Hodgkin's lymphoma (Hodgkin's disease) & Non-Hodgkin's lymphomas (NHL)

DEFINITION

1. The **lymphomas** are malignant conditions affecting principally lymph nodes or the spleen. Lymphoma is a loosely defined term covering processes involving lymph node swelling or splenic enlargement but not due to infection or metastasis. For practical purposes, the term is applied to a spectrum of conditions which are progressive, invasive and destructive.

2. There are two main types, **Hodgkin's lymphoma** and **non-Hodgkin's lymphoma**. Less than 25% of lymphomas are Hodgkin's diseases. Of the remainder, more than half originate from B-cell lymphocytes, 10% from T-cell lymphocytes and 5% from monocytes or macrophages. Diagnosis is by biopsy and histology.

3. Lymphomas are relatively uncommon. In Western countries, they account for about 6% of all malignant disease in adult males (one-seventh the incidence of lung cancer) and 5% in females (one-fifth the incidence of breast cancer).

4. About a quarter of all primary lymphomas arise in lymphoid tissue at extranodal sites, such as the gut or skin.

HODGKIN'S LYMPHOMA

5.

5.1. **Hodgkin's disease** is a lymphoma characterised by destruction of the normal lymph node architecture and the presence of the pathognomonic **Reed-Sternberg cells** The disease is heterogeneous, and four histological variants are recognised, based on the relative preponderance of cell types and the amount of lymph node tissue affected.

5.2. Hodgkin's is about 50% more common in males than females, and there are two peaks of an age-specific incidence, the first in young adults and the second, smaller peak in the over-50s (a view that the second peak is an artefact is not widely accepted).

5.3. There are four types, namely: lymphocyte-predominant, nodular sclerotic, mixed cellularity and lymphocyte- depleted (LDHD).

CLINICAL MANIFESTATIONS

6. Symptoms and signs primarily relate to the site, amount and extent of lymph node enlargement. Hodgkin's is more often localised than widespread, as it spreads to contiguous sites via the lymphatic system. Its rate of progression depends mostly on the histological subtype.

7. Most patients present with the discovery of painless enlarged lymph nodes in the neck and/or axillae and sometimes the groins, without systemic complaints. A chest X-ray usually reveals mediastinal lymph node enlargement, and some cases present with this as an incidental finding.

8. Alcohol-induced pain may occur in the nodes, and intense pruritus may be an early symptom. Fever, night sweats and weight loss are frequent when internal nodes, liver or bone marrow are involved. An occasional feature is Pel-Ebstein fever.

9. Rarely at presentation, the lymph node enlargement is massive, causing obstructive symptoms, including superior vena caval syndrome.

10. Both liver and splenic enlargement may occur. Bone marrow invasion can cause pancytopenia, and pressure on the spinal cord or nerves can result in various effects, including neuralgic pain. Urinary obstruction can also occur.

11. Intracranial, gastric and skin lesions are rare in Hodgkin's disease, and their presence is suggestive of concomitant HIV infection.

12. Both cell-mediated immunity and antibody production become depressed as the disease advances, rendering patients very prone to infection. Cachexia may ensue. Many of those who succumb die of overwhelming infection.

13. **Treatment**

    13.1. Modern treatment has improved the prognosis so that the 5-year survival rate is now about 75%, and about 50% are still free of the disease 10 years from diagnosis. On the other hand, patients successfully treated for Hodgkin's are at higher risk of developing second malignancies, particularly myelodysplasia and acute myeloid leukaemia. The risk is greatest in those receiving extended-field radiotherapy and chemotherapy.

    13.2. Radiotherapy, used alone or in combination with chemotherapy, is effective in most cases of Hodgkin's, but carries an increased risk of causing tumours of tissues in the irradiated field as a late complication. Patients surviving 15 years after treatment of Hodgkin's with radiotherapy have a 2.8-fold higher than expected cumulative risk of developing second tumours, and a year-on-year risk of 0.5-1% persists for at least 30 years. Consequently, there is currently a move away from treatment with radiotherapy and towards chemotherapy.

