CHAPTER 104
LYMPHOMAS

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Introduction

Lymphoma is a generic term used to describe malignant expansion of any of the lymphoid cell series. The nosology of lymphoma is an evolving science with clinical, morphological, and phenotypic studies contributing to the final diagnosis. The historical classification of lymphomas based purely upon morphological appearances under the light microscope has led to confusion and had little prognostic significance, so the Revised Euro-American Lymphoma (REAL) classification is in current use,[1] albeit modified by the World Health Organisation (WHO) to include cytogenetic factors.[2]

Currently, about 15% of lymphomas are regarded as Hodgkin's disease, defined by the presence of Reed-Sternberg cells on light microscopy, and the remaining 85% as non-Hodgkin's lymphoma (NHL). NHL may stem from cells that have B-cell or T-cell, including natural killer (NK) cell, lineage. Amongst NHL, B-cell phenotypes account for about 85% of the diagnosed cases, and within Africa, Burkitt lymphoma is the most common B-cell tumour. REAL divides lymphomas into high-, intermediate-, and low-grade tumours, giving prognostic information that is of value. Burkitt lymphoma is regarded as a high-grade tumour and is one of the fastest-growing neoplasms known, with a tumour doubling time of between 24 and 48 hours.[3]

Aetiology/Pathophysiology

The transformation of cellular behaviour from "normal" to a pattern that we recognise as "malignant" occurs when the genes controlling cellular behaviour are altered in some way. In lymphoid cells, this commonly occurs as a result of chromosomal translocations (e.g., t(8;14) in Burkitt lymphoma, in which a proto-oncogene *cmyc* is moved from its normal site on chromosome 8 to a site on chromosome 14), chromosomal deletions, or oncogenic viruses.

There is a strong association between the Epstein-Barr virus (EBV) and endemic Burkitt lymphoma; although a causal relationship is not certain, EBV antigen can be detected in up to 90% of children affected by Burkitt lymphoma. Many viruses may, through chronic antigenic stimulation, result in chronic B-cell proliferation, thereby increasing the probability of spontaneous chromosomal aberration. It is possible that the origin of the genomic injuries in endemic Burkitt lymphoma is more complex, involving malaria, EBV, arborviruses,[4] and possibly also plant products.[5]

In only 15% of patients with sporadic Burkitt lymphoma seen outside Central Africa is there an associated EBV infection. Sporadic Burkitt lymphoma also has a different pattern of presentation but is histologically identical to the endemic form. It is likely that sporadic Burkitt lymphoma is a disease different from the African form that shares a similar cellular morphology.

Within each subgroup of NHL, cell size and pattern of growth (nodular or diffuse) reflect the gene products of the altered genome, and these in turn determine the innate aggression of the tumour. Anatomical staging also contributes to treatment decisions.

In Africa, the human immunodeficiency virus (HIV) pandemic has greatly altered the epidemiology of lymphoma, resulting in a considerable increase in primary cerebral lymphoma and a substantial increase in the numbers of patients with B-cell NHL.[6,7] Burkitt lymphoma is regarded as an acquired immune deficiency syndrome (AIDS)-defining disease in HIV-infected individuals.[8] HIV-related Burkitt lymphoma seems to be biologically closer to sporadic Burkitt than to the endemic form and is less responsive to chemotherapy, even for those patients in whom the HIV status allows full chemotherapy doses.[3]

Clinical Presentation

Patients with lymphoma may present with the following symptoms:

- Lympadenopathy similar to tuberculosis
- Mediastinal mass
- Pleural effusion
- Splenomegaly
- Maxillary mass (Burkitt lymphoma)
- Right iliac fossa mass
- Intussusception
- Bowel obstruction
- Bowel perforation
- Fever, weight loss, night sweats
- Pel-Ebstein fever

Hodgkin's lymphoma is primarily a disease of lymph nodes, and the clinical presentation largely depends upon which group of nodes is predominantly affected. The classical presentation is of painless lymph node swelling that proceeds to displace structures and may reach massive proportions, causing secondary pressure effects (Figures 104.1–104.3).

