Hodgkin Lymphoma

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Hodgkin lymphoma (HL) is an uncommon B cell lymphoid malignancy. There are two main types of HL—classical Hodgkin lymphoma (cHL) and nodular lymphocyte predominant Hodgkin lymphoma (NLPHL). cHL accounts for 95% and NLPHL for 5% of all HL cases. This chapter will provide a summary of the epidemiology, clinico-pathological features, staging and prognostication of cHL. NLPHL is also discussed briefly.

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1.1 Epidemiology

The incidence of cHL is around three cases per 100,000, with about 1700 new cases diagnosed per year in the UK. It is the third most common cancer in young adults aged between 20–34 years, with a much lower incidence in other age groups. There is a slight male predominance.

1.2 Clinical Presentation

cHL typically presents with painless lymphadenopathy, most often in the neck and supra-clavicular areas. A mediastinal mass is present in over 50% of patients, and this can be asymptomatic or present with dyspnoea, cough, or superior vena cava obstruction (SVCO). Abdominal nodal involvement is less common, often in older patients or when fever or night sweats are present.

A quarter of patients have B symptoms, which include fevers of >38 ºC, drenching night sweats, and loss of more than 10% of body weight over 6 months. Other symptoms such as pruritis, fatigue, and alcohol-related pain may occur but are less specific and are not classified as B symptoms.

About 5–8% of patients with cHL have bone marrow involvement at diagnosis using conventional staging. Rarely, cHL presents with spinal cord compression, central nervous system disease, Waldeyer's ring involvement, testicular masses, or gastro-intestinal masses.

If the disease is left untreated, death usually occurs within 1–2 years, with fewer than 5% of patients alive at 5 years.

Although not an AIDS-defining illness, an association between cHL and HIV infection is well recognised.

1.3 Diagnosis

Surgical excision biopsy of an abnormal node is recommended, although needle core biopsy offers a less invasive alternative, with generally good diagnostic yield. Fine needle aspirate (FNA) is discouraged for lymphoma diagnosis due to poor sample quality for accurate diagnosis.

When the disease is primarily within the chest, involvement of a cardiothoracic team to obtain tissue through mediastinoscopy or by endo-bronchial ultrasound (EBUS) guided biopsy should be considered. Histopathological analysis with immuno-histochemistry is essential for accurate diagnosis, and should be confirmed by an experienced haematopathologist.

1.4 Pathology and Classification

The hallmark of cHL is the presence of malignant Reed-Sternberg (RS) cells scattered within a cellular infiltrate of non-malignant inflammatory cells that make up the majority of the tumour tissue. The RS cells have been shown to be B cells with an altered B-cell programme and, therefore, do not express typical B-cell antigens. They are usually CD15 and CD30 positive. About half of cases harbour Epstein Barr virus (EBV) DNA although the precise role of EBV in the pathogenesis of cHL remains unclear.

cHL is in turn subclassified into four subtypes: nodular sclerosis (70%), mixed cellularity (20%), lymphocyte-rich (5%), and lymphocyte-depleted (rare), according to the cellular background of the RS cells. There are some differences in presentation, sites of involvement, epidemiology, and association with EBV between these four cHL subtypes; however, there are no differences in the prognosis or management of the different subtypes of cHL.

1.5 Staging

Table 1.1 shows the modified Ann Arbor staging system used for HL. The stage highlights the anatomical distribution of the disease but also factors known to be of prognostic significance, such as the absence or presence of B symptoms (A or B), bulky disease (X), and extranodal disease (E). The 2014 Lugano Classification has suggested removing the term X and instead to measure the longest tumour size on CT. It however retains the presence of a single nodal mass of 10 cm or greater than

Table 1.1 Modified Ann Arbor staging criteria for Hodgkin lymphoma

Stage	*Areas involved*
I	**One lymph node region or lymphoid structure**
II	**≥2 lymph node regions on the same side of the diaphragm**
III	**Lymph nodes on both sides of the diaphragm**
IV	**Extranodal sites other than one contiguous or proximal extranodal site or bone marrow**
Qualifier	*Clinical features*
A	No systemic symptoms present
B	Unexplained fevers >38 °C; drenching night sweats; or weight loss >10% of body weight (within 6 months prior to diagnosis)
X	Bulky disease (mediastinal mass larger than a third of thoracic diameter, or any nodal mass >10 cm in diameter)
E	Involvement of one contiguous or proximal extranodal site

a third of the transthoracic diameter at any level of thoracic vertebrae as determined by CT as the definition of bulky disease for cHL.

