Atlas of Genetics and Cytogenetics
in Oncology and Haematology

OPEN ACCESS JOURNAL

INIST-CNRS

Leukaemia Section
Review

t(2;11)(p21;q23) without KMT2A (MLL) rearrangement

Ana L. Ruano, Shashirekha Shetty

Robert J. Tomisch Pathology, Laboratory Medicine Institute, Cleveland Clinic, Cleveland, Ohio (ALR, SS), and University Hospitals, Case Western Reserve University, Cleveland, Ohio (SS), USA; ruanoa@ccf.org and Shashirekha.shetty@UHhospitals.org

Published in Atlas Database: August 2016

Online updated version : http://AtlasGeneticsOncology.org/Anomalies/t0211p21q23ID1333.html

Printable original version : http://documents.irevues.inist.fr/bitstream/handle/2042/68254/08-2016-t0211p21q23ID1333.pdf

DOI: 10.4267/2042/68254

Abstract

Forty five cases carrying the t(2;11)(p21;q23) have been reported in the literature, mostly in myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML). Some of these cases involve rearrangements of the the MLL gene (also known as KMT2A), on 11q23, which confers a more aggressive behavior in myeloid neoplasms. Several individual case reports, as well as series such as 19 cases reported by Bousquet et al., 2008 and 7 cases by Dvorak et al., 2014, describe myeloid neoplasms carrying the t(2;11)(p21;q23) without an MLL gene rearrangement, with possible prognostic implications. The authors of this paper describe two additional cases from their institution.

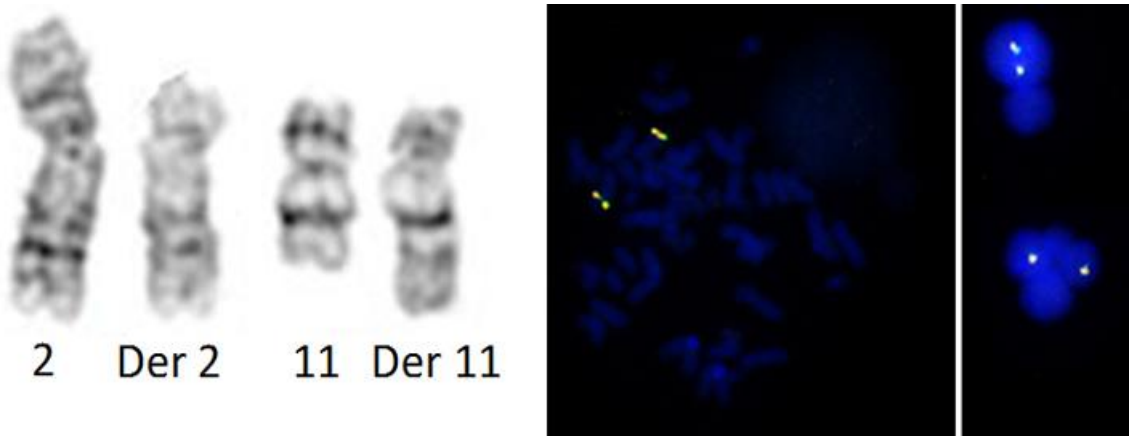
Keywords

Myelodysplastic syndrome, acute myeloid leukemia, t(2;11).

Identity

Other names

Acute myeloid leukemia and myelodysplastic syndrome with t(2;11)(p21;q23) without MLL gene rearrangement.



Representative images of karyotype showing rearrangement between chromosomes 2 and 11, and FISH images showing lack of MLL gene rearrangement.

Clinics and pathology

Disease

Phenotype/cell stem origin

Myeloid blasts.

Thirty two case are available: 2 chronic myeloproliferative cases, 18 myelodysplastic syndromes (MDS), and 12 cases of acute myeloid leukemia (AML). Diagnoses were: chronic myelogenous leukemia harbouring the t(9;22)(q34;q11) (CML, 1 case), polycythemia vera (PV, 1 case), myelodysplastic/myeloproliferative overlap syndrome (MDS/MPN, 1 case), refractory anemia (RA, 1 case), refractory anemia with excess blasts (RAEB, RAEB-I, RAEB-II, 5 cases), refractory cytopenia with multilineage dysplasia (RCMD, 2 cases), RCMD with ring sideroblasts (RCMD-RS, 1 case), unclassifiable MDS (MDS-U, 1 case), low grade MDS NOS (7 cases); AML NOS (3 cases), AML-M0 (1 case), AML-M1 (1 case), AML-M2 (3 cases), AML-M4 (2 cases) and AML-M5 (2 cases). Ten of the twelve AML cases were classified either as having multilineage dysplasia or as arising from MDS (chronic myelomonocytic leukemia , refractory anemia). In two cases, dysplasia could not be assessed (Harrison et al., 1998; Gozzetti et al., 2003; Royer-Pekora et al., 2003; Bousquet et al., 2008; Dvorak et al., 2014; McCormick et al., 2014; Ruano and Shetty, unpublished observation)

