



CASE REPORT



Adult Burkitt lymphoma- an Island between lymphomas and leukemias

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ABSTRACT

Background: Burkitt lymphoma is a rare, aggressive and rapidly fatal, B-cell non-Hodgkin's lymphoma. It has an incidence of 0.4/100,000 age-adjusted to the USA standard population. Here we describe the case of a 77-year-old patient who presented with Burkitt lymphoma.

Case: A 77-year-old male presented to his primary care physician with fatigue and listlessness and was referred to the hospital with a white blood cell count (WBC)-23.7 K/uL (neutrophils 37%, lymphocyte 11%, blasts 9%) and platelets-19 K/uL. During his stay in the hospital, repeat investigations revealed WBC-29.9 K/uL (neutrophils 22%, lymphocyte 27%, atypical lymphocytes 5%, blasts 20%) and platelets-10 K/uL with no evidence of mucosal bleeds, neck or abdominal masses or generalized lymphadenopathy. Bone marrow aspirate revealed the presence of MYC rearrangements (8q24) on flow cytometry and fluorescent in-situ hybridization (FISH), indicative but not typical of BL. He was transfused with platelets due to a rapidly deteriorating platelet count and episodes of epistaxis. He was discharged after four days with a plan of outpatient chemotherapy over a period of 4 months. An Ommaya reservoir was placed in the right ventricle for intrathecal chemotherapy. After four months of chemotherapy, computerized tomography of the chest, abdomen, and pelvis confirmed remission. A magnetic resonance imaging of the brain a month after completion of chemotherapy revealed metastatic lymphoma in the temporal, parietal and occipital lobes. He was discharged to hospice for palliative care.

Conclusion: Unconventional presentations, as seen in our case of a leukemia-like picture in the absence of a bulky disease, are the quagmire that might delay aggressive management and result in poorer outcomes.

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1. Introduction

Burkitt lymphoma is a rare, aggressive and rapidly fatal, B-cell Non-Hodgkin's lymphoma (NHL). The World Health Organization (WHO) defines it as a highly aggressive but curable lymphoma that often presents in extra-nodal sites or as acute leukemia" [1]. It was first described in 1958 by Dr. Dennis Parsons Burkitt in a 5-year old boy from Uganda who presented with swelling of both jaws. The symmetrical nature and progression of these swellings to other parts of the body piqued Dr. Burkitt's curiosity. He described the disease as a tumor of lymphatic origin, which now bears his eponym. Currently, the disease is known to have an incidence of 0.4/100,000 age-adjusted to the USA standard population [2]. It has trimodal age-specific incidence peaks in males at ages 10, 40 and 75 years, and bimodal pediatric and geriatric peaks in females [3]. The cure rate decreases significantly with age, dramatically in patients > 60 years of age.

Here we describe the case of a 77-year-old male who presented with BL.

2. Case

A 77-year-old male, with a past medical history of atrial fibrillation and an unremarkable sexual history, presented to his primary care physician with fatigue and listlessness. He had a hemoglobin-14.4 gm/dl, hematocrit-40.8%, red blood cell count 4.53 M/uL, white blood cell count (WBC) 23.7 K/uL (neutrophils 37%, lymphocyte 11%, monocytes 13%, eosinophil 8% and blasts 9%) and platelets 19 K/uL. He was referred to the hospital for a suspicion of acute leukemia.

An examination was unremarkable with temperature: 98.4°F, pulse:72/minute and blood pressure:134/75 mmHg. No mucosal bleeds, neck/abdominal masses or generalized lymphadenopathy were noted. Repeat investigations were significant for WBC:29.9 K/uL (neutrophils 22%, lymphocyte 27%, monocytes 13%, atypical lymphocytes 5%, blasts 20%) and platelets:10 K/uL. A peripheral smear showed a predominance of lymphoid elements with occasional cytoplasmic vacuoles. The computed tomography of the neck, chest, abdomen and pelvis were significant for a non-enhancing mass deep to the

right sternocleidomastoid (3.3 x 2.6 x 4.6 cm), hepatosplenomegaly and an aneurysmal thoracic aorta. A Flow cytometric analysis and fluorescent in-situ hybridization (FISH) test of the bone marrow aspirate revealed phenotypic findings of CD 10+, BCL 6+, BCL 2-, CD 34- and TdT- and presence of MYC rearrangements (8q24), indicative of a likely diagnosis of BL. However, the findings of CD 19-, dim CD 45+ and a dim surface immunoglobulin expression were not typical for BL.

He was transfused platelets due to his rapidly deteriorating platelet count and episodes of epistaxis, with a post-transfusion count of 29 K/uL. He was discharged after four days with a plan of outpatient chemotherapy consisting of six cycles of EPOCH (etoposide, vincristine, doxorubicin, oral prednisone and cyclophosphamide) over a period of four months. An Ommaya reservoir was placed in the right ventricle for intrathecal chemotherapy. After completion of chemotherapy, a computerized tomography chest, abdomen and pelvis confirmed remission. A month after completion of chemotherapy a magnetic resonance imaging of the brain, for acute onset facial numbness, revealed new lesions in the temporal, parietal and occipital lobes suggestive of a metastatic lymphoma. He was discharged to hospice for palliative care.

