Human Pathology: Case Reports (2016) 3, 12–18

ELSEVIER

Human PATHOLOGY Case Reports

http://www.humanpathologycasereports.com

GATA1 mutation negative acute megakaryoblastic leukemia with acquired trisomy 21 presenting with extensive bone marrow necrosis in an adult: A case report and review of the literature☆,☆☆

Todd P. Williams[1], **Richard D. Hammer MD***

Department of Pathology and Anatomical Sciences, University of Missouri, One Hospital Drive, M214-C MSB, Columbia, MO 65212, United States

Received 6 June 2015; revised 22 August 2015; accepted 2 September 2015

Keywords:
GATA1;
Megakaryocytic leukemia;
Necrosis;
Trisomy 21

Abstract

Context: Acute megakaryoblastic leukemia (AMKL) is a rare myeloid leukemia, occurring in 1%–5% of all adult acute myeloid leukemia (AML) cases. AMKL is characterized by a leukemic blast population positive for factor VIII, CD41a, CD42b, and/or CD61 with extensive myelofibrosis. Although various cytogenetic abnormalities are commonly reported, the association between constitutional trisomy 21 and AMKL has been of particular interest, because of the near universal presence of *GATA1* mutation in such cases.

Objective and Design: We report a case of AMKL in an adult presenting with extensive bone marrow necrosis in which cytogenetic studies revealed three copies of chromosome 21 as part of a complex karyotype; however, sequencing of the *GATA1* gene revealed no mutation.

Results: The patient was an adult male who presented with extensive bone marrow necrosis, making definitive diagnosis difficult. Autopsy studies using a multimodality approach identified AMKL with a complex karyotype, including trisomy 21. Sanger sequencing of the *GATA1* gene showed a germline configuration without a mutation.

Conclusions: To our knowledge, this is the first reported case of an adult with AMKL with acquired trisomy 21 in which the GATA1 mutation was investigated and the second reported case of AMKL presenting with extensive bone marrow necrosis. We will present a diagnostic approach to AMKL in which extensive bone marrow necrosis renders examination of the bone marrow difficult. Furthermore, we will examine the absence of the GATA1 mutation in a case of AMKL with trisomy 21 in an adult.

☆ An abstract of this manuscript was presented at the American Society of Clinical Pathology meeting in Tampa FL on October 8–10, 2014.

☆☆ Financial support was provided by the Department of Pathology and Anatomical Sciences, University of Missouri Medical School, Columbia, MO.

* Corresponding author at: Department of Pathology and Anatomical Sciences, Director, Hematopathology and Coagulation, University of Missouri School of Medicine, One Hospital Drive, M214-C MSB, Columbia, MO 65212, United States. Tel.: +1 573 882 6552, +1 512 699 1261 (cell); fax: +1 573 884 4612.
E-mail addresses: tpwmt4@mail.missouri.edu (T.P. Williams), hammerrd@health.missouri.edu (R.D. Hammer).
[1] University of Missouri School of Medicine.

http://dx.doi.org/10.1016/j.ehpc.2015.09.003

1. Introduction

Acute megakaryoblastic leukemia (AMKL) is rare in adults, occurring in about 1%–5% of all acute myeloid leukemia (AML) cases [1,2]. The diagnosis is typically made from morphologic and immunohistochemical (IHC) analysis of bone marrow aspirate and biopsy, which shows a leukemic blast population identified by IHC for factor VIII, CD41a, CD42b, and/or CD61 with at least $\geq 50\%$ of the blasts being megakaryoblasts, and often accompanied by extensive myelofibrosis demonstrated with a reticulin stain [1–3].

Unlike adults, AMKL is a relatively common form of AML in children, especially those with Down syndrome (DS) who have a 500-fold higher risk of developing AMKL [4]. Several studies have demonstrated that nearly all children with DS-associated AMKL have a mutation in the gene *GATA1*, a transcription factor essential for maturation and apoptosis of megakaryocytes [5–7]. Even though it is apparent that trisomy 21 is a key cytogenetic abnormality that predisposes to the development of AMKL in children, relatively few cases of adult AMKL without DS show a somatic gain of chromosome 21, such that there is no significant association between a somatic gain of chromosome 21 and the development of adult AMKL [8]. A search of the Mitelman database of chromosome aberrations and gene fusions in cancer showed 179 cases of adult AMKL and only 15 cases with a somatic gain of chromosome 21, and 10 of these 15 cases showed a complex karyotype (with at least 3 chromosomal aberrations). None of these cases showed somatic gain of chromosome 21 as a sole abnormality [9]. Only one reported case of adult AMKL has demonstrated a mutation in *GATA1*, and this patient did not have acquired trisomy 21 [6,10].