The authors of this paper describe two additional cases, above included (Ruano and Shetty, unpublished observation): one in a patient diagnosed with myelodysplastic/myeloproliferative (MDS/MPN) overlap syndrome best classified as atypical chronic myeloid leukemia (CML), BCR/ABL negative; another patient presented with acute monoblastic leukemia, later classified as AML with myelodysplasia-related changes after obtaining knowledge on the cytogenetic findings.

Epidemiology

Two cases consisted of a 44 year old female and a 54 year old male (Ruano and Shetty, unpublished observation).

Altogether, there were 26 male and 6 female patients. Median age at diagnosis was 56-57 years (range 37-74).

Clinics

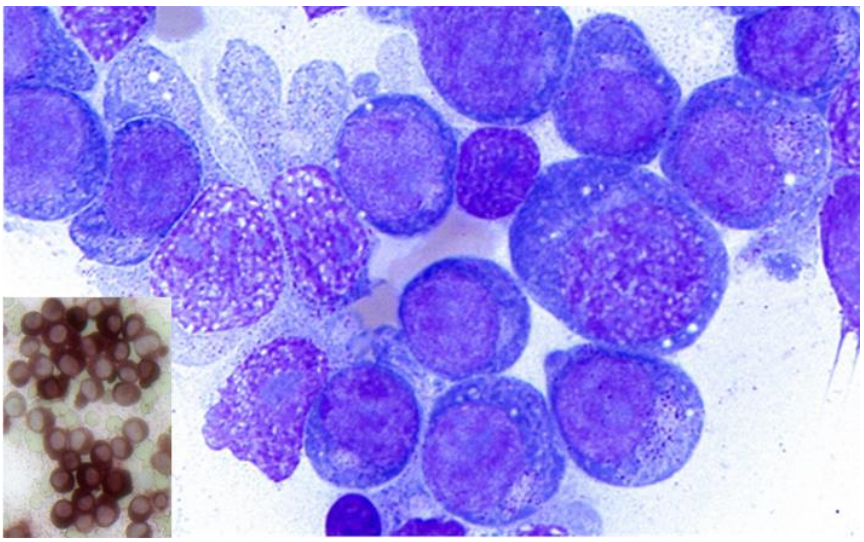
The authors describe a case of a 54 year old male that initially presented with ankle swelling and left upper quadrant discomfort noted to have marked leukocytosis (WBC=237,000/µL) and macrocytic anemia (Hb=10.1 g/dL ; MCV=101.9 fl) associated with massive splenomegaly.

This patient was diagnosed with atypical CML, BCR/ABL negative. The second patient is a 44 year old female with no significant medical history that presented with upper and lower extremity pain and found to be pancytopenic with 2% circulating blasts. She was eventually diagnosed with acute myeloid leukemia with myelodysplasia-related changes.

