Acute Myeloid Leukemia With t(10;11): A Pathological Entity With Distinct Clinical Presentation

Courtney D. DiNardo,[1] Guilin Tang,[2] Naveen Pemmaraju,[1] Sa A. Wang,[2] Allison Pike,[1] Guillermo Garcia-Manero,[1] Jorge Cortes,[1] Carlos Bueso-Ramos,[2] Hagop M. Kantarjian[1]

Abstract

t(10;11)(p12;q23) is a rare recurrent translocation involving the mixed lineage leukemia (*MLL*) gene translocation, most commonly seen in pediatric and young adult acute myeloid leukemia (AML), associated with early morbidity including diffuse intravascular coagulation and tumor lysis syndrome with multiorgan system failure from leukocytosis. With supportive care, first remissions are frequently attained, but patients have a high risk of relapse, extramedullary disease, and poor long-term outcomes.

Introduction: Acute myeloid leukemias with *MLL* rearrangements are frequently associated with myelomonocytic and monoblastic/monocytic morphology, with an increased risk of leukocytosis and leukostasis-related complications. Yet, little is known regarding the clinical presentation of adult AML patients with *MLL* translocations based on the specific translocation partner. **Patients and Methods:** Two recent AML cases with t(10;11)(p12;q23) translocations are detailed, with their shared presenting symptoms highlighted, followed by a review of the current literature. **Results:** The specific t(10;11)(p12;q23) *MLL* translocation is a rare recurrent translocation partner, most commonly seen in pediatric and young adult AML. A high incidence of early morbidity from leukocytosis-related complications are frequently seen, including diffuse intravascular coagulation and tumor lysis syndrome with multiorgan system failure, even without a true leukocytosis. **Conclusion:** With prompt therapy and intensive supportive care first remissions are frequently attained, however, patients have a high risk of relapse, extramedullary disease, and poor long-term outcomes.

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Introduction

Rearrangements involving the mixed lineage leukemia (*MLL*) gene on chromosome 11q23 are well described pathogenic alterations associated with myeloid and lymphoid acute leukemias. *MLL* rearrangements occur in infant, pediatric, and adult populations and are typically associated with an overall poor prognosis, with notable exceptions including the t(9;11) translocation which appears to confer an intermediate prognosis and the t(1;11)(q21;q23) translocation in children conferring a favorable prognosis.[1-4] Although the t(9;11) translocation is the most frequent *MLL* alteration and occurs in approximately 30% to 50% of *MLL*-rearranged cases, > 120 different translocation partners have been identified to date.[5] The specific *MLL* fusion partner is known to impart some lineage specificity, for example, the t(4;11)(q21;q23) translocation is found predominantly in B-cell acute lymphoblastic leukemia (ALL), and other translocations, such as t(9;11) and t(10;11)(p12;q23) are overrepresented in acute myeloid leukemia (AML).[5-8]

Pathologically, the AMLs with recurrent *MLL* translocations are often characterized as myelomonocytic or monoblastic leukemias (ie, French-American-British (FAB) classification of M4 or M5), with a tendency for biphenotypic expression patterns.[9] Yet, little is known with regard to the clinical phenotype of *MLL*-rearranged AML patients, in particular, based on the specific translocation partner.

[1]Department of Leukemia
[2]Department of Hematopathology
The University of Texas M.D. Anderson Cancer Center, Houston, TX

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Address for correspondence: Courtney DiNardo, MD, Department of Leukemia, University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Blvd, Unit 428, Houston, TX 77030
Fax: 713-563-0289; e-mail contact: cdinardo@mdanderson.org

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Two remarkable recent AML cases with t(10;11)(p12;q23) at the M.D. Anderson Cancer Center (MDACC) are herein detailed, with their shared presenting symptoms highlighted, followed by a review of the current literature.

Case 1

A 39-year-old Caucasian man with a medical history of hypothyroidism while taking levothyroxine and a history of occupational radiation exposure presented to his local emergency room for a 1-week history of shortness of breath and fevers. He described generalized fatigue for approximately 1 month. Imaging revealed a multifocal pneumonia and a complete blood count identified an increased white blood cell count of 18,300/μL, with 80% circulating blasts, a hemoglobin of 12.4 g/dL, and platelet count of 42,000/μL. He was urgently transferred to the MDACC for further evaluation and treatment. He was noted on arrival to MDACC to have evidence of chemical diffuse intravascular coagulation (DIC) with a protime of 18.3 s, partial thromboplastin time (PTT) of 45.3 s, d-dimer > 20 μg/mL, and hypofibrinogenemia of 174, and mild spontaneous tumor lysis with lactate dehydrogenase (LDH) level of 2312 IU/L, creatinine (Cr) level of 1.2 mg/dL, and uric acid level of 6.7 mg/dL. A bone marrow biopsy performed on hospital day 2 was consistent with an acute monoblastic leukemia, with 81% blasts (FAB classification AML-M5a) in a 90% hypercellular marrow with $CD13^+$ $CD33^+$ $CD34^-$ $CD38^+$ $CD56^-$ $CD123^+$ HLA-DR^+ MPO^- TdT- blasts. Cytogenetics revealed a hyperdiploid clone of neoplastic cells with a t(10;11) translocation resulting in an *MLL* rearrangement confirmed using fluorescence in situ hybridization (FISH; Table 1 and Figure 1). Treatment was started with systemic chemotherapy of fludarabine 30 mg/m^2 daily for 5 days, idarubicin 10 mg/m^2 intravenous (I.V.) for 3 days, and cytarabine 1 g/m^2 I.V. for 3 days on hospital day 6 after his diagnosis was confirmed. Before his induction regimen he was temporized with hydroxyurea 3 g orally daily starting on the day of admission and cytarabine 1 g/m^2 I.V. once on hospital day 3.

