Burkitt’s Lymphoma:
Clinicopathologic Features and Differential Diagnosis

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Key Words. Burkitt’s lymphoma • Immunophenotype • c-myc • Outcome • Differential diagnosis

LEARNING OBJECTIVES
After completing this course, the reader will be able to:

1. Describe the events leading to the initial identification and description of Burkitt’s lymphoma and the discovery of its association with the Epstein-Barr virus.
2. Outline the WHO Classification of Burkitt’s lymphoma, including the clinical and pathological variants of this lymphoma.
3. Discuss the treatment strategies used for treating Burkitt’s lymphoma.
4. List the criteria for establishing a diagnosis of Burkitt’s lymphoma and discuss the entities that may enter its differential diagnosis.

ABSTRACT
Burkitt’s lymphoma is a highly aggressive lymphoma identified and described in the last century by Denis Burkitt in Africa, in areas endemic for malaria. Since its description in African children, it has been recognized outside areas with endemic malaria, frequently also in children as well as among individuals with an underlying immunodeficiency. Since its initial designation as Burkitt’s lymphoma, this type of lymphoma and lymphomas closely resembling it have received a variety of names in different classifications of lymphomas and leukemias: undifferentiated lymphoma, Burkitt’s and non-Burkitt’s type in the modified Rappaport Classification, malignant lymphoma, small non-cleaved cell, Burkitt’s type in the Working Formulation, Burkitt’s lymphoma and high-grade B-cell lymphoma, Burkitt-like in the REAL Classification, and acute lymphoblastic leukemia, L3 type in the FAB Classification. With the publication of the WHO Classification of Haematopoietic and Lymphoid Tumors, the nomenclature of this lymphoma has come full circle, and it is once again known simply as Burkitt’s lymphoma. In recent years, efforts have focused on improving therapy for this rapidly proliferating neoplasm while minimizing, to the extent possible, treatment-associated toxicity. These efforts have led to the development of high-intensity, short-duration combination chemotherapy that has proven extremely effective for a high proportion of Burkitt’s lymphoma patients. The differential diagnosis of Burkitt’s lymphoma is broad, and precise diagnosis based on histologic, immunophenotypic, and genetic features remains the critical first step in planning appropriate therapy. The Oncologist 2006;11:375–383

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**Historical Background**

In the middle of the last century, when Denis Burkitt, a surgeon, was working in central Africa in Kampala, he noted children with grossly distorted faces, with lesions involving one or both sides of the face and upper and lower jaws, sometimes accompanied by proptosis. He noted that some children had huge abdominal masses, sometimes accompanied by disease in the facial bones, although there was usually no lymph node involvement. This malignancy, initially thought to be a sarcoma [1–3] and later established to be a lymphoma and given the name Burkitt’s lymphoma, was the most common tumor in children in that area [2]. This lymphoma was found to occur throughout tropical Africa except at high altitudes or in areas where the climate was relatively cool. Occurrence was greater in areas with greater rainfall. These geographic and climatic associations suggested an association with falciparum malaria. In 1961, Burkitt made the acquaintance of Epstein, an experimental pathologist, and shared samples of the lymphoma with him. Within these lymphomas, Epstein and colleagues identified the virus that has come to be known as Epstein-Barr virus (EBV); this was the first description of a virus involved in the pathogenesis of a tumor in humans. In the setting of the florid reactive lymphoid hyperplasia that occurs in response to malaria, it was proposed that EBV could be oncogenic [2]. Although only limited chemotherapeutic agents were available at that time and in that place, an excellent response could be obtained, eventually attaining up to 80% long-term survival [2]. In present-day Africa, Burkitt’s lymphoma continues to account for most childhood malignancies [4]. A second form of Burkitt’s lymphoma is now found in Africa: HIV-associated Burkitt’s lymphoma, occurring mainly in adults [4].

