ABC of clinical haematology

Malignant lymphomas and chronic lymphocytic leukaemia

G M Mead

The malignant lymphomas (non-Hodgkin's lymphoma and Hodgkin's disease) are a clinically and pathologically diverse group of cancers of largely unknown cause that are rapidly increasing in incidence. They are highly treatable and sometimes curable. Chronic lymphocytic leukaemia, the commonest adult leukaemia, shares many features with these cancers. The whole group constitutes about 5% of malignant diseases.

Management of the malignant lymphomas is complex and is best carried out in specialised treatment centres

Pathology and staging

The non-Hodgkin's lymphomas arise from malignant transformation of lymphocytes, deriving from B cells in about 85% of cases and T cells in most of the rest. Chronic lymphocytic leukaemia is largely a B cell malignancy, but the cell of origin of the Reed Sternberg cell, which characterises Hodgkin's disease, remains uncertain.

Histopathologically, lymphomas comprise an admixture of identical (monoclonal) malignant cells with variable amounts of reactive lymphoid cells and stroma. The lymphomas are variably subcategorised by pathologists into about 20 different types on the basis of conventional cytological staining and special stains to determine subtype and lineage.

A diagnosis of lymphoma (or even B or T cell lymphoma) gives no clue to the natural course of the disease in an individual patient. Clinicians treating these patients take account of the histopathology and the history provided by the patient, as well as many other factors (for example, stage and age), before recommending treatment or advising about prognosis. The complexity of non-Hodgkin's lymphomas requires a simplified management approach, on the basis of division of cases into low grade (or indolent), intermediate, and high grade disease.

All patients with lymphoma or chronic lymphocytic leukaemia require careful initial staging, usually comprising physical examination, computed tomography, and a bone marrow biopsy. Lymphomas are staged with the Ann Arbor system and chronic lymphocytic leukaemia with the Binet system. Increasingly, treatment is decided on the basis of allocated stage together with an examination of other known prognostic factors.

Ann Arbor staging system for lymphoma

Site
- Stage I—Single lymphoid area or extranodal site (stage IE)
- Stage II—Two lymphoid areas or extranodal sites on the same side of the diaphragm
- Stage III—Lymphoid areas (including the spleen) on both sides of the diaphragm
- Stage IV—Diffuse involvement of an extranodal organ(s) (liver, bone marrow)

Symptoms
- A—No symptoms
- B— $>10\%$ Weight loss, drenching night sweats, or unexplained fevers $\geq 38^{\circ}C$

Binet staging system for chronic lymphocytic leukaemia

Stage A	No anaemia or thrombocytopenia; fewer than three enlarged lymphoid areas
Stage B	As for stage A but three or more enlarged lymphoid areas
Stage C	Anaemia (concentration <100 g/l) and/or platelet count $<100\times10^{9}$/l

Low grade non-Hodgkin's lymphoma and chronic lymphocytic leukaemia

The low grade non-Hodgkin's lymphomas and chronic lymphocytic leukaemia are rare in patients aged under 40 years and are predominantly diseases of elderly people (90% of patients are aged >50 years).

Presenting features of low grade non-Hodgkin's lymphoma
- Painless peripheral lymphadenopathy
- Abdominal mass (nodal or spleen)
- Weight loss
- Night sweats

Nodal non-Hodgkin's lymphomas and chronic lymphocytic leukaemia

This group includes most of the follicular lymphomas and constitutes about 30% of the cases of non-Hodgkin's lymphoma. Chronic lymphocytic leukaemia has a similar natural course. Diagnosis may be incidental (for example, from a routine blood count, as in chronic lymphocytic leukaemia) or

Presenting features of chronic lymphocytic leukaemia
- As for low grade non-Hodgkin's lymphoma
- Asymptomatic—diagnosed coincidentally
- Fatigue
- Anaemia
- Infection

may follow a period of (often fluctuating) localised or generalised enlargement of lymph nodes or the spleen. These lymphomas are usually widespread at diagnosis, commonly (as in non-Hodgkin's lymphoma) or always (chronic lymphocytic leukaemia) involving the bone marrow. Because of their indolent nature, however, there may be little or no initial effect on quality of life. Some patients, however, present with B symptoms or bulky widespread disease and need early treatment.

