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CASE REPORT

B-acute lymphoblastic leukemia/lymphoma (B-ALL) with precedent or concurrent myelodysplastic syndrome (MDS) with deletion 5q

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Abstract Progression to acute leukemia is an inherited feature of myelodysplastic syndrome (MDS). While majority of acute leukemia cases in this setting is acute myeloid leukemia (AML), rare cases of acute B-lymphoblastic leukemia/lymphoma (B-ALL) also exist. Therefore, detection of increased blasts in a patient with MDS should not be equated with a diagnosis of AML; full immunophenotyping of blasts is required. Previous reports indicate that dysplastic myeloid cells and B-lymphoblasts belong to the same clone. However, dysplastic myeloid cells and B-lymphoblasts could be clonally unrelated. Decitabine in addition to hyperCVAD (fractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone alternating with high-dose methotrexate and cytarabine) could be a good treatment option in this particular clinical setting.

Keywords MDS · B-all · Del (5q)

Introduction

Myelodysplastic syndrome (MDS) is a clonal hematopoietic disease characterized with ineffective hematopoiesis (cytopenia), morphologic dysplasia in hematopoietic cells and increased risk of transformation to acute leukemia [1]. While extremely rare cases of acute B-lymphoblastic leukemia/lymphoma (B-ALL) in patients with MDS have been described, the overwhelming majority of acute leukemia cases in this setting is acute myeloid leukemia (AML). Therefore, there is a potential danger to attribute the increased blasts in a patient with MDS to AML without proper immunophenotyping of blasts. Herein, we present two patients with B-ALL arising in a patient with precedent MDS and a patient with co-existing B-ALL to raise awareness of this rare incidence.

Clinical history

Patient 1

A 68 year old man presented with progressive macrocytic anemia and thrombocytopenia in December 2014. Bone marrow biopsy revealed refractory cytopenia with multilineage dysplasia in 12/2014 according to 2008 WHO classification system. Ring sideroblasts were present in 25% of nucleated red cell precursors. Conventional karyotype demonstrated 46,XY,del(5)(q22q35)[7]/46,XY[13]. No significant mutations were detected in 28 tested genes by our clinically validated next generation sequencing-based assay (CM28) [4]. He was treated with lenalidomide 10 mg orally daily and achieved cytogenetic remission in the following bone marrow biopsy in 04/2015 although anemia and thrombocytopenia persisted. The patient had been stable, transfusion independent and tolerated lenalidomide therapy except diarrhea. In April 2017, when patient came for follow-up visit, he had underwent a follow-up bone marrow biopsy.

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Patient 2

An 81 year old woman complained of 4-month history of progressive fatigue and weakness. Peripheral blood demonstrated pancytopenia with hemoglobin 9.2 g/dL, hematocrit 28.3%, WBC 2.0 × 10^9/L (neutrophils 53%, metamyelocytes 2%, blasts 1%, lymphocytes 40%, monocytes 3%, and eosinophils 1%) and platelet 55 × 10^9/L. Bone marrow biopsy was performed in 07/2015 to evaluate pancytopenia.

Materials and methods

Immunohistochemistry

After the tissue blocks were formalin-fixed, they were embedded in paraffin, then cut in 4-μm-thick sections and processed with heat-induced epitope retrieval. Immunohistochemical staining was performed in an automated immunostainer (Ventana Medical Systems, Tucson, AZ). Assessed antibodies against the following antigens were CD3 (Dako), CD10, CD11c, CD19, CD20 (Dako), CD22, CD34 (BD Biosciences), CD61, CD79a (Dako), MPO and TdT (Novoscatra/ Leica).

Flow cytometry immunophenotyping

Flow cytometric immunophenotyping was performed using bone marrow aspirate as described previously [5]. Routine flow cytometry immunophenotypic analysis for B-acute lymphoblastic leukemia included a comprehensive panel of markers including: CD2, cytoplasmic CD3, surface CD3, CD4, CD5, CD7, CD8, CD10, CD11b, CD13, CD14, CD15, CD16, CD19, CD20, CD22, CD25, CD33, CD34, CD36, CD38, CD41, CD45, CD56, CD64, CD66c, cytoplasmic CD79a, CD117, CD123, HLA-DR, MPO, TdT, cytoplasmic IgM, CRLF2, Kappa and Lambda immunoglobulins.

