

BURKITT LIMPHOMA - CASE REPORT

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Abstract

We present the case of a 2 years and 8 months old girl admitted into the hospital for abdominal tumor. We come up with an exploratory laparotomy and we diagnosed tumor of the right colon with stenosis of the lumen, infiltrating the terminal part of the ileum with extension to the mezeneter and retroperitoneum. The treatment in this case was surgical procedure (right hemicolectomy) associated with chemotherapy. The microscopic pathological exam showed the infiltration of the large bowel wall with lymphocytes and macrophages with an overall appearance of „starry sky”.

Key words: Burkitt lymphoma, mature B-cell lymphoma, infant.

Introduction

Burkitt lymphoma is named after Denis Parsons Burkitt, who mapped its peculiar geographic distribution across Africa. It is a high-grade B-cell neoplasm and epidemiologically has 3 major forms: the endemic (African) form, nonendemic (sporadic) form and immunodeficiency-associated variants. Burkitt lymphoma is one of the fastest growing malignancies in humans, with a very high growth fraction. It is a type of highly aggressive non-Hodgkin lymphoma (NHL), and it often presents in extranodal sites or as acute leukemia. The sporadic variant is present in North America and Europe and the endemic variant is observed in equatorial Africa. HIV-associated BL accounts for about 30% of lymphoma patients with HIV. These lymphomas have a rapid and aggressive clinical course, commonly presenting in children and young adults, with frequent bone marrow and peripheral blood involvement. It is considered to be a medical emergency and requires immediate diagnostic and therapeutic intervention.

Pathophysiology

Burkitt lymphoma (BL) is a mature B-cell lymphoma. All the symptoms are caused by rapid turnover of the mature B lymphocytes and the involvement of extranodal sites and invasion of contiguous organs. The characteristic feature of this entity is the dysregulation and mutation of the c-MYC oncogene. It often resulted from translocation of

chromosome 8 and 14 t(8:14). Other translocations are also reported causing c-MYC overexpression. The activation of C-MYC resulted in increased cell cycle progression, decreased apoptosis, increased cell growth and arrest of cell differentiation, increased cellular metabolism, and decreased cell adhesions.^[1]

Frequency Western Europe and United States: The incidence of sporadic BL is 2-3 cases per million individuals in the United States. It accounts for 1-2% of adult lymphoma cases, and up to 40% of lymphoma cases in children. Thirty to forty percent of HIV-related non-Hodgkin lymphoma (NHL) cases are Burkitt lymphoma.

International: Incidence of endemic BL in African children is much higher than in the United States. The children are usually 4-7 years. It was estimated to be 50 times higher. EBV (Ebstein-Barr Virus) infection is found in nearly all cases.

Race: No racial predilection is reported, although the endemic BL observed primarily in equatorial Africa has primary jaw involvement (70% in children aged 4-7 years versus 15-20% in the sporadic US variety).

Sex: The male-to-female ratio is 2-3:1.

Age: Endemic BL is common in children (30% of non-African pediatric lymphomas), but it is rare in adults (1-2% of all cases of NHL). Twenty to thirty percent of non-Hodgkin lymphomas (NHL) in HIV patients are Burkitt lymphoma (BL). It can present as an AIDS-defining illness and does not correlate with the CD4 counts.

Clinical forms: Three different clinical variants of Burkitt lymphoma (BL) are described: endemic, sporadic, and immunodeficiency related. Their presentations may vary^[2].

The endemic form is most commonly seen in patients in equatorial Africa, with face and jaw involvement. Other clinical presentations include abdominal masses, and ileal, cecal, ovarian, and breast involvement have also been documented. The geographic distribution of the tumor corresponds to the epidemiologic distribution of malarial infections.

The sporadic forms most often present with abdominal tumors with bone marrow involvement. Patients usually present with extranodal disease. It can also present as a leukemic type such as L3 lymphocytic

leukemia. Generalized lymphadenopathy is rare. Approximately 90% of patients with sporadic BL and 50% of patients with endemic BL have abdominal masses upon presentation.