The management of these cancers is adjusted to their natural course. Cure can rarely be achieved, and the median overall survival in most series is five to eight years. Prognosis relates to age (poorer when older) and particularly to the extent of disease judged in terms of bulk and effect of tumour. The outlook for chronic lymphocytic leukaemia worsens with increasing extent of disease at presentation and cytopenias (Binet stage B and C).

Patients who are well with non-threatening disease may initially be watched without treatment—on occasions for many years. Initial treatment when needed generally comprises an alkylating agent—usually intermittent chlorambucil—with or without steroids for four to six months and will often be highly successful in causing disease regression; relapse is, however, inevitable. After several years these lymphomas may become refractory to treatment or may "transform" with change in histology and clinical course to an intermediate grade non-Hodgkin's lymphoma. If this occurs then combination chemotherapy is recommended, but the outlook is usually poor.

Promising new treatments that are being evaluated include fludarabine, a new chemotherapy agent, and antibody treatment. Monoclonal antibodies directed against B cell antigens may be used alone or coupled to a toxin (or therapeutic dose of a radio isotope) and can "target" the malignant lymphoid cell. High dose therapy with stem cell rescue is also used.

Extranodal lymphoma (maltoma)

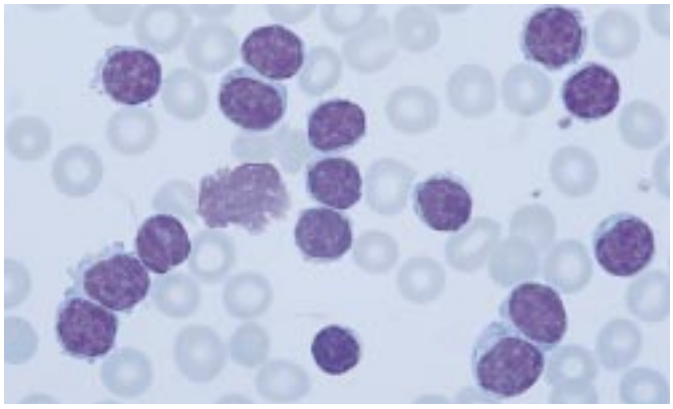
The maltomas (mucosal associated lymphoid tumours) were first described about 15 years ago. These are indolent lymphomas that arise most commonly in the stomach, thyroid, parotid, and lung—often evolving from a pre-existing inflammatory or autoimmune disease (for example, gastritis related to *Helicobacter pylori* or Sjögren's syndrome). These tumours have been successfully managed with local resection or radiotherapy, or both. There is, however, increasing evidence suggesting that gastric maltoma can be controlled or cured by use of appropriate antibiotics, a highly unusual example of malignant regression by treatment of infection.

The maltomas can progress to intermediate grade tumours. In addition they can metastasise, usually to the other maltoma sites described above.

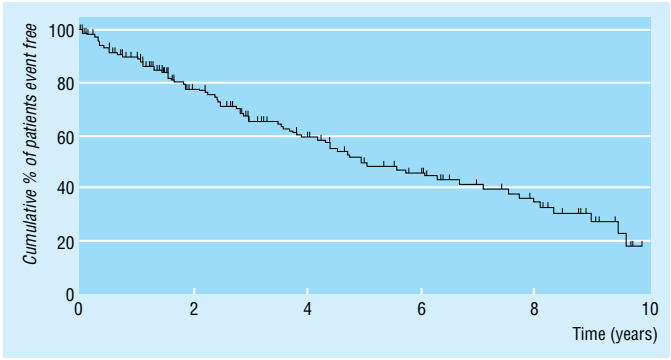
Intermediate grade non-Hodgkin's lymphoma

This is the most common grade of non-Hodgkin's lymphoma (65%) and affects any age group. It is rapidly increasing in incidence, although the reasons for this are uncertain. Two thirds of cases of this type of cancer arise within lymph nodes—patients present because of lymph node enlargement. The remaining cases may arise in almost any other tissue or organ (for example, gastrointestinal tract, skin, brain, and bone), with symptoms appropriate to each site.

