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Case Report

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B Cell Acute Lymphoblastic Leukemia Associated with t(8;22)(p11.2q11.2): Role of Additional Cytogenetic Anomalies

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ABSTRACT

B lymphoblastic leukemia (B-ALL) may be associated with recurrent cytogenetic and molecular abnormalities. We describe the fourth-known case of B-ALL associated with the t(8;22)(p11.2q11.2) – a translocation seen more frequently in T lymphoblastic leukemia and acute myelogenous leukemia. This patient's leukemia involves a combination of additional cytogenetic anomalies not yet described in the literature, including del(11)(q13q23), add(9)(p22), and monosomy 7. Given the role in B cell differentiation of genes in the affected regions, including MEN1 (11q13), ATM (11q22), ETS1(11q23), MLL (11q23), AF9 (9p22), and IKZ-F1 (7p12), this case may provide further insight into B cell leukemogenesis associated with the t(8;22). Deletion or mutation of these genes may be critical in targeting the B cell population, and this cytogenetic profile of a B-ALL suggests additional gene targets for diagnostic and therapeutic consideration.

INTRODUCTION

B cell acute lymphoblastic leukemia (B-ALL) may be associated with recurrent cytogenetic and molecular abnormalities. We describe the fourth-known case of B-ALL associated with the t(8;22)(p11.2q11.2) [1-3]. In addition, this B-ALL has associated cytogenetic anomalies not yet described in the literature; a del(11)(q13q23), an add(9)(p22), and a monosomy 7 were also present. Important gene groups for B cell differentiation were identified on these chromosomes, which may provide further insight into B cell leukemogenesis associated with the t(8;22).

CASE REPORT

The patient, a 78-year-old woman, presented with a two-week history of chest pain, shortness of breath, and severe abdominal pain with accompanying nausea and night sweats. The complete blood count (CBC) revealed a leukocytosis and thrombocytopenia [white blood cell count (WBC) 70.93x10^3/ul and platelets 13x10^3/uL] as well as anemia (hemoglobin 9.7g/dL and hematocrit 29.5%). Evaluation of the peripheral blood smear revealed 60% blasts. The blasts on the peripheral smear were intermediate in size with a high nuclear/cytoplasmic ratio, ovoid to irregular nuclei with fine chromatin, and with inconspicuous nucleoli and scant blue cytoplasm (Fig 1A).

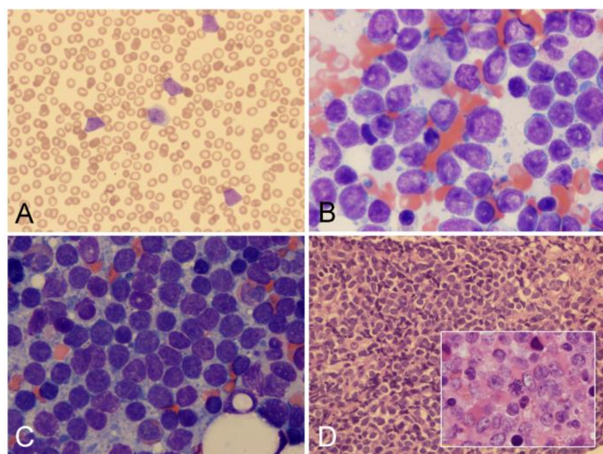

Figure 1: Blast cells in peripheral blood: Wright-Giemsa stain, 50x (A). Bone marrow aspirate: Wright-Giemsa stain, 50x (B,C). Bone marrow: hematoxylin and eosin stain, 40x (D), mitotic figure of leukemic blast, hematoxylin and eosin stain,100x (D inset).

Approximately 90-100% of the cells in the bone marrow aspirate were blasts similar to those observed in the peripheral blood (Fig 1B,C). The bone marrow biopsy was hypercellular (90-100%) with a monotonous infiltrate of blasts with frequent mitotic figures (Fig 1D). Flow cytometric analysis of the peripheral blood revealed a blast population that was CD 10, 19, 20, 33, 34 and HLA-DR positive, consistent with B-ALL. Immunohistochemical staining of the bone marrow core biopsy confirmed a population of CD34, CD10, CD79a and CD20 positive cells (Fig 2).

