

- A 32 year old woman comes to your clinic with neck masses for the last several weeks. Masses are discrete, non matted, firm and rubbery on examination. She also has fever, weight loss, and sweats.

- What is the diagnosis?

Lymphoma

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Introduction

- These neoplasms arise from lymphoid tissues, and are diagnosed from the pathological findings on biopsy as Hodgkin or non-Hodgkin lymphoma.
- The majority are of B cell origin.

- Non-Hodgkin lymphomas are classified as low- or high-grade tumours on the basis of their proliferation rate.
- *High-grade tumours* divide rapidly, are typically present for a matter of weeks before diagnosis, and may be life-threatening.

- *Low-grade tumours* divide slowly, may be present for many months before diagnosis, and typically behave in an indolent fashion.

Hodgkin lymphoma

- The histological hallmark of Hodgkin lymphoma (HL) is the presence of Reed–Sternberg cells, large malignant lymphoid cells of B cell origin.
- They are often only present in small numbers but are surrounded by large numbers of reactive non-malignant T cells, plasma cells and eosinophils.

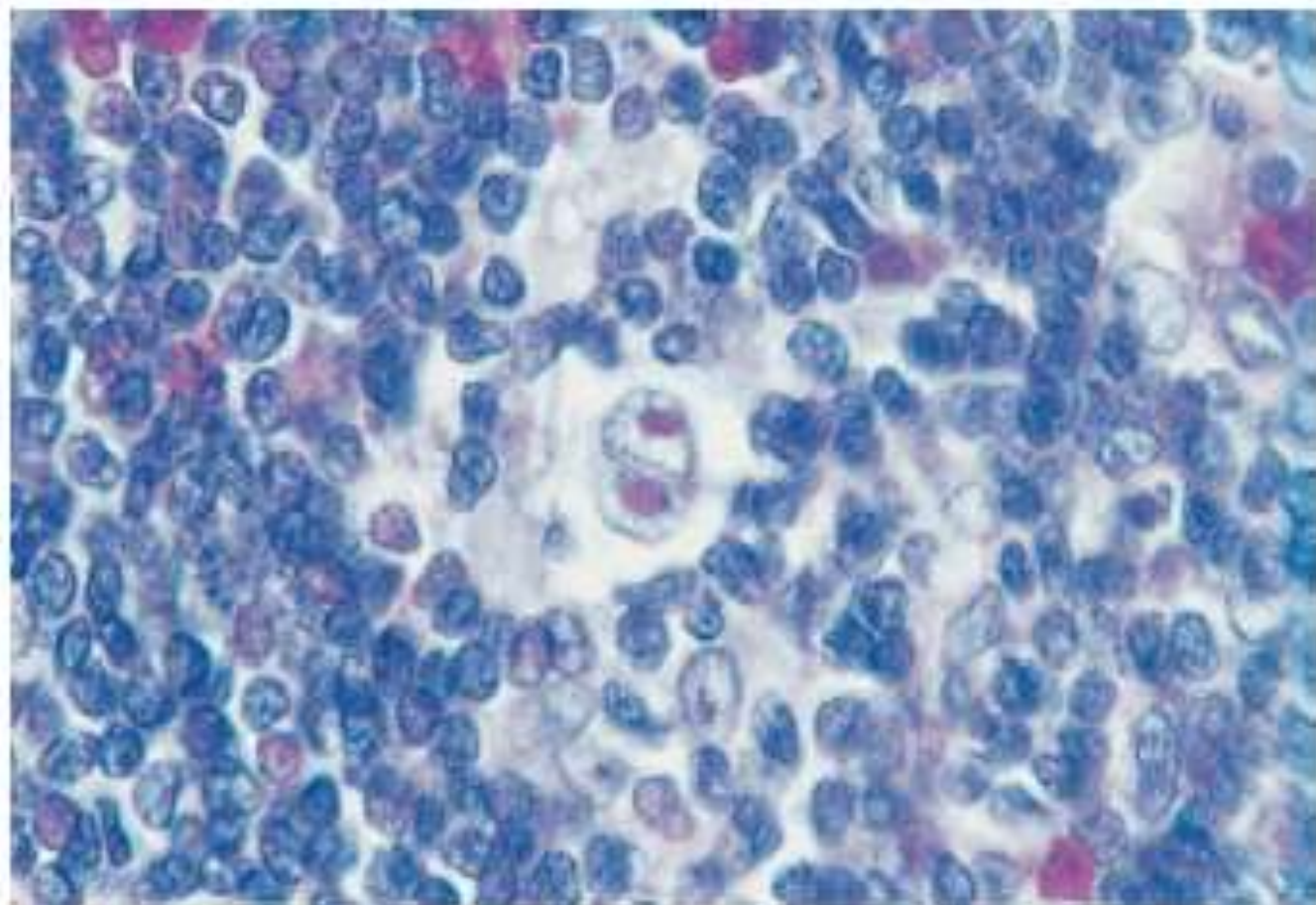




Fig. 24.28 Hodgkin lymphoma. In the centre of this lymph node biopsy is a large typical Reed–Stenberg cell with two nuclei containing a prominent eosinophilic nucleolus.