The Lugano Classification also incorporates CT neck, chest, abdomen, and pelvis combined with functional imaging with ^{18}F-fluorodeoxyglucose-PET (PET/CT) as the optimal staging modality in Hodgkin lymphoma. PET/CT upstages 13–24% of cases compared to CT only. PET/CT may however be positive in sites of infection or inflammation and careful interpretation is required.

PET/CT is highly sensitive for focal bone marrow infiltration, and non-targeted pelvic bone marrow biopsy for staging is now rarely performed. Diffuse bone marrow uptake on PET/CT usually reflects a reactive process, while focal lesions are usually due to disease. Where there is uncertainty, a bone marrow biopsy is advisable.

1.6 Prognostic Factors at Baseline

At diagnosis, cHL is sub-classified into three main prognostic categories (Box 1.1), namely, early favourable, early unfavourable, and advanced, according to the modified Ann-Arbor stage and, for early stage cHL, the presence of clinical risk factors. The treatment and outcomes are in turn influenced by the

Box 1.1 Prognostic Categories in cHL

Early favourable

- Stages I–IIA/B without any risk factors

Early unfavourable

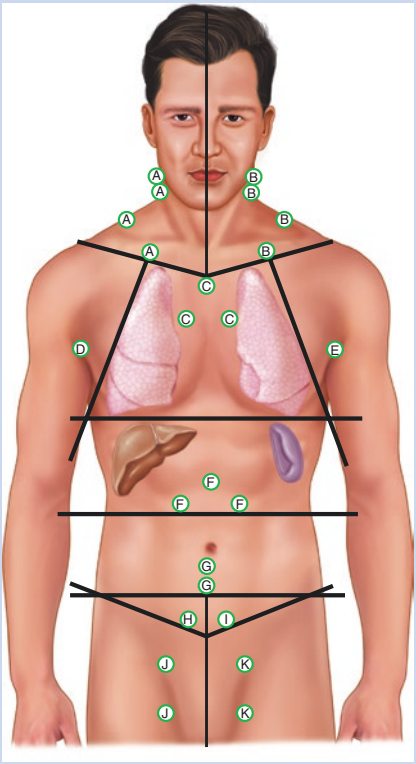
- Stage IA/B and stage IIA with one or more risk factors
- Stage IIB with high ESR and/or involvement of ≥3 lymph node areas as only risk factors

Advanced stages

- Stage IIB with extranodal involvement and/or large mediastinal mass
- Stages III–IV

German Hodgkin Study Group Risk Factors for early stage cHL

- Large mediastinal mass ≥one third of the maximum thorax diameter
- Involvement of one contiguous or proximal extranodal site
- Involvement of three or more nodal areas (see Fig. 1.1)
- Elevated ESR (>50 mm/h in stages I–IIA and >30 mm/h in stages I–IIB)



A: right cervical + infra-/supra-clavicular/nuchal
B: left cervical + infra-/supra-clavicular/nuchal
C: right/left hilar + mediastinal
D: right axillary
E: left axillary
F: upper abdomen (spleen hilum, liver hilum, coeliac)
G: lower abdomen (Para-aortic, iliac, mesenteric)
H: right iliac
I: left iliac
J: right inguinal + femoral
K: left inguinal + femoral

Fig. 1.1 Definition of main lymph node areas (German Hodgkin Study Group)

prognostic category the patient falls into. The precise definition of the risk factors differs somewhat among study groups. The German Hodgkin Study Group risk factors are widely used in early stage disease. Bulky disease has been shown to be an independent adverse prognostic marker in early stage cHL, as is extranodal extension, presence of 3 or more nodal sites (see Fig 1.1) and a raised ESR.

With current treatment regimens, the prognosis of early stage cHL is excellent, with overall 5-year survival approaching 95%. About 10% of early stage patients will experience a relapse or have primary refractory disease.

Box 1.2 IPS/Hasenclever Index Risk Factors in Advanced cHL

1. Serum albumin <40 g/L
2. Haemoglobin <10.5 g/dL
3. Male sex
4. Ann Arbor stage IV
5. Age ≥45 years
6. White cell count ≥15 × 109/L
7. Lymphocyte count <0.6 × 109/L

In advanced cHL, 5-year disease-free survival is variable, between 75 and 90%. A seven-point International Prognostic Score, also known as the Hasenclever Index (Box 1.2), identifies seven risk factors, with each point reducing the 5-year progression-free survival by about 8%. Overall, about 20–30% of advanced stage cHL will experience a relapse or have refractory disease. Unfortunately the baseline IPS is not a very reliable tool in predicting outcome at an individual level.

