Hodgkin lymphomas

Lymphomas are a group of diseases caused by malignant lymphocytes that accumulate in lymph nodes and other lymphoid tissue and cause the characteristic clinical feature of lymphadenopathy. Occasionally, they may spill over into blood (‘leukaemic phase’) or infiltrate organs outside the lymphoid tissue. The major subdivision of lymphomas is into Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL) and this is based on the histological presence of Reed–Sternberg (RS) cells in Hodgkin lymphoma.

History and pathogenesis

Thomas Hodgkin was curator of the Anatomy Museum at Guy's Hospital in London and described the disease in 1832. Dorothy Reed and Carl Sternberg were pathologists who identified the abnormal cell that defines this subtype of lymphoma in 1898. The characteristic RS cells, and the associated abnormal mononuclear cells, are neoplastic, whereas the infiltrating inflammatory cells are reactive. Immunoglobulin gene rearrangement studies suggest that the RS cell is of B-lymphoid lineage and that it is often derived from a B cell with a 'crippled' immunoglobulin gene caused by the acquisition of mutations that prevent synthesis of full-length immunoglobulin. HLA class I expression is usually lost on the tumour cells and mutation of the β2-microglobulin gene is frequent. The Epstein–Barr virus (EBV) genome has been detected in over 50% of cases in Hodgkin tissue but its exact role in the pathogenesis is unclear.

Clinical features :The disease can present at any age but is rare in children and has a peak incidence in young adults. There is an almost 2 : 1 male predominance. The following symptoms are common.

1. Most patients present with painless, asymmetrical, firm and discrete enlargement of superficial lymph nodes. The cervical nodes are involved in 60–70% of patients, axillary nodes in approximately 10–15% and inguinal nodes in 6–12%. In some cases the size of the nodes decreases and increases spontaneously and they may become matted. Typically the disease is localized initially to a single peripheral lymph node region and its subsequent progression is by contiguity within the lymphatic system. Retroperitoneal nodes are also often involved but usually only diagnosed by computed tomography (CT) scan.
2. Modest splenomegaly occurs during the course of the disease in 50% of patients. The liver may also be enlarged because of liver involvement.

3. Mediastinal involvement is found in up to 10% of patients at presentation. This is a feature of the nodular sclerosing type, particularly in young women. There may be associated pleural effusions or superior vena cava obstruction

4. Cutaneous Hodgkin lymphoma occurs as a late complication in approximately 10% of patients. Other organs may also be involved, even at presentation, but this is unusual.

5. Constitutional symptoms are prominent in patients with widespread disease. The following may be seen: (a) fever occurs in approximately 30% of patients and is continuous or cyclic; (b) pruritus, which is often severe, occurs in approximately 25% of cases; (c) alcohol-induced pain in the areas where disease is present occurs in some patients; (d) other constitutional symptoms include weight loss, profuse sweating (especially at night), weakness, fatigue, anorexia and cachexia.

Haematological and biochemical findings

1. Normochromic normocytic anaemia is most common. Bone marrow involvement is unusual in early disease, but if it occurs bone marrow failure may develop with a leucoerythroblastic anaemia.
2. One-third of patients have a neutrophilia; eosinophilia is frequent.
3. Advanced disease is associated with lymphopenia and loss of cell-mediated immunity.
4. The platelet count is normal or increased during early disease, and reduced in later stages.
5. The erythrocyte sedimentation rate (ESR) and C-reactive protein are usually raised. The ESR is useful in monitoring disease progress.
6. Serum lactate dehydrogenase (LDH) is raised initially in 30–40% of cases.
7. The HIV status should be determined.

Diagnosis and histological classification

The diagnosis is made by histological examination of an excised lymph node. The distinctive multinucleate polyploid RS cell is central to the diagnosis of the four classic types and mononuclear Hodgkin cells are also part of the malignant clone. These cells stain with CD30 and CD15 but are usually negative for B-cell antigen expression. Inflammatory components consist of lymphocytes, neutrophils, eosinophils, plasma cells and variable fibrosis. CD68 detects infiltrating macrophages and if this is strongly positive it is an unfavourable feature. Histological classification is into four classical types and nodular lymphocyte predominant disease. There is no difference in the prognosis or management of the different sub-types of classical HL. Nodular sclerosis is the most frequent in Europe and the USA, whereas lymphocyte depleted is more common in developing countries and has a particularly strong association with EBV infection. Nodular lymphocyte predominant does not show RS cells and has many features of non-Hodgkin lymphoma and may be treated as such.