3. Discussion

BL is a highly malignant disease with rapid growth and dissemination. It is known to have one of the highest mitotic rates, with a doubling rate of 24 hours [4]. Prompt diagnosis and treatment prevents the high mortality rate. According to data published by WHO in 2017, BL accounts for 0.8% of all adult B-cell lymphomas [1].

3.1. Epidemiology and etiology

BL is characterized by translocation between *c-MYC* gene and one of the immunoglobulin (Ig) chains on chromosome 8 [5,6]. The dysregulation causes activation of the *c-MYC* proto-oncogene located at 8q24. The promoter sequences of Ig genes most commonly involved are chromosome 14q32 (heavy chain), in 80% of cases, chromosome 2p12 (kappa light chain) in 10%–15% of cases and chromosome 22q11 (lambda light chain) in 5% of cases [6–8].

Infections such as Epstein-Barr Virus (EBV) and human immunodeficiency virus (HIV) influence this translocation. It is suggested that the expression of latent genes (latent membrane protein 2A) increases the probability of acquiring a p53 mutation, thereby playing a role in early development of BL by allowing an expansion of cells containing a MYC translocation [9]. A better understanding of this mechanism may help develop target-specific treatments in the future. The disease is known to have endemic, sporadic and immunodeficiency-related variants. The association with EBV is higher in

the endemic and immunodeficiency-associated variant compared to the sporadic variant (95% vs 25–40%) [10]. In patients with prolonged immunosuppression, the immobilization of cytotoxic T-cells allows for proliferation of EBV-infected B-cells. These variants are histologically similar but differ in their epidemiology, clinical features and genetic features.

3.1.1. Endemic

It is most commonly seen in children, with an incidence of 3–6 cases/100,000/year [11]. Studies show an ecological link to *Plasmodium falciparum* malaria, arboviruses, herpes viruses (HHV5 and HHV8) and schistosomiasis, suggesting a polymicrobial pathogenesis of the disease [1].

3.1.2. Sporadic

This is the most common variant in the USA (0–8.8 cases/million in both children and adults), Europe (0–4.6 cases/million) and in Asia (0–4.9 cases/million) [12–14]. It has a higher male prevalence with a 3–4:1 ratio [13] and a median age of 31 years [15]. It involves the breast, bone marrow (30–38%), central nervous system (CNS; 13–17%) and other sites (6%) [16].

3.1.3. Immunodeficiency-related

In HIV-associated patients, it occurs despite a higher CD4 cell count (>100/mm³) and highly active antiretroviral treatment (HAART) [1].

3.2. Clinical presentation

The clinical presentation depends on the variant. All the variants typically present with unexplained fever, night sweats and unexplained weight loss > 10%. A laboratory evaluation usually reveals elevated lactate dehydrogenase (LDH) and uric acid levels at diagnosis. The endemic variant often presents in the jaw or kidneys. The immunodeficiency-related variant typically presents with the involvement of nodes, bone marrow and the CNS. The sporadic variant most commonly has an abdominal presentation with abdominal pain, nausea, vomiting, bowel obstruction, gastrointestinal bleeding, or syndromes mimicking acute appendicitis or intussusception. However, some cases may present atypically with a leukemia-like picture, as seen in our patient, which is often associated with early infiltration of the CNS [1].

3.3. Diagnosis

A combination of morphology, immunophenotyping and genetic analysis with clinical correlation is currently used for diagnosis as no diagnostic gold standard exists.

The initial diagnostic panel includes a complete blood count with a differential, peripheral smear, serum electrolytes, renal function tests and liver

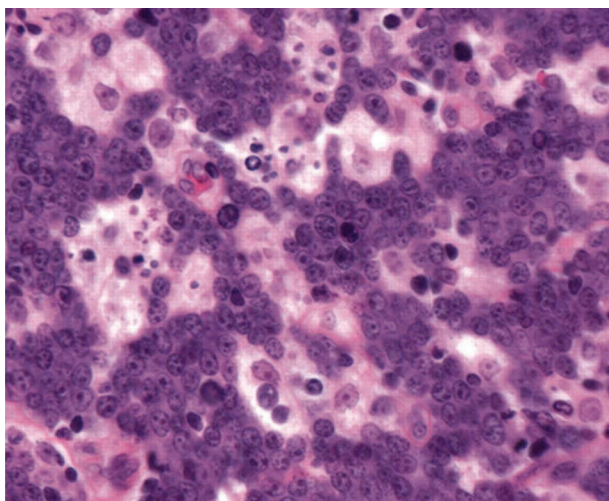


Figure 1. Sporadic classic BL: Diffuse infiltrate of atypical lymphoid cells with numerous mitoses and a prominent Starry-Sky pattern.

function tests. The initial findings are anemia, thrombocytopenia or acute leukopenia in cases with extensive bone marrow involvement at presentation.