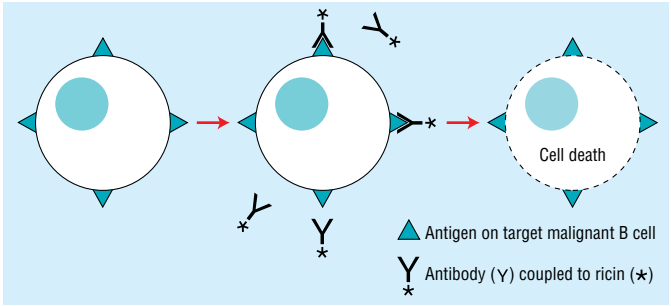
The most common type is diffuse large cell lymphoma, a B cell neoplasm. These lymphomas occur at any age (median 65



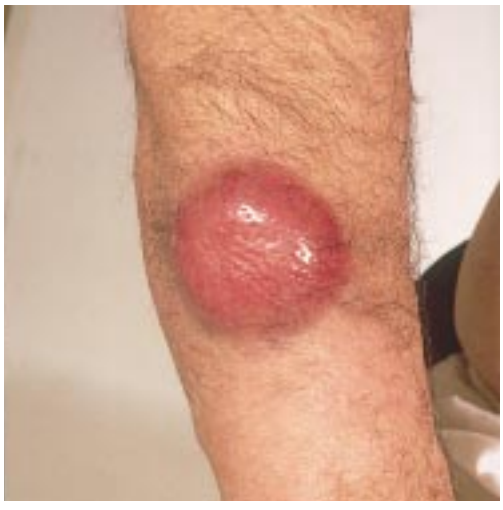
Peripheral blood film of patient with chronic lymphocytic leukaemia showing numerous malignant lymphocytes.



Survival curve of 160 patients with advanced follicular lymphoma: survival is prolonged, but there is no evidence of cure.



"Targeted" antibody therapy of lymphoma. The antibody delivers a toxin (ricin) to the lymphocytes bearing the appropriate surface antigen.

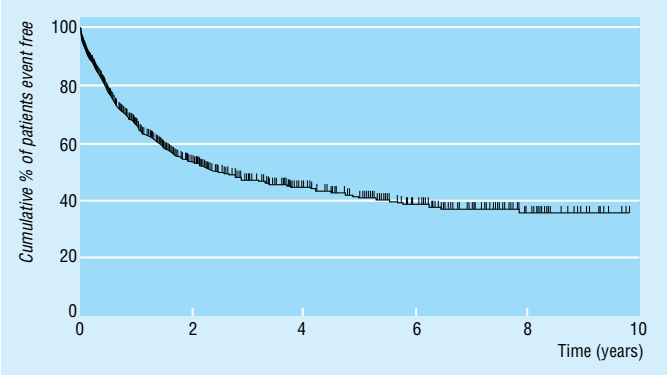


Intermediate grade non-Hodgkin's lymphoma arising in skin.

years) and are rapidly progressive cancers that are often associated with B symptoms. Diagnosis and staging should be urgently performed then treatment with chemotherapy started. These are curable cancers in about 40% of cases. The prognosis relates to the patient's age, extent of spread, lactate dehydrogenase concentration, and performance status.

The standard chemotherapy is a combination of cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) given intravenously at intervals of three weeks in outpatient clinics on six occasions and sometimes supplemented by radiotherapy.

Relapse is not uncommon and in the past was associated with a poor outlook. However, younger patients with disease that has remained sensitive to chemotherapy may now be cured in up to 50% of cases using high dose chemotherapy. Survival in remaining patients is often measurable in months.



Survival of 760 patients with large cell non-Hodgkin's lymphoma (40% cure rate).

