Global Health Case

A Case from the University Campus Emergency Room in Worcester: Sharp abdominal pain in the right lower quadrant in a well-appearing 12 y.o. boy

Global Health Pathway
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Sarah J. Palmer, M.D. Candidate
University of Massachusetts Medical School

Case

A well-appearing 12 y.o. boy arrives to the emergency room at the University Campus in Umass with sharp pain in his lower right abdomen. He experiences a loss of appetite, nausea and vomiting, as well as abdominal swelling. Upon examination, his lower right abdomen is enlarged and tender to touch.

What do you think is happening?

Hypothesis: Appendicitis

• These are the classic signs of appendicitis
• Since we are in a world-class hospital, we take a CT scan to confirm our hypothesis.
• What are we expecting to find?
Our Patient’s CT Scan

What do you see? Is this what we were expecting?
Do we still think our patient has appendicitis?

Kidney
Spine
Colon
Aorta and IVC

Where is his stomach?
Where is his liver?

He has a soft tissue mass (M) within the loop of his right colon with thickened wall (open arrow) and fat stranding (solid arrow) surrounding this loop of bowel.

What’s next?

We biopsy the tumor and send to pathology

• How would you describe these cells?
• “Diffuse infiltrating pattern, a medullary, cohesive proliferation of medium sized neoplastic cells, monomorphic, medium sized cells with round nuclei, multiple nucleoli, and a "starry-sky" pattern was observed." (BUJM.org)
• These are phenotypical markers of Burkitt Lymphoma.
• What if we do cytogenetic analysis?

Cytogenetic Testing

• >95% of cases with show a c-myc translocation on Chromosome 8.
• This is considered the hallmark of Burkitt Lymphoma.
Burkitt Lymphoma (BL)
Definition
• Highly aggressive B cell non-Hodgkin lymphoma
• Caused by translocation and deregulation of c-MYC gene on chromosome 8. (Present in 95% of cases)
• Three distinct clinical forms
  • Endemic
  • Sporadic
  • Immunodeficiency-associated

Endemic BL
• Incidence in Africa is 50 times that found in the US
• Accounts for 30-50% of all childhood cancer in equatorial Africa
• Incidence: 3 to 6 cases/100,000 children/year
• Peak incidence in children 4-7 years of age
• Twice as common in boys as it is in girls.

Sporadic BL
• Seen in the US and Western Europe
• In the US: 30% of pediatric lymphomas and <1% adult non-Hodgkin lymphomas
• US: Three cases per million persons per year in both children and adults
• Europe: 2.2 cases per million persons per year in both children and adults
• Peak incidence is at 11 y.o. in children and median age at diagnosis is 30 y.o. in adults. BL is not typically seen in patients younger than 35.
• More common in Caucasians than African or Asian Americans, and may be more common in Central America.
• Across the board, male:female ratio is 3 or 4:1.
**Immunodeficiency-associated BL**

- Associated with HIV infection
- Typically affects those with relatively high CD4 counts (>200 cells/microl) and no opportunistic infections.
- Rate of BL has not decreased with the advent of highly active antiviral therapy.

**Epidemiology**

- BL is most commonly found in equatorial Africa.
- The exact worldwide incidence of BL is unknown because of the lack of resources that would be needed for accurate diagnosis in the developing countries where it is most common.

**Geographic Correlation**

(A) mosquitoes  
(B) Burkitt's lymphoma
Associated Diseases & Current Research

- As early as 1970, Kafuko & Burkitt described a correlation between extremely endemic malaria, Epstein Barr Virus, and BL.
- The connection with Epstein Barr Virus and BL has been firmly established.
- There is a strong geographic correlation between malaria and BL.
- Yet, nearly 100% of children in Kenya are infected with EBV by 2 y.o., and of those that survive repeated malaria infections, the majority do not develop BL. (Moorman)
- The correlation has been described and maps show a strong correlation, but this is an active area of research seeking to explain the biological causation.