Epidemiology and Aetiology

 24.55 Epidemiology and aetiology of Hodgkin lymphoma
Incidence
<ul style="list-style-type: none">• ~4 new cases/100 000 population/yr
Sex ratio
<ul style="list-style-type: none">• Slight male excess (1.5:1)
Age
<ul style="list-style-type: none">• Median age 31 yrs; first peak at 20–35 yrs and second at 50–70 yrs
Aetiology
<ul style="list-style-type: none">• Unknown• More common in patients from well-educated backgrounds and small families• Three times more likely with a past history of infectious mononucleosis but no definitive causal link to Epstein–Barr virus infection is proven

WHO Classification of Hodgkin Lymphoma

 24.56 WHO pathological classification of Hodgkin lymphoma		
Type	Histology classification	Proportion of HL
Nodular lymphocyte-predominant HL		5%
Classical HL	Nodular sclerosing	70%
	Mixed cellularity	20%
	Lymphocyte-rich	5%
	Lymphocyte-depleted	Rare

- Mixed cellularity is more common in the elderly.
- Lymphocyte-rich HL usually presents in men.
- Lymphocyte-depleted HL is rare and probably represents large-cell or anaplastic non-Hodgkin lymphoma.

- Nodular lymphocyte-predominant HL is slowgrowing, localised and rarely fatal.
- Classical HL is divided into four histological subtypes from the appearance of the Reed–Sternberg cells and surrounding reactive cells.
- The nodular sclerosing type is more common in young patients and in women.

Clinical features

- There is painless, rubbery lymphadenopathy, usually in the neck or supraclavicular fossae; the lymph nodes may fluctuate in size.
- Young patients with nodular sclerosing disease may have large mediastinal masses which are surprisingly asymptomatic but may cause dry cough and some breathlessness.

- Isolated subdiaphragmatic nodes occur in fewer than 10% at diagnosis.
- Hepatosplenomegaly may be present but does not always indicate disease in those organs.
- Spread is contiguous from one node to the next and extranodal disease, such as bone, brain or skin involvement, is rare.

Investigations

- Treatment of HL depends upon the stage at presentation; therefore investigations aim not only to diagnose lymphoma but also to determine the extent of disease.



24.57 Clinical stages of Hodgkin lymphoma (Ann Arbor classification)

Stage	Definition
I	Involvement of a single lymph node region (I) or extralymphatic* site (I _E)
II	Involvement of two or more lymph node regions (II) or an extralymphatic site and lymph node regions on the same side of (above or below) the diaphragm (II _E)
III	Involvement of lymph node regions on both sides of the diaphragm with (III _E) or without (III) localised extralymphatic involvement or involvement of the spleen (III _s), or both (III _{SE})
IV	Diffuse involvement of one or more extralymphatic tissues, e.g. liver or bone marrow
Each stage is subclassified:	
A	No systemic symptoms
B	Weight loss > 10%, drenching sweats, fever
*The lymphatic structures are defined as the lymph nodes, spleen, thymus, Waldeyer's ring, appendix and Peyer's patches.	

- *FBC* may be normal. If a normochromic, normocytic anaemia or lymphopenia is present, this is a poor prognostic factor. An eosinophilia or a neutrophilia may be present.
- *ESR* may be raised.

- *Renal function tests* are required to ensure function is normal prior to treatment.
- *Liver function* may be abnormal in the absence of disease or may reflect hepatic infiltration. An obstructive pattern may be caused by nodes at the porta hepatis.

- *LDH measurements* showing raised levels are an adverse prognostic factor.
- *Chest X-ray* may show a mediastinal mass.

- *CT scan* of chest, abdomen and pelvis permits staging. Bulky disease (> 10 cm in a single node mass) is an adverse prognostic feature.
- *Lymph node biopsy* may be undertaken surgically or by percutaneous needle biopsy under radiological guidance.

