Pediatric Extranodal Lymphoma

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KEYWORDS

• Lymphoma • Children • Non-Hodgkin lymphoma • Burkitt lymphoma • Lymphoblastic lymphoma • Diffuse large B-cell lymphoma • Anaplastic large cell lymphoma

KEY POINTS

- Compared with non-Hodgkin lymphoma (NHL) in adults, the histologic spectrum of pediatric disease is quite narrow and consists of aggressive forms causing widespread disease.
- Burkitt lymphoma is the most common type of pediatric NHL and the most common site of involvement is the ileocecal region, often presenting acutely with intussusception.
- Lymphoblastic lymphoma, as well as other types of NHL, can manifest with rapidly enlarging mediastinal masses causing compression of the airway and superior vena cava.
- Staging and assessment of treatment response are usually performed with fluorodeoxyglucose (FDG)-PET/computed tomography, although alternative techniques with no or lower radiation dose are being evaluated.

Lymphoma is the third most common pediatric neoplasm after leukemia and central nervous system (CNS) tumors, accounting for 10% to 15% of cancers in children. In the United States seven hundred new cases are diagnosed annually, nearly half of which are non-Hodgkin lymphomas (NHLs).[1] NHL is more often extranodal in children than is Hodgkin lymphoma or NHL in adults. NHL shows a predilection for male and white patients and is more common than Hodgkin disease in children younger than 10 years of age.[1]

Pediatric NHL differs from adult disease. NHL that affects children is far less varied in histology and more likely to derive from primitive precursor cells.[2] Disease is typically widespread at presentation in children, and indolent types of lymphoma seen in adults do not occur in pediatric patients. Only 4 types of NHL commonly occur in children: Burkitt lymphoma, lymphoblastic lymphoma, diffuse large B-cell lymphoma (DLBCL), and anaplastic large cell lymphoma (ALCL).

BURKITT LYMPHOMA

Burkitt lymphoma is an aggressive mature B-cell lymphoma and the most common subtype of NHL in children, accounting for 40% of cases in the United States.[3] Burkitt lymphoma primarily involves extranodal sites and, as one of the fastest growing malignancies, generally presents with widespread disease.[4,5] There is a strong male predilection with a male-to-female ratio of 4 to 1. The

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age range is 0 to 20 years with a median age of 8 years. Children between the ages of 5 to 9 comprise more than one-third of cases.[3]

The tumor is named for the surgeon, Denis Parsons Burkitt, who identified a group of children with rapidly enlarging jaw masses while working in Uganda.[6] The World Health Organization now recognizes 3 clinical variants: endemic, sporadic, and immunodeficiency-related Burkitt lymphoma.[7]

The endemic type afflicts children in equatorial Africa and Papua New Guinea where it is the most common childhood malignancy. The peak age of incidence is 4 to 7 years.[7] Endemic Burkitt lymphoma is an Epstein-Barr virus (EBV)-mediated tumor; nearly all tumors (95%) are latently infected.[8] Additionally, the geographic distribution of the endemic form overlaps with that of malaria, although the relationship between malaria, EBV, and Burkitt lymphoma has not yet been fully elucidated. The disease usually involves the jaw and facial bones of young children with characteristic involvement of the developing molar teeth. Disease of the gastrointestinal (GI) tract, kidneys, bone, gonads, and breasts is also common. CNS and peripheral lymph node disease is less frequent.

The sporadic variant, previously known as American Burkitt lymphoma, occurs worldwide and also affects young adults. In the United States 500 cases are diagnosed annually.[9] There is a male predilection with a male-to-female ratio of 2–3 to 1 in adults, likely higher in children.[7] Associated EBV infection is found in 25% to 30% of cases.[5,8] Jaw tumors are rare in this form. The GI tract is most frequently involved and 30% to 40% of patients present with acute abdominal complaints mimicking acute appendicitis.[4,10,11]

The immunodeficiency-associated form occurs primarily in patients with human immunodeficiency virus (HIV) but also in patients with congenital immunodeficiency (eg, Wiskott-Aldrich syndrome, ataxia telangiectasia) and in allograft recipients. This is the most common subtype of lymphoma in children with HIV accounting for 40% of cases.[2] There is also an association with EBV infection, though less than in the endemic form, involving 25% to 40% of cases.[5,8] This association is higher for HIV-infected patients and solid organ transplant recipients.[12]

Pathology Findings

Macroscopically, a fleshy pink to tan mass frequently involving the bowel wall and encasing mesenteric vessels is seen (**Fig. 1**). Due to the short doubling time, central tumor necrosis is common.[4,11] At histology, the tumor consists of medium-sized, monomorphic cells with round or oval nuclei, coarse chromatin, several nucleoli, and a moderate amount of densely basophilic cytoplasm. High mitotic index is typical, along with many apoptotic cells, the nuclear remnants of which are ingested by macrophages. These pale tingible body macrophages are interspersed among the deeply basophilic tumor cells, creating the characteristic starry-sky pattern seen on light microscopy (**Fig. 2**).[7,13]

The tumor cells are of B-cell lineage and express mature B-cell markers: CD20, CD19, CD2, and CD79a. The morphologic and immunophenotypic features may be indistinguishable from those of DLBCL; however, genetic analysis reveals the characteristic t(8:14)(q24;q32) translocation that leads to deregulation of the c-MYC proto-oncogene.[5,9,14] The c-MYC coding sequence is partnered to strong immunoglobulin-promoter and enhancer elements, which drive its expression.[12]

Imaging Features

Extranodal sites are predominantly involved, typically with bulky disease. The most common site of involvement in sporadic and immunodeficiency-associated Burkitt lymphoma is the GI tract with abdominal and pelvic masses evident in 31% to 64% of cases.[4] The most frequently affected sites are distal ileum, cecum, and appendix, a predilection that is presumably due to the concentration of lymphoid tissue in these regions in the form of Peyer patches (see **Fig. 1**). The tumor spreads circumferentially from the submucosa and deep mucosal layers, manifesting as diffuse bowel wall thickening and/or as mural masses on imaging (**Fig. 3**). The mural masses may serve as pathology lead points for intussusception and Burkitt lymphoma is the most common cause of intussusception in children older than 4 years of age.[15] The bowel lumen may be either narrowed due to mass effect or dilated due to tumor invasion of the autonomic plexus and muscularis propria. The latter process disrupts peristalsis and leads to bowel wall dilation and an aneurysmal appearance that is characteristic of Burkitt lymphoma (see **Fig. 3**).[4,14,16] Enlarged abdominal lymph nodes may be seen.[2,17] Complications of tumor mass effect may be evident on imaging, including bowel, biliary, or ureteral obstruction. Malignant ascites is seen in up to one-quarter of cases.[4,11,15,18]

On ultrasound, tumor invasion of the bowel wall produces hypoechoic bowel wall thickening with loss of the normally stratified appearance. A focal hypoechoic, complex mass may be seen.[17] In