Clinical staging:

The disease may be suspected on the basis of clinical presentation, chest X-ray and CT scan. The selection of appropriate treatment depends on accurate staging of the extent of disease. shows the scheme that is used. Staging is performed by clinical examination together with combined positron emission tomography (PET) and CT scans. CT scan alone can be used if PET is not available. Magnetic resonance imaging (MRI) scanning may be needed for particular sites. Bone marrow trephine is sometimes carried out and liver biopsy may also be needed in difficult cases. PET/CT scanning is useful in monitoring response to treatment and for detection of small foci of residual disease. Patients are also classified as A or B according to whether or not constitutional features (fever or weight loss) are present

Positron emission tomography (PET)

^{18}F-fluorodeoxyglucose positron emission tomography (FDGPET) is now used widely in the management of lymphoma and other haematological malignancies. It utilizes the fact that rapidly dividing malignant cells readily take up glucose from their environment. Radiolabelled glucose is infused into the patient and the tissues that have taken up the label can then be visualized by the PET scanner. As well as detecting the presence of active disease at the time of diagnosis, PET/CT scans can also be used to assess the response to treatment and to potentially guide the treatment course. These 'interim PET/CT' scans are reported according to the Deauville 5 point criteria, which uses the uptake in the mediastinum and liver as an internal control, from which to assess the activity of the tumour. Scores 1 and 2 are generally considered 'negative', whereas 4 and 5 are 'positive' and a score of 3 must be interpreted according to the clinical context.

- Score 1 no uptake
- Score 2 uptake ≤ mediastinum
- Score 3 uptake > mediastinum but ≤ liver
- Score 4 moderately increased uptake > liver
- Score 5 markedly increased uptake > liver

Classical Hodgkin lymphoma (95% of cases)	
Nodular sclerosis	Collagen bands extend from the node capsule to encircle nodules of abnormal tissue. A characteristic lacunar cell variant of the Reed–Sternberg cell is often found. The cellular infiltrate may be of the lymphocyte-predominant, mixed cellularity or lymphocyte-depleted type; eosinophilia is frequent
Lymphocyte rich	Scanty Reed–Sternberg cells; multiple small lymphocytes with few eosinophils and plasma cells; nodular and diffuse types
Mixed cellularity	The Reed–Sternberg cells are numerous and lymphocyte numbers are intermediate
Lymphocyte depleted	There is either a reticular pattern with dominance of Reed–Sternberg cells and sparse numbers of lymphocytes or a diffuse fibrosis pattern where the lymph node is replaced by disordered connective tissue containing few lymphocytes. Reed–Sternberg cells may also be infrequent in this latter subtype
Nodular lymphocyte-predominant (5% of cases)	
Reed–Sternberg cells are absent; lymphocyte predominant (LP) tumour B cells are present	