    13.3. Chemotherapy alone is always used when there is significant extranodal spread, and has not been associated with the same risk. However, combined chemotherapy, particularly with MOPP (mustine, vincristine, procarbazine and prednisolone), carries a 2% risk of the development of myelodysplasia and/or acute myeloid leukaemia within six years, and a lesser risk over a further four years. It also carries the risk of infertility.

AETIOLOGY

14. The cause of Hodgkin's lymphoma is unknown. In common with most malignancies, it probably results from interaction of genetic and unidentified environmental factors. It is likely that a series of events, one or more of which may be infection, initiates the malignant change.

15. The evidence of genetic susceptibility is strong. Twin studies reveal that the identical twin of a sufferer is 99-fold more likely to develop the disease than expected from the incidence in the general population, and same-sex siblings have a 10-fold risk. Chromosomal abnormalities are found in the cells of patients, but they are not of any consistent pattern. However, significant concordance of certain human leukocyte antigens (HLA) have been found in affected family members.

16. There have been reports of case clustering, but critical examination of the evidence does not support the theory that a specific infective causative agent is transmitted from case to case. There is evidence of a causal role for the Epstein-Barr virus (EBV) in a subset of cases, particularly those of mixed cellularity, and there is an association between LDHD and HIV infection.

17. There is an increased risk of Hodgkin's disease in patients with all immunodeficiencies and autoimmune diseases.

18. Hodgkin's lymphoma has not been shown to be linked with exposure to ionising radiation, climatic conditions, trauma, or to physical or mental stress.

NON-HODGKIN ' S LYMPHOMAS (NHL)

19. **Non-Hodgkin's lymphomas** are defined as **lymphomas without Reed-Sternberg cells**. Unlike in Hodgkin's disease, the normal architecture of lymph node is not always disturbed. As noted above, most are of B-cell origin. A smaller proportion arise from T-cells, and the remainder from monocytes or macrophages. The majority are monoclonal.

20. As in Hodgkin's, the incidence is about 50% higher in males than females. The age-specific incidence rises steadily between infancy and old age. The incidence of NHL is increasing, especially in populations at increased risk for AIDS.

21. The various types in this diverse group of disorders are thought to represent neoplastic lymphoid cells arrested at different stages of normal maturation.

22. **Classification** is problematic, and the existence of differing classifications is confusing. Several methods have been used, based on histology, immunology or clinical features:

    22.1. In 1982, an international panel devised a *Working Formulation of NHL for Clinical Use* to provide a common language for clinicians and researchers. NHL was classified into three grades of malignancy, with subgroups, according to histological features. A fourth group is miscellaneous, including mycosis fungoides, composite lymphoma and histiocytic lymphoma, and unclassifiable.

22.2. Most European clinicians use a 1988 updated version of an older *Kiel classification,* incorporating material from cell-marker studies. This has good prognostic value.

22.3. A new **REAL** (*Revised American-European Lymphoma*) classification was devised at a Berlin conference in 1993 and is gaining favour. It incorporates immunophenotyping, genotyping and cytogenetic information, and concentrates on clinicopathological entities.

22.4. Whichever classification is used, about 70% of NHLs are low-grade (relatively benign) and the remainder are high-grade (more aggressive). The intermediate grade of the Working Formulation has proved to be of no practical value.

23. Non-Hodgkin's lymphomas tend to involve structures other than lymph nodes, either by direct invasion (eg. from mediastinal nodes into pleura, lung or pericardium) or more remotely. This contrasts with Hodgkin's, in which **extra-nodal** spread is relatively rare. Primary extranodal presentation of lymphoma is almost exclusive to NHL, and up to 40% of cases of NHL arise in extra-nodal sites.

