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AML with t(10;11): A pathological entity with distinct clinical presentation

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Abstract

t(10;11)(p12;q23) is a rare recurrent MLL translocation, most commonly seen in pediatric and young adult 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 (AML) 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.

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 (DIC) 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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Keywords

AML; MLL; leukostasis; DIC; TLS

Introduction

Rearrangements involving the mixed lineage leukemia (*MLL*) gene on chromosome 11q23 are well described pathogenic alterations associated with both 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) While the t(9;11) translocation is the most frequent *MLL* alteration and occurs in approximately 30–50% of *MLL* rearranged cases, over 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 ALL, while other translocations such as t(9;11) and t(10;11)(p12;q23) are overrepresented in AML.(5–8) Pathologically, the acute myeloid leukemias with recurrent *MLL* translocations are often characterized as myelomonocytic or monoblastic leukemias (i.e. FAB classification M4 or M5), with a tendency for biphenotypic expression patterns.(9) Yet little is known with regards to the clinical phenotype of *MLL*-rearranged AML patients, in particular based on the specific translocation partner. Two remarkable recent AML cases with t(10;11)(p12;q23) at the MD Anderson Cancer Center 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 past medical history of hypothyroidism on levothyroxine and a history of occupational radiation exposure presented to his local emergency room for a one-week history of shortness of breath and fevers. He described generalized fatigue for approximately one month. Imaging revealed a multifocal pneumonia and a complete blood count identified an elevated white blood cell count of 18.3 K/ul, with 80% circulating blasts, a hemoglobin of 12.4 g/dl and platelet count of 42 K/ul. He was urgently transferred to the MD Anderson Cancer Center (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 sec, PTT 45.3 sec, d-dimer >20 mcg/mL and hypofibrinogenemia of 174, as well as mild spontaneous tumor lysis with LDH 2312 IU/L, Cr 1.2 mg/dl, and uric acid 6.7mg/dl. A bone marrow was performed on hospital day 2 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 by FISH (Table 1). He was started on systemic chemotherapy with fludarabine 30mg/m2 daily x 5 days, idarubicin 10mg/m2 IV x 3 days, and cytarabine 1 g/m2 IV x 3 days on hospital day 6 after his diagnosis was confirmed. Prior to his induction regimen he was temporized with hydroxyurea 3 grams orally daily starting on the day of admission and

cytarabine 1g/m² IV x 1 on hospital day 3. His peak white blood cell count was 26.2 K/ul on hospital day 2. He had only two documented fevers, on the night of admission at 38.3 and the morning of hospital day 2 at 38.4 degrees Celsius. Despite resolution of his leukocytosis and disappearance of circulating blasts, as well as 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 1). During week 1 he also developed severe clinical DIC with PT 52.1, PTT 70.2, fibrinogen 34 and d-dimer >20 with recurrent epistaxis, hemoptysis, and persistent oozing from all indwelling lines. On day 7 he complained of a headache and a head CT was performed which revealed a left frontal lobe parenchymal hematoma measuring 13mm as well as a subarachnoid hemorrhage in the left parietooccipital region. He was supported with continuous platelet infusions, FFP, DDAVP, aminocaproic acid and three doses of recombinant human factor VIIa (Novo7).

During week 1 of hospitalization he also developed oliguric acute renal failure in the setting of tumor lysis with maximum LDH 21113, phos 7.3, BUN 166 and creatinine 6.2. With continued intensive supportive care his multiorgan failure slowly resolved and the patient clinically improved. He was able to be extubated on day 12, and his renal function subsequently recovered and dialysis was permanently discontinued on day 20. His blood counts recovered without circulating blasts and a day 28 bone marrow confirmed a complete remission with no residual leukemic blasts by morphology or flow cytometry, with diploid cytogenetics present in all metaphases. He was able to be discharged on hospital day 39 with no residual complications apart from a new baseline creatinine of approximately 2. He continues on consolidation therapy and a stem cell transplant is imminently planned.

Case #2

A 20 year old Hispanic male with no past medical history was admitted to the intensive care unit of MD Anderson Cancer Center. He noted a 2–3 month history of progressive gingival swelling and gum irritation, and he had recently undergone a “gum stripping” dental procedure for a presumed gingivitis complicated by fevers and poor wound healing, and for which he had been prescribed oral antibiotics without relief. He was admitted to his local hospital for persistent fevers and oral pain, and a CBC on admission revealed leukocytosis of 85 K/ul with circulating blasts and he was transferred to MDACC for a concern of acute leukemia. On arrival to MDACC his CBC was 94 K/ul with 80% circulating blasts, hemoglobin 6.6 g/dl, and platelets 61 K/ul. He had laboratory evidence of DIC on arrival with PT 20.1, PTT 62.1, fibrinogen 157 and d-dimer > 20. He was started immediately on oral hydroxyurea and IV cytarabine 1g/m² IV given his leukocytosis. A bone marrow revealed an acute monocytic leukemia (M5b) with 75% monoblasts in a 95% hypercellular marrow, cytogenetics with pseudodiploid clones with an inversion 11q and t(10;11) translocation resulting in MLL rearrangement confirmed by FISH (Table 1). He was started on fludarabine 30mg/m² daily for 5 days with cytarabine 2g/m²/day x 5 days and idarubicin 6mg/m² IV x 2 days.