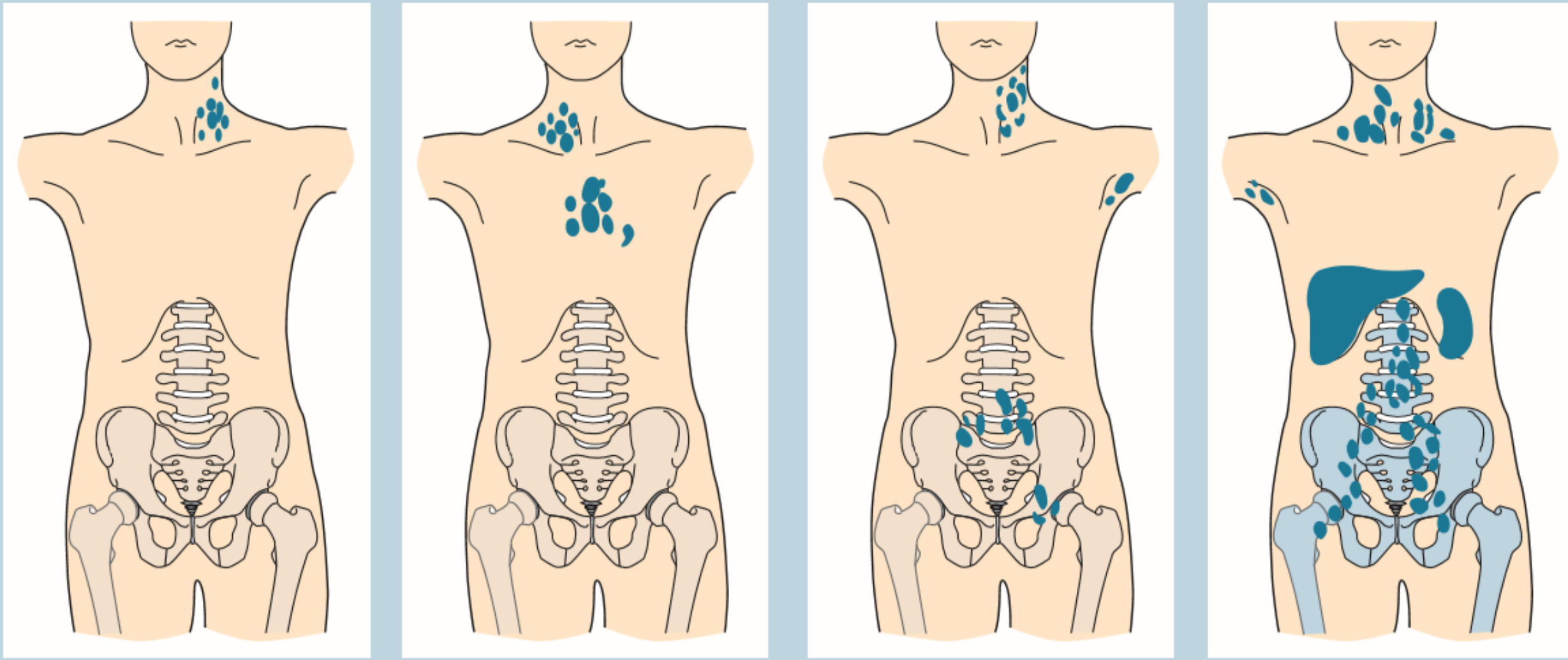
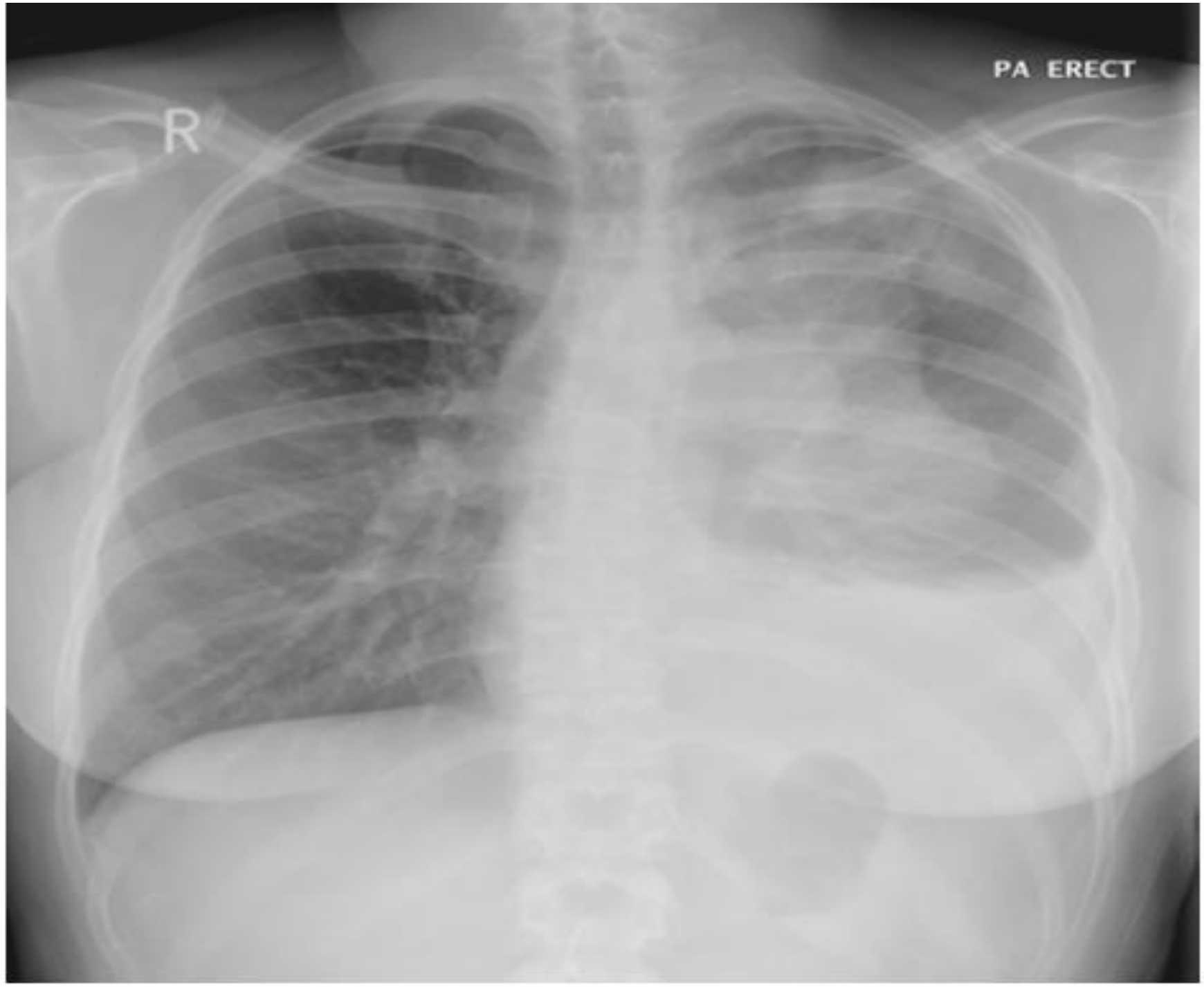