In AIDS patients with Burkitt lymphoma, the disease usually is advanced at diagnosis and tends to involve extranodal sites. Most of these patients present with wide dissemination and bone marrow involvement. Because of their underlying immune deficiency and leukopenia, most of these patients tolerate systemic chemotherapy poorly. Death usually occurs shortly after diagnosis.

Clinical findings and symptoms

Face and jaw involvement in endemic BL (it only occurs in 15-20% of sporadic cases.) ,mandibular or maxillary mass

Abdominal masses can cause abdominal pain and distention, ascites, nausea and vomiting

Loss of appetite and/or change in bowel habits

Gastrointestinal bleeding

Signs and symptoms of acute abdomen (intestinal perforation ,right iliac fossa mass)

Renal failure as a result of retroperitoneal disease and renal involvement

Bone marrow involvement is common in BL.

CNS involvement is common, which includes the following: meningeal infiltration with or without cranial nerve (frequently third and seventh nerve) involvement .

Headaches, visual impairment, and paraplegia from spinal involvement may be initial presenting features in some cases

"B" systemic symptoms fever, weight loss, night sweats, fatigue

Ethyopathogenesis

The following are considered etiologic factors that are implicated in the pathogenesis of BL:

Viral: EBV is associated with 95% of endemic SNCC lymphomas and 20-30% of sporadic BL cases.

c-MYC oncogene activation: The classic t(8;14)(q24;q32) reciprocal translocation (85%) results in the transposition of the c-MYC proto-oncogene on chromosome 8 with one of the immunoglobulin genes on chromosome 14, which results in activation of the c-MYC gene and is considered responsible for tumor proliferation. The variant translocations involving c-MYC transposition to the other immunoglobulin genes, t(2;8) and t(8;22), are also found in BL. C-MYC mutations are also presented. ^[3]

P53 gene: Abnormalities in P53 genes have also been reported and are thought to be associated with the pathogenesis of BL

Lab Studies

Flow cytometry of biopsied tissue or bone marrow may reveal expression of immunoglobulin M (IgM) surface immunoglobulins (most common) as well as other mature B-cell markers such as CD19, CD20, CD22, CD79a, and CD10. Tdt, CD5, CD23, and CD34 negative. ^[4,5]

Cytogenetic studies may reveal one of 3 reciprocal chromosomal translocations: t(8;14)(q24;q32) in 85% of cases, t(2;8)(p12;q24), and t(8;22)(q24;q11). ^[4,5]

Serum chemistries :electrolyte imbalances occur as a result of renal infiltration with lymphoma. The rapid turnover of the Burkitt lymphoma (BL) cells may cause primary tumor lysis. Oliguric renal failure may be a presenting feature of patients with a high tumor burden, resulting in uric acid nephropathy. Serum lactate dehydrogenase (LDH) level, if elevated, corresponds with tumor burden and the extent of disease. It is also a useful indicator of the patient's response to treatment and can be used as an early nonspecific indicator of disease relapse. Liver function test results, if abnormal, may be indicative of visceral involvement with lymphoma. Beta2 microglobulin is a predictor of the extent of disease and is used as a surrogate marker for early relapse. Serum uric acid levels, if high, reflect the high-grade nature of the disease and correlate with the probability of tumor lysis syndrome with initiation of cytotoxic therapy. Complete blood counts may reveal pancytopenia (anemia, thrombocytopenia, and/or leukopenia) due to the involvement of the bone marrow.

Imaging Studies

CT scan of the abdomen and pelvis can be used to evaluate for abdominal and pelvic lymphadenopathy, masses, and visceral involvement. This helps in determining the extent of the disease and may aid in determining the most suitable site for biopsy. CT scanning of the chest should be performed to complete the staging workup. CT scan or MRI of the brain or spinal cord is indicated if neurologic signs are present. Findings on gallium scan provide an estimate of the extent of disease, and gallium scan is used as a follow-up tool in assessing sites of relapse.