Supplemental oxygen for shortness of breath with a concern of leukostasis and multifocal pneumonia was required on the day of admission, and by hospital day 3 he had progressed to

acute respiratory failure requiring 100% supplemental oxygen. Imaging confirmed a multifocal infiltrate suspicious for pneumonia, diffuse alveolar infiltrates and/or leukemic infiltrates. He required mechanical ventilation on hospital day 6, with diffuse alveolar hemorrhage identified by direct visualization in the setting of clinical DIC for which he was initiated on high-dose corticosteroids and aminocaproic acid infusion. He also developed tumor lysis syndrome with maximum values of LDH 18,988, BUN 64, Cr 2.3, and Phos 9.1. He was supported without the need for hemodialysis. With continued empiric therapy and maximum support he slowly improved and was extubated on day 10. On day 14, he complained of abdominal pain and imaging revealed pancreatitis and splenic infarcts in the setting of elevated amylase and lipase of 232 and 919, respectively, also managed conservatively. All cultures obtained during his hospital stay were without growth. A day 28 recovery bone marrow confirmed a complete remission with no residual leukemic blasts by morphology or flow cytometry and diploid cytogenetics. He received one consolidation cycle with additional fludarabine, idarubicin and cytarabine which he tolerated without toxicity or adverse events. Unfortunately he recovered from his first consolidation cycle with relapsed disease, with recurrence of his previously identified t(10;11) with evidence of additional clonal evolution (Table 1). He is currently receiving salvage therapy with a plan to proceed with myeloablative stem cell transplant upon achievement of CR2.

Discussion

The myelomonocytic (M4) and monoblastic/monocytic (M5) myeloid leukemias are often associated with higher rates of leukocytosis and extramedullary disease. AML with MLL-rearrangements are frequently characterized as M4/M5 leukemias with a propensity to extreme leukocytosis, skin involvement and CNS disease.(10)

Leukocytosis is typically defined as $> 50,000$ blasts/mm³ and has been traditionally explained as an extreme overcrowding of large leukemic blasts in the circulation leading to hyperviscosity and vascular events.(11) However, more recent evidence describes endothelial damage occurring through abnormal cytokine profiles and altered interactions predominantly among adhesion molecules.(12) This may explain why certain leukemia subtypes are more at risk of “leukostasis”-related complications, and in particular clarifies why this phenomenon may even be observed in leukemia patients without significant leukocytosis, such as Case #1.

The striking clinical phenotype observed in these two young male patients with t(10;11) MLLrearranged AML consisted of rapid multiorgan failure including acute respiratory and renal failure, along with severe clinical DIC and tumor lysis syndrome, which developed despite appropriate and aggressive intensive chemotherapy with effective early leukoreduction.

Due to the overall rarity of this translocation, the clinical characteristics and outcome of patients with a t(10;11)(p12;q23) translocation is not well described. A historical study of 20 patients by Lillington *et al*, describes a cohort of younger patients with male predominance, in whom the majority achieve a first complete remission, yet in whom overall survival (OS) is less than 24 months and the only long-term AML survivors those receiving stem cell

transplants.(9) Notably, in a recent analysis of over 1590 MLL-rearranged leukemias identified over the past decade, primarily from European centers, 120 patients were found to have a t(10;11), and yet only 23 of them were adults (the remainder comprising infants and children). Our finding of 2 young adults with t(10;11) AML within the same time period at our institution was significant and inspired our review of this entity.

At MDACC since 2006, we have treated 5 adults with t(10;11) and a confirmed MLL rearrangement (Table 2). Our analysis confirms the high risk of relapsed leukemia and poor long-term survival suggested in this cytogenetically defined cohort, although one patient is alive and disease-free now more than 8 years post a stem cell transplant in CR1, suggesting that transplant in first remission should remain the goal for these patients whenever possible.

The t(10;11)(p12;q23) translocation involves the *MLLT10* (previously *AF10*) gene on chromosome 10p12, and typically arises from a complex rearrangement resulting from the insertion of chromosome 11 material, including the *MLL* gene, into chromosome 10p.(13) The *MLLT10* gene encodes a nuclear protein which functions within the DOT1L protein network, leading to transcriptional elongation and increased histone H3 methylation signatures, and innovative therapeutic approaches including the DOT1L inhibitors provide the hope of novel and effective targeted therapy for this high risk disease. Whether dysregulation of *MLLT10* in t(10;11) patients predisposes patients to endothelial cell damage via altered cytokine signaling or adhesion interactions warrants future investigation.