Figure 19.1 Cervical lymphadenopathy in a patient with Hodgkin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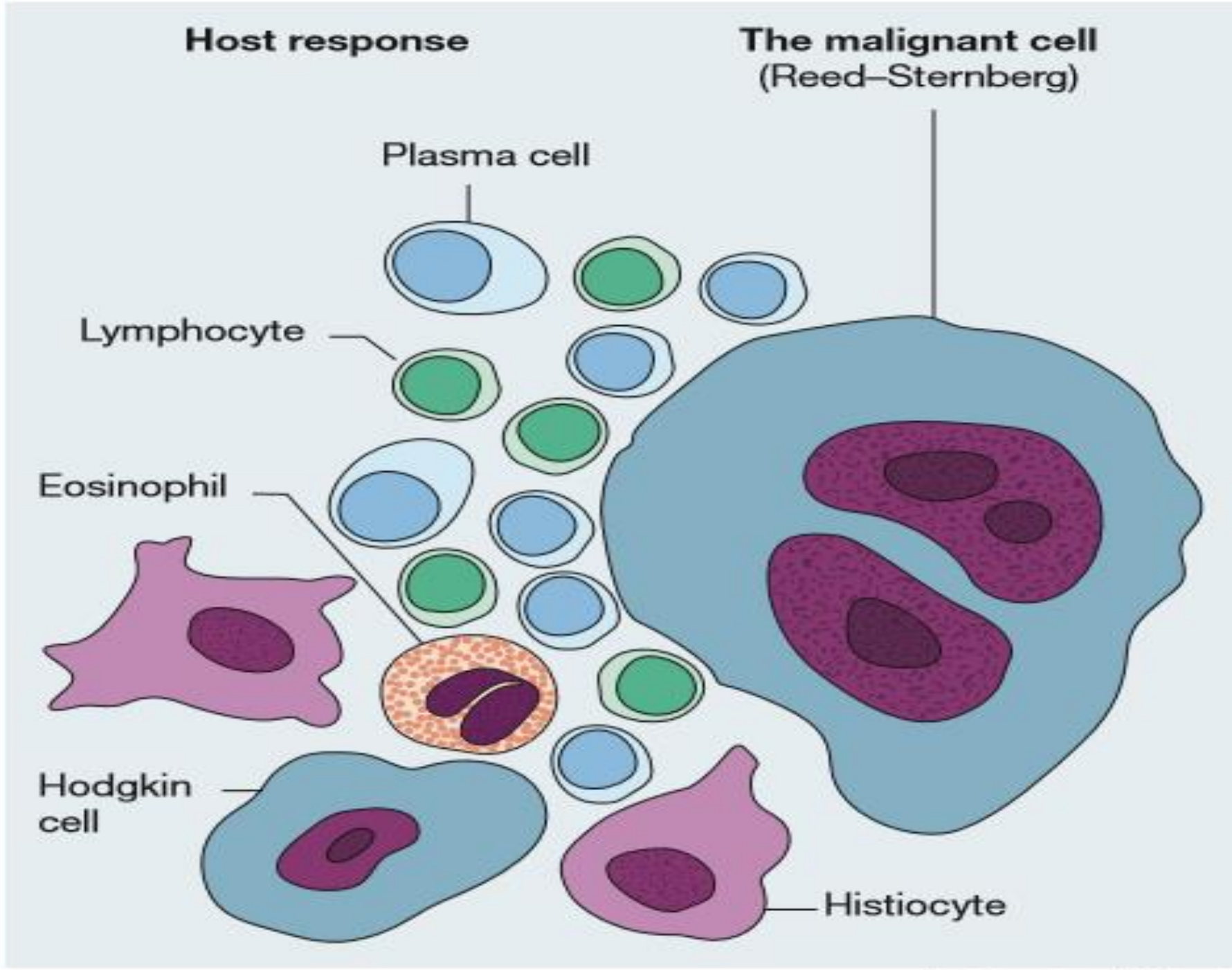
Host response
The malignant cell
(Reed–Sternberg)
Plasma cell
Lymphocyte
Eosinophil
Hodgkin
cell
Histiocyte

