

Precursor B-Cell Lymphoblastic Lymphoma (PBLL) in Children: Pattern of Presentation and Outcome

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ABSTRACT

Purpose and Background: Precursor B-cell lymphoblastic lymphoma (PBLL) is a rare subtype of NHL seen primarily in children or young adults. There are approximately 100 immunophenotyped cases of PBLL; reported in the literature; most as single case reports or very small series. In this report, we describe patterns of presentation, and results of a retrospective study looking at patients with PBLL treated at KFSH and RC between 1993 and 2000.

Patients and Methods: We present results of a retrospective study looking at patients with PBLL treated at KFSHRC between 1993 and 2000, younger than 14 years of age (cut-off age for pediatric department). Six cases of PBLL were lacking evidence of blood and bone marrow involvement. Histologic sections were available for review in all cases.

Results: Twenty one patients were treated for lymphoblastic lymphoma, of which six had a precursor B-cell phenotype. There were three boys and the median age at diagnosis was 6 years (range 3-13). In four of the patients the primary involved were oro-nasopharynx or the paranasal sinuses. One patient had a soft tissue mass in the upper thigh while one patient had a solitary bone lesion in the distal tibia. Four of the patients had limited stage disease (2 stage I and stage II), while 2 were stage IV. Both patients with stage IV disease had CNS involvement with blasts in the CSF. Both had paranasal primaries and had bone infiltration involving the base of the skull, with radiological documentation of intracranial extension in one patient. Median LDH level was 542 IU/L (range 463-5000).

Five patients were treated according to B-cell NHL type protocols. Because of the specific diagnosis of PBLL, two of these patients were switched to an ALL-type protocol following post induction intensification; one died in remission due to encephalitis, while the other remained in CR almost 2 years after diagnosis. A third patient suffered a loco-regional relapse 17 months after completing first line therapy, and was re-treated on an ALL-type protocol, and currently is in remission 25 months following relapse. The fourth patient, who received 9 months of post induction therapy, remains free of disease 7 years following

diagnosis. The fifth patient had local and CNS progression on therapy, and died of his disease. The last patient with a solitary bone lesion was misdiagnosed as Ewings' Sarcoma and received treatment for that disease. He suffered an isolated CNS relapse, and is in CR 12 months following the relapse, on an ALL treatment protocol.

Conclusion: PBLL is a distinct B-cell NHL which involves extralymphatic sites, with particular predisposition for the upper aerodigestive tract. Patients should not be treated on short intensive protocols used for other B-cell NHL but should receive treatment based on ALL protocols like those for treating T-cell LL

Key Words: PBLL - Presentations - Chemotherapy.

INTRODUCTION

Lymphoblastic lymphoma (LL) is a neoplasm of immature lymphoid cells. The cells are morphologically identical to the lymphoblasts of acute lymphoblastic leukemia (ALL). Commonly used criteria to distinguish LL from ALL are as follows: (1) manifestations as bulky mass in solid organs, (2) focal (<25%) or absent bone marrow involvement; and (3) absence of peripheral blood involvement [18].

These immature B-lymphoid cells are morphologically of small to medium size, with fine chromatin, inconspicuous nucleoli, and a high mitotic rate [10]. Immunophenotypically, the neoplastic cells express terminal deoxynucleotidyl transferase (TdT) and B-cell antigens such as CD10, CD19, CD22, and CD79a [4,27,29]. There are approximately 100 immunophenotyped cases of PBLL reported in the literature; most as single case reports or very small series [1-3,5,8,11,13,15-17,19-22,25,26,28,29,31,34].

The Revised European-American classification system of lymphoid neoplasms (REAL)

has merged the categories of precursor B-cell ALL and PBLL in a single entity [7], but the existing data of LL are insufficient to validate this proposal. These tumors are considered by many researchers to represent different clinical presentations of the same neoplasm and are grouped in the category of precursor B-cell lymphoblastic leukemia lymphoma in the proposed World Health Organisation classification of lymphoid neoplasms [6].

In this report, we describe patterns of presentation, and results of a retrospective study looking at patients with PBLL treated at KF-SH&RC between 1993 and 2000.

