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Case Report

Mixed phenotype acute leukemia, B/myeloid, NOS with near-tetraploidy: a case report

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Abstract: Acute leukemia in adults is usually associated with a myeloid phenotype, and less commonly presents as an acute lymphocytic leukemia. Rarely, the leukemic blast cells express more than one lineage phenotype and satisfy the diagnostic criteria for an acute leukemia of ambiguous lineage (ALAL), further subclassified as mixed phenotype acute leukemia (MPAL). Near-tetraploidy is an unusual presentation of acute leukemia where the blasts contain 80-104 chromosomes. More commonly associated with acute lymphocytic leukemia, near-tetraploidy has been described in only a limited number of cases of acute myeloid leukemias, and near-tetraploid ALAL is rare. We describe the first report of near-tetraploid MPAL, B/myeloid, not otherwise specified.

Keywords: Acute leukemia of ambiguous lineage (ALAL), mixed phenotype acute leukemia (MPAL), B/myeloid, near-tetraploidy

Introduction

Diagnosis of acute leukemia requires integration of morphologic, immunophenotypic, and molecular/cytogenetic findings [1]. Acute leukemia can be diagnosed when bone marrow or peripheral blasts represent ≥ 20% of the nucleated cell differential, or whena cytogenetic abnormality of diagnostic significanceis present [2, 3]. Acute myeloid leukemia (AML) is the most common type of acute leukemia in adults, while acute lymphocytic leukemia is most common in children. In the majority of these cases, leukemic blasts are relatively uniform in terms of morphologic and immunophenotypic features [2]. Rarely, multiple lineage criteria are satisfied in a single diagnostic sample. These cases are classified as acute leukemias of ambiguous lineage (ALAL) in the most recent edition of the WHO Classification of Tumours of Hematopoietic and Lymphoid Tissues [4, 5]. ALAL is further subclassified based on immunophenotype and molecular/cytogenetic abnormalities. The so-called mixed phenotype acute leukemias (MPAL) are diagnosed when more than one blast cell lineage is identified at presentation, namely T/myeloid or B/myeloid, and rarely T/B. MPAL is rare, representing no more than 5% of all acute leukemias [3]. In most reported cases, outcomes for MPAL are inferior to outcomes for AML or ALL, and stem cell transplantation is commonly offered as a mainstay of therapy, despite lack of evidence for treatment [6].

Cytogenetic abnormalities in acute leukemias are common, and may be of prognostic or diagnostic significance. Near-tetraploidy is a nearly complete duplication of the entire genome, and is defined as 81-103 chromosomes. Morphologically, near-tetraploid acute leukemias have characteristically large blast cells [7] and may be associated with erythrophagocytosis [8]. Near-tetraploidy occurs in ~1% of AML cases, where it is thought to portend a worse prognosis [9]. The etiology of the near-tetraploid cytogenetic abnormality is unknown, but likely represents a late karyotypic evolution of diploid cells, and is often found in association with other chromosomal abnormalities [8]. Interestingly, near-tetraploidy may occur more commonly in male patients with certain leukemias [10]. This uncommon cytogenetic abnormality has been reported in a limited number of cases

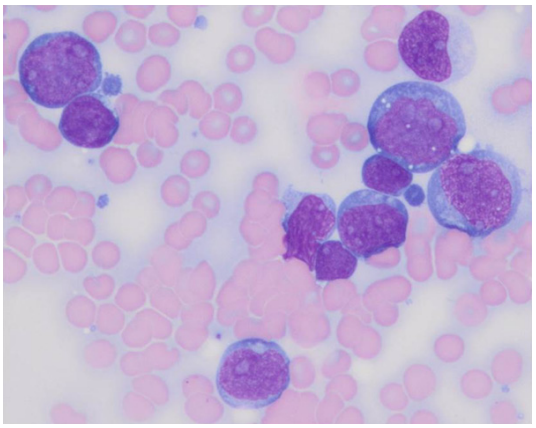

Figure 1. Bone marrow aspirate smear showing predominantly blast cells. The blast cell size varied, with distinctly large and small forms seen. Write-Giemsa, 50× optical magnification.

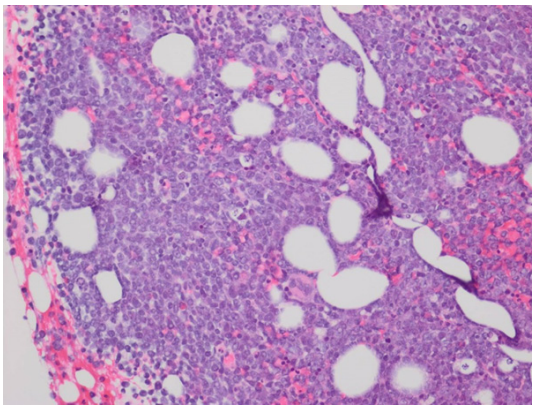

Figure 2. Bone marrow core biopsy section demonstrating a markedly hypercellular bone marrow with predominantly blasts present and markedly decreased trilineage hematopoiesis. Hematoxylin & Eosin, 20× optical magnification.

of ALAL [9, 11]; however, to our knowledge there are no reported cases of near-tetraploid MPAL, B/myeloid, not otherwise specified (NOS).

