Childhood lymphomas – a brief overview

Lymphoma is a malignant proliferation of lymphoid cells.

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The term 'lymphoma' refers to malignant proliferation of lymphoid cells, usually in association with and arising from lymphoid tissues (i.e. lymph nodes, thymus, spleen).[1] Lymphomas are closely related to lymphoid leukaemias, which also originate in lymphocytes but typically involve only circulating blood and the bone marrow (where blood cells are generated in a process termed haematopoiesis) and do not usually form static tumours.[2,3]

Hodgkin's disease

Thomas Hodgkin published the first description of a lymphoma in 1832, which was therefore named after him as Hodgkin's lymphoma.[4] Hodgkin's lymphoma or Hodgkin's disease (HD) is characterised by progressive enlargement of the lymph nodes. It is considered unicentric in origin and has a predictable pattern of spread by extension to contiguous lymph nodes.[5] Hodgkin's disease was the first cancer to be cured with radiation therapy alone or with a combination of several chemotherapeutic agents, even before the understanding of the biology of Hodgkin's disease improved. Since then, the cure rate for children and adolescents with Hodgkin's disease has steadily improved, particularly with the introduction of combined radiation and multi-agent chemotherapy.[6]

Lymphomas are closely related to lymphoid leukaemias.

Aetiology and epidemiology

The cause of HD is unknown. Epstein-Barr virus (EBV) is associated with HD as demonstrated by epidemiology and serological studies. HD is also associated with several immune disorders such as systemic lupus erythomatosus (SLE), rheumatoid arthritis, ataxia telangiectasis and other congenital immunodeficiency disorders.[5,7] The incidence of HD varies, ranging from 1 to 10 per 100 000 population. Two peak ages have been identified, with a peak at 15 - 35 years of age and another above 50 years of age. There is a male predominance, with a male to female ratio of 3:1.[5] Clustering of cases of HD within families or races may suggest a genetic predisposition to the disease or a common exposure to an aetiological agent. Analysis of familial HD kindred, however, fails to reveal a germline mutation, while the risk of developing HD is higher in identical twins than in other first-degree relatives .[5,7]

Pathophysiology

HD is a B-cell malignant disorder that affects the reticulo-endothelial and lymphatic systems. Invasion can affect other organs and systems, predominantly the lungs, bone, bone marrow, liver parenchyma, and rarely the CNS.[7] The spread of HD occurs mostly by contiguity from one chain of lymph nodes to another. Involvement of the left supraclavicular nodes often follows abdominal para-aortic node involvement, whereas involvement of the right supraclavicular nodes tends to be associated with mediastinal adenopathy.[5]

Histopathology

The diagnosis of HD is based on the recognition of tumour giant cells (Reed-Sternberg cells) surrounded by benign-appearing host inflammatory cells (Fig. 1). For purposes of diagnosis, tumor cells must have two or more nuclei or nuclear lobes and two or more large, inclusion-like nucleoli.[5]

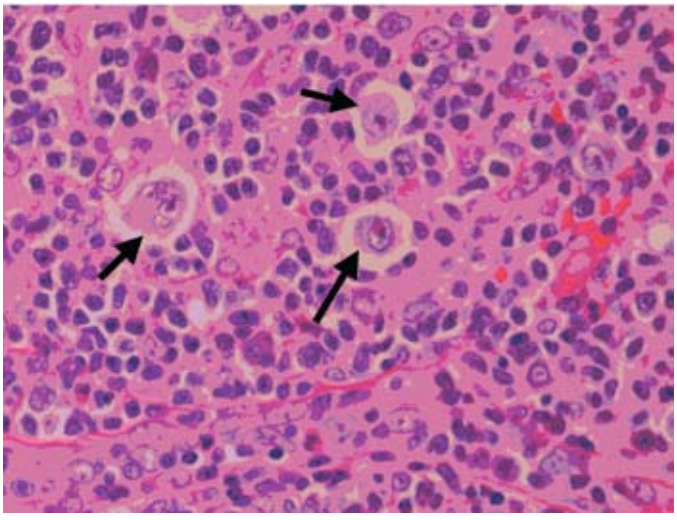

Fig. 1. Hodgkin-Reed-Sternberg (HRS) cells (arrows). (Image obtained from Dr Dinkel, Department of Anatomical Pathology, University of Pretoria.)