MATERIALS AND METHODS

Patients:

A retrospective review of the medical records at King Faisal Specialist Hospital and Research Centre & King Fahd Children Cancer Centre and Research Centre, from 1993 through 2000, of patients younger than 14 years of age (cut-off age for pediatric department). Six cases of PBLL were lacking evidence of blood and bone marrow involvement. Histologic sections were available for review in all cases.

Diagnosis:

The diagnosis of PBLL was based on the presence of extramedullary primary and $\leq 5\%$ blasts in BM, the presence of lymphoblastic histology and/or FAB-L1 or L2 cytomorphology, and the presence of at least one b-lineage antigen as well as the absence of surface immunoglobulin (slg) and of t-lineage antigens.

Staging:

Staging included physical examination, peripheral blood and bone marrow aspiration smears, cerebrospinal fluid (CSF) analysis, ultrasonography, CXR, computed tomography (chest) or magnetic resonance imaging (MRI), and skeletal scintigraphy according to site of presentation. The St. Jude staging system was used [29] Initial CNS disease was diagnosed if lymphoblasts were present in the CSF and the number of cells in the CSF was $>5/\text{micro L}$ and/or if cerebral infiltrates were detected on cranial CT or MRI. Treatment; Five patients were treated according to B-cell non-Hodgkin's lymphoma (NHL) type protocols. Because of the specific diagnosis of PBLL, two of these patients were switched to an ALL-type protocol

following post induction intensification. The last patient (6th) with a solitary bone lesion was misdiagnosed as Ewings' sarcoma and received treatment for that disease. He suffered an isolated CNS relapse for which he was started on an ALL-type protocol.

RESULTS

Clinical Manifestations and Staging:

Table (1) summarized the clinical and radiologic features for 6 patients with PBLL. The M/F ratio was 1:1. The median age at diagnosis was 7.5 years [range 3-13]. In four of the patients, the primary involved the oro-nasopharynx or the paranasal sinuses. One patient had a soft tissue mass in the upper thigh while one patient had a solitary bone lesion in the distal tibia. The head and neck region was the initial site of diagnosis in 4 of 6 cases. According to the St. Jude classification for non-Hodgkin's lymphoma in children [19], 4 of 6 had limited stage disease (2 had stage I, and 2 had stage II), while 2 had stage IV disease. Both patients with stage IV disease had CNS involvement with blasts in the CSF. Both had paranasal primaries and had bone infiltration involving the base of the skull, with radiological documentation of intracranial extension in one patient. Median LDH level was 542 m/L (range 463->5000; n=5).

Treatment and Outcome:

Five patients were treated according to B-cell non-Hodgkin's lymphoma type protocols. Because of specific diagnosis of PBLL, two of these patients were switched to an ALL-type protocol following post induction intensification; one died in remission due to encephalitis, while the other remains in CR1 almost 2 years after diagnosis. A third patient suffered a loco-regional relapse 17 months after completing first line therapy. She was re-treated on an ALL-type protocol, and currently is in remission 25 months following her relapse. The fourth patient, who received 9 months of post induction therapy, remains free of disease 7 years following diagnosis. The fifth patient had local and CNS progression on therapy, and died of his disease. The last patient with a solitary bone lesion was misdiagnosed as Ewings' Sarcoma and received treatment for that disease. He suffered an isolated CNS relapse, and is in CR2 12 months following the relapse, on an ALL-type treatment protocol.

Table (1): Clinical features in cases of precursor B-cell lymphoblastic lymphoma.

| Case No./ Sex / Age at diagnosis | Presentations | Clinical findings |
|----------------------------------|---|---|
| 1/M/3 | Palpable mass left cheek, 6m rapid increase for 3m | Multiple nodes in the left supraclavicular region; normal chest and abdomen on CT |
| 2/F/6 | Dysphagia and weight loss, 2m | Right tonsillar mass |
| 3/M/8 | Left anterior cervical adenopathy, 2-3m | Oropharyngeal mass, multiple nodes, left cervical chain; normal chest and abdomen on CT |
| 4/F/ 10 | Non-tender mass, upper left thigh, 2m | Multiple bilateral inguinal nodes; left iliac nodes; normal chest and abdomen on CT |
| 5/M/13 | Non-tender mass, right cheek; 4-6m | Multiple nodes left supraclavicular region; normal chest and abdomen |
| 6/F/7 | Solitary bone lesion in the distal right tibia; 2 month | No evidence of lymphadenopathy |

DISCUSSION

In the revised European-American Lymphoma classification, lymphoblastic lymphoma (LL) is divided into precursor B- and T-cell types. Both types of LL are cytologically identical, and the immunophenotype cannot be predicted reliably from microscopic examination alone. Sites of manifestations of LL depend on the immunophenotype of the neoplastic cells. Patients with T-cell LL frequently have a mediastinal (thymic) mass. If lymphadenopathy is present, it is generally above the diaphragm, although mediastinal involvement by PBLL also has been rarely described [12,24]. Common sites of involvement in PBLL include the skin, particularly of the head and neck, bone, and lymph nodes [5,17].