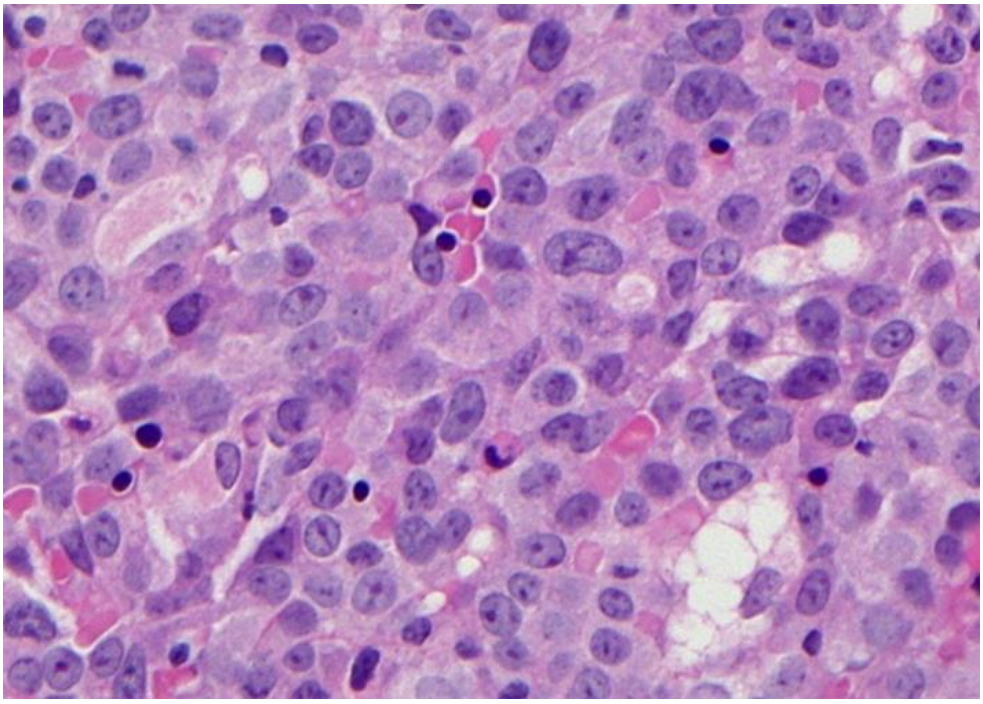
Pathology

Five of the seven cases reported by Dvorak et al., 2014 showed marked megakaryocytic dysplasia.

The case described by McCormick et al., 2014 showed a hypercellular bone marrow (95%) with increased megakaryoctyes ranging from small hypolobated forms to large and normally lobated.



Bone marrow aspirate showing intermediate size blasts with fine nuclear chromatin and moderate basophilic cytoplasm with occasional small azurophiic granules and vacuoles. The blasts were diffusely positive for alpha-naphthyl butyrate esterase and negative for myeloperoxidase cytochemistries (insert).



Hypercellular bone marrow (>95%) showing sheets of immature mononuclear cells with fine chromatin and prominent nucleoli, consistent with blasts.

From the cases reported by the authors of this paper, the bone marrow aspirate and biopsy from the 54 year old patient with atypical CML, BCR/ABL negative showed granulocytic hyperplasia with left shift with occasional dyserythropoiesis and dysgranulopoiesis. There was more prominent dysmegakaryopoiesis consisting of small, hypolobated forms with occasional micromegakaryocytes. Blasts represented 3% of bone marrow elements. One year later, the patient presented with acute myeloid leukemia with 40% circulating blasts expressing CD5, CD7, CD13, CD33, CD34, CD117, and HLA-DR, with dim expression of CD56. Two follow-up bone marrows showed persistent involvement by AML.

The bone marrow aspirate and biopsy from the 44 year old female with AML showed 89% blasts expressing CD13 (dim), CD33, CD38, CD45 (dim), CD56, CD64, CD65 (bright), HLA-DR, and CD117 (on a subset). performed on the bone marrow aspirate shows 69% blasts which are positive for CD4, CD13 (dim), CD33, CD38, CD45 (dim), CD56, CD64, CD65 (bright), HLA-DR, and CD117 (subset). Cytochemical stains showed that the blasts were negative for myeloperoxidase and positive for alpha-naphthyl butyrate esterase. See Figure 2 and 3.

Treatment

The patient reported by Gozzeti et al., 2003 was treated with cytarabine for 7 days, achieving a partial remission. His disease progressed afterwards for what he was treated with various
chemotherapeutic regimens but died 1 year after diagnosis. The patient reported by Royer-Pokora et al., 2003 was treated with imatinib achieving complete response that lasted for 22 months, when the case report was written.

The seven patients reported by Dvorak et al., 2014 were treated either with symptomatic or cytoreductive therapy. One patient with deletion 5q was treated with lenalidomide but had only a partial response to treatment. Two patients underwent peripheral stem cell transplantation, after which one had stable disease but the other transformed to AML. The median overall survival for this small cohort was 72 months and at the time of publication, 2 patients were alive and 5 had died.

The patient reported by McCormick et al., 2014 remained clinically stable 70 months after initial diagnosis, requiring only periodic phlebotomies.

The 54 year old patient described by this page's authors was initially treated with hydroxyurea after being diagnosed with atypical CML. He transformed to AML 14 months later and was treated with 7+3, ara-C and idarubicin. Due to persistent disease he was started on a new cycle of chemotherapy which was complicated by fever and altered mental status eventually leading to patient's death approximately 1 month later. The 44 year old patient diagnosed with AML with myelodysplasia related changes was treated with 7+3 regimen, with cytarabine and daunorubicin and had 2 negative bone marrows at 14 days and 1 month after treatment was started.