**Pathologic Features**

In the World Health Organization (WHO) Classification, three clinical variants of Burkitt’s lymphoma are described: endemic, sporadic, and immunodeficiency-associated types. Endemic Burkitt’s lymphoma refers to those cases occurring in African children, usually 4–7 years old, with a male:female ratio of 2:1, involving the bones of the jaw and other facial bones, as well as kidneys, gastrointestinal tract, ovaries, breast, and other extranodal sites [5]. The incidence is estimated to be 50 times higher than in the U.S. [6]. EBV is found in nearly all cases. Sporadic Burkitt’s lymphoma occurs worldwide; it includes those cases occurring with no specific geographic or climatic association. It accounts for 1%–2% of lymphoma in adults and up to 40% of lymphoma in children in the U.S. and western Europe [6]. The abdomen, especially the ileocecal area, is the most common site of involvement; the ovaries, kidneys, omentum, Waldeyer’s ring, and other sites may also be involved (Fig. 1 and Fig. 2). Bilateral involvement of the breasts may occur in association with the onset of puberty or with lactation [5]. Lymph node involvement is more common among adults than among children [7]. Patients may also have malignant pleural effusions or ascites [5, 7]. Rarely, patients present with disease that is primarily leukemic (classified as acute lymphoblastic leukemia [ALL], L3 type in the French-American-British [FAB] Classification). Neoplastic cells are EBV+ in 15%–30% of cases, or fewer in some series [8]. Immunodeficiency-associated Burkitt’s lymphoma occurs mainly in patients infected with HIV (Fig. 3) but also occurs in allograft recipients [9, 10] and individuals with congenital immunodeficiency. In the early years of the AIDS epidemic, several cases of Burkitt’s lymphoma were described in homosexual men [11, 12]; these were the first descriptions of non-Hodgkin’s lymphoma arising in association with what was later recognized as HIV infection. Information accumulated since that time indicates that Burkitt’s lymphoma accounts for 30%–40% of non-Hodgkin’s lymphoma in HIV+ patients [6, 13, 14].

**Figure 1.** Burkitt’s lymphoma, sporadic, with classical morphology, involving the tonsil of a child. (A): There is a diffuse infiltrate of atypical lymphoid cells with numerous mitoses and a prominent starry-sky pattern because of the presence of multiple tingible body macrophages. (B): High-power magnification shows that the neoplastic cells are medium-sized, round, and uniform, with nuclei that are similar in size to or slightly smaller than the nuclei of the tingible body macrophages.

**Figure 2.** Burkitt-like lymphoma, sporadic, involving the ileum of an elderly woman; there was also ovarian involvement. (A): There is a diffuse infiltrate of atypical lymphoid cells with abundant apoptotic debris and scattered tingible body macrophages. (B): Compared with Figure 1B, the neoplastic cells in this figure are somewhat more pleomorphic and overall slightly larger.
In a study performed before widespread use of highly active antiretroviral therapy (HAART), Burkitt’s lymphoma was estimated to be 1,000 times more common in HIV+ individuals than in the general population [14]. Compared with other HIV+ patients with non-Hodgkin’s lymphoma of the diffuse large B-cell type, those with Burkitt’s lymphoma are younger, less often carry a prior diagnosis of AIDS, and have higher mean CD4 counts (usually >200 cells/μl). The diagnosis of Burkitt’s lymphoma in an HIV+ individual often represents the first AIDS-defining criterion [14, 15]. HIV-associated Burkitt’s lymphoma shares some pathogenetic features with endemic Burkitt’s lymphoma. HIV infection, analogous to malaria, leads to polyclonal B-cell activation, and permits poorly controlled proliferation of EBV+ B cells. The genetic instability of the EBV+−, aberrantly regulated B cells leads to a greater risk of c-myc rearrangement, and then to lymphoma. HIV is not directly involved in lymphomagenesis but is indirectly involved via cytokine deregulation, chronic antigenic stimulation, and decreased immune surveillance [14, 15]. Lymphoma often involves lymph nodes, bone marrow, and extranodal sites, most often in the abdomen [14]. Burkitt’s lymphoma occurring in transplant recipients tends to occur after a relatively long interval post-transplant (mean, 4.5 years in one series) [9]. Most patients are solid organ recipients, but recipients of stem cells are rarely affected as well. EBV is commonly but not uniformly present [9, 10].