Case presentation

A fit, active 70-year-old male presented with new onset pre-syncope, night sweats, weakness, weight loss and fatigue that developed over a one-week period. His medical co-morbidities included well-controlled hypertension and dyslipidemia. A small rash of unknown etiology was noted on the abdomen; physical exam findings were otherwise unremarkable.

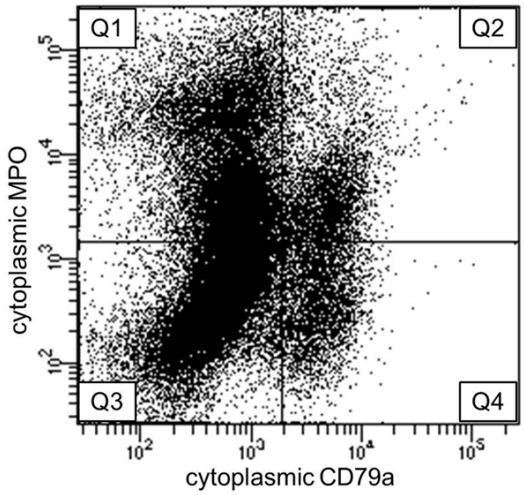

Figure 3. Flow cytometric analysis of the blasts identified cells that are positive for cytoplasmic myeloperoxidase (MPO; Q1 and Q2) and positive for cytoplasmic CD79a (Q2 and Q4). Cells that are negative for MPO and CD79a are also identified (Q3).

A complete blood cell count was significant for pancytopenia. The patient was admitted to hospital and bone marrow specimens were collected. The bone marrow aspirate contained markedly hypercellular bone marrow particles and 80% blasts. There were distinctly large and small blast populations present. The blasts had a high N:C ratio with prominent nucleoli. Some blast cells demonstrated cytoplasmic vacuolation. Auer rods were not seen (**Figure 1**).

The bone marrow biopsyspecimen was markedly hypercellular. There was a significant expansion of blasts and markedly decreased trilineage hematopoiesis (**Figure 2**). The neoplastic cells were positive for CD34, cKIT, TdT, CD79a, PAX5, and myeloperoxidase (MPO) by immunohistochemistry. With flow cytometry, several distinct blast cell lineages were identified including MPO+ (**Figure 3**, Q1 and Q2), CD79a+ (**Figure 3**, Q2 and Q3), and blasts that were positive for both MPO and CD79a (**Figure 3**, Q2). Based on the burden of blasts and their unusual immunophenotypic profile, the patient was diagnosed as MPAL, B/myeloid, NOS.

G-banded karyotyping performed on metaphases obtained from a 24 hour culture prepared from bone marrow aspirate identified an abnormal near-tetraploidy clone presenting with a 91, XXYY, -7 [9]/46, XY [5] karyotype (**Figure 4**). A single metaphase was noted to have a 92, XXYY karyotype. The remaining

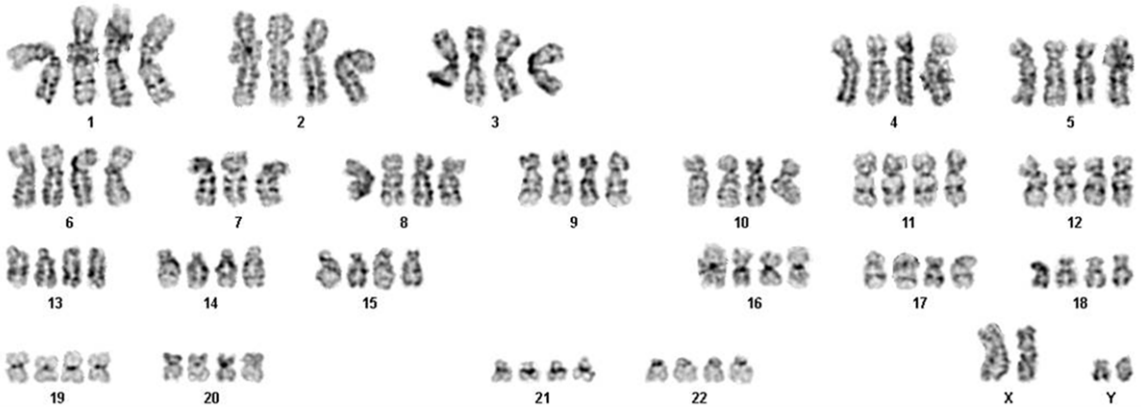

Figure 4. The 91 XXYY abnormal mosaic karyotype, with only 3 copies of chromosome 7, identified in 9 of 15 G-banded metaphases.