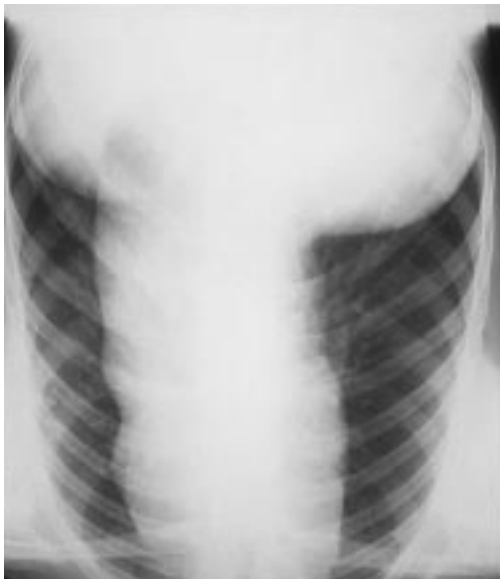
High grade non-Hodgkin's lymphoma

This grade of the disease is rare (under 5% of all cases) and comprises rapidly progressive cancers of children and young adults.

Lymphoblastic lymphoma is a T cell lymphoma predominantly of young males that usually presents with a mediastinal mass. Involvement of the bone marrow and central nervous system commonly occur. Burkitt's lymphoma as seen in Europe and America is a rare B cell neoplasm of young adults that usually arises at extranodal sites most commonly in the gastrointestinal tract—for example, the ileocaecal region. This lymphoma also commonly spreads to the bone marrow and the central nervous system.

Both these lymphoma types are curable with intensive combination chemotherapy; the role of high dose therapy is under evaluation.

Treatment of these cancers is urgent and may, if adequate precautions are not taken, be complicated by the acute tumour lysis syndrome resulting from breakdown of the lymphoma. This can lead to renal failure and possible death. Prophylaxis against relapse in the central nervous system is routinely used. Overall cure rates generally exceed 50%.



Anterior mediastinal mass in adolescent male: histological tests reveal lymphoblastic lymphoma.

AIDS related non-Hodgkin's lymphoma

The immunosuppression associated with HIV infection has been associated with a noticeable increase in the incidence of non-Hodgkin's lymphoma and Hodgkin's disease.

These diseases arise in many cases because of uninhibited expansion of multiple clones of lymphocytes infected with Epstein-Barr virus. They are commonly high grade B cell neoplasms that arise at extranodal sites—for example, the brain and the ileocaecal area.

Treatment of AIDS related non-Hodgkin's lymphoma

- Treatment is often difficult because of pre-existing immunosuppression and AIDS related infection
- Chemotherapy is usually indicated; the prognosis relates to the degree of immunosuppression at diagnosis
- Cure of these lymphomas is possible, although the outlook is usually very poor

Hodgkin's disease

Hodgkin's disease is an uncommon form of lymphoma occurring mainly at ages 15-35 years and affects slightly more men than women

Pathology

Hodgkin's disease has classically been divided into four types. Recent studies suggest, however, that one type—lymphocyte predominance—is a clinically distinct B cell lymphoma often presenting with isolated enlargement of a peripheral lymph node.

The nodular sclerosing type constitutes 70-80% of cases of Hodgkin's disease and classically presents in young women with mediastinal and cervical nodal disease.

Symptoms and signs of Hodgkin's disease

- Painless lymphadenopathy
- B symptoms
- Pruritus

Mixed cellularity disease occurs predominantly in older males and is more commonly widespread. Lymphocyte depleted Hodgkin's disease is rare.

Clinical presentation and management

Hodgkin's disease most commonly presents as enlargement of supradiaphragmatic lymph nodes with or without B symptoms. Generalised pruritus can be a presenting feature in some cases. The spleen is involved in at least 30% of cases, and in the past the disease was detected with splenectomy. This procedure has now been abandoned as studies suggested no overall survival benefit from this procedure, and modern management instead relies on assessment of prognostic factors—which are used to assess the likelihood of early stage disease being encompassed by radiotherapy with a reasonable chance of cure. Staging is, as for non-Hodgkin's lymphoma, with the Ann Arbor system.

Patients with early stage disease (non-bulky stage I and IIA) are managed with radiotherapy. Treatment confined to the involved area is used for localised lymphocyte predominant disease. The remaining cases receive at least mantle radiotherapy (treatment of bilateral cervical and axillary nodes combined with treatment to the mediastinum), resulting in cure iin 60-70% of cases.

