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ORIGINAL ARTICLE

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Pulmonary involvement in pediatric lymphoma

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Abstract *Background*: The prevalence of pulmonary lymphoma in the pediatric age group is not documented in the literature. *Objective*: This study was designed to assess the prevalence of pulmonary parenchymal lymphoma in children with Hodgkin disease (HD), non-Hodgkin lymphoma (NHL) and post-transplant lymphoproliferative disorder (PTLD). *Materials and methods*: A 10-year retrospective analysis of 161 lymphoma patients (62 girls and 99 boys), mean age of 12.4 years, was performed. The definition of pulmonary lymphoma excluded those with isolated pleural disease and/or mediastinal adenopathy. *Results*: Eighty-two patients had HD, 65 had NHL, and 14 had PTLD. Overall prevalence of pulmonary parenchymal involvement was 13% (21/161), including 12% of patients with HD, 10% of patients with NHL, and 29% of patients with PTLD. CT findings included: pulmonary nodules (90%) or mass (38%); interstitial (9%) or alveolar (9%) disease; cavitation (9%); and pleural based mass (9%). *Conclusions*: Pulmonary parenchymal disease in our pediatric lymphoma population was more prevalent than expected (13%). This is significant for patient management. New pulmonary lesions in patients with known lymphoma should be regarded with suspicion. In the setting of immune suppression, pulmonary lesions treated as infection may actually represent lymphoma. Expeditious biopsy of lesions failing to respond promptly to antibiotic therapy should be considered.

Keywords Lymphoma · Hodgkin's · PTLD · Lungs · Children

Introduction

Before the current era of computed tomography (CT), pulmonary parenchymal involvement with lymphoma was reported in 11.6% of patients with Hodgkin disease (HD) and 3.7% of patients with non-Hodgkin lymphoma (NHL) [1]. More recent CT-based studies reported that 8% of HD patients had pulmonary parenchymal disease at diagnosis [2, 3] and 12% at recurrence [3]. These three study populations all included a majority of adult patients. There are no reports in the literature assessing the prevalence of pulmonary parenchymal lymphoma in a purely pediatric population.

HD and NHL together account for approximately 15% of pediatric malignancies. The typical presentation, natural history, and treatment modalities of these diseases are well established. Recently, the increasing sophistication and success of pediatric organ transplantation has brought with it an increase in the incidence of post-transplant lymphoproliferative disorder (PTLD). This entity is less well understood, but has been reported to differ substantially from the spontaneously arising lymphomas in both presentation and response to

treatment [4]. The majority of PTLD cases are associated with Epstein-Barr virus (EBV) infection, particularly primary EBV infection in patients who were EBV seronegative before transplantation [4]. Similar to NHL, abdominal and thoracic clinical presentations are the most common [4, 5].

Pulmonary parenchymal involvement in the pediatric population with lymphoma has not been specifically quantified in the era of CT. We have observed that a diagnostic dilemma emerges when a patient who has either known lymphoma or immune suppression presents with pulmonary disease. The presentations of pulmonary parenchymal lymphoma are varied, the index of suspicion may be low, and the pulmonary disease may be attributed to the more common etiology of infection [5, 6]. The purpose of this study was to examine the prevalence of pulmonary parenchymal involvement in the pediatric lymphoma population at our institution (a tertiary care children's hospital), and to determine whether any differences in frequency of pulmonary disease existed among the lymphoma subgroups.

Materials and methods

IRB approval was obtained for retrospective analysis of the pediatric lymphoma population at our institution during a 10-year period, including review of hospital charts, pathology reports, and CT studies. The radiology information database was searched for the keyword 'lymphoma' in patients under the age of 18 years at the time of examination. We also ran a list of all children with gallium scans at this institution. The entire list was then cross-referenced with the pediatric oncology list of lymphoma patients. We believe we captured all the pediatric lymphoma patients. In total, 161 children with lymphoma (62 girls and 99 boys) with a mean age of 12.4 years (range 1–20 years) were identified.