Cytogenetic analyses

Conventional chromosome analysis (karyotyping) was performed on G-banded metaphase cells prepared from unstimulated 24-h and 48-h bone marrow cultures as described previously [6].Twenty metaphases were analyzed. Karyotype was written following the current International System for Human Cytogenetics Nomenclature [7]. Fluorescence in situ hybridization performed using probes for *BCR-ABL1*, *MYC* and chromosome 5 when necessary.

Array CGH

Extracted DNA is digested, labeled and subjected to microarray-based comparative genomic hybridization (array CGH) versus a reference sample using an oligonucleotide genomic array (4 × 180 K format) targeting cancer genes (human genome build 19) as described previously [8]. The Agilent GeneChip microarray scanner was used for imaging and data analysis was performed using Cytogenomic workbench software. The findings were reported using ISCN 2016 recommendations [7].

Next-generation sequencing

Next-generation sequencing to assess mutational hotspots in 28 genes (*ABL1, ASXL1, BRAF, DNMT3A, EGFR, EZH2, FLT3, GATA1, GATA2, HRAS, IDH1, IDH2, IKZF2, JAK2, KIT, KMT2A, KRAS, MDM2, MPL, MYD88, NOTCH1, NPM1, NRAS, PTPN11, TET2, TP53*, and *WT1*) was performed on the bone marrow aspirate specimens using a MiSeq sequencer (Illumina, San Diego, CA) as described previously [4].

Results

Patient 1

Peripheral blood showed pancytopenia with hemoglobin 9.9 g/dL, hematocrit 31.3%, white blood cell (WBC) 2.4 × 10^9/L (neutrophils 30%, lymphocytes 60%, monocytes 3%, and eosinophils 7%) and platelet 64 × 10^9/L. No circulating blasts were present. Bone marrow was hypercellular (90%) for his age and sheets of immature cells replaced hematopoietic cells (Fig. 1-A). Numerous (54%) blasts were present in bone marrow aspirate smears, which were variable in size with vesicular chromatin, slightly irregular nuclear contours, small nucleoli, and agranular cytoplasm without Auer rods (Fig. 1-B). Cytochemical stain for myeloperoxidase was negative in blasts. Background hematopoietic cells were decreased, but dysplasia was present in all three lineages. Ring sideroblasts were seen in 62% of nucleated red cell precursors (Fig. 1-C). By immunohistochemistry, the blasts expressed PAX-5 and TdT. CD3 was negative in the blasts.

Flow cytometry using bone marrow aspirate sample demonstrated B-lymphoblasts accounting for 17.2% of total cell analyzed, which were positive for CD4 (partial), CD19, CD22 (partial), CD25 (partial), CD33 (partial), CD34, CD38, CD45 (dim), CD66c (partial), cytoplasmic CD79a, CD123, HLA-DR, and TdT (Fig. 1-D). The immature population was negative for CD2, cytoplasmic CD3, surface CD3, CD5, CD7, CD10, CD13, CD14, CD15, CD20, CD36, CD41, CD56, CD64, CD117, cytoplasmic IgM, CRLF2 and myeloperoxidase.

Conventional karyotype showed 46,XY[20]. Fluorescence in situ hybridization (FISH) was negative for *BCR-ABL1* rearrangement and del (5q31) or monosomy 5. CM28 (NGS