24. A wide variety of tissues may be involved, especially the mucosa-associated lymphoid tissues of the gut (the so-called **MALTomas**), thyroid, lung, salivary glands and the tonsils, eyes and skin. Primary lesions rarely occur in the central nervous system. Of the extranodal sites, the skin and gastrointestinal tract are the most common.

25. **Skin**
Primary skin lymphomas are of the T-cell type. Two forms are identified: **mycosis fungoides** and a generalised, insidious, leukaemic variant of this, called the **Sézary Syndrome**.

26. **The gastrointestinal tract**
Primary gastrointestinal lymphomas arise in the abundant lymphoid tissue of the gut wall. 5% of all gastric neoplasms are lymphomas, and 80% of gastrointestinal lymphomas arise in the stomach.

27. **Primary small intestinal lymphomas** include three clinically important forms:

27.1. In the West, small intestinal non-Hodgkin's lymphoma may take the form of a solitary tumour.

27.2. Another important association in Western society is **enteropathy-associated lymphoma**. This occurs where non-Hodgkin's lymphoma is found in association with villous atrophy and crypt hyperplasia. There may be active overt coeliac disease, well-controlled coeliac disease or no history of coeliac disease, but the characteristic histology is evident. In this form the tumours are multifocal.

27.3. **Mediterranean type lymphoma,** or immunoproliferative small intestinal disease (IPSID). This presents with malabsorption, and is characterised by infiltration of the bowel by lymphoplasmacytic and plasma cells.

28. In their early stages, gastrointestinal MALTomas regress dramatically in response to broad-spectrum antibiotics.

29. **Burkitt's lymphoma** is a tumour occurring in the jaws and abdomen of young children in parts of Africa.

CLINICAL MANIFESTATIONS

30. **Lymphoblastic lymphomas**, including Burkitt's, are predominant in children. The commonest presentation is as a mediastinal mass. They are often of T-cell type, having a shared cellular lineage with acute lymphatic leukaemia. With this exception, non-Hodgkin's lymphomas are rare below the age of 40, having a peak incidence in the 60-70 age group.

31. The presenting features include generalised (less often localised) lymph node enlargement, usually painless, sometimes with systemic symptoms. In some cases, it may be difficult to differentiate clinically between NHL and Hodgkin's. Pointers include the involvement of unusual lymph node sites or tonsillar tissue. Presentation with a mediastinal mass is uncommon in adult NHL.

32. Presentation with a variety of effects of enlarged extranodal tissue, superior vena caval syndrome, pleural effusion, ascites, jaundice etc is far more common in NHL than in Hodgkin's.

33. **Mycosis fungoides** may be suspected where a middle-aged man develops a non-specific intensely pruritic eruption. Eventually, plaques develop, then tumours which may ulcerate, and ultimately there will be systemic spread. In Sézary syndrome the clinical picture is similar, but more severe and generalised. There may be periods of remission.

34. The presenting features of **gastric lymphoma** are those of any gastric disorder, including pain, vomiting, weight loss and haemorrhage.

35. **Solitary small intestinal** lymphoma can present with abdominal obstruction, haemorrhage or perforation. **Enteropathy-associated** lymphoma presents as an abdominal emergency. **Mediterranean-type** lymphoma occurs in young adults, and presents with severe malabsorption.

AETIOLOGY

36. The aetiology of the non-Hodgkin's lymphomas is unclear, despite a vast amount of research and the identification of factors listed below. Recent interest has focused on immunological aspects of aetiology and the role of viruses.

37. A **family history** of lymphoma or leukaemia is associated with a threefold risk of developing low-grade NHL, but not the high-grade type. Some familial aggregations are associated with familial immunodeficiency, but there is no such abnormality in many others. In any case, familial cases account for less than 5% of cases of NHL.

38. The white races have about a 50% higher incidence of NHL compared with blacks. Further evidence of racial genetic factors is the virtual absence of B-cell chronic lymphocytic leukaemia (which is closely related to NHL) in Asians.