5/15 metaphases analyzed demonstrated a normal male 46, XY karyotype.

The patient was given chemotherapy with curative intent. He developed sepsis after Linker IA and required ICU admission. A bone marrow biopsy collected post cycle IA showed no residual acute leukemia. The patient completed cycles IB and IC without complications. Unfortunately, dosing in cycle IIA was reduced due to rising liver enzyme levels, and cycle IIB was not completed due to an invasive fungal rhinosinusitis. No subsequent bone marrow biopsies were performed.

Discussion

Here we report the first identified case of MPAL, B/myeloid, NOS with near tetraploidy. While two reported cases [9, 11] discuss near tetraploidy in leukemia of ambiguous lineage, no literature was available to guide the management of this unique MPAL patient. We turn to other acute leukemia for reference, with a slightly greater pool of evidence. In AML and ALL, a low frequency of tetraploidy has been reported at approximately 1% prevalence [12], and recent literature reviews cite less than 70 tetraploid or near tetraploid cases that have been reported for AML [8]. Morphologically, tetraploidy presents with larger, abnormal blasts consistent with increased nuclear chromosomal material, and is often accompanied by additional gene mutations of chromosomes 5, 7, 1, 2, 3, or 17 [7, 8] One acute leukemia study noted a higher prevalence of tetraploidy in males [10], but with a small sample size of only 13 patients, this may be due to reporting bias.

It is thought that molecular events such as loss of p53 might result in instability of the chromosome, leading to premature DNA synthesis, mitotic arrest and subsequent polyploidy [13]. The p53 gene deletion specifically has been discussed in near-tetraploid or tetraploid hematological malignancy, and was present in 23% of near-tetraploid and tetraploid hematologic malignancies in one study [10]. The mechanisms of this endoreduplication remain unclear, but may be due to S/M uncoupling [10]. Common cytogenetic changes in MPAL include t(9;22)(q34;q11.2) (BCR/ABL1) and 11q23 (MLL) abnormalities [11]; however, our patient did not express any of these.

There is suggestion of favorable prognosis of near tetraploid ALL in children [10, 12]. Among AML adult patients with near tetraploidy, results are more conflicted [7, 9, 10]. Overall, for adults with near-tetraploidy in acute leukemia, there is some evidence to support a worse prognosis compared to non-tetraploid acute leukemia, but an improved prognosis compared to other degrees of ploidy such as triploidy [9, 10]. It has been suggested that the variety of chromosome numbers is suggestive of global cell cycle control defects, and thus poorer response to chemotherapy [9]. Presence of the BCR-ABL translocation in MPAL may contribute to a poorer prognosis, regardless of tetraploidy [11].

An additional interesting cytogentic feature of this MPAL is the trisomy involving chromosome

7, since 4 copies of chromosome 7 would be expected in a tetraploid karyotype. This was the only reported chromosome loss, and was considered to be clonal, since it was seen in 9/15 metaphases analyzed. It is possible that this was a secondary chromosomal loss following the endoreduplication, as we would expect to see only two copies in a primary loss [14]. Six other cases in the literature describe chromosome 7 loss in AML, and one other paper reports a near tetraploidy with hidden monosomy 7 associated with MPAL [14]. We are unsure of the significance of the reduced chromosome 7 copy number in a near tetraploid karyotype in MPAL due to the lack of published examples.

Treatment of MPAL is controversial [11, 14], as the physician must determine whether to use a myeloid or lymphoid protocol, and whether chemotherapy will be followed by a stem cell transplant [11]. There is some evidence suggesting an ALL approach may have a higher response rate [14]. Complete remission was attained in three of five MPAL patients who underwent autologous stem cell transplantation, suggesting a relatively positive outcome for this treatment regimen; however this sample size is small and insufficient to draw a conclusion of efficacy [7]. Our patient responded well to the ALL Linker protocol administered, but was met with multiple serious complications related to the intensive induction chemotherapy. Longer follow-up is required to draw conclusions from the treatment effect.

To our knowledge, this is the first reported case of near-tetraploidy with loss of one chromosome 7in a patient with MPAL, B/myeloid,NOS. Near-tetraploidy in acute leukemia is a rare finding, with a paucity of evidence in MPAL. While there is some suggestion of poorer prognosis among some patients with near-tetraploidy in acute leukemia, the implications of this abnormal karyotype are yet to be determined. An ALL approach with stem cell transplant may be a reasonable treatment consideration for some patients. Further study is needed to optimize the managements of all MPAL patients, including those with near-tetraploidy.

Disclosure of conflict of interest

None.

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