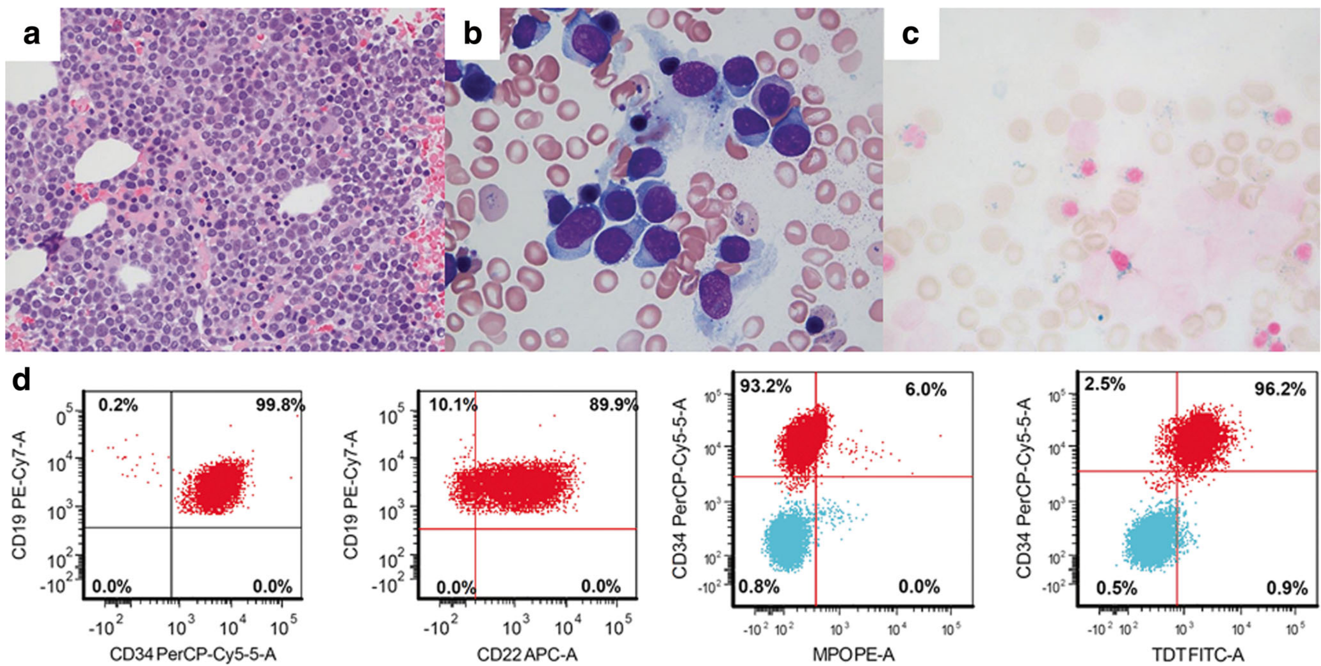

Fig. 1 Bone marrow and flow cytometry findings in patient #1. 1-A. Sheets of immature cells replace hematopoietic cells (Hematoxylin and eosin, 400X). 1-B. Blasts are variable in size with vesicular chromatin, slightly irregular nuclear contours, small nucleoli, and agranular cytoplasm without Auer rods (Wright-Giemsa stain, 1,000X with oil). 1-C. Ring sideroblasts are commonly seen in the nucleated red cell precursors (Iron stain, 1,000X with oil). 1-D. Blasts (red population) are B-lymphoblasts based on flow cytometric immunophenotyping (CD19+, CD34+, CD22+, TdT+ and MPO-). Blue population depicts mature lymphocytes. MPO; myeloperoxidase, TdT; Terminal deoxynucleotidyl transferase

panel) detected *EZH2* p.L71* [4]. Microarray-based comparative genomic hybridization (array CGH) did not detect any aberrations.

The patient is under treatment with hyperfractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone alternating with high-dose methotrexate and cytarabine (hyperCVAD). A day-21 BM showed persistent MDS with positive minimal residual disease for B-ALL (0.19% of total analyzed events).

Patient 2

Bone marrow was hypercellular (80%–100%) for her age with sheets of blasts. The blasts were intermediate-sized and had open chromatin and scant cytoplasm (Fig. 2-A). Bone marrow aspirate smears show numerous blasts with open chromatin, inconspicuous nucleolus and scant agranular basophilic cytoplasm without Auer rods (Figs. 2-B). Dysplasia is present in all three lineages of hematopoietic cells. Iron stain on bone marrow aspirate smear revealed no ring sideroblasts.

Immunohistochemical stains demonstrated that the blasts express CD19, CD20, CD22, CD34, CD79a and TdT, consistent with B-lymphoblasts (Figs. 2-C). The blasts were negative for CD3, CD10, CD11c, CD61 and MPO immunohistochemically. Flow cytometry using bone marrow aspirate sample showed a distinct population of B-lymphoblasts accounting for 7% of total cells analyzed, which were positive for CD10 (dim/partial), CD13 (dim/partial), CD19, CD20, CD33 (dim/partial), CD34, CD38 (decreased), CD45 (dim), TdT, and HLA-DR (decreased). They were negative for CD2, cytoplasmic CD3, surface CD3, CD4, CD5, CD7, CD11b, CD14, CD56, CD64, CD117, CD123, myeloperoxidase, and immunoglobulin kappa and lambda light chain (Figs. 2-D).