With respect to morphology, the WHO Classification describes classic Burkitt’s lymphoma and two variants: Burkitt’s lymphoma with plasmacytoid differentiation and atypical Burkitt’s/Burkitt-like lymphoma [5]. Classic Burkitt’s lymphoma is found in cases of endemic Burkitt’s lymphoma and most cases of sporadic Burkitt’s lymphoma affecting children (Fig. 1) but in only a minority of sporadic and immunodeficiency-associated adult cases. Neoplastic cells are uniform and medium-sized (their nuclei are no larger than the nuclei of admixed histiocytes), with round nuclei and several or multiple small basophilic nucleoli. Cytoplasm is moderately abundant, and with formalin fixation there may be slight cytoplasmic retraction, leading to squared-off edges between neighboring cells. The RNA-rich cytoplasm is deep blue on Giemsa or Wright stain and usually shows multiple vacuoles (Fig. 3) because of the presence of lipid, when marrow aspirates or Wright-stained touch preps are available. The mitotic rate is unusually high. Characteristically there are numerous admixed tingible body macrophages, phagocytosing abundant apoptotic debris, creating a starry-sky pattern [5]. Many cases of sporadic Burkitt’s lymphoma occurring in adults have Burkitt-like morphology. Those with plasmacytoid differentiation tend to occur in association with immunodeficiency. Burkitt-like lymphoma and Burkitt’s lymphoma with plasmacytoid differentiation both tend to have greater nuclear pleomorphism than classic Burkitt’s lymphoma, and both tend to have a smaller number of more prominent nucleoli (Fig. 2). The plasmacytoid variant has, in addition, monotypic cytoplasmic immunoglobulin. Burkitt’s lymphoma, regardless of subtype, typically expresses monotypic surface IgM, pan-B-cell antigens, including CD19, CD20, CD22, and CD79a, and coexpresses CD10, Bcl-2, CD43, and p53, but not CD5, CD23, Bcl-2, CD138, or TdT. The proliferation fraction is very nearly 100% [5, 16]; accordingly, the doubling time of the tumor is very short, between 24 and 48 hours. Rare cases have been reported that lack surface immunoglobulin [8], including some occurring in allograft recipients [9]. The immunophenotype suggests follicle center origin for this lymphoma.

A defining feature of Burkitt’s lymphoma is the presence of a translocation between the c-myc gene and the IgH gene (found in 80% of cases [t(8;14)]) or between c-myc and the gene for either the kappa or lambda light chain (IgL) in the remaining 20% [t(2;8) or t(8;22), respectively]. Other specific lymphoma-associated translocations, such as IgH/bcl-2 and translocations involving bcl-6, are absent. The myc/Ig translocation may not be detected by routine cytogenetics; performing fluorescence in situ hybridization (FISH) or long-segment polymerase chain reaction may increase the chance of identifying the translocation [8]. In endemic Burkitt’s lymphoma, the break point in c-myc is more than 100 kb upstream from the first coding exon, and the break point in the IgH gene is in the joining segment. In sporadic and HIV-associated Burkitt’s lymphoma, the
break point in myc is between exons 1 and 2, and the break point in \( IgH \) is in the switch (S\( \mu \)) region, suggesting a different pathogenesis and suggesting that neoplastic transformation affects B cells at different maturational stages for these subtypes of Burkitt’s lymphoma [5, 17]. It should be noted however, that results have not been uniform; in a study of sporadic Burkitt’s lymphoma, most presenting as leukemia, one third of cases had chromosomal break points in the joining region of \( IgH \) [8].

Proliferating tissues typically express at least one member of the myc family, most often c-myc. myc is downregulated when cells are terminally differentiated (or when lymphoid cells become memory lymphocytes) [18]. c-myc rearrangement is a pivotal event in lymphomagenesis; it results in a perpetually proliferative state. It has wide ranging effects on progression through the cell cycle, cellular differentiation, apoptosis, and cell adhesion [6]. c-myc rearrangement is an early event; lymphomagenesis most likely involves accumulation of other genetic events as well. \( p53 \) gene mutation, for example, is common in Burkitt’s lymphoma, occurring in immunocompetent and immunosuppressed patients, including HIV\(^+\) individuals and transplant recipients [9, 19].