Early stage disease :

The outcome for early stage disease is excellent and an important aim is to avoid over-treatment and the risk of late complications. Two broad options are chemotherapy alone or ‘combined modality treatment’ (CMT) using chemotherapy and radiotherapy. CMT achieves better short-term disease control but in the longer term there is no clear increase in overall survival. Individual treatment decisions will depend on local regimens and patient choice. As examples, favourable prognosis disease could be treated with two courses of A (Adriamycin = Doxorubicin), B (Bleomycin), V (Vinblastine), D (Dacarbazine) (ABVD) chemotherapy followed by 20 Gy radiotherapy. If lymph nodes are not bulky radiotherapy can be omitted but at least three courses of ABVD given. In contrast, unfavourable disease (1B or 2B) could be treated with four to six courses of ABVD followed by 30 Gy radiotherapy for bulky disease. Alternatively the first two cycles of ABVD can be replaced by more intensive chemotherapy, such as escalated BEACOPP (Bleomycin, Etoposide, Adriamycin, Cyclophosphamide, Vincristine = Oncovin, Procarbazine and Prednisolone).

Advanced stage disease Cyclical chemotherapy is used for stage III and IV disease. Six to eight cycles of ABVD are most widely used. Six cycles of escalated BEACOPP may be given to achieve higher complete

remission rates at the expense of greater toxicity. Subsequent radiotherapy is given if residual nodes are more than 1.5 cm diameter, or smaller but remain PET positive, or to sites of originally bulky disease.

Assessment of response to treatment

Clinical examination and imaging (PET/CT scans) are used to assess response to treatment. Regular pulmonary function assessment is needed, in older patients and those receiving bleomycin. Patients with HL often show residual masses following treatment which may be because of the large degree of fibrosis present within lymph nodes. PET/CT scanning reveals the areas of active disease. Clinical trials are assessing if PET/CT can be used to define the management of individual patients. For example, it may be used after the first two cycles of ABVD and if there is residual active disease, treatment might be switched to more intensive chemotherapy. Alternatively, if the PET scan is negative, bleomycin might be omitted from subsequent chemotherapy and there is generally no need to repeat the PET/CT scan at the end of therapy. For patients PET/CT-positive at the end of therapy, repeat biopsy and close clinical and imaging assessment is needed. Inflammatory tissue may cause a false positive PET scan.