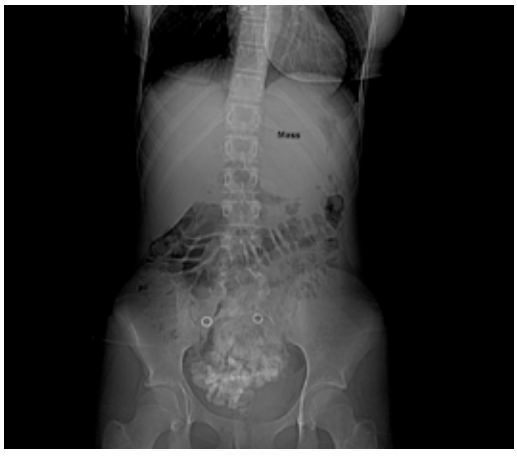

Figure 104.1: Abdominal radiograph with a mass.

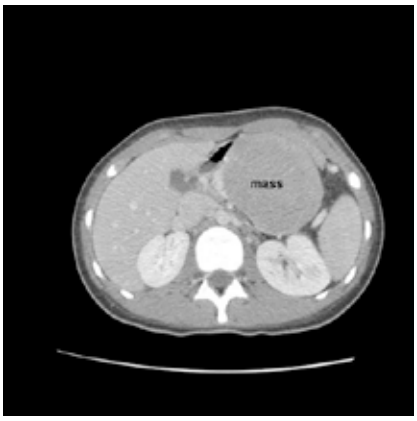

Figure 104.2: Abdominal computed tomography (CT) scan with a mass.

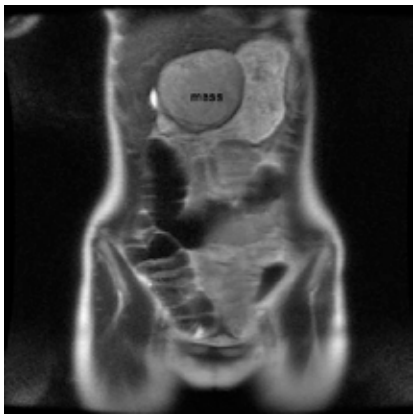

Figure 104.3: Abdominal magnetic resonance imaging (MRI) with a mass.

Figure 104.4: Burkitt lymphoma.

In NHL, extra-nodal disease is common and is often related to the gastrointestinal (GI) tract or other lymphoid organs, such as the spleen. Lymphoblastic lymphoma, which is difficult to differentiate from a lymphoblastic leukaemia, typically presents with a mediastinal mass or pleural effusion.

In Equatorial Africa, the classic picture of Burkitt lymphoma (Figure 104.4) is of a rapidly growing jaw or maxillary tumour in a small child under the age of 5 years. Additional abdominal disease is seen in about half of the patients. Endemic Burkitt lymphoma rarely presents as a right iliac fossa mass that can be confused with an inflammatory lesion, but intestinal involvement can provoke intussusception, intestinal obstruction, and occasionally intestinal perforation, although these symptoms are more common in sporadic cases. However, the pattern of disease presentation varies widely across relatively small geographic areas, suggesting that environmental factors may play a role.[9]

Constitutional symptoms of fever, weight loss, and night sweats, known as B symptoms, are associated with extensive extranodal disease and a poorer prognosis, irrespective of the lymphoma subtype.[10] B symptoms are more commonly present in patients with HIV-related lymphoma. The well-known Pel-Ebstein fever seen occasionally in patients with Hodgkin's lymphoma is simply a B symptom with a name.

Investigation and Staging

Appropriate treatment can only follow tissue diagnosis and accurate staging. Because the intranodal pattern of growth still has an important bearing on classification, an entire node should be submitted for examination. Fine needle aspirates and needle biopsies give limited information, but they may suffice in areas where more detailed studies are not available or are irrelevant to management decisions. In children with jaw tumours clinically thought to be Burkitt lymphoma, the diagnosis can often be confirmed by removing one of the free-floating teeth that are characteristic of the lesion. Usually this can be achieved without an operation, as the tooth can be extracted digitally, and the tissue attached to the tooth is adequate for diagnosis.