Diferential diagnosis

Burkitt lymphoma must be distinguished from other primary abdominal tumors in childhood, including Wilms tumor, neuroblastoma, and peripheral neuroectodermal tumor. In the bone marrow, it must be differentiated from B and T precursor and myeloid leukemias. In peripheral B-cell lymphomas, the major

differential diagnosis is with diffuse large B-cell lymphoma.^[6]

Procedures for diagnosis

Laparotomy was indicated for initial diagnosis and for resection of the disease years ago; it is not recommended by current guidelines. The diagnosis of BL or BLL(Butkitt-like lymphoma) is made by obtaining a biopsy of the tumor mass for histopathology, immunochemistry, and flow cytometry. Cytogenetic studies to identify C-Myc mutation will aid in the diagnosis. *Bone marrow aspirate and biopsy*: the aspirate should be sent for cytogenetic studies. If lymphoma cells are present in the aspirate, flow cytometry/immunophenotyping should be ordered to further characterize the disease.^[6] Bone marrow is involved in 20% of sporadic cases and 8% of endemic cases. Obtaining bilateral biopsy and aspirate specimens is highly recommended. *Lumbar puncture* (LP) is considered part of the staging workup. LP should be performed to ascertain meningeal involvement. The CSF should be sent for cytology and, possibly, flow cytometry in addition to the usual studies. Intrathecal chemotherapy is usually given at the time of initial LP.

Histologic Findings

Extranodal involvement shows monotonous morphology with cells of uniform size and shape. The cytoplasm is scanty, and the nucleus is round or slightly irregular with slightly coarse chromatin and several nucleoli. Mitotic figures are frequently seen. The description of "starry sky appearance" is because of the scattered macrophages with phagocyte cell debris under the microscope. However, the starry sky pattern is not pathognomonic for BL and may be observed in other highly proliferative lymphomas. Immunophenotype and cytogenetic studies are aiding the diagnosis of BL.

Staging

Ann Arbor system and Jude/Murphy staging are commonly used.

Stage I Single tumor (extranodal)
Single anatomic area (nodal)

Stage II Single tumor (extranodal) with regional node involvement

Primary gastrointestinal tumor
Lymphoma involving sites on the same side of the diaphragm

Stage III Lymphoma involving sites both above and below the diaphragm

Stage IV Any of the above with CNS or bone marrow involvement at presentation

Medical Care

Patients in whom BL is suspected should be admitted to the hospital. These patients experience rapidly progressive of extranodal sites; therefore, a diagnostic workup should be completed as soon as possible. Consultation with a hematologist and hematopathologist should be obtained as soon as possible. Measures should be taken to prevent tumor lysis syndrome

Surgical Care

The role of surgical debulking in patients with BL has become controversial because of improved response rates (ie, up to 90%) with combination chemotherapy alone. Historically, most patients who presented with large masses, particularly abdominal disease, underwent an exploratory laparotomy, at which time an effort was made to debulk as well. With newer sophisticated interventional radiology approaches, an adequate diagnosis can be reached in almost all patients without major surgical intervention. In current clinical practice, effective and durable responses are observed with combination chemotherapy, obviating the role of surgical debulking.

Tracheotomy is indicated if the patient's airway is compromised from the physical pressure of a large tumor mass and exploratory laparotomy due to bowel obstruction (often before the diagnosis was made)

Patients with uncontrolled gastrointestinal bleeding also may need exploratory laparotomy or endoscopic procedures for hemostasis.

Pericardiocentesis is indicated for patients presenting with cardiac tamponade.

Paracentesis is indicated if large ascites is one of the presenting complaints.

An excisional lymph node biopsy is usually necessary to reach an accurate diagnosis.

A semipermanent intravenous catheter such as a peripherally inserted central catheter (PICC) line or medicine port should be arranged with interventional radiology or surgery to aid chemotherapy, medications, blood products, and fluid management.

Treatment

Systemic combination chemotherapy is the treatment of choice for all stages of Burkitt lymphoma (BL). It should be started as soon as possible as the diagnosis is made. With current short, intensive chemotherapy approaches, cure rates have been reported in the range of 90% for children and up to 89% in adults. Most protocols incorporate cyclophosphamide, methotrexate, vincristine, and

doxorubicin, with or without corticosteroids. Two to 3 months of treatment is now considered sufficient depending on the stage of disease, with reported cure rates of 90-100%. Radiation has no role in the management of any stage of disease. BL is considered to be a systemic disease^[7,8].