39. There is a strong association with immunodeficiency, both primary and secondary. The incidence of NHL in patients with secondary immunodeficiency, eg. due to immunosuppressive therapy or HIV infection, is up to 100 times higher than that in the general population. In these patients, the lymphomas-tend to be of higher grade and to be primarily extranodal, often in the brain.

40. Gastric MALTomas may be driven by antigenic stimulation from *Helicobacter pylori* infection, which is common in patients with gastric lymphoma. Seropositivity to *H. Pylori* is associated with a sixfold increased risk of developing this type of lymphoma, which can regress with the elimination of infection.

41. Mediterranean type lymphoma (IPSID) is thought to arise from a chronic immune stimulation within the gastrointestinal tract from repeated infection, possibly related to poor hygiene.

42. The regression of gastrointestinal MALTomas in response to treatment with broad-spectrum antibiotics suggests that the lesions may be infective, pre-neoplastic and reversible.

43. EBV is consistently found in HIV-related central nervous system tumours and in the cerebrospinal fluid, as well as in some systemic HIV-related NHLs, but its role is uncertain. Otherwise, with the exception of Burkitt's and some T-cell lymphomas, EBV is rarely found in NHLs.

44. Burkitt's lymphoma is closely associated with EBV infection, but EBV is so very common that other co-factors must exist. These are probably a genetic defect and malaria, which is known to reduce immunity. It is thought that malarial infection enhances the tendency to neoplasia induced by EBV, which usually causes only non-malignant lymphoid proliferation.

45. Another strong association between NHL and an infective agent is in areas where the human T-lymphotropic virus (HTLV-I) is endemic, and is thought to be the main causative factor in most cases of lymphoma.

46. Exposure to phenoxyacetic acid **herbicides,** particularly 2,4-D, is associated with an increased risk of NHL in agricultural workers.

47. Research into the possible involvement of **organochlorine residues** has revealed a positive association between exposure to polychlorinated biphenyls (PCBs) and the risk of developing NHL. The effect appears to be potentiated by EBV infection. Until their dangers were recognised, PCBs were extensively used in transformers and capacitors, also in sealants, rubbers, plasticisers, inks, paints etc. The industrial use of PCBs ceased in the USA in 1977, and about 7 years later in Britain. However, there is still some risk of exposure through dismantling and disposal. By contrast, high serum concentrations of DDT were not found to be associated with such a risk.

48. Besides farming, employment in other occupations has been linked, through cohort studies, with an increased risk of NHL. The groups involved include rubber workers, chemists, chemical workers, dry cleaners, oil refinery workers, printers, abattoir workers, workers exposed to ethylene dioxide, beauticians and hairdressers, and wood workers of various types. Case control studies confirm these occupational risks, as well as risks associated with exposure to chlorophenols and organic solvents.

49. **Solvent exposure** has been linked to increased NHL risk in industrial settings, including chemical manufacturing, rubber industry, aircraft maintenance, and dry cleaning. It is probable that solvent exposure is responsible for the increased risk in some of the other occupational groups mentioned above.

50. It is accepted that non-Hodgkin's lymphomas have an increased incidence following exposure to excess **ionising radiation.**

51. It has been suggested that excessive exposure to solar **ultraviolet radiation** is a factor contributing, by immunosuppression, to the increased incidence of NHL, but this has not been confirmed, and an American study found contrary evidence.

52. Exposure to **hair dyes,** particularly permanent black, is associated with an increased risk of NHL.

53. **Dietary factors** appear to affect the risk of developing NHL. There is a positive association with high levels of milk consumption, especially in men, but the responsible agent is unknown. There is no evidence that frequent animal protein consumption, including fish and eggs, is generally associated with increased risk, although an American study suggests that there may be such an increase in older (over 55) women. Several studies have revealed an inverse association with high intakes of fruits, vegetables, carotenes and vitamin C.

54. Contamination of drinking water with **nitrates,** from agricultural or natural sources, is associated with an increased risk of NHL. Nitrates are converted by bacteria to nitrites and, thence, to nitrosamines, which are carcinogens.