The immunophenotype of the stages of normal T- and B-cell differentiation that take place in the thymus and bone marrow, respectively. The vast majority (80-90%) of LLs have a T-cell phenotype, while only 10% to 20% of LLs are B-cell type.

Apart from lymphoblastic histology and FAB-L1 or L2 cytology, the expression of nuclear TdT, a highly specific marker for lymphoblastic lymphoma [33], and the lack of surface Ig expression are decisive parameters for distinguishing PBLL from mature B-cell neoplasm such as Burkitt's lymphoma.

The differential diagnosis of precursor B-cell LL includes T-cell LL as well as malignant neoplasms of the small blue cell category such

as Ewing's Sarcoma. Although the mean ages for precursor B-cell LL and T-cell LL are virtually identical, T-cell LL has a much higher proportion of cases occurring in the mediastinum, 50% to 65%, compared with 4% for precursor B-cell LL [8]. Most T-cell LLs also express TdT and CD99, while up to a third express CD10 [14,16,31]. However, reactivity for at least 1 pan T-cell marker (CD2, CD3, CD5, CD7) is present in all cases T-cell LL.

Precursor B-cell LL can manifest as a primary bone lesion [14,16,31], and Ewing's Sarcoma need to be excluded because of overlapping patient populations, as happened with one of our patients.

Both precursor b- and T-cell LL express CD99, which at one time was thought to be unique to Ewing's sarcoma [23]. Moreover, only two thirds of precursor B-cell LL express CD45 (LCA), and, thus, a CD99±, LCA-negative tumor should not be equated with a diagnosis of Ewing's sarcoma.

Additional immunohistochemical stains such as TdT, CD34, or CD79a, which are negative in Ewing's Sarcomas, are needed to exclude precursor B-cell LL [32]. CD43 is another commonly expressed antigen found in both B- and T-cell LL that is not present in Ewing's Sarcomas [31]. The demonstration of an (11; 22) translocation or the EWS-FLI1 fusion product characteristic of Ewing's Sarcomas is helpful in establishing the correct diagnosis, to avoid erroneous diagnosis, treatment of this group of patients.

Because of its biological relationship to ALL, treated patients with pre-B LL according to an ALL-type strategy consisting of intensive induction, consolidation and extra compartment therapy, intensive re-induction for advanced-stage disease and maintenance, this strategy proved to be highly efficacious for PBLL patients. In our series, five patients were treated according to B-cell NHL protocol. Because of the specific diagnosis of PBLL, two of these patients were switched to an ALL-type protocol following post induction intensification; one died in remission due to encephalitis, while the other remains in CR1 almost 2 years after diagnosis. The third patient had a loco-regional relapse 17 months after completing first line therapy, for which she was re-treated on an ALL-type protocol, and currently is in remissions 25 months following her relapse. The fourth patient, who received 9 months of post induction therapy, remains free of disease 7 years following diagnosis. The fifth patient had progressive local and CNS disease on therapy, died of his disease. The last patient, who was misdiagnosed as a case of Ewing's Sarcoma and received treatment for that disease, suffered from isolated CNS relapse, and is in CR2 12 months following the relapse, on an ALL-treatment protocol.

In conclusion, PBLL is a distinct B-cell NHL which involves extralymphatic sites, with particular predisposition for the upper aerodigestive tract. Patients should not be treated on short intensive protocols used for other B-cell NHL but should receive treatment based on ALL protocols like those for treating T-cell LL. Therefore, correct diagnosis, including cytomorphology, histopathology, immunophenotyping, and genetics to distinguish patients with PBLL from those suffering from mature B-cell neoplasms, is essential for the allocation of patients to the appropriate treatment strategy.

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