Based on the extent of disease and LDH level and cytogenetic studies, patients can be stratified into low-risk and high-risk categories.^[9]

Low-risk category: Patients have low tumor burden, as determined by low LDH level, completely resected abdominal disease, or a single extra-abdominal site of disease. In such cases, combination chemotherapy (preferably via a clinical trial) should be considered.

High-risk category: Patients have high tumor burden, as determined by a high LDH level, and extensive abdominal or extra-abdominal disease. These patients are at high risk for relapse. Combination chemotherapy in the setting of a clinical trial is the recommended way to treat these patients. High-dose methotrexate, anthracyclines, alkylating agents, and intrathecal chemotherapy are usually used. Patients who have CNS or bone marrow disease should be considered for enrollment in clinical trials involving consolidation with high-dose chemotherapy with autologous stem cell rescue^[10,11].

Mortality/Morbidity

Approximately 90% of pediatric patients with BL treated with current intensive chemotherapy regimens have long-term disease-free survival. For those experience relapse, as many as 25% of patients may be able to achieve a long-term disease-free survival through high-dose therapy with autologous hematopoietic stem-cell transplantation.

Case report

We present the case of a 2 years and 8 months old girl, who was admitted in Pediatric Surgery Clinic after transferring her from a pediatric department with the following symptoms: colic-like abdominal pain in the right hemiabdomen and abdominal distension, bilious vomiting ,fever, nocturne sweats., change in bowel habits with present intestinal transit. Two months ago she was admitted into Pediatric Clinic with an acute viral pneumonia, Mallory-Weis syndrome and intestinal parasitizes (Giardia lamblia).After that she had recurrent abdominal pain, fatigue, loss of the appetite with weight loss.

Objective exam at admission: altered general state,deficitary nutritional state (G=11 kg, High=84 cm),anorexia, pouched eyes, pale teguments and mucosa, abdominal painful tumor in the middle right quadrant, with a diameter of about 4/5 cm, firm consistency, with not-well limited borders, fixed on the subjacent plains.

Laboratory data reveals :high number of leucocytes and thrombocytes, high acute phase reactants, high serum lactate dehydrogenase,nutritional disturbances (decreased proteins and albumins),feriprive anemia,acute dehydration with hyponatremia.The other laboratory findings were within normal limits(alpha-fetoprotein, alkaline phosphatase, serum aminotransferase, gama-GT,urea, creatinine, glycaemia, urine brief exam).

Imagistic data: X-ray thoracic and abdominal did not offer useful diagnostic information. Barium enema showed the barium column stopped below the hepatic angle of colon which is more dilated. MRI abdominal: revealed posterior pancreas displacement ,dilatated ascendant part of the large intestine with enlarged and dualised wall, much thicker than normal, with ileum displacement to the right,small quantities of liquid in the interhepato-diaphragmatic and parietocolic right space; normal findings for liver, kidneys, spleen; (Fig.1).

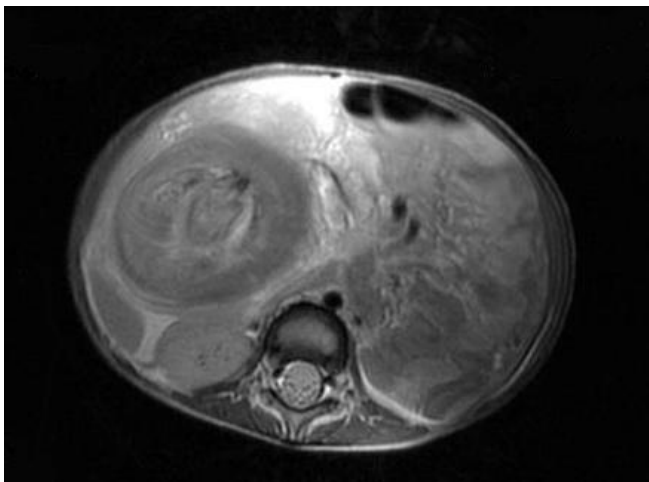


Fig. 1: Burkitt lymphoma, abdominal MRI.