Relapsed cases

Approximately 25% of patients suffer from disease relapse or are refractory to initial therapy. Treatment is generally given as an alternative combination chemotherapy to the initial regimen and, if necessary, with radiotherapy to sites of bulky disease. Brentuximab vedotin is an anti-CD30 antibody linked to a microtubule-disrupting agent and may produce favourable responses. If the disease remains chemosensitive, high-dose chemotherapy and autologous stem cell transplantation improve the probability of cure and are given for most patients below the age of 65 years. Allogeneic transplantation may also be curative in a minority of patients who fail other therapies. A new therapy is the use of antibodies which block the inhibitory molecule PD-1 on T cells .Hodgkin lymphoma often expresses high levels of the PD-1 ligand PD-L1 and this acts as a mechanism for evading the T cell immune response. PD-1 blockade is proving to be highly effective in management of relapsed HL and is now likely to be investigated earlier in the treatment pathway

Prognosis:

The prognosis depends on age, stage and histology. Overall approximately 85% of patients are cured.

The late effects of Hodgkin lymphoma and its treatment:

Long-term follow-up of patients has revealed a considerable burden of late disease following treatment. Secondary cancers, such as lung cancer and breast cancer, appear to be related to radiotherapy, whereas myelodysplasia or acute myeloid leukaemia are more associated with the use of alkylating agents. NonHodgkin lymphoma and other cancers also occur with greater frequency than in controls. Non-malignant complications include sterility, intestinal complications, coronary artery disease and pulmonary complications of the mediastinal radiation or bleomycin chemotherapy. Vinblastine may cause a permanent neuropathy. These features are the main reason why less intensive treatment regimens are now being explored for this disease.

Non-Hodgkin lymphoma

Introduction to non-Hodgkin lymphoma:

These are a large group of clonal lymphoid tumours, about 85% of B cell and 15% of T or NK (natural killer) cell origin. Their clinical presentation and natural history are much more variable than Hodgkin lymphoma. They are characterized by an irregular pattern of spread and a significant proportion of patients develop disease outside the lymph nodes. Their frequency has increased markedly over the last 50 years and, with an incidence of approximately 17 in 100 000, they now represent the fifth most common malignancy in some developed countries

Classification

The lymphomas are classified within a group of mature B-cell and T-cell neoplasms, which also includes some chronic leukaemias and myeloma. The World Health Organization (WHO) classification recognizes age (paediatric or elderly) and site of involvement (e.g. skin, central nervous system (CNS), intestine, spleen, mediastinal) as well as the disease histology, immunophenotype and genotype important in disease classification. In this chapter we consider the more common lymphoma subtypes within this classification

Cell of origin

The normal B-cell development stages are illustrated in -cell lymphomas tend to mimic normal B cells at different stages of development. This is shown by their phenotypic patterns on immune histology or flow cytometry. They can be divided into those resembling precursor B cells found in the bone marrow, and those which resemble germinal centre (GC) cells or post-GC cells from lymph nodes. T-cell lymphomas resemble precursor T cells in the bone marrow and thymus, or peripheral mature T cells.

Low- and high-grade non-Hodgkin lymphoma

sThe non-Hodgkin lymphomas (NHL) are a diverse group of diseases and vary from highly proliferative and potentially rapidly fatal diseases to some very indolent and well-tolerated malignancies. For many years clinicians have subdivided lymphomas into ‘low-grade’ and ‘high-grade’ disease. This approach is valuable as, in general terms, the low-grade disorders are relatively indolent, respond well to chemotherapy but are very difficult to cure, whereas high-grade lymphomas are aggressive and need urgent treatment but are more often curable.