**STAGING, TREATMENT, AND OUTCOME**

Staging is performed using the Ann Arbor or, more often, the St Jude/Murphy staging system [5, 6, 13, 20]. Approximately 30% of patients present with limited-stage disease (I or II), while 70% present with widespread disease (stage III or IV) [5]. Patients often present with bulky disease, frequently with an elevated lactate dehydrogenase (LDH) level. Patients with any of the three clinical variants are at risk for spread to the central nervous system (CNS) and bone marrow. The bone marrow is positive in 30%–38%, and the CNS is involved in 13%–17% of adult cases [6]. In a study of children with disseminated disease, 12% had CNS involvement, and 22% had marrow involvement [21].

Sporadic and immunodeficiency-associated Burkitt’s lymphoma do not share endemic Burkitt’s lymphoma’s exquisite sensitivity to chemotherapy, so that historically the prognosis had been poor, particularly among adults. Short-duration, high-intensity chemotherapy, sometimes combined with CNS prophylaxis, yields excellent survival in children: patients with localized disease have a >90% 5-year survival rate [21], and children with widespread disease (including leukemic presentation) may achieve a >90% complete response (CR) rate, with an event-free survival (EFS) rate at 4 years of 65% in patients with leukemic presentation, and 79% for those presenting with stage IV lymphoma reported in one series [22]. When similar aggressive chemotherapeutic regimens have been administered to adults, good outcomes have been achieved, with CR rates of 65%–100% and overall survival (OS) rates of 50%–70% [6, 13, 23]. The institution of the CODOX-M/IVAC regimen (Magrath protocol)—two cycles of CODOX-M (cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate, and intrathecal therapy) alternating with IVAC (ifosfamide, etoposide, high-dose cytarabine, and intrathecal therapy)—for high-risk disease, and for those with low-risk disease (e.g., one extranodal site or completely resected abdominal disease with normal LDH), three cycles of CODOX-M, represented a major step forward in the treatment of Burkitt’s lymphoma. Children and adults treated with this regimen had similar outcomes; the EFS rate at 2 years was 92% for the group as a whole [23]. However, there were significant associated toxicities, including frequent myelosuppression, mucositis, neuropathy, and some treatment-related deaths [6, 13]. In addition, because of the rapid, effective tumor cell killing with this aggressive protocol, careful monitoring is required to avoid the complication of tumor lysis syndrome [5]. Some modifications have been suggested to minimize the significant toxicities associated with the CODOX-M/IVAC protocol. The United Kingdom Lymphoma Group, for example, used this protocol with slight modifications, such as decreases in vincristine, achieving a 2-year EFS rate of 65% overall (83% in the low-risk cohort and 60% in the high-risk cohort) [13, 24]. The Dana-Farber Cancer Institute has treated patients with a modified Magrath protocol, aimed at decreasing toxicity while maintaining good outcome. In this modification, the schedule of fractionated cyclophosphamide was altered and the vincristine dose was capped, but the dose of doxorubicin was escalated. In this cohort, there were no treatment-related deaths, one instance of severe mucositis, and no severe neurotoxicity. The 2-year EFS rate was 64% for all patients, 100% for low-risk patients, and 60% for high-risk patients [13, 25]. When relapses occur, it is usually within 1 year of diagnosis, so those who survive 2 years without recurrence can be considered cured [5].

Rituximab, a monoclonal anti-CD20 antibody, may improve outcome; a study of a small series from the M.D. Anderson Cancer Center used rituximab in conjunction with hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone), with CNS prophylaxis, and achieved a complete remission rate of 89%: most patients had advanced-stage disease, and some were HIV\(^+\) [13, 26]. These results are promising, but additional investigation is required to determine the role of rituximab in the treatment of Burkitt’s lymphoma [13]. Similarly, the role of autologous or allogeneic stem cell transplantation for possible consolidation or salvage therapy is not established [6]. Although in recent years tremendous progress has been
made, new therapies are required to minimize toxicities, especially in older patients. Relapses remain a problem, particularly among higher-risk patients [13]. Novel therapies that have not been tested but could be useful include those targeted against the c-myc gene, DNA methyltransferase inhibitors, proteasome inhibitors, cyclin-dependent kinase inhibitors, and others [6].