Cytogenetic studies allow lymphoma to be categorised more precisely, but therapeutic decisions can be made on morphological assessment alone combined with clinical staging. The St. Jude modification of the Ann Arbor Hodgkin's staging system based on clinical assessment, plain radiology, and ultrasound (Table 104.1) can be applied to NHL.

Burkitt lymphoma should be staged according to the Uganda Cancer Institute staging system. This reflects the high incidence of abdominal disease, even in patients presenting primarily with jaw disease, and recognises the effect of complete surgical resection when this is possible (Table 104.2).

All lymphomas should further be categorised as to the presence or absence of B symptoms. The presence of B symptoms should be signified by an addition of the suffix "B" after the stage shown in Table 104.1. If present, B symptoms would justify an increase in treatment intensity.

Table 104.1: St. Jude modification of the Ann Arbor staging system for non-Hodgkin's lymphoma.

Stage	Description
Stage 1	• Single nodal or extranodal tumour, excluding the mediastinum and abdomen
Stage 2	• Single extranodal tumour with regional lymph nodes affected • Primary gastrointestinal tract disease; regional nodes may or may not be affected • Lymphoma in two or more areas of lymph nodes on the same side of the diaphragm
Stage 2R	• Primary abdominal tumour that has been completely removed by surgery
Stage 3	• Two single extranodal tumours on opposite sides of the diaphragm • Origin in the lungs, chest, or thymus gland • Two or more nodal areas affected on opposite sides of the diaphragm
Stage 3A	• Abdominal tumour only that cannot be removed by surgery
Stage 3B	• Tumour affecting more than one organ within the abdomen
Stage 4	• Any of the above, plus—at the time of diagnosis—the central nervous system (CNS; brain and spinal cord) and/or the bone marrow also affected

Table 104.2: Uganda Cancer Institute staging system for Burkitt lymphoma.

Stage	Description
Stage A	• Single extraabdominal tumour
Stage AR	• Completely resected abdominal tumour without extraabdominal disease
Stage B	• Multiple extraabdominal tumours
Stage C	• Intraabdominal tumour with or without a single jaw tumour
Stage D	• Intraabdominal tumour with extraabdominal sites other than a single jaw tumour

Serum lactate dehydrogenase (LDH) is a useful marker of tumour activity and can be measured serially to assess response to treatment. Most high-risk lymphomas have initially high levels of LDH; a rapid fall reflects tumour responsiveness and is associated with a more favourable prognosis.[11]

Treatment

The actual treatment of lymphoma does not usually involve the surgeon, as it is based primarily on chemotherapy with selective use of radiotherapy. The surgeon may be involved in the diagnosis of lymphoma, particularly in differentiating between tuberculosis nodal enlargement and lymphoma in the HIV-positive child, the definition and resection of localised intraabdominal disease, as well as in the management of complications of either the disease itself or its treatment.

High-grade lymphomas, by virtue of their rapid cell proliferation, generally respond well—often dramatically—to chemotherapy. Indeed, the rapidity of cell death after initiating treatment may present the kidney with unmanageable quantities of purines, pyrimidines, phosphate, and other cellular detritus, leading to tumour lysis syndrome. Oncology treatment protocols should include measures, such as prophylactic urate oxidase, hyperhydration, and urine alkalinisation[12] to minimise this occurrence.

The outcome for children with Burkitt lymphoma is clearly related to access to effective chemotherapy. This is such a rapidly growing tumour that those in whom there is a delay—either pending histopathology confirmation or pending recovery from laparotomy at which extensive disease precluded total resection—fare worse.[13] In addition to systemic chemotherapy, intrathecal methotrexate should be given to reduce the risk of CNS relapse.[14]

A considerable amount of energy has been expended in attempting to develop a low toxicity, high efficacy regimen for the treatment of Burkitt lymphoma that would be practicable in a resource-limited environment.[14] This effort is being cofunded by the International Society for Pediatric Oncology (SIOP). Resource limitations not only impact the actual affordability of treatment drugs but also the availability of supportive care, such as antibiotics, and the ability to manage treatment-related toxicity, particularly bone marrow suppression with, among others, blood component therapy. An ideal regimen should therefore be nontoxic as well as effective, inexpensive, and easy to administer.[15] The results of the SIOP studies have been encouraging, and relapse, should it occur, can also be effectively treated within a resource-constrained service.[16]

Patients with HIV-related lymphomas, excluding cerebral lymphomas, can tolerate effective chemotherapy protocols when treatment is given in conjunction with highly active antiretroviral therapy (HAART).