The most recent and currently accepted classification is the Revised European-American Lymphoma (REAL) classification as modified and adopted by the WHO: [7-9]

Classic nodular sclerosing. There are fibrous bands that result in a nodular pattern with lacunar-type Hodgkin-Reed-Sternberg (HRS) cells, where the cytoplasm in formalin-fixed specimens retracts, forming a lacuna around the nucleus. This is the most common type in all age groups (77% of adolescents and 72% of adults), although it affects only 44% of younger children.

Classic mixed cellularity. This type may have interstitial fibrosis, but fibrous bands are not observed. HRS cells are classic in appearance or mononuclear. Lymphocytes may predominate in the cellular background. This subtype is more common in young children (33%) than in adolescents (11%) or adults (17%).

Classic lymphocyte rich. This type is extremely rare, and has classic or lacunar-type HRS cells with rare or absent eosinophils on a cellular background.

Classic lymphocyte depleted. There are large numbers of HRS cells with sarcomatous variants and a hypocellular background due to fibrosis and necrosis. This type is also extremely rare.

Nodular lymphocyte predominance (NLP). This form may be nodular and fibrosis is unusual. The HRS cell variants are known as lymphocytic and histiocytic (L&H) or popcorn cells. The nuclei are multi-lobed and vesicular with small nucleoli. The characteristic halo of the classic H-RS cell is absent. The background consists of histiocytes and lymphocytes with B-cell predominance in contrast to the cellular background in classic HD, which has T-cell predominance.

Clinical features[5]

Lymphadenopathy is the presenting symptom in 90% of cases and consists of with painless swelling of one or more groups of superficial lymph nodes. Cervical nodes are involved in 60 - 80% of cases and associated with mediastinal involvement in 60% of cases. Axillary, inguinal and retroperitoneal nodes are also frequently involved. Involved nodes are discrete, elastic, and usually 'rubbery'. Mediastinal adenopathy occurs in 60% of all cases and includes the following nodal subgroups: prevascular, aortopulmonary, paratracheal, subcarinal and posterior mediastinal.

Splenomegaly is often present, but this is not always indicative of splenic involvement. Lymphocyte depletion (LD) subtype most commonly involves the spleen.

Systemic symptoms occur in 30% of all cases and include intermittent fever (Pel-Ebstein), anorexia, fatigue, weakness, night sweats, and weight loss. Mild itching may be seen in 15 - 25% of patients. Pruritus is generally more common in patients with advanced-stage disease and resolves when HD is successfully treated.

Pulmonary involvement is seen in 17% of cases, presenting as contiguous lesions, peribronchovascular disease, subpleural spread with plaque-like pleural thickening or effusion, and intraparenchymal involvement, either nodular or alveolar in nature.

Neurological manifestation is usually late and occurs due to spread from haematogenous dissemination, para-vertebral lymph nodes along nerve roots, blood vessels, or perineural lymphatics into the spinal canal by way of the intervertebral foramina and similarly into the intracranial region. These patients present with signs and symptoms of raised intracranial pressure, focal neurological signs and cranial nerve palsies.

Bone disease occurs only in 2% of cases and usually carries an ominous prognosis, but survival has improved in the last 10 years. Bone marrow involvement is seen in 5% of patients with HD presenting with anaemia, leucopenia and thrombocytopenia. Multiple biopsies are indicated, because HD tends to involve the marrow in a focal fashion.

Liver disease occurs in 2% of cases and usually occurs together with splenic disease. Liver biopsy is the only method for accurate diagnosis of liver involvement. The presence of jaundice in patients is an ominous prognostic sign and may be terminal or preterminal.

Skin involvement is thought to be caused by obstruction of regional lymphatics, direct extension from underlying nodes, or haematogenous dissemination. Lesions usually consist of erythematous nodules or papules.

Splenomegaly is often present, but this is not always indicative of splenic involvement.