Although the most important prognostic features have yet to be determined, some features that have been associated with adverse outcome in adults and children include older age, advanced stage, poor performance status, bulky disease, high LDH, and CNS or marrow involvement [6, 27]. Among pediatric patients, a poorer prognosis is associated with age over 15 years [27]. A good prognosis is associated with resectable abdominal disease [5]. Failure to achieve a CR is a very poor prognostic sign [6, 27]. A granulomatous response to the lymphoma has been associated with localized disease and a favorable outcome in cases of sporadic Burkitt’s lymphoma [28, 29].

A minority of patients with Burkitt’s lymphoma presents with leukemic disease, previously classified as ALL, L3 type. Therapy traditionally used to treat lymphoblastic leukemia worked poorly in Burkitt’s patients, but newer chemotherapeutic regimens are associated with better outcome, although they too are associated with serious toxicities [13].

HIV+ patients may be treated with intensive therapy but require especially close observation, with transfusion support and antibiotic therapy as needed. HAART may improve outcome, allowing patients a better chance of being able to tolerate full-dose chemotherapy [13]. Patients developing Burkitt’s lymphoma in a post-transplant setting may also be difficult to treat, but may show a good response to therapy that includes a combination of chemotherapy, decreased immunosuppression, and rituximab [9], although mortality appears to be high among the small numbers of cases reported [9, 10], with three of five patients in one series succumbing to complications of therapy [10].

**Differential Diagnosis**

The main entity in the differential diagnosis of Burkitt’s lymphoma is other types of high-grade B-cell lymphoma, especially diffuse large B-cell lymphoma (Fig. 4). This problem is most pertinent for adults rather than children because a much lower proportion of non-Hodgkin’s lymphoma in adults is Burkitt’s lymphoma, and because adults often have the atypical Burkitt’s variant, which has morphologic features closer to those of diffuse large B-cell lymphoma than classic Burkitt’s lymphoma. Features that favor Burkitt’s lymphoma include morphology as described above (see Pathologic Features), an immunophenotype that is CD20+, CD10+, Bcl-6+, Bcl-2−, TdT−, and monotypic sIg+, with virtually all cells Ki67+ (proliferation), and a translocation involving c-myc and IgH or IgL, without rearrangements involving the bcl-2 or bcl-6 genes (Table 1) [30–32]. c-Myc protein expression has been suggested to favor Burkitt’s lymphoma over diffuse large B-cell lymphoma, but different studies vary with respect to their results on this point, and some large B-cell lymphomas also express c-Myc protein [30]. Childhood lymphomas with the morphology of Burkitt’s lymphoma appear to be uniform with respect to immunophenotype and cytogenetics; this is not true of such lymphomas in adults [16]. Although the immunophenotype of bona fide examples of Burkitt’s lymphoma is uniform from case to case, the features of diffuse large B-cell

![Figure 4](http://theoncologist.alphamedpress.org/downloaded_from)
Table 1. Burkitt’s and Burkitt-like lymphoma: differential diagnosis