In addition, a small population of aberrant myeloid blasts was also present. The aberrant myeloblasts were positive for CD13 (decreased), CD33, CD34 (decreased), CD38 (dim), CD117, CD123 (decreased), and HLA-DR (decreased). Abnormal patterns and abnormal antigen expression in myelomonocytic cells were also present. No immunophenotypically abnormal T cells were detected.

Conventional karyotype demonstrated 46,XX,del(5)(q13q33)[14]/46,XX[6]. FISH was positive for del (5q31) [29/200]. Del (5q)-harboring cells were dysplastic myelocytes and granulocytes, not lymphoblasts. FISH was negative for *BCR-ABL1* and *MYC* rearrangements. CM28 detected *TP53* p.Y126C and *TET2* p.I1762fs. Array CGH showed loss of 5q14.3-q34.

Patient was treated with mini-hyperCVD (50% dose reduction in cyclophosphamide and dexamethasone and 75% dose reduction in methotrexate compared to hyperCVAD), ofatumumab and decitabine. A day-28 bone marrow showed no morphologic support for acute leukemia, but flow cytometry demonstrated persistent B-lymphoblasts

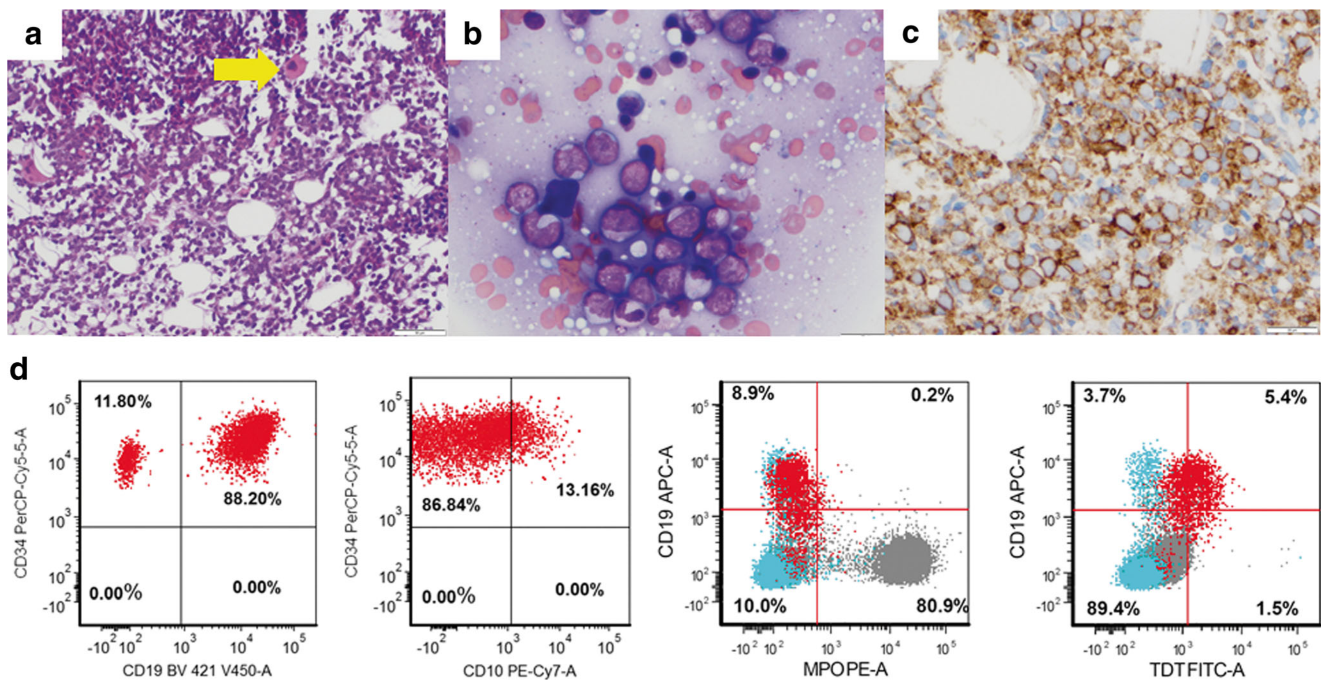

Fig. 2 Bone marrow and flow cytometry findings in patient #2. 2-A. Numerous immature cells replace hematopoietic cells. Dysplastic megakaryocyte (yellow arrow) is present (Hematoxylin and eosin, 200X). 1-B. Blasts are large-sized cells with high nuclear: cytoplasmic ratio, open chromatin and occasional cytoplasmic vacuoles (Wright-Giemsa stain, 500X). 1-C. CD34 expression is seen in the blasts (TdT stain, 500X). 1-D. Blasts (red population) are positive for CD19+, CD34+ , CD10 (dim/partial), TdT+ and MPO-, consistent with B-lymphoblasts. Blue and gray populations depict mature lymphocytes and granulocytes, respectively. MPO; myeloperoxidase, TdT; Terminal deoxynucleotidyl transferase