Epstein Barr Virus and BL

*Epstein Barr Virus is necessary but not sufficient to cause [endemic] BL. A more dynamic model encompasses incremental contributions from both chronic and acute p. Falciparum malaria leading to alterations in EBV persistence and EBV-specific immunity that culminate in endemic BL.*

- Moorman et. al., 2011

Malaria, EBV and BL

2 Compatible theories
1) Malarial infection will increase polyclonal B-cell expansion and lytic EBV reactivation, which would lead to the expansion of latently infected B cells and the likelihood of a c-myc translocation.
2) EBV-specific T-cell immunity is impaired during malaria co-infection, which leads to the loss of viral control.

This is an active area of research.
Signs & Symptoms

- Patients present with rapidly growing tumor masses
- Spontaneous tumor lysis
- High serum lactate dehydrogenase (LDH) concentration
- Elevated uric acid levels
- Tumor doubling time is 25 hours, which is extremely short
- All three distinct types of BL are histologically identical and are clinically similar: they differ in clinical presentation and genetic features.

Endemic

- Jaw/Facial bone tumor 50-60% of the time
- Bone marrow involvement in <10% of patients at the time of initial presentation, but is common in recurrent or resistant disease.
- Primary involvement of the abdomen is less common
- The primary tumor can spread to extranodal sites: mesentery, ovary, testis, kidney, breast, and meninges.

Sporadic

- Most often has abdominal presentation
- 25% Involvement of jaw or facial bones
- 30% Involve Bone Marrow
- 15% Involve CNS
- Bone Marrow and CNS involvement are commonly seen in recurrent or resistant disease
- Most of the disease affect the distal ileum, stomach, cecum, as well as the mesentery, kidney, testis, ovary, breast, bone marrow, or CNS.
- Presenting symptoms can include those related to bowel obstruction and GI bleeding, often mistaken for appendicitis or intussusception.
Immunodeficiency-related BL

- Accompanied by underlying immunodeficiency
- AIDS, congenital or acquired immunodeficiency
- These cases more often involve lymph nodes, bone marrow, and CNS.

Self Quiz

- What category does our patient’s BL fall into?
  - Sporadic
- Where can we assume our patient is from, based on this category?
  - The United State or Europe
- This type of lymphoma makes up what percentage of pediatric cancers in the US?
  - 30%

Thought question
Is our patient likely to survive this disease?

Diagnosis

As we did in our case study, diagnosis of BL is based on a pathologic evaluation using a sample of the tissue involved.
- Pathologist will look for morphology and immunophenotype
- We are looking for a C-myc mutation on Chromosome 8
  - CD20+, CD10+, BCL6+, BCL2-
- These markers will confirm a diagnosis of BL
- If the tissue is missing one, a FISH assay can be done to locate it.
- If the patient is a child, this is enough to confirm a BL diagnosis.
- If the patient is an adult, further testing must be done to confirm the BL diagnosis.
Treatment

• Prevent tumor lysis syndrome through hydrating with intravenous fluids 24 hr before administering chemotherapy
• Aggressive chemotherapy with prophylaxis for CNS involvement is proven to work
• CODOX-M/IVAC Regimen
• CALGV 9251 Regimen
• Hyper-CVAD Regimen
• Rituximab

Outcomes, prognosis & prevention

• Untreated, BL is fatal
• For children, prompt, intensive chemotherapy usually cures them of BL
• Long term survival rates with appropriate treatment is 60-90%
• Despite this effective treatment, rates of survival in equatorial Africa are estimated to be around 40% (blfundafria.org).
• This vast difference is due to the lack of access to care. BLFA (Burkitt’s Lymphoma Fund Africa) is an organization working to fund this care.

Self Quiz

What is the cause of Burkitt Lymphoma?

a) Malaria  
b) Epstein Barr Virus  
c) C-myc B cell mutation  
d) Immunodeficiency

Answer: C) C-myc B cell mutation
Sources

• http://www.bjui.org/ContentFullItem.aspx?id=687&SectionType=1&title=Female-Paraurethral-Primary-Burkitt%E2%80%99s-Lymphoma-presenting-with-symptoms-of-bladder-outlet-obstruction, successfully treated with chemoimmunotherapy
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