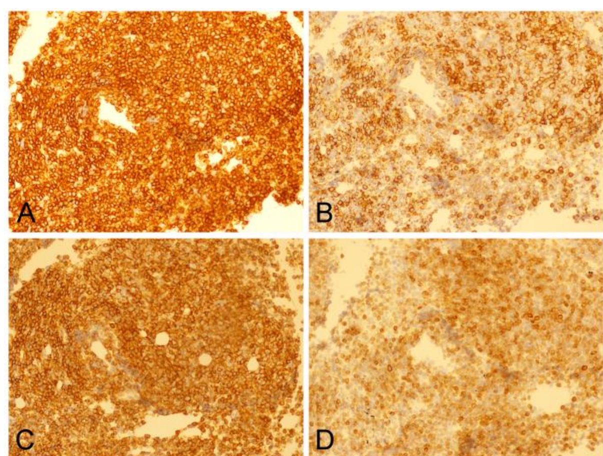

Figure 2: Immunohistochemical staining of the bone marrow core biopsy: CD10 (A), CD20 (B), CD34 (C), CD79a (D). (All at 20x.)

Cytogenetic analysis revealed a t(8;22)(p11.2;q11.2) in all metaphases analyzed. In addition to the translocation, 30% of this cell population had additional chromosomal abnormalities, including del(11)(q13q23), add(9)(p22) and monosomy 7. FISH showed no fusion of ETV6 (TEL; 12p13) and RUNX1 AML1; 21q22) regions. The patient received Rituximab, to which she had an anaphylactic reaction. She refused further chemotherapy and was lost to follow-up.

DISCUSSION

B-ALL is a neoplasm of lymphoblasts committed to the B-cell lineage. The genetic profile of the blasts is of critical importance regarding prognosis and therapeutic management of the leukemic process. Considering this, the World Health Organization has classified certain subgroups of B-ALL according to the chromosomal translocation expressed by the malignant population of cells. There are several such translocations commonly associated with B-ALL, such as such as t(9;22) and t(12;21). These translocations produce identifiable fusion proteins, the downstream affects of which are thought to influence features of this leukemia. Whereas this has been helpful for estimating patient outcome and determining treatment regimen, it does not necessarily provide reliable insight into the initial steps of leukemogenesis. The translocation associated with a lesion may be sufficient to drive cancer pathogenesis, but a direct correlation between translocation expressed and the leukemia it produces is inconsistent [4]. This suggests that along with the chromosomal translocation, additional genetic mechanisms are involved in determining which blast population is affected and at which stage the cells are arrested.

The translocation t(8;22)(p11.2q11.2) has been shown to produce a fusion protein, combining regions of the gene coding for fibroblast growth factor receptor 1 (FGFR1) with regions of the gene coding for breakpoint cluster region (BCR). Constitutive activation of the FGFR1 kinase region is generated by the relocation of this region to a location downstream of the BCR region in t(8;22)(p11.2q11.2). The activity of this fusion protein has been previously shown to arrest the neoplastic population at an early B-cell stage [5]. In addition, it allows this population to proliferate in a cytokine independent manner [6] conferring oncogenic potential. The mechanisms underlying these capabilities have yet to be fully elucidated, but studies have identified some aspects of the molecular activity. For example, the BCR-FGFR1

protein has been shown to constitutively activate STAT5, which may underlie the cytokine independence of the cells and the subsequent ability of this population to survive and expand [7].