Renal manifestations are seen in 13% of cases and may involve one or both kidneys. Myelosuppression in HD may be caused by hypersplenism or bone marrow infiltration.

The most common endocrine abnormality associated with HD is hypercalcaemia, which has been associated with advanced stage and poor prognostic features. The aetiology seems to be related to altered 1,25-(OH)2-D3 levels.

Laboratory features

Haematological findings

- Anaemia: normocytic and normo-chromic
- Neutrophilia: 50% of patients
- Eosinophilia: 15% of patients
- Lymphocytopenia: sign of advanced disease.

Biochemical findings

- Elevated serum copper level – may also be elevated in infections and inflammatory disorders
- Elevated serum ferritin and decreased serum transferase levels (associated with advanced stage)
- Elevated ESR
- Elevated fibrinogen level
- Elevated haptoglobin level
- Elevated ALP (alkaline phosphatase) level – may indicate bone or liver involvement of HD.

Staging

After a tissue diagnosis is made, the disease is staged by using imaging studies, evaluating the bone marrow and assessing for B symptoms.

- The most widely used staging system is the Ann Arbor staging system:
  - Stage I – single lymph node region or single extranodal site
  - Stage II – two or more lymph node regions on the same side of the diaphragm
  - Stage III – lymph node regions on both sides of the diaphragm
  - Stage IV – diffuse or disseminated involvement of one or more extralymphatic organs (liver, bone marrow, lung) or tissues with or without associated lymph node

involvement (the spleen is considered a nodal site).

- A or B designations are also used:
  - B includes the presence of at least one of the following symptoms: drenching night sweats, unexplained fevers with temperature more than 38°C, and more than 10% loss of body weight in the past 6 months
  - A involves the absence of symptoms described above.
- The E designation is extension or contiguous involvement of extranodal sites by large mediastinal masses that are not considered metastatic or stage IV.

Treatment

Children with HD should be treated at a paediatric oncology unit where paediatric oncologists, radiation therapists, and full ancillary services are available for children with malignancies. HD is one of the most curable malignancies of childhood and can be cured with radiation therapy, chemotherapy, or a combination of both. Acute and late toxicity vary substantially according to the treatment modality used. Most modern paediatric treatment strategies focus on reducing late effects of therapy while achieving excellent cure rates with risk-adapted chemotherapy alone or response-adjusted combined-modality regimens.[5] With rare exceptions, all children and adolescents are treated with chemotherapy alone or combined with radiation therapy. Chemotherapy alone is effective and prevents radiation-associated treatment complications. This approach is recommended especially in centres where paediatric radiation therapy is not feasible but where chemotherapy can be reliably administered. However, in paediatric oncology units with well-developed paediatric radiation programmes, combined-modality therapy is preferred to avoid the high cumulative doses of alkylating agents, bleomycin, and anthracyclines. Although combined chemotherapy and radiation broadens the spectrum of potential toxicity, the incidence and severity of individual drug or radiation-related toxicity are generally reduced because of the lowered doses of chemotherapy and radiation. Here are a couple of the more commonly used chemotherapy regimens currently used for the treatment of HD, which are administered for 2 - 6 cycles 3 - 4 weeks apart, depending on stage:

- cyclophosphamide, vincristine, procarbazine, and prednisone (COPP)
- adriamycin, bleomycin, vinblastine and dacarbazine (ABVD)
- doxorubicin (adriamycin), bleomycin, vincristine and etoposide (ABVE)
- vincristine (Oncovin), etoposide, prednisone and doxorubicin (adriamycin) (OEPA).

Prognosis

The overall 5-year survival rate for Hodgkin lymphoma is 91%. Patients with localised disease have a higher rate than those with advanced-stage disease (>90% v. as low as 70%). Therefore, the importance of early referral to any paediatric oncology unit cannot be overemphasised.