Surgery

The surgeon may be required to biopsy either a nodal mass, gonad, or mediastinal tumour, although frequently in Africa the diagnosis can be reached with sufficient precision to allow rational treatment following needle biopsy or bone marrow biopsy.

The role of the surgeon in the primary management of children with B-cell lymphoma remains controversial. In endemic areas, localised intraabdominal disease is, unfortunately, not as frequent as it is in sporadic cases occurring outside Equatorial Africa. There is, however, no doubt that on rare occasions abdominal disease is localised, complete resection is beneficial but biopsy only or debulking does not improve survival.[17,18] As chemotherapy regimens become more successful and more widely available, pressure on the surgeon is easing.[19]

In patients who present with an abdominal emergency, such as perforation, obstruction, or intussusception, the decision to operate is easy. The procedure that can be performed is defined by the findings at the time of surgery. Complete resection is ideal if circumstances allow, but the extent of disease may limit this ambition to a bypass procedure or biopsy alone. In patients with residual intraabdominal disease after laparotomy, delay in the administration of chemotherapy should be avoided.[17]

In patients in whom there is no crisis but an abdominal mass is palpable, the likelihood of complete resection must be judged from clinical assessment and preoperative imaging.

If abdominal disease is associated with extraabdominal lymphoma, then the initial strategy should be chemotherapy.[20] If the tumour is judged by the surgeon to be unresectable, the initial treatment should also be chemotherapy.

Staging laparotomy is not required. Even in the absence of sophisticated radiological techniques, it is usually possible to define the extent of disease within the abdomen with ultrasound, and, if necessary, to obtain tissue by using a needle biopsy. In some patients, a diagnostic laparotomy will have been indicated for symptoms at presentation. It is not necessary to remove the spleen or any other organ in order to stage or effectively treat the tumour.

In patients with primary bowel lymphoma, chemotherapy can be so effective that the tumour regresses, leaving a hole in the bowel.[21] This constitutes a surgical emergency. Surgical management will depend upon the clinical status of the patient as well as the findings at laparotomy. Exsanguinating haemorrhage from the bowel has also been reported in patients while on treatment for intestinal lymphoma. If the bleeding does not respond to conventional resuscitation, operative treatment may be necessary.[21]

Outcomes

Patients with T-cell and large-cell lymphomas fare worse than those with lymphomas of B-cell lineage.[22] Generally, patients with lymphoma and coexistent HIV disease do less well than patients who are not HIV-infected. The advent of HAART may change this perception, as improvement in immune status will allow HIV-infected individuals to tolerate more aggressive chemotherapy with shorter rest periods.[10,23]

Patients in the developed world have a higher incidence of resectable abdominal disease, and treatment with aggressive chemotherapy, including stem cell rescue, is available. With such aggressive treatment, 5-year survival rates reach 90% for localised disease and 70% for disseminated disease.[3]

In Africa, outcomes vary according to local geographic and economic factors. The most convincing data come from the Malawi Burkitt Lymphoma Project, which used initial cyclophosphamide monotherapy and later introduced intrathecal methotrexate for CNS prophylaxis. Initially, 63% of those with lesions in the head and neck secured complete remission with monotherapy, but only 33% of those with abdominal or other sites did so.[14] More recent studies have shown a 53% event-free survival for stage 3 patients[13] and a 71% complete clinical remission in those who relapsed or had primarily resistant tumours.[15]

These results are encouraging and show that much can be achieved even in the most resource-constrained countries.

Key Summary Points

1. The most common type of lymphoma is non-Hodgkin's lymphoma, which includes Burkitt type in association with the Epstein-Barr virus.
2. Presentation is variable.
3. Tissue diagnosis is essential.
4. Staging is best done by following the Uganda Cancer Institute staging system (see Table 104.2).
5. Chemotherapy is the mainstay of treatment.
6. Surgical input is mainly for tissue sampling and for acute abdominal presentation.
7. The prognosis is good where a chemotherapy programme is available.

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