Leukaemias and lymphomas:

The difference between lymphomas, in which lymph nodes, spleen or other solid organs are involved, and leukaemias, with predominant bone marrow and circulating tumour cells, may be blurred. Chronic lymphocytic leukaemia and small lymphocytic lymphoma are identical lymphoproliferative diseases but show leukaemic and lymph node distribution respectively. Acute lymphoblastic leukaemia and acute lymphoblastic lymphoma are also similar and have comparable treatment regimens. Small numbers of malignant cells circulate in the blood in many forms of NHL

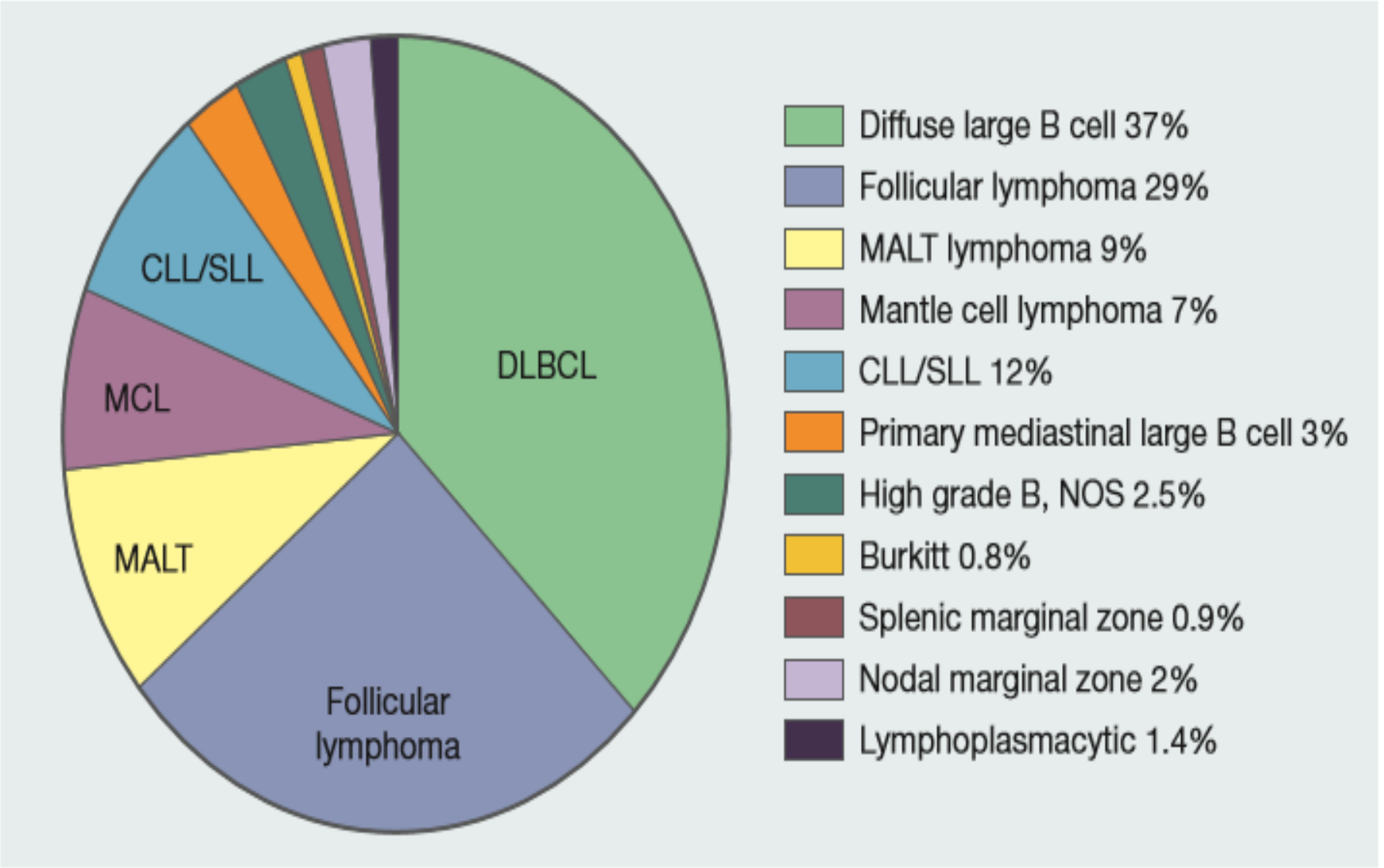

Figure 20.1 The relative frequencies of B-cell non-Hodgkin lymphomas. CLL, chronic lymphocytic lymphoma; DLBCL, diffuse large B-cell lymphoma; MALT, mucosa-associated lymphoid tissue; MCL, mantle cell lymphoma; NOS, not otherwise specified; PMLBCL, primary mediastinal large B-cell lymphoma; SLL, small lymphocytic lymphoma.

Clinical features of non-Hodgkin lymphoma:

1. Superficial lymphadenopathy The majority of patients present with asymmetric painless enlargement of lymph nodes in one or more peripheral lymph node regions.

2. Constitutional symptoms Fever, night sweats and weight loss occur less frequently than in Hodgkin lymphoma. Their presence is usually associated with disseminated disease.

3. Oropharyngeal involvement In 5–10% of patients there is disease of the oropharyngeal lymphoid structures (Waldeyer's ring) which may cause complaints of a 'sore throat' or noisy or obstructed breathing.

4. Symptoms due to anaemia, infections due to neutropenia or purpura with thrombocytopenia may be presenting features in patients with diffuse bone marrow disease. Cytopenias may also be autoimmune in origin or due to sequestration in the spleen.

5. Abdominal disease The liver and spleen are often enlarged and involvement of retroperitoneal or mesenteric nodes is frequent. The gastrointestinal tract is the most commonly involved extranodal site after the bone marrow, and patients may present with acute abdominal symptoms.

6. Other organs Involvement of the skin, brain, testis or thyroid is not infrequent. The skin is also primarily involved in two closely related T-cell lymphomas, mycosis fungoides and Sézary syndrome.