Non-Hodgkin's lymphoma (NHL)

NHL is also due to malignant proliferation of cells of lymphocytic lineage and while malignant lymphomas are generally restricted to lymphoid tissue such as lymph nodes, Peyer's patches and spleen. It is not uncommon to find bone marrow involvement in children, in which case it is referred to as leukaemia.[5] As recently as the 1970s, fewer than 20% of children with NHL were projected to survive their disease and the majority died within 2 years of diagnosis. Virtually all survivors were patients with localised disease. Progress in therapy of childhood NHL is a wonderful success story and developments in modern therapy in the last two decades have lead to cure for more than 75% of children. Currently, many recent studies focus on less intensive therapy to reduce the acute and long-term consequences of treatment. The success is due not to new drugs, but rather to rational classification systems based on an improved understanding of the biology, immunology and molecular biology of the NHLs; improvements in imaging; advances in supportive care to reduce the life-threatening complications of NHL and therapy; and the empirical development of intensive regimens for children presenting with advanced-stage disease.[8]

Aetiology and epidemiology

NHL accounts for 6 - 7% of malignant diseases in childhood and is the third most common childhood malignancy, with an overall incidence of 10.5 per 1 000 000. NHL accounts for 45% of all lymphomas in children and adolescents less than 20 years of age. Isolated cases of familial NHL occur. The overall male to female ratio is 2.5:1, and is relatively similar across all ages, with a peak at age 15 - 19 years, largely because of a significant increase in the incidence of diffuse large-cell lymphoma. NHL is associated with Bruton's agammaglobulinaemia, common variable agammaglobulinaemia, ataxia telangiectasia, Wiskott-Aldrich syndrome and severe combined immunodeficiency. Children treated with chemotherapy and radiotherapy for Hodgkin's disease are at risk of developing secondary NHL. There is an association between NHL and Epstein-Barr virus (EBV) infection, as well as HIV.[5]

HD is one of the most curable malignancies of childhood and can be cured with radiation therapy, chemotherapy, or a combination of both.

Pathophysiology

NHL is a systemic disease due to the unique anatomy of the lymphoid system and because of the physiology of lymphoid cells, which migrate whether they are normal or malignant.[10]

Childhood NHL generally manifests as bulky extramedullary (usually extranodal) disease with or without demonstrable dissemination. The distinction between NHL and acute leukaemia is arbitrary. Therefore, these entities are best considered in terms of a spectrum ranging from clinically localised disease to overt leukaemia.[5]

In most treatment protocols, acute leukaemia is now defined on the basis of marrow involvement with a blast count of more than 25% irrespective of the presence of bulky extramedullary disease. In contrast, a tumour accompanied by marrow involvement below this threshold constitutes stage 4 lymphoma.[5]

Table I presents the World Health Organization (WHO) classification for NHL from the International Lymphoma Study Group.[5] This classification for NHL is based on the currently recognised histological (morphological), immunophenotypic and genetic features and clinical presentation. This updates the Revised European-American Lymphoma (REAL) classification and is the preferred classification for NHL.

Clinical features

The presenting symptoms of NHL depend mainly on the location of the tumour. It may present in a variety of ways, occasionally providing a diagnostic dilemma.[5] The primary site is the

abdomen in 35%, especially the ileocecal region, appendix, ascending colon, or a combination of these sites. These patients usually present with abdominal pain, nausea and vomiting, constipation or diarrhoea, abdominal distension, palpable mass, intussusception, peritonitis, ascites, acute gastrointestinal bleeding, obstructive jaundice, hepatosplenomegaly or right iliac fossa mass.

In 13% of cases the head and neck are involved with enlargement of the cervical nodes and parotid gland, jaw swelling, and unilateral tonsillar hypertrophy. The disease may present with nasal obstruction, rhinorrhoea, hypoacousia, and cranial nerve palsies.

The mediastinum is involved in 26% of cases. Patients may present with superior vena cava (SVC) syndrome, a medical emergency. The clinical signs include distended neck veins, oedema of the neck and face, marked dyspnoea, orthopnoea, dizziness, headache, dysphagia, epistaxis, altered mental status, and syncope associated with bending. A large anterior mediastinal mass compresses the SVC due to the thinness of its wall and its close apposition to the vertebral column. Pleural effusion may be produced by direct pleural involvement and/or result from compression of lymphatics by the mediastinal mass. The presence of pericardial effusion may cause cardiac tamponade.