55. Studies in Sweden and America have detected an increased risk of NHL in recipients of blood transfusions, suggesting that a blood-borne agent may be responsible for some cases of the disease.

CONCLUSION

56. Hodgkin's and non-Hodgkin's lymphomas are malignant diseases of lymphoid tissue in lymph nodes and elsewhere in the body. It is considered that they are caused by combinations of constitutional and environmental factors, immunodeficiency being the strongest risk factor. Some environmental factors have been identified, but are lacking in most cases. Trends in known risk factors and diagnostic procedures can account for only a small part of the large, accelerating world-wide increase in the incidence of NHL. The incidence of Hodgkin's is stable.

57. Lymphomas are not caused by climatic extremes, trauma, physical or mental stress, or lowered resistance arising from hardship. Immunodeficiency may result from other diseases and their treatments. Infections which have been associated with the development of lymphomas include EBV, HTLV-I, HIV and (in the case of MALTomas) *H. pylori.*

58. The progress of lymphomas is independent of external factors, other than medical treatment.

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GLOSSARY for LYMPHOMAS

AIDS	Acquired immunodeficiency syndrome. A deficiency of cellular immunity induced by infection with the human immunodeficiency virus (HIV-I) and characterised by opportunistic diseases.
Antibody	A substance, naturally present or induced by exposure to an antigen, which has the capacity to react with a specific antigen.
Antigen	A substance which, as a result of coming into contact with appropriate cells, induces a state of sensitivity and/or immune responsiveness after a latent period and which reacts in a demonstrable way with antibodies and/or immune cells of the sensitised subject.
Autoimmune	Cells and/or antibodies arising from, and directed against, an individual's own tissues.
Cachexia	General weight loss and wasting occurring in the course of a chronic disease.
Carcinogen	Any cancer-producing substance or organism.
Epstein-Barr virus (EBV)	A herpes virus which causes infectious mononucleosis (glandular fever).
Helicobacter Pylori	A bacterial species which produces the enzyme urease, causes gastritis and is involved in most cases of peptic ulcer.
Heterogeneous	Comprising elements with various and dissimilar properties.
Histiocyte	A tissue macrophage.
HIV	The human immunodeficiency virus, HIV-I.
Lymphocyte	A white blood cell formed in lymphatic tissue anywhere in the body.
Macrophage	A mononuclear, actively phagocytic cell arising from mononuclear stem cells in the bone marrow.
Metastasis	The spread of a disease process from one part of the body to a remote part.
Mediastinum	The median part of the thoracic cavity, containing all the thoracic viscera except the lungs.

Monoclonal (in this context)	Arising as clones from single mutant cells.
Monocyte	A large mononuclear leucocyte, usually 3-7% of the leucocytes in the circulating blood and normally found in lymph nodes, spleen, bone marrow and loose connective tissue.
Mycosis fungoides	A chronic progressive lymphoma arising in the skin and initially simulating eczema.
Myelodysplasia (in this context)	Abnormal proliferation of cells in bone marrow.
Neoplasia	A pathological process resulting in the production of a tumour.
Pancytopenia	Depletion of blood cells of all types.
Pel-Ebstein fever	A remittent fever, in which a few days of high fever alternate with longer periods of normal, or even subnormal, temperature.
Plasma cells	Ovoid cells derived from B-lymphocytes, involved in the production and secretion of antibodies.
Reed-Sternberg cells	Large binucleate or multinucleate transformed lymphocytes.
Seropositive	Containing antibody of a specific type in serum. Used to indicate immunological evidence of a specific infection, or the presence of a diagnostically useful antibody.
Sézary Syndrome (reticulocytosis)	Exfoliative dermatitis with infiltration by atypical monocytes, which are also present in the peripheral blood.
Superior vena caval syndrome	Complete or partial obstruction of the superior vena cava, usually by cancer, resulting in oedema and venous engorgement in the face, neck and arms, cough and dyspnoea.

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