<table>
<thead>
<tr>
<th>Type of lymphoma</th>
<th>Clinical features</th>
<th>Morphology</th>
<th>Usual immunophenotype</th>
<th>Genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burkitt’s and Burkitt-like</td>
<td>Children &gt; adults, male &gt; female, extranodal &gt; nodal, bulky, rapidly growing masses</td>
<td>Uniform or slightly pleomorphic medium-sized cells, starry-sky pattern</td>
<td>CD20+, CD10+, Bcl-6+, Bcl-2-, CD5-, TdT-, monotypic sIg+, Ki67 ~100%</td>
<td>t(8;14), t(2;8), or t(8;22) (myc and IgH or IgL); no bcl-2 or bcl-6 translocation</td>
</tr>
<tr>
<td>Diffuse large B-cell</td>
<td>Adults &gt; children, nodal or extranodal, sometimes large mass lesions, often localized</td>
<td>Large oval, irregular or lobated nuclei, scant cytoplasm</td>
<td>CD20+, CD10+/− Bcl-6−, Bcl-2−, monotypic sIg−</td>
<td>bcl-2 and bcl-6 abnormalities common, myc abnormal in a minority</td>
</tr>
<tr>
<td>Precursor B-lymphoblastic leukemia</td>
<td>Children &gt; adults, leukemia &gt; lymphoma</td>
<td>Small- to medium-sized cells, variable size and shape</td>
<td>CD19+, CD20−, CD10+, CD7+, TdT+, sIg−</td>
<td>Variable, often hyperdiploid, no myc rearrangement</td>
</tr>
<tr>
<td>Precursor T-lymphoblastic leukemia</td>
<td>Adolescents and young adults &gt; children and older adults, male &gt; female; mediastinum often involved</td>
<td>Small- to medium-sized cells, variable size and shape</td>
<td>CD3−, CD7+, CD4+/8+, CD1a−, TdT−</td>
<td>Variable</td>
</tr>
<tr>
<td>Mantle cell lymphoma, blastoid variant</td>
<td>Middle-aged and older adults &gt; male &gt; female; usually widespread disease in nodes and other sites</td>
<td>Medium- to large-sized lymphoblast-like or pleomorphic cells with scant cytoplasm</td>
<td>CD20+, CD5+, CD10+, Bcl-2−, cyclin D1+, monotypic sIg+</td>
<td>t(11;14) (bcl-1 and IgH)</td>
</tr>
<tr>
<td>Florid follicular hyperplasia</td>
<td>Children &gt; adults, common in early HIV infection; lymphadenopathy</td>
<td>Large irregular follicles with many blast cells and mitoses</td>
<td>CD20+, CD10+, Bcl-6+, Bcl-2−, Ki67 ~100%, polyclonal Ig expression</td>
<td>No clonal abnormalities</td>
</tr>
</tbody>
</table>

Burkitt’s and Burkitt-like lymphomas are heterogeneous, and a subset of them has an immunophenotype that is the same as that seen in Burkitt’s lymphoma (Fig. 4). In a study of diffuse large B-cell lymphoma, the lymphoma is subjected to immunophenotyping with a panel that includes the markers that are characteristic of Burkitt’s lymphoma, and with an immunophenotype that is similar or identical to that seen in Burkitt’s lymphoma, sometimes with cytogenetic abnormalities overlapping those seen in Burkitt’s lymphoma [31]. Although the WHO Classification states that finding a proliferation fraction approaching 100% is presumptive evidence of myc translocation, a recent study did not find such a correlation [16]. Morphologic examination does not accurately predict which of these lymphomas has the immunophenotype and genotype of Burkitt’s lymphoma, underscoring the need for thorough evaluation of such cases [8, 16, 18, 31, 34].

At Massachusetts General Hospital, when confronted with a diffuse, high-grade B-cell lymphoma with morphology suggesting Burkitt’s lymphoma, we perform immunophenotyping with a panel that includes the markers that are characteristically present or absent in Burkitt’s lymphoma (Table 1). If the immunophenotype is that characteristic of...
Burkitt’s lymphoma, cyogenetic analysis, usually using FISH on touch preps prepared from fresh or frozen tissue, is obtained. If a c-myc rearrangement is present, and rearrangements of bcl-2 and bcl-6 are absent, a diagnosis of Burkitt’s lymphoma is made. If there is morphologic, immunohistologic, or cyogenetic departure from the results expected in Burkitt’s lymphoma, then the diagnosis is usually B-cell lymphoma, high-grade, not subclassified if neoplastic cells are overall medium-sized, or diffuse large B-cell lymphoma if neoplastic cells are large, with a notation that the lymphoma has features suggesting high-grade behavior.