1.7 Nodular Lymphocyte Predominant Hodgkin Lymphoma

NLPHL is a distinct clinical entity with a histology and clinical course distinct from cHL. NLPHL accounts for about 5% of cases of HL in adults and adolescents and 10–20% of cases in children. Most NLPHL patients (70%) are male. Incidence peaks at 13–14 years in children and 30–35 years in adults. Three-quarter patients present with early-stage disease, often with solitary lymph node involvement. B symptoms are rare in NLPHL.

NLPHL lacks the classical Reed-Sternberg cells but is characterized by the presence of atypical cells, sometimes termed ‘popcorn’ or L&H cells. NLPHL usually displays a nodular growth pattern, which may or may not be accompanied by diffuse areas. L&H cells are typically positive for B-cell-associated antigens such as CD20, unlike cHL cells.

The clinical course in NLPHL is usually indolent and the prognosis is favourable, although late relapses 10–15 years later may occur. Transformation to high-grade B-cell lymphoma is reported in about 12% of patients at 10 years after diagnosis. The risk of transformation increases over time and occurs more frequently in advanced stage disease, especially when disease involves organs such as the spleen and bone and when associated with B symptoms. Histological confirmation at relapse is important to exclude transformation.

Key Points

- Hodgkin lymphoma (HL) is an uncommon cancer of the lymphatic system.
- There are two main types of HL—classical Hodgkin lymphoma (cHL) and nodular lymphocyte predominant Hodgkin lymphoma (NLPHL).
- cHL accounts for 95% and NLPHL for 5% of all HL cases.
- cHL typically presents with painless lymphadenopathy, most often in the neck and supraclavicular areas (mediastinal mass is present in over 50% of patients).
- A quarter of patients have B symptoms.
- About 5–8% of patient with cHL have marrow involvement at diagnosis.
- If the disease is left untreated, death usually occurs within 1–2 years from progression (fewer than 5% of patients alive at 5 years).
- Although not an AIDS-defining illness, an increased incidence of cHL is seen in the setting of HIV infection.
- Surgical excision biopsy of an abnormal node is recommended, although needle core biopsy offers a less invasive alternative, with generally good diagnostic yield.
- Fine needle aspirate (FNA) is discouraged for lymphoma diagnosis due to poor yield.
- When the disease is primarily within the chest, involvement of a cardiothoracic team to obtain tissue through mediastinoscopy should be considered.
- Histopathological analysis with immunohistochemistry is essential for diagnosis, and the diagnosis of HL should be confirmed by an experienced haematopathologist.
- Contrast-enhanced CT neck, chest, abdomen, and pelvis is used for anatomical staging, and this is now often combined with functional imaging with ^{18}F-fluorodeoxyglucose-PET (PET/CT), which upstages 13–24% compared to CT only.
- PET/CT is highly sensitive for focal bone marrow infiltration, and nontargeted pelvic bone marrow biopsy for staging is now performed less often.
- With current treatment regimens, the prognosis of early and intermediate stage cHL is excellent, with overall survival at 5 years approaching 95%.

- In advanced cHL, 5-year disease-free survival is variable, between 75 and 90%.
- NLPHL is a distinct clinical entity characterized by the presence of atypical cells, sometimes termed ‘popcorn’ or L&H cells
- Most NLPHL patients (70%) are male and the disease primarily affects children, adolescents and young adults.
- NLPHL has an excellent prognosis, although late relapses 10–15 years later may occur.

Further Reading

1. Townsend W, Linch D. Hodgkin’s lymphoma in adults. Lancet. 2012;380(9844):836–47.
2. Ansell SM. Hodgkin lymphoma: 2016 update on diagnosis, risk-stratification, and management. Am J Hematol. 2016;91(4):434–42.
3. Ansell SM. Hodgkin lymphoma: diagnosis and treatment. Mayo Clin Proc. 2015;90(11):1574–83.
4. Hoppe RT, Advani RH, Ai WZ, Ambinder RF, Aoun P, Bello CM, et al; National Comprehensive Cancer Network. Hodgkin lymphoma, version 2.2015. J Natl Compr Canc Netw. 2015;13(5):554–86.
5. McKay P, Fielding P, Gallop-Evans E, Hall GW, Lambert J, Leach M, Marafioti T, McNamara C. Guidelines for the investigation and management of nodular lymphocyte predominant Hodgkin lymphoma. Br J Haematol. 2016;172(1):32–43.
6. Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, Lister TA. Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification. J Clin Oncol. 2014;32(27):3059–67.