Other sites include the skin, subcutaneous tissue, orbit, thyroid, bone, kidney, epidural space, breast and gonads. There are occasionally constitutional symptoms present. Fever and weight loss are relatively uncommon except in anaplastic large-cell lymphoma. Weight loss may also occur secondary to mechanical bowel obstruction.

Table I. WHO classification of neoplastic diseases of haemat-opoietic and lymphoid tissues[5]

Precursor B-cell neoplasms
Precursor B-lymphoblastic leukae-mia/lymphoma
Mature (peripheral) B cell neoplasms
B-CLL/small lymphocytic lymphoma
B-cell prolymphocytic leukaemia
Lymphoplasmacytic lymphoma
Mantle cell lymphoma
Follicular lymphoma (grade 1, 2 or 3)
Nodal marginal zone B-cell lym-phoma
Extranodal marginal zone B-cell lymphoma of MALT type
Splenic marginal zone B-cell lym-phoma
Hairy cell leukaemia
Plasma cell myeloma/plasmacytoma
Diffuse large-B-cell lymphoma
Burkitt's lymphoma/Burkitt's cell leukaemia
Precursor T-cell neoplasms
Precursor T-lymphoblastic leukae-mia/lymphoma
Mature (peripheral) T-cell neoplasms
Predominantly leukaemic/dissemi-nated
Predominantly nodal
Predominantly extranodal

Burkitt's lymphoma

This type of lymphoma is common among children, especially in Africa. Burkitt's lymphoma (or Burkitt's tumour, or malignant lymphoma Burkitt's type) is a cancer of B lymphocytes, named after Denis Parsons Burkitt, a surgeon who first described the disease in 1956 while working in equatorial Africa.[11] There are three main clinical variants: the endemic, the sporadic and the immunodeficiency-associated variants, which are all associated with HIV and AIDS.

The endemic variant occurs in equatorial Africa and characteristically involves the jaw or other facial bone (Fig. 2). Children affected by the disease often also have chronic malaria and Epstein-Barr virus (EBV). The sporadic variant of Burkitt's lymphoma is found outside Africa and usually involves the abdomen, especially the ileo-caecal region. The tumour cells have a similar appearance to the cancer cells of classic African or endemic Burkitt's lymphoma. There is also an association with EBV. Immunodeficiency-associated Burkitt's lymphoma is usually associated with HIV infection or post-transplantion due to immunosuppressive drugs. Burkitt's lymphoma can be one of the diseases associated with the initial manifestation of AIDS.[12]

Diagnosis of NHL

- Biopsy
  - A histological diagnosis must be obtained.
  - For patients with an abdominal tumour, tissue is generally available from resection or intraoperative biopsy.
  - Patients with mediastinal disease frequently have enlarged supraclavicular or cervical nodes, which can enable diagnosis without thoracotomy.
  - As an alternative, a diagnosis may be made by using pleural fluid or by using involved bone marrow (especially if CBC counts are abnormal and/or if imaging studies demonstrate abnormal signal intensity of the marrow). In rare cases, cerebrospinal fluid (CSF) can be used.
- Lumbar puncture with determination of the CSF cell count and differential. This test is done to assess CNS involvement, the presence of which alters therapy.
- Bilateral (superior to unilateral) bone marrow aspiration and biopsy
  - Biopsy is necessary to assess for evidence of bone marrow involvement in patients with lymphomas.
  - A finding of more than 25% marrow blasts is generally regarded as diagnostic of acute leukaemia. Levels of involvement lower than this with lymphoma indicate stage 4 disease.

Progress in therapy of childhood NHL is a wonderful success story and developments in modern therapy in the last two decades have lead to cure for more than 75% of children.