Biopsy
needle

Enlarged
lymph nodes

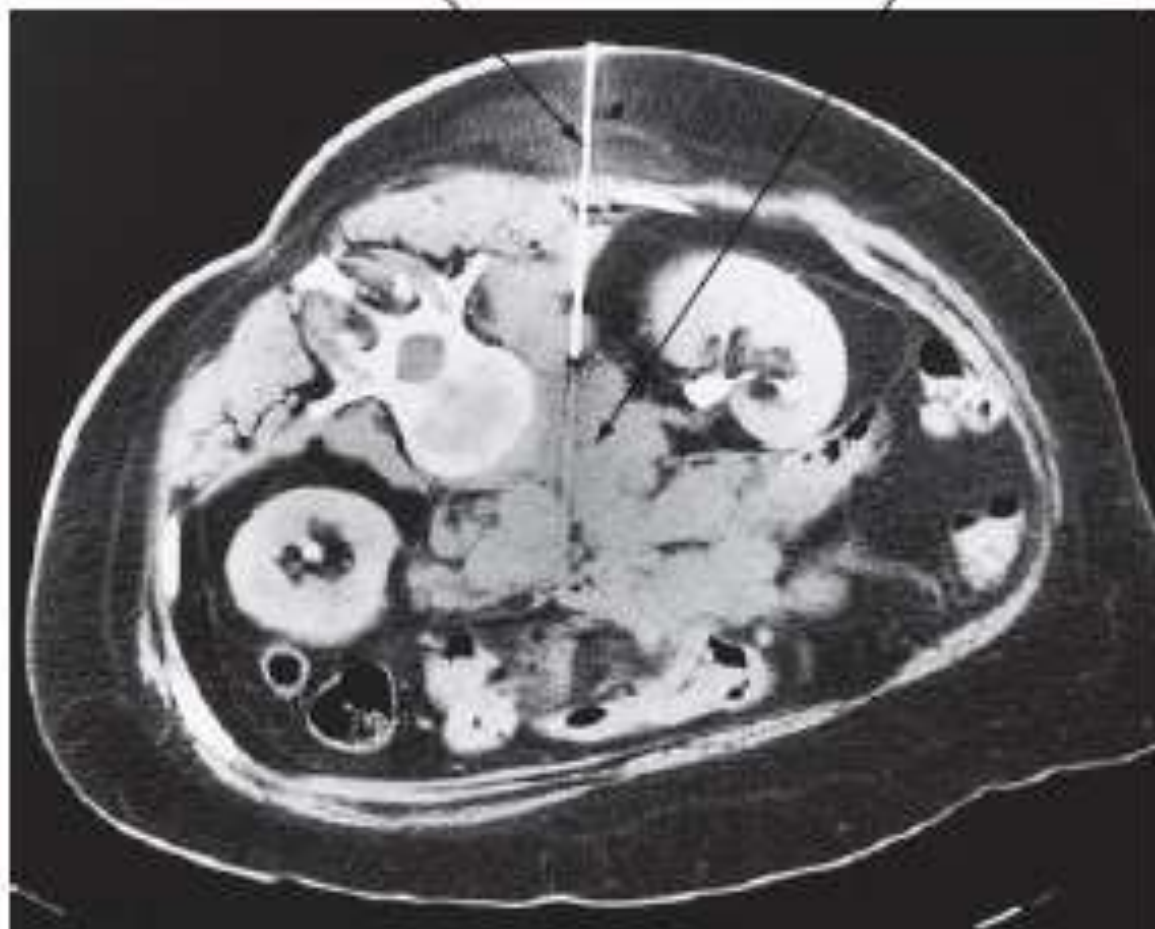


Fig. 24.29 CT-guided percutaneous needle biopsy of retroperitoneal nodes involved by lymphoma.

Management

- Historically, radiotherapy to lymph nodes alone has been used to treat localised stage IA or stage IIA disease effectively, with no adverse prognostic features.

- Clinical trials have shown that patients with early stage disease have better outcomes if chemotherapy is included in their treatment.
- The majority of HL patients are now treated with chemotherapy and adjunctive radiotherapy.
- The ABVD regimen (doxorubicin, vinblastine, bleomycin and dacarbazine) is widely used in the UK.

- Patients with advanced-stage disease are most commonly managed with chemotherapy alone.
- Standard treatment in the UK is 6–8 cycles of ABVD, followed by an assessment of response.

- Patients with disease which is resistant to therapy may be considered for autologous HSCT.

Prognosis

- Over 90% of patients with early-stage HL achieve complete remission when treated with chemotherapy followed by involved field radiotherapy, and the great majority are cured.