Chest CT images were reviewed by the primary author and one or both pediatric radiologist coauthors. The chest CT protocol for evaluation of the child with known or suspected lymphoma consisted of axial or helical acquisition of images at 5-, 7-, or 10-mm thickness depending on the age and size of the patient. Except in cases of renal failure, all studies were performed with intravenously administered contrast medium (2 cc/kg to a maximum of 75 cc). Staging CT included a minimum of chest, abdomen, and pelvis CT, and depending on the clinical presentation, neck and head CT were occasionally added. Follow-up CT of the chest was obtained in those patients with chest involvement at diagnosis or clinical suspicion of new intrathoracic disease. CT findings were categorized based on the most frequent manifestations of pulmonary lymphoma described in the radiologic literature [5]: nodule (< 1 cm); mass (> 1 cm); cavitation; alveolar (definition used was air-space disease), and interstitial disease (definition used was bronchovascular thickening); pleural based mass; pleural effusion; hilar or mediastinal lymphadenopathy. Some of the patients had more than one manifestation of pulmonary lymphoma.

Patients were divided into HD, NHL, and PTLD groups based on medical record review and further subdivided according to the presence or absence of biopsy-proven pulmonary parenchymal disease. Our criteria for PTLD required malignant monoclonal lymphoproliferative disease with definitive tissue diagnosis. Our definition of pulmonary lymphoma excluded those patients with isolated pleural disease and/or isolated mediastinal lymphadenopathy. The chi-square test was used for statistical analysis.

Results

Eighty-two patients (51%) had HD, 65 (40%) had NHL, and 14 (9%) had PTLD. Of the PTLD patients, 12 had non-Hodgkin type lymphoproliferative disease and one had Hodgkin type. One additional patient had an atypical monoclonal B cell lymphoproliferative disorder related to congenital immune deficiency (Evans syndrome). This patient was included in the PTLD group because his lymphoproliferative disorder arose in the setting of immunosuppression. Among the 12 transplants, there were six livers, five hearts, one kidney, and one bone marrow transplant. Bone marrow is by far the most common pediatric transplantation procedure at our institution. Although a few pediatric lung transplant patients are followed here, none appeared in our PTLD population.

The sites of lymphoma involvement in all patients were tabulated. Fifty-five of 82 (67%) patients with HD, 32 of 65 (49%) patients with NHL, and 4 of 14 (29%) PTLD patients had entirely node-limited disease (at both presentation and recurrence, when applicable). The distribution of extranodal disease varied widely, including: bone, bone marrow, eye, kidney, lung parenchyma, mucosa-associated lymphoid tissue, parotid gland, pleura, skin, spleen, and thyroid gland. Among PTLD patients, the site of lymphomatous involvement was related to transplant site: five of five cardiac transplant patients had only supradiaphragmatic disease and four of six hepatic transplant patients had only infradiaphragmatic disease. The single renal transplant patient had only infradiaphragmatic disease.

Overall, 26 patients had lung or pleural findings on CT at some point during their therapeutic course. Three had pleural effusions without pulmonary parenchymal disease, one of which was lymphomatous by thoracentesis. These patients were not included in the pulmonary lymphoma group. One had pulmonary nodules which resolved after antibiotic therapy; another died of respiratory failure before a biopsy specimen was obtained. These patients were also excluded.

Nineteen patients underwent lung biopsies, all of which were positive for lymphoma. One patient had multiple pulmonary nodules unresponsive to antibiotics that regressed after chemotherapy; another had massive pulmonary disease in the setting of a fatal multisystem lymphoma recurrence and was presumed by clinicians to have had pulmonary parenchymal lymphoma. These 21 patients were included in the pulmonary lymphoma group. In 16 children the

diagnosis of pulmonary lymphoma was at presentation, in two children during the initial presentation with progressive disease, and in 3 additional children at relapse.

Thus, the overall prevalence of pulmonary parenchymal involvement in our lymphoma population was 13% (21/161). This included 12% (10/82) of patients with HD, 10% (7/65) of patients with NHL, and 29% (4/14) of patients with PTLD.

The Chi-square test was used to examine the relationship between the prevalence of pulmonary parenchymal involvement in the PTLD population and the spontaneously arising lymphoma population (both HD and NHL). The results did not indicate a significant difference in the frequency of pulmonary parenchymal disease between the two groups of children ($P = 0.19$).CT findings in patients with pulmonary involvement included: solitary or multiple pulmonary nodules (90%), pulmonary mass (38%), interstitial (9%) or alveolar (9%) disease, cavitation (9%), pleural based mass (9%), pleural effusion (9%), and mediastinal adenopathy (67%) (tabulated in Table 1). Findings are shown in (Figs. 1, 2, 3, 4). Most patients had at least two findings. No differences in the CT pattern of lung disease were observed between the PTLD and spontaneously arising lymphoma groups.