Staging

Several systems for classifying NHL have been proposed. The Murphy system is as follows:

- Stage I – single extranodal tumour or single anatomical area (nodal), excluding the mediastinum or abdomen

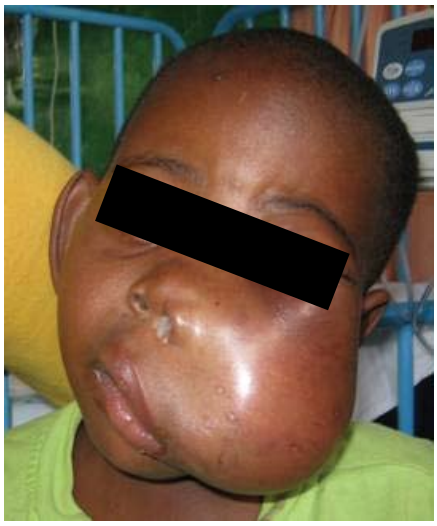

Fig. 2. A 4-year-old boy with Burkitt's lymphoma at presentation.

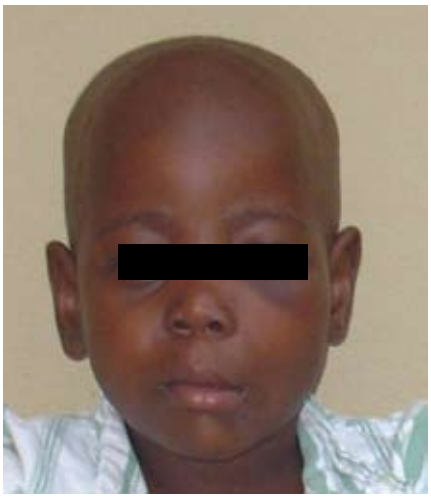

Fig. 3. Marked response seen in the same patient after 3 months of chemotherapy.

- Stage II – single extranodal tumour with regional node involvement; primary gastrointestinal tumour with or without associated involvement of mesenteric nodes, with gross total resection; or, on same side of diaphragm, 2 or more nodal areas, or 2 single (extranodal) tumours with or without regional node involvement.

Immunodeficiency-associated Burkitt's lymphoma is usually associated with HIV infection or post-transplantion due to immuno-suppressive drugs.

- Stage III – any primary mediastinal, pleural, or thymic intrathoracic tumour; any extensive and unresectable abdominal tumour; any primary paraspinous or epidural tumour regardless of other sites; or, on both sides of the diaphragm, 2 or more nodal areas, or 2 single (extranodal) tumours with or without regional node involvement.
- Stage IV – any of the above with initial CNS or marrow (<25%) involvement.

Treatment

Treatment is according to stage:

- Localised (stage I and II) lymphoblastic lymphoma (LL)
- Advanced (stage III and IV) LL
- Localised (completely resected stage I and abdominal stage II) Burkitt's lymphoma and diffuse B-cell, large cell lymphoma (DLCL)
- CNS involvement
- Bone marrow involvement
- Large cell anaplastic NHL.

The two most widely used treatment protocols in South Africa are the BFM-NHL and LMB protocols, which include a number of chemotherapeutic drugs (including prednisone, high-dose methotrexate, cyclophosphamide, vincristine, doxorubicin, cytarabine and VP16) given precisely at specified times, consisting of a number of cycles depending on the stage of the disease as induction, consolidation and in certain instances maintenance therapy. These tumours show a significant response to chemotherapy (Fig. 3). Radiotherapy is not routinely indicated, but only used for acute life-threatening complications refractory to chemotherapy, such as superior vena cava syndrome. Cranial irradiation was used in the past for CNS prophylaxis and CNS disease. This has now been replaced with high-dose systemic intravenous methotrexate and intrathecal therapy. The role of surgery in NHL treatment is limited and it should only be performed in patients in whom there is good reason to believe that total resection can be achieved without a mutilating procedure, or if the procedure is not excessively risky.[5]

Prognosis

The 3-year event-free survival depends on the type of lymphoma and the stage of disease, ranging from 99% for localised completely resected stage I Burkitt's lymphoma to 70% 5-year event-free survival for stage IV large cell anaplastic lymphoma.[5] The event-free survival in a recent South African study was 87% for all B-cell NHL with most patients being stage III and IV.[13]

Conclusion

The importance of early referral for any patient with a suspected malignancy cannot be overemphasised. Poor outcome in developing countries is mostly due to late presentation. Early and urgent referral to a paediatric oncology unit is essential, and this alone will make a huge difference, especially in the South African setting

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