Patients with more extensive or symptomatic disease and those for whom initial radiotherapy fails receive combination chemotherapy incorporating doxorubicin. About two thirds of patients receiving chemotherapy will remain permanently free of disease as a result of this treatment. At the time of relapse treatment may comprise further chemotherapy or high dose chemotherapy with peripheral stem cell rescue—radiotherapy often also has a role.

Long term studies suggest that the overall cure rates for Hodgkin's disease are stable at 70-80%, although it is hoped that high dose chemotherapy may improve these figures. In the past chemotherapy was invariably associated with infertility and premature menopause—newer treatments carry much less risk of these problems. Late toxicity—particularly second malignancy—remains the source of concern in patients that have been treated with wide field radiotherapy or chemotherapy. Patients with early stage disease are increasingly being managed with limited radiation fields combined with brief courses of chemotherapy in an attempt to avoid this complication.

Clinical features of Hodgkin's disease *v* non-Hodgkin's lymphoma

	Hodgkin's disease	*Non-Hodgkin's lymphoma*
Incidence	Stable	Increasing
Age	Median 29 years	Increasing incidence with age
Sites	Nodal; supradiaphragmatic	Nodal or extranodal; any site
Clinical features	Mediastinal mass; itching; alcohol induced pain	Nil specific
Prognosis	70-80% cure	Highly variable by type; most incurable

Further reading

- O'Brien S, del Giglio A, Keating M. Advances in the biology and treatment of B-cell chronic lymphocytic leukaemia. *Blood* 1995;85:307-18.
- Aisenberg AC. Coherent view of non-Hodgkin's lymphoma. *J Clin Oncol* 1995;13:2656-75.
- DeVita VT, Hubbard SM. Hodgkin's disease. *N Engl J Med* 1993;328:560-5.

Dr Dina Choudhury provided the blood film showing chronic lymphocytic leukaemia.

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The ABC of Clinical Haematology is edited by Drew Provan, consultant haematologist and honorary senior lecturer at the Southampton University Hospitals NHS Trust, and Andrew Henson, clinical research fellow, university department of primary care, Royal South Hants Hospital, Southampton.

WHEN I USE A WORD …

Sloe gin

Last autumn I went down to the banks of the Cherwell looking for blackthorn bushes *(Prunus spinosa)* to pick sloes with which to make that nectar of homemade liqueurs, sloe gin. I had already looked up the recipe in *The Alice B Toklas Cook Book*, actually wanting an excuse to reread Brian Gysen's notorious recipe for hashish fudge, which includes a pulverised bunch of *"canibus sativa"* (obtaining which "may present certain difficulties"). The fudge, we are told, "should be eaten with care. Two pieces [about the size of a walnut] are quite sufficient."

Alice got her recipe for sloe gin from the Princess D de Rohan: "To each bottle of gin allow 1 pint sloes and 1/2 lb rock candy.... Prick the sloes with a fork (silver for preference).... Allow to stand for three months, shaking every day. Then strain through muslin and bottle.... Leave at least a year before drinking ... at seven years it's a dream." Had she been English, Alice would surely have recommended barley sugar, not rock candy, but in the end I just used granulated.

Sloe is an old word for a plum, like the Polish word sliwa (hence slivovitz). Gin, on the other hand, is a contraction of geneva or genever, themselves corruptions of juniper, from whose berries the drink is distilled, although not all spirits called geneva or gin were necessarily made from juniper berries. Gin is said to have been introduced by Francois le Boë or Franciscus Sylvius, the famous anatomist (remember the Sylvian fissure?) and professor of medicine at the State University of Leyden (1614-72), who recommended it for its diuretic properties. Because it was originally made in the Netherlands it was also called Hollands or Schiedam, the name of a town near Rotterdam.

A few years ago the Anglia and Oxford Regional Health Authorities joined forces, and the new headquarters are in Milton Keynes. Milton means a middle farmstead or estate and Keynes is named after the family de Cahaignes, who came over with William the Conqueror and later settled in Buckinghamshire. And cahaignes is derived from an old Celtic word meaning a juniper—like St Keyne, the patron saint of the Cornish town of that name.

So the next time I visit the regional health authority headquarters I shall take some sloe gin to celebrate the home of the juniper.

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