3.3.1. Morphology

Hemorrhagic and necrotic abdominal masses with a fish-flesh appearance are seen on gross examination. Microscopically, a starry-sky appearance due to several tingible body macrophages is a hallmark of BL (Figure 1) [1].

3.3.2. Immunophenotype

The tumor cells express surface antigens for IgM, light chains, B-cells (CD19, CD20, CD22 and CD79a) and a Ki67+proliferation of nearly 100%. The cells also express germinal center markers (CD10 and BCL6), HLA-DR, CD38, CD77 and CD43 [1].

3.3.3. Cytogenetics

FISH demonstrates the activation of MYC gene at 8q24 through translocation with one of the three immunoglobulin loci (Figure 2).

3.3.4. Staging

Contrast-enhanced CT and positron emission tomography are used to stage BL using the modified Ann Arbor staging (Table 1).

3.4. Treatment

Due to a lack of standard treatment protocol, Various combinations of chemotherapy, based on the pediatric population treatment regimen, are available for treatment of BL. The Magrath regimen is most frequently used consisting of a combination of CODOX-M

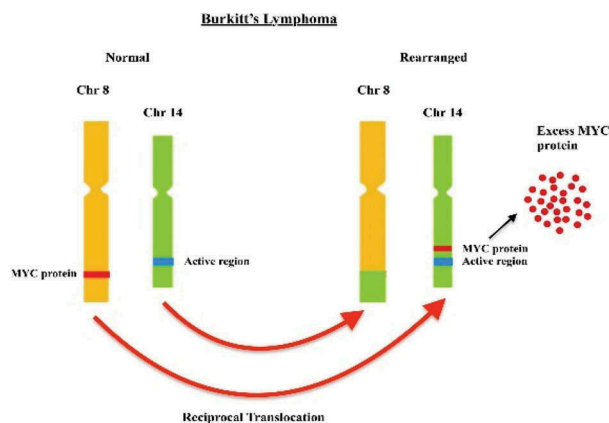


Figure 2. Translocation leading to activation of c-MYC proto-oncogene.

Table 1. Modified Ann Arbor Staging of NHL [21].

Stage	Description
I	Involvement of a single lymph node region
II	Involvement of ≥ 2 lymph node regions on the same side of the diaphragm
III	Involvement of lymph node regions on both sides of the diaphragm
IV	Multifocal involvement of ≥ 1 extra lymphatic sites \pm associated lymph nodes or isolated extra lymphatic organ involvement with distal nodal involvement

[cyclophosphamide (CYT), vincristine, doxorubicin and high-dose methotrexate (MTX)] with IVAC (ifosfamide, cytarabine, etoposide, and intrathecal MTX). The adult B-cell ALL treatment protocol is the basis of two treatment regimens. The first consists of a combination of one seven-day cycle of CYT and prednisone followed by alternating 21-day cycles of ifosfamide or CYT, high-dose MTX, vincristine, dexamethasone, either doxorubicin or etoposide/cytarabine, in addition to triple intrathecal therapy (MTX, cytarabine, hydrocortisone). The other, called HyperCVAD, consists of a combination of hyperfractionated CYT, vincristine, doxorubicin, and dexamethasone (with or without rituximab) alternating with high-dose MTX and cytarabine. For older and less fit patients, infusional chemotherapy with dose adjusted EPOCH (etoposide, vincristine, doxorubicin, oral prednisone, CYT) is a suitable alternative being less aggressive with lower toxicity. Intrathecal MTX is added as prophylaxis due to poor CNS penetration. Mostly used in the immunodeficiency-associated variant, its use in the sporadic variant is not well understood. The addition of rituximab or filgrastim to combination chemotherapy regimens improves the overall survival and response rates. Tumor lysis syndrome is treated with aggressive hydration, rasburicase and correction of electrolyte imbalances.

Prophylactic chemotherapy for CNS reduces the relapse rate from 30–50% to 6–11%, with most relapses occurring in first year [17,18].

3.5. Prognosis

Older age and advanced stage at presentation, pre-existing co-morbidities, bulky disease and high LDH are indicative of poor prognosis [16,19]. Despite new aggressive chemotherapy, the prognosis remains poor in adults >60 years of age with an absolute five-year survival of 27% [20].

4. Conclusion

Burkitt lymphoma has a characteristic presentation depending on the variant. However, an atypical presentation as seen in our case of a leukemia-like picture in the absence of a bulky disease may delay the diagnosis due to a lack of characteristic signs and diagnostic discordance. The unconventional presentations of this disease are the quagmire that might delay aggressive management and result in poorer outcomes.

Disclosure statement

No potential conflict of interest was reported by the authors.

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