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Case Report

Pediatric Philadelphia-positive B lymphoblastic leukemia with CD56 expression and L2 morphology: Case report and review of the literature

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ABSTRACT

We present a unique case of pediatric B lymphoblastic leukemia with Philadelphia chromosome, CD56 expression, and predominantly L2 morphology. A review of the current literature demonstrates that this distinct combination of features is rare and may portend a worse prognosis, although there are too few cases to determine whether these features are prognostically independent of one another.

1. Introduction

B lymphoblastic leukemia (B-ALL) is predominantly a disease of children and typically presents with cytopenias and increased blasts in the peripheral blood and bone marrow [1]. The lymphoblasts are most commonly small and round with smooth chromatin and scant cytoplasm (L1 morphology). Less commonly, the blasts appear larger and more monocytoid with irregular nuclear contours and folds (L2 morphology), which could be confused with acute myeloid leukemia. The typical immunophenotype includes B-lineage markers such as CD19, cytoplasmic CD79a, and cytoplasmic CD22, as well as markers of immaturity such as CD10, CD34, and nuclear TdT. Aberrant non-B-cell antigen (i.e. CD13, CD33, etc.) expression does occur, though the expression of CD56 is exceedingly rare. A Philadelphia chromosome [t(9;22) BCR-ABL1 translocation] is uncommon in pediatric B-ALL and is frequently associated with aberrant myeloid antigen expression, sometimes to such an extent that a diagnosis of mixed phenotype acute leukemia is considered. Historically this rare B-ALL variant portended a very poor prognosis [2,3], but with the advent of tyrosine kinase inhibitor therapies, its overall survival has improved [4]. Here we present a unique case of pediatric B-ALL with a combination of rare features and review the literature for other cases with similar features.

2. Case presentation

A 6-year-old previously healthy boy presented to the local emergency department following one week of fatigue, fever, and a syncopal episode. CBC at the time revealed a hemoglobin of 4.1 g/dL, leukocytes 8.8 $\times 10^9$/L, platelets 225 $\times 10^9$/L, and 0.43% reticulocytes. The peripheral smear was normal, and hemolysis workup was negative. He was admitted to our hospital overnight for a red blood cell transfusion, and was later dismissed the following morning with a hemoglobin of 9.8 g/L and a presumptive diagnosis of transient erythroblastopenia of childhood. At follow-up two weeks later his CBC was improved with hemoglobin 9.7 g/L, leukocytes 6.5 $\times 10^9$/L, and platelets 565 $\times 10^9$/L. He was transfused two weeks later when a local CBC revealed hemoglobin 7.3 g/L. He returned for follow-up at our institution six weeks from initial presentation, at which point CBC revealed a hemoglobin of 8.6 g/L, leukocytes 20.3 $\times 10^9$/L, platelets 49 $\times 10^9$/L, and 37% circulating blasts which were confirmed by peripheral blood smear review.

Bone marrow aspirate smear showed 70% blasts with dimorphic morphology (Fig. 1A, Wright-Giemsa stain, 1000× oil) including a few smaller blasts with smooth chromatin and scant cytoplasm and a majority of larger monocytoid blasts with finely reticulated chromatin, prominent nucleoli, and delicate nuclear folds (Fig. 1A, inset). The blasts were negative for myeloperoxidase (MPO), butyrate esterase, and chloroacetate esterase by cytochemical stains, arguing against myeloid or monocytic origin. By flow cytometry, the blasts were positive for CD34, CD19, CD10 (partial), CD45 (dim), CD13, HLA-DR, CD56 (partial), CD38, nuclear TdT, cytoplasmic CD22 (dim), cytoplasmic CD79a, CD9 (partial), and CD66c (partial). They were negative for CD2, CD3, CD7, CD15, CD16, CD20, CD33, CD36, CD64, CD117 and cytoplasmic MPO.