The important question that remains is whether the high-grade lymphomas with some but not all features of Burkitt’s lymphoma should be treated as Burkitt’s lymphoma or as diffuse large B-cell lymphoma. The presence of an 8q24 (c-myc) aberration has been associated with a worse prognosis in all histologic groups, not just those with the morphology of Burkitt’s lymphoma [34]. A recent study of de novo lymphomas classified by histology as diffuse large B-cell lymphoma or Burkitt-like lymphoma, with analysis of immunophenotype and cyogenetic features, showed that, among adults, survival was better for diffuse large B-cell lymphoma than for lymphomas with histologic features of Burkitt-like lymphoma (independent of immunophenotype or cyogenetics); the prognosis for lymphomas with histologic features of Burkitt-like lymphoma without myc translocation was better than for those with a myc translocation. For all adult cases of diffuse large B-cell lymphoma and those classified morphologically as Burkitt-like lymphoma, those with neither myc nor bcl-2 translocation had a better outcome than those with IgH/bcl-2 fusion; that group in turn did better than those with IgH/myc fusion, and the worst prognosis was associated with dual fusion (translocations involving both myc and bcl-2) [15]. These dual translocation or “double-hit” lymphomas have a c-myc translocation that enhances cell proliferation and a bcl-2 translocation that inhibits apoptosis and thus prolongs cell survival. This devastating combination leads to a lymphoma with a very poor prognosis (Fig. 5). There were no survivors with double-hit lymphomas (some of which were transformed follicular lymphomas) at 2 years in one series [18]; other reports have confirmed the aggressive behavior of these lymphomas [35–37].

These findings indicate that there are high-grade B-cell lymphomas that do not fulfill strict criteria for a diagnosis of Burkitt’s or Burkitt-like lymphoma but that have some histologic, immunophenotypic, or genetic features that overlap with the features characteristic of Burkitt’s lymphoma. Although these may not be true examples of Burkitt’s lymphoma, they are aggressive lymphomas that may require more intensive therapy than that usually considered adequate for diffuse large B-cell lymphoma. Such cases should be subjected to full morphologic, immunophenotypic, and cyogenetic characterization, and the best therapy determined by treating patients in clinical trials.

Other entities in the differential diagnosis of Burkitt’s lymphoma include lymphoblastic lymphoma/leukemia and blastoid mantle cell lymphoma. Lymphoblastic lymphomas are usually more variable in size and shape and have more finely dispersed chromatin and less cytoplasm. Mantle-cell lymphoma, blastoid variant, has cells that resemble lymphoblasts or medium- to large-sized cells more pleomorphic than those seen in Burkitt’s or Burkitt-like lymphoma. The striking starry-sky pattern and very high mitotic rate of Burkitt’s lymphoma would be very unusual in lymphoblastic neoplasms and mantle-cell lymphoma; immunophenotyping establishes a diagnosis in difficult cases. When analyzed by flow cytometry, follicular lymphoma can have an immunophenotype similar to or identical to that of Burkitt’s lymphoma, although examination of histologic sections allows easy distinction between these two entities. On occasion, Burkitt’s lymphoma involves follicles and has a follicular pattern. The appearance of florid follicular hyperplasia, with highly active follicle centers with many blast cells and tingible body macrophages, overlaps with the appearance of Burkitt’s lymphoma. The immunophenotype of Burkitt’s lymphoma is very similar to that of the reactive follicle center (CD10+, Bcl-6+, Bcl-2−, Ki67 nearly 100%). Demonstration of monotypic immunoglobulin can definitively exclude a reactive process.

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Figure 5. High-grade B-cell lymphoma with concurrent c-myc and bcl-2 rearrangements (“double-hit” lymphoma) involving peripheral blood. The neoplastic cell shown is medium-sized with several prominent nucleoli. It lacks the cytoplasmic vacuoles seen in the Burkitt’s lymphoma in Figure 3. This lymphoma followed an aggressive course and was rapidly fatal.
SUMMARY
Burkitt’s lymphoma is a unique neoplasm that has taught us much regarding lymphomagenesis. It is the first human tumor to be causally associated with a virus (EBV). The c-myc of Burkitt’s lymphoma is the first oncogene to be described in a lymphoma [38]. It is the first type of non-Hodgkin’s lymphoma to be described in association with HIV infection. Among human neoplasms, it has the shortest doubling time. Its unequalled proliferation rate creates special challenges for diagnosis and treatment.

DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST
The author indicates no potential conflicts of interest.

REFERENCES


