Imaging of Pediatric Lymphomas

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KEYWORDS

• Lymphoma • Children • Non-Hodgkin • Hodgkin • Burkitt

Lymphoma is the third most common malignancy in the pediatric age group following leukemia and malignant brain tumors.[1,2] Hodgkin lymphoma (HL) and non- Hodgkin lymphoma (NHL) account for 10% to 15% of all cancers in children and adolescents younger than 20, with nearly 1700 new cases per year reported in the United Sates.[1] The incidence of lymphoma increases with age, representing 3% of cancers in children younger than 5 and 24% of cancers in adolescents aged 15 to 19. Although the total number of new cases of HL per year exceeds new cases of NHL, NHL is more frequent in children younger than 10 and HL is more common in adolescents.[1] Pediatric HL and NHL each include several different histologic subtypes. Pediatric lymphomas may not be limited to a single organ system. Classic HL involves contiguous nodal groups at presentation, unlike NHL, which is more commonly extranodal.

HODGKIN LYMPHOMA

HL was first described as a separate entity in 1832 by Thomas Hodgkin, MD, a pathologist at Guy's Hospital in London. He reported ''peculiar enlargement'' of cervical and other lymph nodes associated with splenic enlargement.[3] In 1856, Samuel Wilks reported similar cases. Crediting Hodgkin with the original description of this entity, Wilks named it ''Hodgkin's Disease'' in 1865. In 1898, Carl Sternberg provided the first histologic description of the neoplastic cell seen in HL. Four years later, Dorothy Reed described the cellular abnormalities and clinical findings in more detail. Reed-Sternberg (RS) cells are considered the hallmark of HL. RS cells are giant multinucleated lymphocytes with eosinophilic nucleoli. The term, HL, is preferred to Hodgkin's disease.

Male incidence is slightly increased under age 15 (male-to-female ratio = 1.3) and significantly increased under age 5 (male-to-female ratio = 5.3).[1] HL is more common, however, in adolescent females over age 15. The incidence is equal in African American and Caucasian children younger than 10. Above this age, the incidence is higher in Caucasians.

Age-adjusted incidence rates comparing 1975–1979 to 1990–1995 time periods reveal comparable rates of decrease in both genders, in patients younger than 15, and a greater male than female decline in the 15- to 19-year-old age group.

The overall 5-year survival for HL diagnosed in patients younger than 20 is reported to be 91%. Although the 5-year survival for both genders and all age groups is similar, the 5-year survival is slightly decreased (84%) in African Americans.[1]

Epstein-Barr virus (EBV) is associated with an increased risk for developing HL. EBV is associated with nearly 50% of HL in developed countries and up to 90% in developing countries. EBV-infected B cells may inhibit normal apoptosis of Reed Sternberg (RS) cells.[4,5] EBV in RS cells occurs more frequently in the mixed cellularity (MC) subtype, male patients, children younger than 10, and lower socioeconomic groups.[6,7] Increasing evidence links EBV-positive HL and infectious mononucleosis. Increased risk factors for developing HL in adolescents and young adults are socioeconomic status, smaller family size, and early birth order.[1] The incidence of HL is increased

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in immunocompromised individuals, congenital and acquired, including HIV-infected patients. Some of these patients also are EBV positive. Such patients have a worse prognosis.[8,9]

The classification of HL is based on morphology, immunohistochemistry, and clinical behavior. The World Health Organization (WHO) classification separates the uncommon nodular lymphocyte predominant (LP) form of HL from the relatively common form, designated classical HL. WHO subtypes of classical HL are nodular sclerosis (NS), lymphocyte rich (LR) (previously LP), mixed cellularity (MC), and lymphocyte depletion (LD). Each subtype is discussed.[10]

National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) statistics for the period 1975–1995 reveal the NS subtype of HL accounted for 70% of cases of HL in patients younger than 20. The incidence of NS is followed by MC (16%), LR (7%), and LD (2%). Age and gender are important factors in pediatric HL. Eighty percent of female patients and 67% of male patients aged 15 to 19 had NS subtype. MC subtype accounts for 32% of all HL cases in children younger than 10 compared with 15% in the 10- to 14-year-old age group and 13% in the 15 to 19 year olds. MC is more common in male (70%) than female patients younger than 20.[1] MC is associated with EBV.[1,6,7] LR is more common in patients younger than 10 with a male predominance.[1,11] LD is rare in the pediatric population and presents with extensive disease frequently involving bone and bone marrow and retroperitoneal lymph nodes. HIV infection and immunosuppression after solid organ transplantation are associated factors in the development of the LD subtype.[1,11,12]

Before the nearly curative current therapy protocols for HL, the ratio of lymphocytes to abnormal cells in the MC, LR, and LD subtypes was associated with prognosis. Response to therapy is in these subtypes currently is independent of histology subtype.[11]

RS cells are most abundant in the NS subtype with fewer numbers in MC and LD subtypes. NS is characterized by lymph nodes that have thickened capsules and are separated into macronodules by collagenous bands. The presence of collagen and fibrous stroma contributes to the presence of residual mediastinal soft tissue even after no viable disease remains. RS cells are rare in the LR subtype of HL often requiring evaluations of multiple tissue sections before the diagnosis can be made. The benign appearance of these lymphocytes and their characteristic cellular proliferation may result in misdiagnosis of lymphoid hyperplasia.[11]

NON-HODGKIN LYMPHOMA

NHL comprises 10% to 15% of all childhood cancers.[13] These lymphomas arise from constituent cells of the immune system that normally circulate throughout the body, thus making NHL a systemic disease. Pediatric NHL differs in several important ways from NHL in adults:

- This group of neoplasms derives from mature and immature cells as compared with the adult population where most tumors derive from mature cells.
- In the pediatric age groups NHL encompasses high-grade tumors that usually are diffuse in nature.[14]
- Pediatric NHLs are divided more evenly between B-cell and T-cell neoplasms as opposed to adults where the majority of tumors are of B-cell origin.

In the pediatric population there are only four major subtypes of NHL as opposed to the many subtypes of NHL in adults (**Table 1**).

The World Health Organization (WHO) divides pediatric NHL into four major histologic subtypes: Burkitt lymphoma (BL), diffuse large B-cell lymphoma (DLBCL), anaplastic large cell lymphoma (ALCL), and lymphoblastic lymphoma (LBL). Each of these subtypes is discussed.

NHL is more common than HL in children younger than 10[1] but less common than HL in older children. The incidence of NHL increases with age. There is a notable male predominance for NHL in children, with 70% occurring in male children.[1] This male predominance is seen in all age groups, although it is more pronounced in those younger than 15. The incidence of NHL among Causasian children is 1.4 times higher than for African Americans younger than 15. The incidence of NHL has remained stable for those younger than 15 from 1975 to 2004. The incidence among 15 to 19 year olds, however, increased from 10.7 per million in 1979 to 16.3 per million in 1995.[1]

Table 1
Incidence of subtypes of non-Hodgkin lymphoma in the pediatric population

Subtype	Incidence (%)
Burkitt lymphoma	40
Diffuse large B-cell lymphoma	20
Anaplastic large cell lymphoma	10
Lymphoblastic lymphoma	30