We report a case of a 54-year-old male that presented with pancytopenia and severe back pain. Cytogenetic analysis revealed a complex karyotype, including trisomy 21. The extensive marrow necrosis made for a challenging work-up; however, a diagnosis of AMKL was made at autopsy by examining extramedullary sites involved by leukemia with electron microscopy and IHC stains. This is only the second report of AMKL presenting with extensive bone marrow necrosis (the previous report was presented in 1984) [11], and the first report of an adult patient with AMKL and acquired trisomy 21 in which the GATA1 mutation was investigated.

2. Materials and methods

Approval was obtained from the institutional IRB at the University of Missouri Hospitals and Clinics, Columbia, Missouri. Bone marrow and paraffin embedded H&E slides were prepared by standard methods. Immunostaining was performed following the standard protocol on a Dako Immunostainer (Dako, Carpinteria, CA). Flow cytometric immunophenotyping was performed on a FacsCanto II flow cytometer (Becton-Dickinson, Franklin Lakes, NJ) using standard protocols. Cytogenetic studies were performed at Mayo Laboratories (Rochester, NY). Extracted DNA from autopsy tissue that was 85%–90% viable and 80% involved with AMKL was sent for *GATA1* Sanger sequencing (bidirectional sequencing of all coding exons (exons 2–6) of the *GATA1* gene) and was performed at Prevention Genetics (Marshfield, WI). The clinical sensitivity of this test is unknown and was validated by comparing 11.3 megabases of Sanger DNA sequence to NextGen sequencing generated at other labs [12]. Transmission electron microscopy was performed using standard methods. The electronic medical records were reviewed for pertinent demographic, past medical history, and physical exam findings.

3. Results

The patient is a 54-year-old male that presented to the emergency department with a one-week history of shortness of breath, fever, chills, night sweats, fatigue, anorexia, right upper quadrant abdominal pain, and lower back pain. Inpatient workup revealed anemia, thrombocytopenia, hepatosplenomegaly, and generalized lymphadenopathy. The differential diagnosis considered by hospital day 12 was hemophagocytic lymphohistiocytosis (ferritin level elevated to 38,459 ng/mL) versus hematopoietic/lymphoid neoplasm. Treatment with rituxan, etoposide, and dexamethasone was started on hospital day 13, due to concerns for hemophagocytic lymphohistiocytosis. During his hospital stay, he developed critical pancytopenia, respiratory failure, and renal failure. He expired on hospital day 17.

Wright's stained peripheral blood smears performed on hospital days 1 and 11 showed thrombocytopenia, anemia, and marked leukocytopenia with occasional blasts. The blasts had large round nuclei and prominent nucleoli with strongly basophilic cytoplasm and azurophilic granules. Flow cytometry performed on the peripheral blood revealed that approximately 1.5% of the cells represented an aberrant CD34+ myeloblast population. The clinical differential diagnosis included myelodysplasia and acute myeloid leukemia as well as other disorders associated with pancytopenia, including sepsis.

Bone marrow biopsies and aspirates were performed on hospital days 3 and 11. The aspirates showed scant cellularity and extensive necrosis. The core biopsies showed scattered immature pleomorphic atypical cells in a background of extensive necrosis (Fig. 1). The initial bone marrow biopsy was diagnosed as extensive necrosis with focal involvement by high-grade hematopoietic/lymphoid neoplasm. Flow cytometry performed on the peripheral blood on hospital day 11 revealed 8%–9% aberrant myeloblasts showing expression of CD7. The complete phenotype showed myeloblasts positive for CD45 (dim), CD34, CD117, CD33, CD13 (dim), and CD7 and