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Please read this section first

The HPCSA and the Med Tech Society have confirmed that this clinical case study, plus your routine review of your EQA reports from Thistle QA, should be documented as a "Journal Club" activity. This means that you must record those attending for CEU purposes. Thistle will not issue a certificate to cover these activities, nor send out "correct" answers to the CEU questions at the end of this case study.

The Thistle QA CEU No is: **MT-2015/009.**

Each attendee should claim THREE CEU points for completing this Quality Control Journal Club exercise, and retain a copy of the relevant Thistle QA Participation Certificate as proof of registration on a Thistle QA EQA.

DIFFERENTIAL SLIDES LEGEND

CYCLE 45 SLIDE 6 – FEBRUARY 2015

BURKITT LYMPHOMA/LEUKAEMIA (BLL)

First described by Dennis Burkitt in 1958, Burkitt lymphoma (BL) is a highly aggressive non-Hodgkin lymphoma (NHL) often presenting in extra-nodal sites or as an acute leukemia. Originally thought to represent 2 different lymphoproliferative disorders, BL was historically classified as a small non-cleaved cell lymphoma in patients with a solid tumour or nodal mass and as L3 acute lymphoblastic leukemia (FAB [French-American-British] L3 ALL) in patients with greater than 25% bone marrow involvement. However, on the basis of shared molecular and genetic features, the World Health Organization (WHO) Classification of Lymphoid Diseases recognizes the lymphoma and leukemic phases of BL as a single entity; a mature B-cell neoplasm, subtype Burkitt lymphoma/Burkitt cell leukemia. The hallmark of this disease is the overexpression of c-Myc, most commonly resulting from t(8;14), although variant translocations have been described.

Clinical presentation of BL

Three different clinical variants of BL have been described: endemic, sporadic, and immunodeficiency BL. Although there is considerable overlap, unique clinical and genetic features have been described among these variants.

- The endemic form is most commonly observed in equatorial Africa, in children aged 4 to 7 years, with frequent involvement of the jaw and kidneys, although ileal, cecal, ovarian, and breast involvement have also been reported. The particularly high incidence of BL in equatorial Africa (50-fold higher than in the United States) and the geographic distribution of this tumour, corresponding to the distribution of endemic malaria, have led to its designation as endemic BL.
- In contrast, in other geographic areas, most patients present with abdominal tumours with no specific geographic or climatic distribution. This clinical variant, designated sporadic BL, accounts for 1% to 2% of all adult lymphomas in Western Europe and the United States.
- The immunodeficiency subtype is frequently observed in the setting of human immunodeficiency virus (HIV) infection and, unlike other HIV-related lymphomas, is frequently noted in patients with CD4 counts exceeding 200 cells/µL.

Adult patients with sporadic or immunodeficiency-associated BL typically present with extranodal disease, with the abdomen being the most frequent site of involvement. Symptoms can include abdominal pain, nausea, vomiting, bowel obstruction, gastrointestinal bleeding, or syndromes mimicking acute appendicitis or intussusception. Intra-abdominal presentations usually affect the bowel or intra-abdominal lymph nodes, although kidney, pancreas, liver, spleen, breast, or ovarian involvement can occur. At diagnosis, patients usually have bulky disease and elevated lactate dehydrogenase and uric acid levels. Bone marrow and central nervous system (CNS) involvement is reported in 30% to 38% and 13% to 17% of adults, respectively.

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Because of the frequency of extranodal disease, several different staging systems have been used for BL. Adult trials frequently reference the Ann Arbor system, although some researchers find this system inadequate because of its inability to fully describe the extent of extranodal involvement. Therefore, some trials report stage according to the St Jude or Murphy staging schema (Table 1). It is important to note that this staging system recognizes Burkitt leukemia as a separate entity, unlike the current WHO classification. Also, this staging system was developed when surgery was often used for both diagnostic and therapeutic purposes, with the goal of surgery often being complete resection of intra-abdominal disease. Current therapy of BL does not routinely incorporate debulking surgery because of the existence of highly effective chemotherapy and an increased rate of local complications and toxic death with early surgery.

Table 1.
St Jude/Murphy Staging System for BL

Stage	Description
I	A single tumour (extranodal) or a single anatomic area (nodal) with the exclusion of the mediastinum or abdomen.
II	A single extranodal tumour with regional node involvement.
	Two single extranodal tumours on the same side of the diaphragm with or without regional node involvement.
	Primary gastrointestinal tumour with or without involvement of associated mesenteric nodes only.
	Two or more nodal areas on the same side of the diaphragm.
IIR	Completely resected intra-abdominal disease.
III	Two single extranodal tumours on opposite sides of the diaphragm.
	All primary intra-thoracic tumours (mediastinal, pleural, thymic).
	All paraspinal or epidural tumours, regardless of other tumour sites.
	All extensive primary intra-abdominal disease.
	Two or more nodal areas on opposite sides of the diaphragm.
IIIA	Localized but non-resectable intra-abdominal disease.
IIIB	Widespread multiorgan abdominal disease.
IV	Any of the above with initial CNS and/or bone marrow involvement (less than 25% involvement; greater than 25% involvement is defined as L3 ALL).

