing with lymphocytic depletion. It has been reported that increased frequency of lymphocytes correlates with improved prognosis. Remembering this sub-classification of Nodular Sclerosing type is a luxury which an over burdened medical student can ill afford.

Hodgkins disease with mixed cellularity.

This entity represents 25% of all the Hodgkins disease in Malta. It mainly occurs in elderly people and is less common in younger age group. No cases were reported in children in Malta. Median age of incidence in Malta is 54 years. The disease is slightly more common in Females that Males. The disease occupies an intermediate position between lymphocytic predominance type and lymphocytic depletion type with respect to prognosis. Abdominal involvement is more common in this type of Hodgkins disease. Histologically, usually, the lymph node is diffusely involved. Focal involvement is rare. Large numbers of plasma cells, eosinophils, atypical mononuclear cells are admixed with classical Reed-Sternberg cells. Focal necrosis with minimal fibrosis may be present.

Hodgkins disease with lymphocytic depletion.

This is the least common type of all the Hodgkins lymphomas in Malta. It constitutes about 11% of all the Hodgkins lymphomas. The disease is more common in Males, Male to Female ratio being 2:1. The disease occurs mainly in adults. Occurence in children is extremely rare. Average age of incidence in Malta is 40 years. Sometimes the disease may present as fever, hepatosplenomegaly and lymphopenia with sub diaphragmatic involvement. This type of Hodgkins disease carries the worst prognosis. Histologically there is diffuse involvement of lymph node with abundant Reed–Sternberg cells, and atypical reticulum cells. There is paucity of lymphocytes. The lymph node usually shows deposits of non fibrillary eosinophilic material which is negative for amyloid.

NON HODGKINS LYMPHOMAS

Incidence 1 in 27,500
Prevalence 1 in 5,500.

Histologic Type	Frequency	Median Age	Male/Female
1. Diffuse lymphocytic lymphosarcoma	34%	54.6 yrs..	2:1
2. Diffuse Reticulum cell lymphosarcoma	17%	53 yrs.	1:1
3. Diffuse lymphoblastic lymphosarcoma	13%	40 yrs.	All Males
4. Unclassified lymphoma	11%	58 yrs.	1:3
5. Nodular lymphomas	10%	48 yrs.	5:1
6. Diffuse Prolymphocytic lymphosarcoma	5%	52 yrs.	All males
7. Mycosis fungoides	5%	60 yrs.	All males
8. Immunoblastic lymphosarcoma	—	51.3 yrs.	—
9. Burkitts tumour	5%	—	—
10. Plasma cytoma	—	—	—

HODGKINS LYMPHOMA

Incidence 1 in 55,000
Prevalence 1 in 11,000

Histologic Type	Frequency	Median Age	Male/Female
40 1. Nodular Sclerosing type	36%	44 yrs.	3:2
15 2. Lymphocytic predominance type	28%	35 yrs.	3:2
30 3. Mixed cellularity type	25%	54 yrs.	3:4
15 4. Lymphocytic depletion type	11%	40 yrs.	2:1