Nine of the 21 patients had a gallium scan at the time of diagnosis of the pulmonary lymphoma. One of these was positive in the lung and a second was positive in the pleural space; the other seven were negative in the lungs.

The prevalence of specific areas of extrapulmonary involvement was assessed in both the pulmonary lymphoma group as a whole and the remaining lymphoma patients. This included tabulation of sites of nodal disease and extranodal involvement. No significant differences existed between the two groups. Apart from the preferential distribution with respect to the diaphragm in PTLD patients discussed above, there was no demonstration of tropism between various sites of involvement.

Table 1 Comparison of pulmonary lymphoma findings with the literature

Finding	This paper, no. of cases	This paper, % of cases	Lewis[a], no. of cases	Lewis, % of cases
Nodule	19/21	90%	19/31	61%
Mass	8/21	38%	21/31	68%
Interstitial + alveolar	4/21	19%	11/31	35%
Cavitation	2/21	9%	10/31	32%
Pleural mass	2/21	9%	17/31	42%
Effusion	2/21	9%	13/31	42%
Mediastinal adenopathy	14/21	67%	11/31	35%

[a]From [5]

Discussion

Pulmonary parenchymal disease was more common in all subsets of our pediatric lymphoma population than has previously been reported [5]. In fact, the specific incidence of pulmonary parenchymal involvement in children, whether in spontaneously arising lymphoma or PTLD, has not been well quantified. We observed more frequent pulmonary parenchymal involvement in the PTLD population than in children with spontaneously arising lymphoma. However, the difference was not

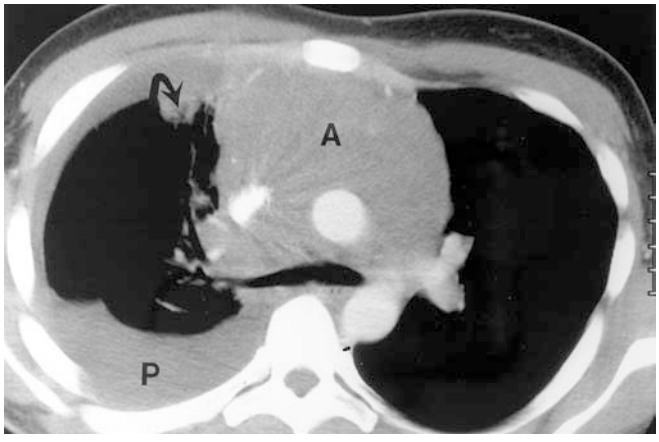

Fig. 1 The definition of pulmonary parenchymal involvement excluded those with findings limited to pleural effusion (*P*) and/or mediastinal adenopathy (*A*). This 17- year-old boy with NHL was included because he had additional pulmonary parenchymal lymphoma, indicated by the *arrow*

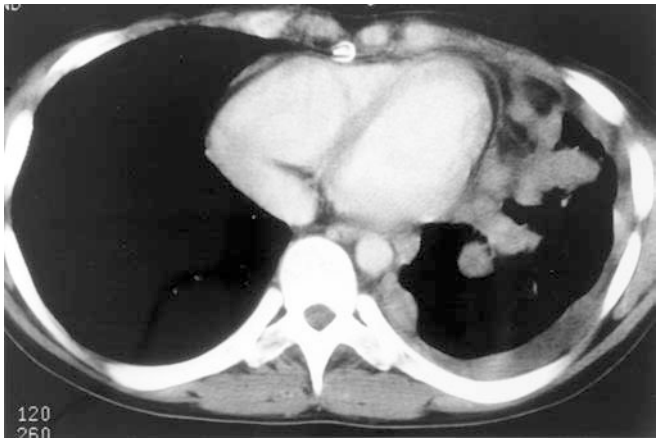

Fig. 2 A 16- year-old boy with NHL with multiple pulmonary masses (> 1 cm) and nodules (< 1 cm)