■ Non-Hodgkin lymphomas are a large group of clonal lymphoid tumours. Approximately 85% are of B-cell origin and 15% derive from T or NK cells.

■ Their clinical presentation and natural history are more variable than Hodgkin lymphoma and can vary from very indolent disease to rapidly progressive subtypes that need urgent treatment.

■ The NHL are divided into low-grade and high-grade disease. Low-grade disorders are typically slowly progressive, respond well to chemotherapy but are difficult to cure, whereas high-grade lymphomas are aggressive and need urgent treatment but are more often curable.

■ Investigation is with lymph node biopsy, blood tests and imaging usually by PET/CT. Immunohistochemistry of the lymph node is essential and cytogenetic or gene mutation analysis is helpful in many cases.

■ Clinical staging is performed as for Hodgkin lymphoma.

■ Some of the more common subtypes include: Small lymphocytic lymphoma is the lymphoma equivalent of chronic lymphocytic leukaemia. Lymphoplasmacytic lymphoma usually produces an IgM paraprotein, when it is also known as Waldenström's macroglobulinaemia, and often leads to anaemia and hyperviscosity. Marginal zone lymphomas arise from marginal zone B cells of lymphoid follicles and can occur as mucosa

associated (MALT) lymphoma, most frequent in the stomach. Follicular lymphoma represents 25% of all NHL and is associated with the t(14;18) translocation. Treatment usually achieves disease remission but the only curative option is allogeneic stem cell transplantation.

- Mantle cell lymphoma is associated with increased expression of the cyclin D1 gene and has clinical features of an ‘intermediate grade’ lymphoma.
- Diffuse large B-cell lymphoma is a common subtype and is an aggressive disease which needs urgent treatment. There is a wide variety of sub-types. Over 50% of cases are cured.
- Burkitt lymphoma is one of the most highly proliferative subtypes of tumour. Endemic cases in Africa are associated with EBV infection. Treatment is with aggressive chemotherapy regimens.
- T-cell lymphomas are less common and include mycosis fungoides, peripheral T-cell lymphomas and anaplastic large cell lymphoma.
- Treatments for NHL are based on a variety of chemotherapy regimens. Anti-CD20 antibodies are used in most cases of B-cell lymphomas and have markedly improved the prognosis