Morphology and immunophenotype of BL

In addition to the different clinical variants of BL, 2 morphologic variants have been identified: classic BL and atypical or Burkitt-like lymphoma (BLL). Medium-sized cells with abundant, basophilic cytoplasm, often containing lipid vacuoles; round nuclei with clumped chromatin and multiple nucleoli; and a diffuse, monotonous pattern of infiltration are characteristic of classic BL. A “starry sky” appearance has been described in this type of NHL because of its abundant proliferative rate, frequent apoptoses, and numerous macrophages containing ingested apoptotic tumour cells.

The Burkitt-like variant, a provisional entity in the REAL (Revised European-American Lymphoma) classification and a subcategory of BL in the WHO classification, has greater pleomorphism in nuclear size and shape, with fewer nucleoli than classic BL. In many cases, BLL has features intermediate between diffuse large B-cell lymphoma (DLBCL) and BL, making pathologic diagnosis difficult. In fact, the degree of consensus among pathologists making the diagnosis of BLL was only 53% using the REAL classification. This lack of reproducibility may be related to the histologic, clinical, and genetic heterogeneity of BLL, with a variety of reviews reporting

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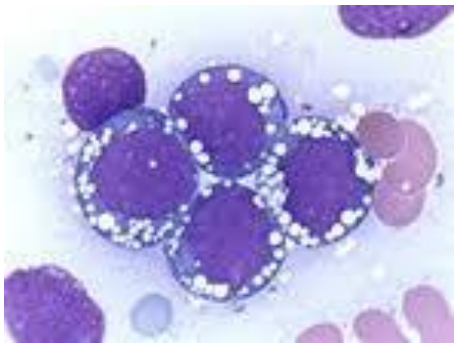
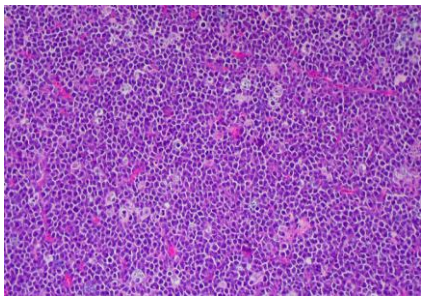
differing characteristics of BLL, including translocation of t(14:18), lack of c-myc rearrangements, and more frequent nodal presentations. Currently, the WHO Classification of Lymphoid Diseases requires that BLL demonstrates a high growth fraction, with Ki67 staining exceeding 99%, with cytogenetic evidence of a c-myc rearrangement, when cytogenetic analysis is available.



Burkitt leukaemia - blasts are large, basophilic, and heavily vacuolated



Starry sky pattern

Genetic features of BL

Eighty percent of BL cases harbor t(8;14), resulting in the juxtaposition of the c-myc gene on chromosome 8 with IgH enhancer elements on chromosome 14 which drive c-Myc mRNA and protein production. In the remaining 20% of BL cases, translocations occurring between chromosomes 2 and 8, t(2;8)(p12;q24), or chromosomes 8 and 22, t(8;22)(q24;q11), place the c-myc gene adjacent to either κ or λ light chain loci and enhancer elements, respectively. As heavy chain and light chain loci are specifically active in mature B cells, it is not difficult to understand how c-myc transcription is favoured in BL harbouring t(8;14), t(2;8), or t(8;22).

Treatment

Burkitt lymphoma/leukemia (BL) has become a very curable mature B-cell neoplasm. Current standard regimens, focused on the unique characteristics of this disease, are composed of cyclical intensive chemotherapy and aggressive intrathecal prophylaxis. Using this approach, complete response rates of 80%-90% are routinely achieved, and survival is now approaching 80% with the addition of rituximab to these intensive regimens. Prophylactic cranial irradiation and prolonged maintenance have no proven benefit and are not recommended.

The more widespread use of highly active antiretroviral therapy in the HIV patient with BL has allowed the use of similar aggressive therapies that are used for the non-HIV BL patients, with commensurate improvements in outcomes in this high-risk population. Future improvements for patients with BL could rely on standardization of gene expression profiling (to ensure more accurate diagnoses and prognostication of disease and to understand mechanisms of treatment resistance) and to develop novel biologically targeted approaches to treatment. The next generation of clinical trials to further improve survival will have the challenge of identifying high-risk patients who might be candidates for novel agents that could be incorporated into existing regimens with the goal of curing all patients with this disease.

References

1. Adult Burkitt leukemia and lymphoma: Kristie A. Blum, Gerard Lozanski, and John C. Byrd
2. Burkitt lymphoma/leukemia: improving prognosis: Kenkre VP, Stock W.

Questions

1. Discuss the morphology and genetic features of Burkitt's lymphoma.
2. Discuss the classification of Burkitt's lymphoma.
3. Discuss the treatment of Burkitt's lymphoma?