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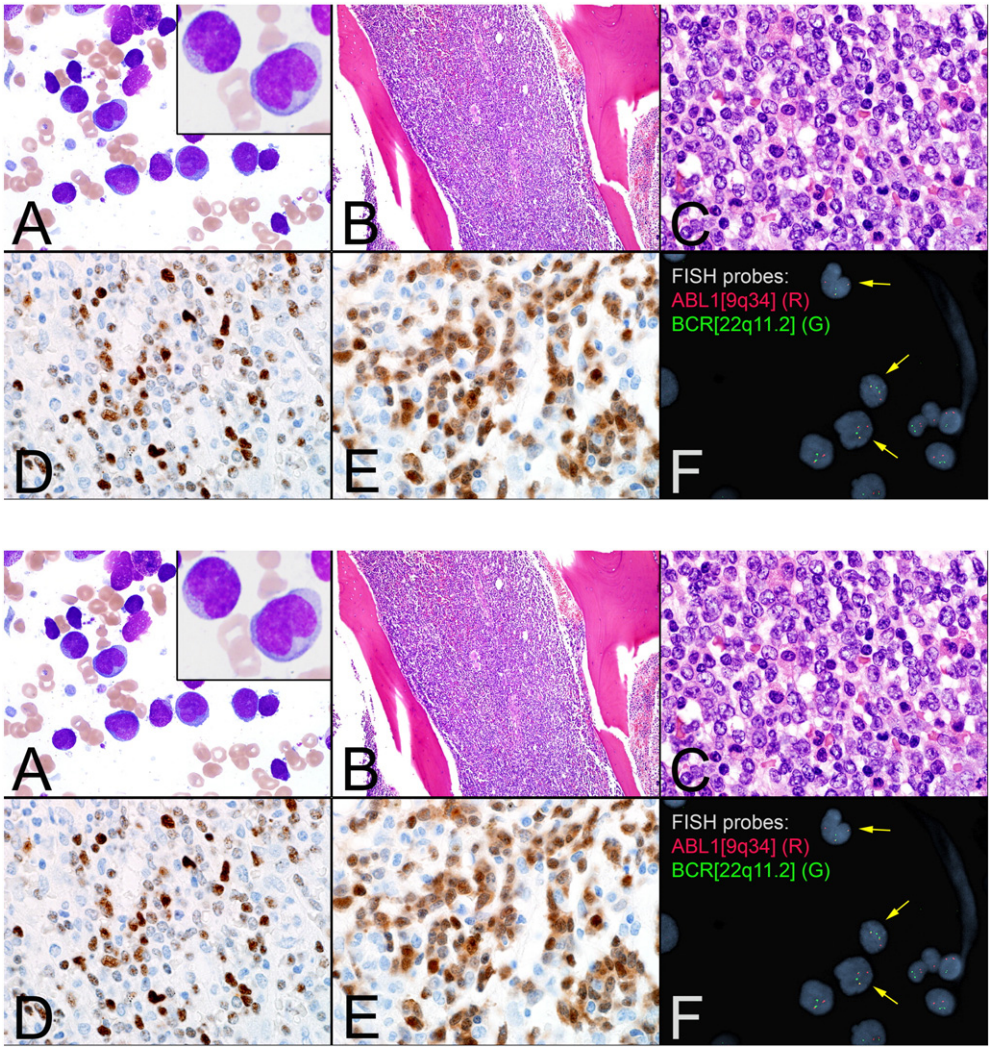

Fig. 1. Morphologic, immunohistochemical and cytogenetic features of the present case. A: Wright-Giemsa stain of bone marrow aspirate smear. Both L1 and L2 morphologic types of lymphoblasts are seen (the L2 type blasts at a higher magnification are demonstrated in the insert). B: Low magnification of H&E stained bone marrow biopsy demonstrates hypercellularity. C: High magnification of H&E stained bone marrow biopsy shows small (L1 type) and large, irregular-shaped (L2 type) blasts. D and E: Immunohistochemical stains of PAX5 and TdT show that both L1 and L2 blasts are positive for PAX5 and TdT, respectively. F: FISH studies confirmed the *BCR-ABL1* fusion. Probe *BCR* is red (R), and probe *ABL1* is green (G). Arrows point to the blasts that contain positive fusion signals.

The bone marrow was hypercellular with sheets of blasts ranging in size from small to intermediate and with open chromatin, prominent nucleoli, and monocytoid morphology (Fig. 1B, H&E, 100× and Fig. 1C, H&E, 1000× oil). Both the small blasts and monocytoid blasts were positive for PAX5 (Fig. 1D, 1000× oil) and nuclear TdT (Fig. 1E, 1000× oil), but were negative for CD68 (not shown). Conventional cytogenetics revealed a t(9;22) and an unbalanced t(1;7) resulting in a duplication of 1q (46,XY,t(9;22)(q34;q11.2)[3]/46,idem, der(7)t(1;7)(q11;q36)[16]/46,XY[1]). FISH studies confirmed the *BCR-ABL1* fusion (Fig. 1F, arrows) and a duplication of 1q23 (not shown) in both the small and monocytoid blasts. Based on these data, a diagnosis of Philadelphia-positive B lymphoblastic leukemia was made. The patient's cerebrospinal fluid (CSF) was not involved by leukemia.

He underwent induction chemotherapy plus imatinib, complicated by febrile neutropenia. His day 28 and day 40 bone marrows were morphologically negative but showed 1.15% and 0.2% residual leukemic blasts demonstrated by flow cytometry analysis. He received two cycles of consolidation therapy with imatinib, after which a bone marrow biopsy was positive for 0.01% *BCR-ABL1* transcripts (p190) by quantitative mRNA analysis but negative by morphologic and cytogenetic methods. He received re-induction chemotherapy at the time of this report.

3. Discussion

Historically, B-ALL was classified by morphology [5] which included L1 (smaller blasts with scant cytoplasm) and L2 (larger blasts with monocytoid cytologic features) classifications. L2 morphology is much less common, being found in approximately 10–15% of cases [6–11]. Patients with L2 morphology tend to be older children and are more likely to be pro-B-ALL than patients with L1 morphology [8,9,12,13]. L2 morphology may be mistaken for monocytic differentiation, especially in the presence of CD56 expression. Thus immunochemical and cytochemical stains should be employed to exclude this possibility. L2 morphology is associated with poor prognosis and delayed early response to therapy as shown in this case, although it is less clear whether cytomorphology is independently prognostic when other clinical and cytogenetic features are also considered [6–11,13,14].

Three unique features of the case are the expression of CD56 by the neoplastic lymphoblasts, the Philadelphia chromosome, and predominantly L2 morphology. To our knowledge, there are a total of 28 reported cases of B-ALL with CD56 expression, including the present case [15–19]. Although rates vary by study population, the overall occurrence of CD56 expression in B-ALL is 3.3% (range 1–12%) (Table 1). In contrast to adult B-ALL, the t(9;22) BCR-ABL1 translocation as seen in this case