- Between 50 and 70% of those with advanced-stage HL can be cured.
- The Hasenclever index can be helpful in assigning approximate chances of cure when discussing treatment plans with patients.
- Patients who fail to respond to initial chemotherapy or relapse within a year have a poor prognosis but some may achieve long-term survival after autologous HSCT.



24.58 The Hasenclever prognostic index for advanced Hodgkin lymphoma

Score 1 for each of the following risk factors present at diagnosis:

- Age > 45 yrs
- Male gender
- Serum albumin < 40 g/L
- Haemoglobin < 105 g/L
- Stage IV disease
- White blood count > $15 \times 10^9/L$
- Lymphopenia < $0.6 \times 10^9/L$

Score	5-yr rate of freedom from progression (%)	5-yr rate of overall survival (%)
0–1	79	90
> 2	60	74
> 3	55	70
> 4	47	59

Non-Hodgkin lymphoma

- Non-Hodgkin lymphoma (NHL) represents a monoclonal proliferation of lymphoid cells of B cell (70%) or T cell (30%) origin.
- The incidence of these tumours increases with age, to 62.8/million population per annum at age 75 years, and the overall rate is increasing at about 3% per year.

- The current WHO classification stratifies according to cell lineage (T or B cells) and incorporates clinical features, histology, chromosomal abnormalities and cell surface markers of the malignant cells.

- Clinically, the most important factor is grade, which is a reflection of proliferation rate.
- High-grade NHL has high proliferation rates, rapidly produces symptoms, is fatal if untreated, but is potentially curable.
- Low-grade NHL has low proliferation rates, may be asymptomatic for many months before presentation, runs an indolent course, but is not curable by conventional therapy.

- Of all cases of NHL in the developed world, over two thirds are either diffuse large B-cell NHL (high-grade) or follicular NHL (low-grade).
- Other forms of NHL, including Burkitt lymphoma, mantle cell lymphoma, MALT lymphomas and T-cell lymphomas, are less common.

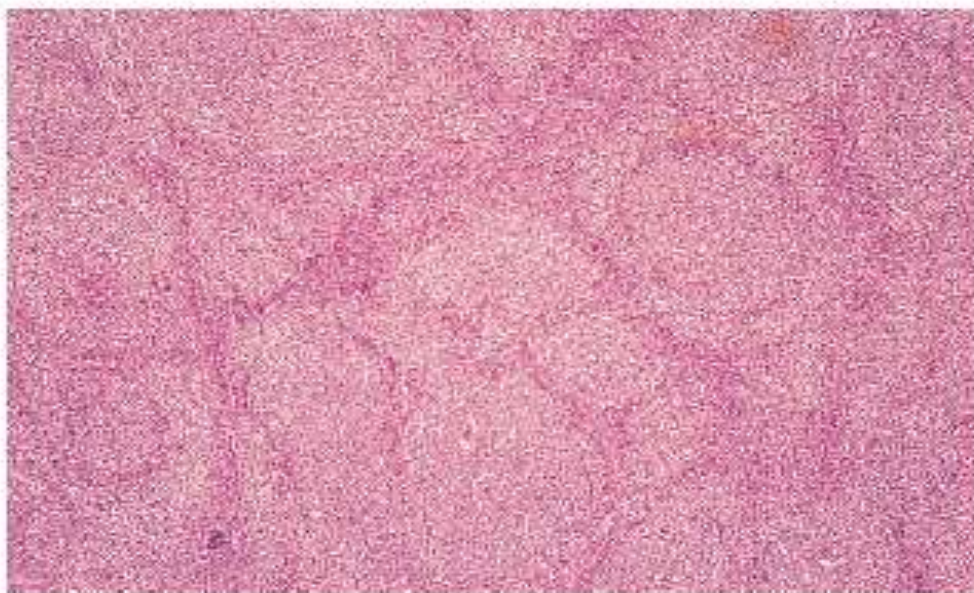
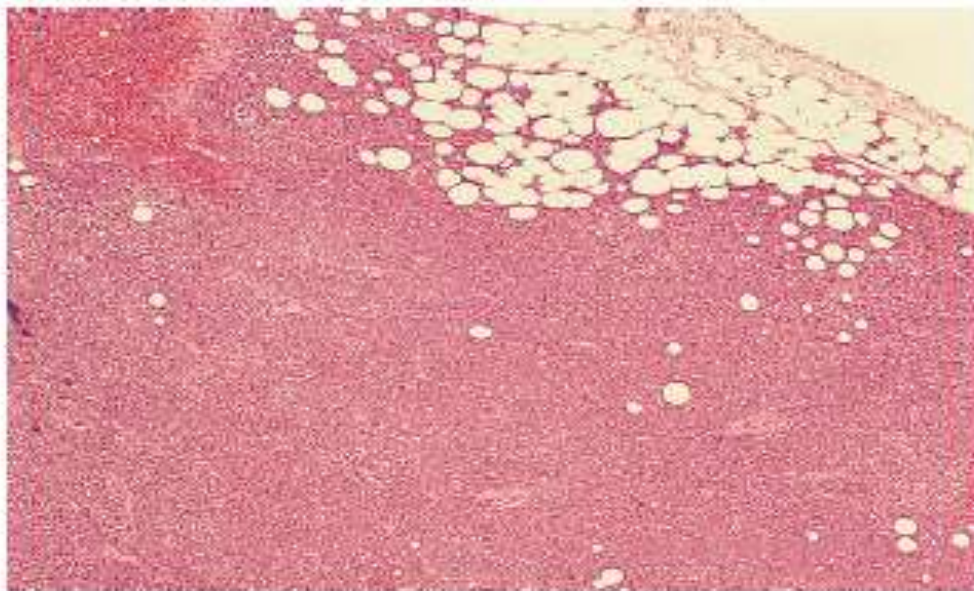
A**B**