Treatment: After all these investigations we decided to do exploratory laparotomy in order to establish the diagnostic and the treatment. After a short period of preoperative preparation we performed a median laparotomy. We found moderate ascite liquid,

endoluminal tumor of the caecum and ascendant colon extended on about 10-15 cm in length, with stenosis of the lumen, infiltrating the terminal part of the ileum with extension to the mezenzer and retroperitoneum.(Fig.2).



Fig. 2: Burkitt lymphoma, intraoperative details.

We practiced right hemicolectomy with ileotransversoanastomosis termino-terminalis, with biopsy of the mesenteric and epiploonal ganglia and peritoneal drainage. The postoperative care was done in the Intensive Care Unit in the first 5 days, then in the Surgery Compartment and it consisted of solution of parenteral nutrition (glucose, amino acids), antibiotics (piperacillin tazobactam), electrolytes, vitamins .The evolution was favorable and she was transfered in Oncology Department for chemotherapy.

medium shapes and scanty cytoplasm , round noncleavated nucleus and several nucleoli with high mitotic activity and macrophages with the appearances of the “starry sky”.The "starry sky appearance" frequently was seen both in ileum and in paracolic and epiploonal ganglia (Fig.3).We have not had possibility to do cytogenetic studies and flow cytometry of biopsied tissue or bone marrow.The diagnostic was Burkitt lymphoma,(abdominal beginning) with high grade of malignancy.

Histopathology findings revealed enlarged bowel wall infiltrated with atypic lymphoid cells with

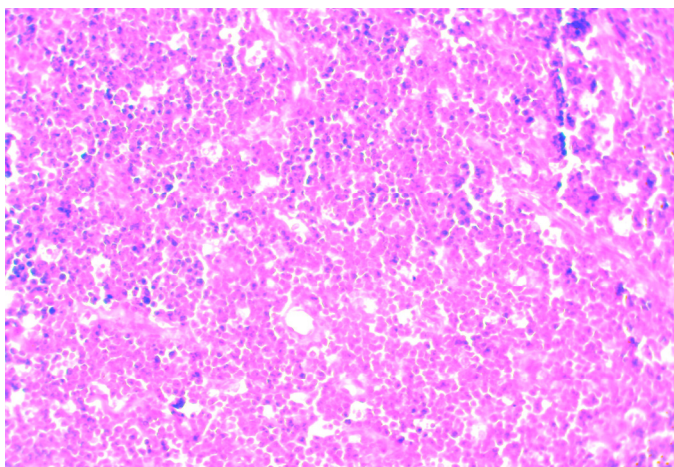


Fig. 3: Burkitt lymphoma showing the “starry sky appearance” (Hx-E, x 20).

Discussions

With newer sophisticated interventional radiology approaches, an adequate diagnosis can be reached in almost all patients without major surgical intervention. CT scan of the abdomen and pelvis helps in determining the extent of the disease and may aid in determining the most suitable site for biopsy. Histopathology, immunochemistry and flow cytometry of the biopsied tissue establish the diagnosis. Effective and durable responses (up to 90%) are observed with combination chemotherapy alone, obviating the role of surgical debulking.

In this case we suspected abdominal tumor according with anamnesis, clinical findings and

laboratory data. In malignancy disease there is pancytopenia, but high number of leucocytes and thrombocytes was showed in blood exam. The abdominal MRI suggests terminal ileum caecum intussusception in the ascendent part of the large intestine and did not offer any information about tumor or lymphadenopathy. We performed exploratory laparotomy with right hemicolectomy with ileotransversoanastomosis termino-terminalis and biopsy of the mesenteric and epiploonal ganglia in order to establish the extend of disease. Lymphoma cells were not presented in the bone marrow aspirate or in central spinal liquid. According to Ann Arbor system and Jude/Murphy staging this case was stage II.

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