His peak white blood cell count was 26,200/μL on hospital day 2. He had only 2 documented fevers, on the night of admission at 38.3°C and the morning of hospital day 2 at 38.4°C. Despite resolution of his leukocytosis and disappearance of circulating blasts, and continued empiric broad-spectrum antibiotics including antibacterial, antifungal, and antiviral coverage, his shortness of breath and oxygen requirement increased, requiring 80% supplemental oxygen by hospital day 3 and mechanical ventilation on hospital day 9 (Figure 2). During week 1 he also developed severe clinical DIC with protime (PT) of 52.1 sec, PTT of 70.2 sec, fibrinogen at 34 mg/dL, and d-dimer > 20 mg/dL with recurrent epistaxis, hemoptysis, and persistent oozing from all indwelling lines. On day 7 he complained of a headache and a head computed tomography scan was performed, which revealed a left frontal lobe parenchymal hematoma measuring 13 mm and a subarachnoid hemorrhage in the left parietooccipital region. He was supported with continuous platelet infusions, fresh frozen plasma (FFP), desmopressin (DDAVP), aminocaproic acid, and 3 doses of recombinant human factor VIIa. During week 1 of hospitalization he also developed oliguric acute renal failure in the setting of tumor lysis with a maximum LDH level of 21,113 IU/L, phosphorus (phos) of

Table 1 Clinicopathologic Characteristics

Characteristic	Patient 1	Patient 2
Age/Sex	39/M	20/M
Ethnicity	Caucasian	Hispanic
Year of Diagnosis	2014	2014
AML FAB	M5	M5
WBC Count at Diagnosis	26	94
BM Blast Percentage	81	75
Cytogenetics	48,XY,del(9)(q12q32),der(10)t(10;11)(p12;q23),t(10;11),+20,+20[20]	46,XY,der(10)t(10;11)(p12;q21)inv(11)(q21q23),der(11)t(10;11)[4]/46,sl,der(5)t(1;5)(q11;q35)[7]/46,XY,der(10)t(10;11)(p12;q21)inv(11)(q21q23),der(11)t(1;11)(q11;p15)t(10;11)[4]/46,XY[2] At relapse: 53∼55,XY,+1,+5,+6,der(10)t(10;11)(p12;q21)inv(11)(q21q23),der(11)t(10;11),+13,add(14)(p11.2),+15,+18,+19,+20,+22,+0∼1mar[cp19]/46,XY [1]
FISH for *MLL* Rearrangement	Positive in 95%	Positive in 65%
Molecular	FLT3, NPM1, CEBPA negative (NRAS and KRAS-positive)	FLT3, NPM1, CEBPA negative
Treatment Regimen	FIA induction with CR1	FIA induction and consolidation ×1 with CR1; CRD1 2 months; salvage DAC-CIA
TLS	Yes (LDH 21,000; Phos 8.3; UA 7.6)	Yes (LDH 18,988; Phos 9.1)
Clinical DIC	Yes (fbgn 32; dd >20); profuse bleeding	Yes (fbgn 78, dd >20); DAH and splenic infarcts
Resp Failure	Yes; 80% Fi02	Yes; 100% Fi02
Renal Failure	Yes; Cr 6, required HD	Yes; Cr 2.3, no HD required
CNS Disease	No	No

Abbreviations: AML = acute myeloid leukemia; BM = bone marrow; Cr = creatinine; CR1 = first complete response; CRD1 = first complete remission duration; DAC-CIA = decitabine, clofarabine, idarubicin, cytarabine; DAH = diffuse alveolar hemorrhage; dd = d-dimer; DIC = diffuse intravascular coagulation; FAB = French-American-British; fbgn = fibrinogen; Fi02 = fraction of inspired oxygen; FIA = fludarabine, idarubicin, cytarabine; FISH = fluorescent in situ hybridization; HD = hemodialysis; LDH = lactate dehydrogenase; M = male; Phos = phosphorus; Resp = respiratory; TLS = tumor lysis syndrome; UA = uric acid; WBC = white blood cell.