Despite this evidence that BCR-FGFR1 has the ability to manifest in a B-cell population, the diagnosis in the majority of reported cases with the translocation producing this fusion protein has clinical features that resemble chronic myelogenous leukemia (CML). This disease is aggressive and rapidly evolves to acute myelogenous leukemia (AML) or less commonly to T lymphoblastic leukemia (T-ALL). Understanding the leukemogenesis in this case of B-ALL, then, necessitates a closer look at the other cytogenetic anomalies identified in the blast population and their potential contribution to the actions of the BCR-FGFR1 fusion protein.

Here, we consider the cytogenetic profile of the presented case. In addition to the t(8;22)(p11.2;q11.2) karyotype, 30% of the cells revealed three additional chromosomal abnormalities, del(11)(q13q23), add(9)(p22) and monosomy 7. Each of these affected regions harbors genes that participate in normal B cell development, and deletion or mutation within these gene regions may therefore have implications in the pathogenesis or progression of this B cell leukemic process. Within the region of the 11q deletion, there are several candidate genes including MEN1 (11q13), ATM (11q22), ETS1(11q23), and MLL (11q23) that have been shown to play critical roles in B cell differentiation.

The MEN1 gene codes for menin, a protein involved in regulation of B lymphoid progenitor differentiation by regulating Hoxa9 expression. Loss of menin function has been associated with impaired B lymphoid progenitor development. In addition, the interaction of menin with MLL fusion proteins is well-documented and may be of interest in our case, as MLL is also within the region of the 11q deletion. The MLL protein is an important component of hematopoiesis -- it acts as part of a complex of proteins that also includes menin to dictate cell fate of progenitor cells through Hox gene expression regulation [8]. Disruption of the MLL gene at 11q23 is characteristic of well-recognized subsets of acute leukemia, often associated with blast cells that generate MLL fusion proteins. The blast populations produced are arrested at an early progenitor stage and proliferate in response to increased levels of Hox9, itself driven by MLL fusion proteins. MLL translocation can be cryptic, often presenting as an 11q23 deletion, detectable only if further studies are performed, such as multiplex FISH analysis [9]. Additional analysis was not performed in this case; however, especially with the finding of addition at 9p22 harboring AF9, a frequent MLL fusion partner, identification of MLL translocation in this cell population may have had implications for diagnosis and treatment.

ATM, ETS1 and IKZ-F1 gene deletions have also been linked to leukemic B-cell transformation. Deletion of these genes interfere with pre-B cell receptor function, inhibiting signaling that is critical to induce the switch from early B cell proliferation to differentiation [10-12]. Of note and relevant to the monosomy 7 present in the current report, IKZ-F1(7p12.2) may be particularly important in targeting B-cells for transformation to leukemia. IKZ-F1 codes for Ikaros, a protein that is required for the ability of the pre-B cell receptor to induce B-cell differentiation, possibly through activation of SLP-65. Deficiency of SLP-65 has been linked to pre-B cell proliferation and pre-B-cell leukemogenesis. The applicability of this information may be further clarified through consideration of recent data examining mechanisms underlying BCR-ABL positive B-ALL. BCR-ABL+ leukemia most often manifests as a chronic myelogenous leukemia. However, recent data comparing the complete cytogenetic profiles of BCR-ABL B-ALL and BCR-ABL CML has revealed the presence of an IKZ-F1 mutation in 84% of BCR-ABL- induced B-ALL, a mutation not seen in the myelogenous leukemia type with this fusion protein. The literature on BCR-FGFR1-induced B-ALL is comparatively sparse. However, Baldazzi et al also described monosomy 7 as part of the cytogenetic profile in their case report of B-ALL with a t(8;22)(p11.2q11.2) [1].

CONCLUSION

Our case suggests that the mechanism of B-ALL with t(8;22)(p11.2q11.2) is multifactorial. This particular cytogenetic profile of B-ALL suggests additional gene targets for diagnostic and therapeutic consideration. In addition, alteration

of genes critical for B cell differentiation provides insight into how the 8;22 translocation, more commonly seen in myelogenous as well as T cell leukemia, may also be associated with disruptions in B cell leukemogenesis.

CONFLICTS OF INTEREST

All authors have no conflicts of interest.

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