Finally, it is worth affirming that prompt effective treatment of the underlying leukemia with intensive cytoreductive chemotherapy, and without leukopheresis, led to resolution of the leukocytosis and reduction of the circulating leukemia blast count in both patients within 48 hours. The secondary organ dysfunction and clinical syndrome, however, took several weeks to fully improve in both patients. With continued intensive supportive care both patients fully recovered, with both patients achieving a complete remission and with the hope of curative therapy with stem cell transplantation.

Conclusion

AML with MLL rearrangements are frequently associated with myelomonocytic and monoblastic leukemias with an increased risk of leukocytosis and leukostasis-related complications at diagnosis. 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. 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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Clinical Practice Points

- AML with MLL rearrangements are frequently associated with myelomonocytic and monoblastic/monocytic leukemias with an increased risk of leukocytosis and leukostasis-related complications at diagnosis.
- The t(10;11)(p12;q23) translocation involving MLL is a rare recurrent translocation partner, most commonly seen in pediatric and young adult 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.

Figure 1.

(a): Non-contrast CT chest of patient #1 portraying diffuse multifocal infiltrates

(b): CT abdomen/pelvis of patient #2 with multiple splenic infarcts and hepatomegaly

Figure 2A

Figure 2B

Figure 2.

(a) Fluorescence in situ hybridization (FISH) using *MLL* break-apart probe on a G-banded metaphase showed a *MLL* rearrangement and der(10),t(10;11),t(10;11) aberrations in patient #1.

(b) Conventional cytogenetic analysis revealed a hyperdiploid neoplastic clone showing del(9q),der(10)t(10;11),t(10;11),+20,+20 aberrations in patient #1.

Table 1

Clinicopathologic characteristics

	Age/Sex	Ethnicity	Year Dx	AML FAB	Dx WBC	% BM Blast	Cytogenetics	FISH for MLL Rearrangement	Molecular
1	39M	Caucasian	2014	M5	26	81	48,XY,del(9)(q12q32),der(10)(10;11)(p12;q23),t(10;11),+20,+20[20]	Positive in 95%	FLT3, NPM1, CEBPA neg (NRAS and KRAS+)
2	20M	Hispanic	2014	M5	94	75	46,XY,der(10)(10;11)(p12;q21)inv(11)(q21q23),der(11)(10;11)[4]/ 46,sl,der(5)(1;5)(q11;q35)[7]/46,XY,der(10)(10;11)(p12;q21)inv(11) (11)(1;11)(q11;p15)(10;11)[4]/46,XY[2] At relapse: 53~55,XY,+1,+5,+6,der(10)(10;11)(p12;q21)inv(11)(q21q23), der(11)(10;11),+13,add(14)(p11.2),+15,+18,+19,+20,+22,+0~1mar [cp19]/46,XY [1]	Positive in 65%	FLT3, NPM1, CEBPA neg

	Tx Regimen	TLS	Clinical DIC	Resp Failure	Renal Failure	CNS disease
1	FIA induction with CR1.	Yes (LDH 21000, Phos 8.3, UA 7.6)	Yes, (Fbgn 32, dd >20) Profuse bleeding.	Yes 80% FiO2	Yes Cr 6, required HD	No
2	FIA induction and consolidation x 1 with CR1. CRD1 2 months. Salvage DAC-CIA.	Yes (LDH 18988, Phos 9.1)	Yes (fbtn 78, dd>20) DAH and splenic infarcts.	Yes 100% FiO2	Yes Cr 2.3, no HD required	No

Table 2

Review of t(10;11)(p12;q23) cases

Age/ Sex	Ethnicity	Year Dx	Dx	Cytogenetics		FISH for MLL Rearrangement	OS and Status
31F	Caucasian	2000	M5 AML	50,XX,+3,+del(5)(q13q33),+6,der(6)t(1;6)(q21;q21), +8,der(10)t(10;11)(p12;q13)inv(11)(q13q23) [19]		Positive in 30%	6 yrs Died in 2 nd salvage with extramedullary and CNS disease (CRI x 5 yrs s/p SCT)
34M	Caucasian	2006	M5 AML	46,XY,t(10;11)(p12;q23)[20]		Positive in 98%	8 yrs Alive in CRI s/p SCT
42F	Hispanic	2008	M5 AML	46,XX,add(1)(p36.1),der(10)t(10;11)(p12;q13)inv(11)(q13q23),der(11)t(10;11)[13]/46,XX[7]		Positive in 49%	17 mo Died in CR2 of post-SCT GVHD and TTP
39M	Caucasian	2014	M5 AML	48,XY,del(9)(q12q32),der(10)t(10;11)(p12;q23),t(10;11),+20,+20[20]		Positive in 95%	2 mo Alive in CRI
20M	Hispanic	2014	M5 AML	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]		Positive in 65%	3 mo Alive with relapsed disease undergoing salvage therapy