Fig. 24.30 Histology of non-Hodgkin lymphoma. **A** (Low-grade) follicular or nodular pattern. **B** (High-grade) diffuse pattern.

Clinical features

- Unlike Hodgkin lymphoma, NHL is often widely disseminated at presentation, including in extranodal sites.
- Patients present with lymph node enlargement, which may be associated with systemic upset: weight loss, sweats, fever and itching.
- Hepatosplenomegaly may be present.

- Sites of extranodal involvement include the bone marrow, gut, thyroid, lung, skin, testis, brain and, more rarely, bone.
- Compression syndromes may occur, including gut obstruction, ascites, superior vena cava obstruction and spinal cord compression.

- The same staging system is used for both HL and NHL, but NHL is more likely to be stage III or IV at presentation.

Investigations

- These are as for HL, but in addition the following should be performed:
- *Bone marrow aspiration and trephine.*
- *Immunophenotyping of surface antigens to distinguish T from B cell tumours.* This may be done on blood, marrow or nodal material.
- *Cytogenetic analysis to detect chromosomal translocations* and molecular testing for T cell receptor or immunoglobulin gene rearrangements, if available.

- *Immunoglobulin determination.* Some lymphomas are associated with IgG or IgM paraproteins, which serve as markers for treatment response.
- *Measurement of uric acid levels.* Some very aggressive high-grade NHLs are associated with very high urate levels, which can precipitate renal failure when treatment is started.
- *HIV testing.* This may be appropriate if risk factors are present

Management

- *Low-grade NHL*

Asymptomatic patients may not require therapy. Indications for treatment include marked systemic symptoms, lymphadenopathy causing discomfort or disfigurement bone marrow failure or compression syndromes.

- In follicular lymphoma, the options are:
- *Radiotherapy*. This can be used for localised stage I disease, which is rare.

- *Chemotherapy*. Most patients will respond to oral therapy with chlorambucil, which is well tolerated but not curative.
- Humanised monoclonal antibodies ('biological' therapy) can be used to target surface antigens on tumour cells, and induce tumour cell apoptosis directly.
- Rituximab (R) in combination with cyclophosphamide, vincristine and prednisolone (R-CVP) is commonly used as first-line therapy.

- *Transplantation.* Particular interest centres on the role of high-dose chemotherapy and HSCT in patients with relapsed disease.

- ***High-grade NHL***
- Patients with diffuse large B-cell NHL need treatment at initial presentation:
- *Chemotherapy*. The majority (> 90%) are treated with intravenous combination chemotherapy, typically with the CHOP regimen (cyclophosphamide, doxorubicin, vincristine and prednisolone).

- *Radiotherapy.* A few stage I patients without bulky disease may be suitable for radiotherapy. Radiotherapy is also indicated for a residual localised site of bulk disease after chemotherapy, and for spinal cord and other compression syndromes.
- *HSCT.* Autologous HSCT benefits patients with relapsed chemosensitive disease.

Prognosis

- Low-grade NHL runs an indolent remitting and relapsing course, with an overall median survival of 10 years.
- Transformation to a high-grade NHL occurs in 3% per annum and is associated with poor survival.

Thank you!