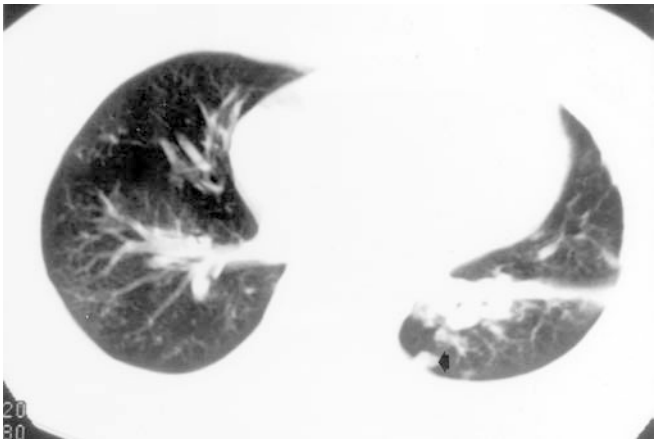

Fig. 3 This 12- year-old boy with HD has interstitial lymphoma and nodules, one of which is included on this image (*arrowhead*)

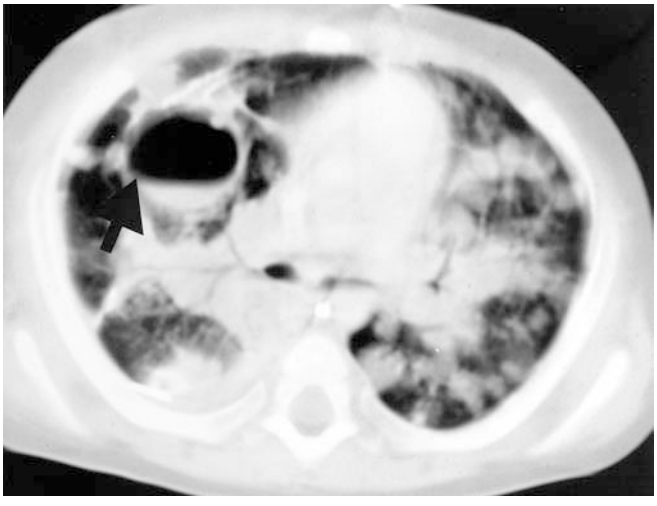

Fig. 4 This 15- month-old boy with PTLD has masses as well as alveolar and interstitial pulmonary lymphoma. The mass (*arrow*) in the right lung with the fluid level was thought to represent a secondary abscess or pneumatocele

statistically significant, probably due to the small size of our PTLD population. The overall prevalence of pulmonary lymphoma was 13%. Similar to the adult-based data (Table 1), pulmonary nodules and pulmonary masses were the most common findings. As noted in this previous study, the absence of mediastinal adenopathy on CT scan does not exclude the diagnosis of pulmonary lymphoma.

Several reports in the literature have linked pulmonary parenchymal PTLD directly to lung transplantation, while others have disputed this relationship [7]. However, such a relationship would not explain the greater than expected prevalence of lung findings in our PTLD population, as none of the children in our series had undergone lung transplantation. In fact, it is probable that our findings actually underestimate the prevalence of pulmonary parenchymal involvement in PTLD (due to the small number of lung transplants followed at our institution).

Bias in this study includes our restriction of the diagnosis in pulmonary lymphoma to those with a chest CT scan. In some children there may have been pulmonary lymphoma evident solely on chest radiographs. Additional bias may have been introduced in our restricted definition of pulmonary lymphoma. Some of the children with pulmonary lymphoma may not have had a biopsy or may have died before demonstrating response to therapy. It has been suggested that the increased prevalence of pulmonary lymphoma in children is a direct result of relapse and longer survival in this era of chemotherapy. Our population had a marked predominance of pulmonary lymphoma at presentation, 16 of the 21 cases. In an additional two children the pulmonary lymphoma was diagnosed in progressive disease with no remission. There were only three children in whom the diagnosis of pulmonary lymphoma was made at relapse.

The clinical implications of these findings are significant. In the setting of immune suppression (whether related to organ transplant or secondary to chemotherapy) new pulmonary parenchymal disease is often treated empirically as infection. The present series suggests that such lesions may represent pulmonary parenchymal lymphoma. Therefore, pulmonary disease failing to respond promptly to antibiotic therapy deserves consideration of biopsy for definitive tissue diagnosis. Pulmonary parenchymal disease in lymphoma appears to be more prevalent than previously noted in the predominantly adult literature, suggesting that new pulmonary disease in all pediatric lymphoma patients should be regarded with heightened suspicion.

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