(0.01% of total analyzed events). Conventional karyotype showed 46,X,t(X;18)(q22;p11.3),del(5)(q13q33)[1]/46,XX[19]. Sanger sequencing for *TP53* detected p.Y126C mutation. Additional follow-up bone marrow study was not performed. Following 8th cycle of her treatment (19 months from B-ALL diagnosis), she succumbed to death due to sepsis.

Discussion

We report two rare cases of patients with B-ALL and MDS. One patient has a previous history of MDS, treated with lenalidomide, who later developed B-ALL in the background of MDS. The other patient presented with concurrent B-ALL and MDS de novo. Progression to B-ALL from MDS is exceedingly rare [2, 3, 10, 12–18]. Previously published literature suggests that dysplastic myeloid cells and B-lymphoblasts belong to the same clone. Three and two patients had del(5q) and trisomy 8 at the time of MDS, respectively, which were also present when B-ALL occurred [12–15, 18]. Abruzzese et al. further demonstrated that particular cytogenetic abnormality (+8) is present not only in myeloid cells but in B-lymphoblasts in a patient who sequentially developed B-ALL after MDS [12]. However, MDS and B-ALL appears to be independent events in the current two patients. The first patient showed MDS with del(5)(q22q35), but it was not seen by conventional karyotype as well as FISH when he developed B-ALL. The second patient showed del(5)(q13q33), but this abnormality was only seen in myeloid cells based on morphology-correlated FISH. These data indicate that dysplastic myeloid cells and B-lymphoblasts may be clonally unrelated.

Intriguingly, both patients harbored an interstitial deletion in the long arm of chromosome 5. Although not identical, del(5q) was the sole cytogenetic abnormality in these two patients. Del(5q) in patients with MDS is associated with decreased miR-145 and miR-146a, and inactivation or *EGR1* [19]. MiR-145 and miR-146a target the Toll-IL-1 receptor domain-containing adaptor protein (TIRAP) and TNF receptor-associated factor-6 (TRAF6). Therefore, decreased miR-145 and miR-146a induces elevation of TIRAP and TRAF6, which provides survival advantage via enhanced nuclear factor-κB (NF-κB) activity. *EGR1* is a zinc-finger transcript factor that plays a role in cell growth, development and stress responses. In hematopoietic stem cells (HSCs), EGR1 expression is enriched in the most primitive subset of HSCs. In a murine model, absence of *EGR1* was shown to induce HSC proliferation in the bone marrow [20]. Given the fact that del(5q) appears to be confined to myeloid cells, it seems that del(5q) provides proliferative and survival signals in

some of HSCs and yet unknown second trigger ushers them to proliferation of B-lymphoblasts.

NGS-based assay did not reveal non-random mutations in these patients. Of note, one patient harbored *TP53* p.Y126C. *TP53* mutations in patients with MDS with del(5q) are associated with increased risk of progression to acute myeloid leukemia [11]. Considering the lineage of blasts in current report, *TP53* mutation could be an early event before the lineage of blasts was determined. *EZH2* and *TET2* mutations are quite rare in B-ALL, so it appears that these mutations are from myeloid clones [9, 21].

Both patients were treated mainly for B-ALL, but decitabine was also given to one patient. Decitabine is an FDA-approved drug for patents with MDS, but was also shown to be safe and effective in some patients with ALL [22]. Considering concurrent MDS, addition of decitabine to B-ALL regimen could be a good treatment option, particularly those who cannot tolerate intensive chemotherapy.

Two patients in the current report emphasizes that AML is not the only leukemia arising from or concomitant with MDS. Diligent efforts to accurately determine the lineage of blasts are required even in patients with obvious dysplasia in hematopoietic cells.

Compliance with ethical standards

Conflict of interest Author Jin Woo Joo, Author Sergej Konoplev, Author Timothy J. McDonnell and Author Chi Young Ok declare that they have no conflict of interest.

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