INTRODUCTION

Natural killer (NK) cell leukemia/lymphoma is a rare and heterogeneous group of disorders. Aggressive NK cell leukemia/lymphoma and extramedullary NK cell lymphoma, nasal type are considered to originate from mature NK cells based on their morphology, immunophenotype, functional NK cell activity, and expression of cytotoxic molecules [1–3]. Precursor NK cell neoplasms have been characterized as CD56-positive immature hematolymphoid tumors [4,5]. In contrast to mature NK cell malignancies, precursor NK cell neoplasms are less recognized with a more complex immunophenotypic profile, overlapping morphology with lymphoblasts, and heterogeneous biological behavior.

NK cell malignancies are much more prevalent in Asia and more common in adults than in children. Most of NK cell neoplasms occur in extramedullary sites and arise from mature NK cells. The very limited number of reports of pediatric patients with precursor NK cell leukemia in Western countries has led to insufficient experience with diagnosis and treatment options. Here we present a pediatric patient with precursor NK cell leukemia and review the literature of the previously reported cases to further help characterize this uncommon tumor.

CASE REPORT

A 4-year-old female presented with a history of bilateral red eyes, anterior uveitis, ankle pain, and bilateral headache. Physical examination was significant for right-sided facial ecchymosis, bilateral scleral hemorrhage, mild icterus, bilateral anterior and posterior cervical and posterior auricular lymphadenopathy, and hepatosplenomegaly. Laboratory data included a white blood cell count of 4,700/μL with 5% circulating blasts, hemoglobin 8.4 g/dl, platelet count of 61,000/μL, and lactate dehydrogenase of 588 IU/L. Chest X-ray, chest and brain computed tomography, and blood culture were unremarkable.

A bone marrow examination detected 90% blasts. The blasts showed lymphoblastoid morphology (Fig. 1a). Azurophilic cytoplasmic granules were absent. Angioinvasion, angiodesstruction, or necrosis was not identified in bone marrow biopsy. Blasts by flow cytometric analysis and immunohistochemical stains exhibited CD2*CD3*CD4*CD7*CD8*CD16*CD56*CD57*CD19*CD20*CD13*CD3* Myeloperoxidase (MPO)*CD34*HLA-DR*CD10*TdT*CD45dim immunophenotype (Fig. 1b). Cytotoxic marker granzyme B was negative. Epstein–Barr virus (EBV) was not detected by real time polymerase chain reaction.

The patient was diagnosed with blastic NK cell leukemia and received initial chemotherapy according to Children’s Cancer Group protocol 3941 for non-Hodgkin lymphoma (NHL). She achieved a complete remission within the first 2 weeks of treatment. After chemotherapy consisting of 3 weeks of induction, 3 weeks of consolidation, and 7 weeks of maintenance, she underwent an autologous bone marrow transplant with a genotypically HLA identical sibling as donor. Her post transplant preparative regimen consisted of total body irradiation (total dose 1200 cGy), cytarabine, and cyclophosphamide. The post transplant course was uneventful with the exception of Grade II acute graft versus host disease noted in the skin. She has been in complete continuous remission for 2 years.

DISCUSSION

Not including the patient described here, four precursor NK cell leukemia cases in childhood are found in the English literature (Table I) [6–8]. Selection criteria included patients with ≥30% bone marrow lymphoid blasts which express at least one NK cell antigen (CD16, CD56, or CD57), without expression of surface CD3, CD19, CD20, CD13, CD33, and MPO. Demographically, the age range was 4–18 years. Two were male and three were female. Four out of the five patients were of Asian, Hispanic, or South American descent while one patient was Caucasian. All cases had extramedullary lesions with lymph node involvement most common. Other sites of leukemia included liver/spleen, skin, and mediastinal and pericardial involvement.

Several common features were noted among all patients diagnosed with precursor NK cell leukemia. (1) The leukemic cells displayed blast appearance without cytoplasmic azurophilic granules and manifested dim CD45 expression, a characteristic of true blasts. A composite phenotype CD3-CD56-CD13-CD33-MPO- in blasts was consistent with a NK cell derivation. (2) Germline configuration of TCR and/or IgH genes was identified.
TABLE 1. Pediatric Patients With Precursor Natural Killer Cell Leukemia

<table>
<thead>
<tr>
<th>Category/Subcategory</th>
<th>Race/Geographic Location</th>
<th>Morphology/EM lesions</th>
<th>Immunophenotype</th>
<th>TCR &amp;/or IgH gene rearrangementCD56</th>
<th>EBV status</th>
<th>Treatment and outcome</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precursor form</td>
<td>Hispanic/USA</td>
<td>Lymphoblastoid/LLular, LN, Splenic</td>
<td>CD3+ “HLA-DR+T�6+ CD10+CD2+CD5+CD3+CD4+CD7+”</td>
<td>ND+</td>
<td>NEL therapy; BMT; alive, 2y</td>
<td>Present case</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Caucasian/USA</td>
<td>Lymphoblastoid/LLular</td>
<td>CD1+/CD3+CD5+CD7+CD19+/CD20+CD13+CD33+MPO+CD45+</td>
<td>TCR/-</td>
<td>ALL therapy; remission; DOD, 35 mos</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Asian/Japanese</td>
<td>Lymphoblastoid/Plasmacytoid, Pericellular</td>
<td>CD1+/CD3+CD5+CD7+CD19+/CD20+CD13+CD33+MPO+CD45+</td>
<td>Germinal configuration</td>
<td>ALL therapy; BMT; alive, 3y</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Precursor form (blastic NK cell leukemia/Lymphoma, CD4+CD56+ hematopoietic neoplasm)</td>
<td>South American/Brazil</td>
<td>Lymphoblastoid/Skin, LN, Spleen</td>
<td>CD1+/CD3+CD5+CD7+CD19+/CD20+CD13+CD33+MPO+CD45+</td>
<td>Germinal configuration/ND</td>
<td>CHOP; DOD, 2 mos</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>South American/Brazil</td>
<td>Lymphoblastoid/Skin, LN, Spleen</td>
<td>CD1+/CD3+CD5+CD7+CD19+/CD20+CD13+CD33+MPO+CD45+</td>
<td>ND/-</td>
<td>ALL therapy; CR, 7 yrs</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>

BMT, bone marrow transplantation; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CR, complete remission; DOD, died of disease; EBV, Epstein-Barr virus; EM, extramedullary; F, female; IgH, immunoglobulin heavy chain; LN, lymph node; M, male; mos, months; MPO, myeloperoxidase; ND, not done; NHL, non-Hodgkin lymphoma; TCR, T cell receptor, yrs, years.

—, negative; +, positive.
none of cutaneous cases had mediastinal lesions. Analysis of additional precursor NK cell leukemia patients will be necessary to more fully define the clinicopathologic features of this disease in pediatric patients.

A standard treatment protocol for precursor NK cell leukemia has not been established. The study by Suzuki et al. [9] showed that adult patients with both cutaneous and non-cutaneous forms responded initially to chemotherapy for lymphoid malignancies, but recurrence was frequent and prognosis of patients with the non-cutaneous form was significantly less favorable. All pediatric patients reviewed in this report received therapy for acute lymphoblastic leukemia (ALL), except our case who received NHL therapy and case 4 in Table I who was treated with cyclophosphamide, doxorubicin, vincristine, and prednisone. Two patients died of disease. Two patients received allogeneic bone marrow transplant in addition to chemotherapy and achieved complete remission for 2–3 years. Additional pediatric experience is necessary to determine if allogeneic bone marrow transplant in the first clinical remission is the optimal therapy for pediatric patients with this rare disease.

REFERENCES