She remained clinically stable but was lost to follow-up 1 year after diagnosis.

Prognosis

Dvorak et al., 2014 determined that the median survival of MDS patients harbouring the t(2;11)(p21;q23) was significantly greater than that of MDS patients with complex karyotype or trisomy 8 as sole abnormality (72 vs 7.5 and 57 months, respectively, p=0.0007). Other studies have placed the t(2;11)(p21;q23) in the intermediate risk category. However, the MLL gene status was not evaluated. Studies in larger groups of patients, also possibly including patients with AML, are needed in order to determine if the t(2;11)(p21;q23) without MLL rearrangement truly conveys a better prognosis.

Cytogenetics

Cytogenetics morphological

The case described by Harrison et al., 1998 showed a 46XX, t(2;11)(p21;q23), del(5q)(q13q33)[24]/46XX[1] karyotype and was negative for MLL gene rearrangements by Southern Blot. The case described by Gozzetti et al., 2003 had a 46XX, t(2;11)(p21;q23)[14] karyotype and was negative for an MLL rearrangement by FISH. The CML case reported by Royer-Pekora et al., 2003 initially had both, a t(9;22)(q34;q11) and a t(2;11)(p21;q23) on all analysed cells. After the patient achieved major molecular and cytogenetic response to imatinib, a new clone containing only the t(2;11) emerged. This translocation was not present on skin fibroblasts from which the authors conclude that it was not present constitutionally.

Among the 19 cases reported by Bousquet et al., 2008, the t(2;11)(p21;q23) was the sole cytogenetic abnormality in 5 cases, and was associated with other abnormalities in the other 14 cases including deletion 5q (8 cases) and chromosome 7 abnormalities (4 cases). All cases were negative for MLL gene rearrangements by FISH, and an alternative breakpoint located downstream from MLL was identified by PCR-based molecular techniques, without a definitively identified gene. They also describe overexpression of microRNA (MiR) -125b in their patient series.

All seven cases reported by Dvorak et al., 2014 showed the t(2;11)(p21;q23). In 2 cases, this was the only cytogenetic abnormality, in 4 cases a deletion of 5q was also present in the main clone, and in 1 patient the deletion 5q was present in a subclone. They were all negative for MLL gene rearrangements by FISH.

Cytogenetic analysis from the case described by McCormick et al., 2014 showed four lines: one showing a 46XY normal male karyotype, two showing the t(2;11)(p21;q23-24), one of which also showed del(5)(q15q31), and a fourth one showing only the del5q. There was no MLL gene rearrangement detected by FISH and allele specific polymerase chain reaction (PCR) was negative for a JAK2V617F mutation. However, a mutation in JAK2 exon 12 was identified.

From the cases described by the authors of this page, the karyotype of the 54 year old male with atypical CML was reported as 46,XY,t(2;11)(p21;q23). The karyotype of the 44 year old female with AML was reported as 47,XX,t(2;11)(p21;q23),+8[16]/47,idem,+i(8)(q10)[4]. Both cases were negative for MLL gene rearrangement by FISH (see Figure 1).

Genes involved and proteins

Note

The gene on 11q23 involved in these translocations has not been yet identified. Bousquet et al., 2008 determined through FISH that the breakpoint in their cases appeared to be located downstream from the MLL region. By PCR, they assessed expression of several genes/sequence tags known to be located in this region but did not find altered expression of any of them. They did find, however, that their series of patients showed overexpression of miR -125b (6- to 90-fold) when compared to other patients with MDS or AML without the translocation. McCormick et al., 2014 also found a 200-fold overexpression of miR-125b in their case.

miR-125b originates from chromosomes 11q24 (MIR125B1) and 21q21 (MIR125B2) It is a regulator of normal hematopoiesis and exerts its oncogenic effect through several mechanisms including arrest of myeloid/monocytic differentiation, promoting stem cell renewal and targeting intermediaries in the TP53 pathway. Besides AML/MDS with t(2;11)(p21;q23), miR-125b has also found to play a role in pediatric acutepromyelocytic leukemia , acute megakaryoblastic leukemia of trisomy 21, and precursor B-cell acute lymphoblastic leukemia (B-ALL) (McCormick et al., 2014).

References

Bousquet M, Quelen C, Rosati R, Mansat-De Mas V, La Starza R, Bastard C, Lippert E, Talmant P, Lafage-Pochitaloff M, Leroux D, Gervais C, Viguié F, Lai JL, Terre C, Beverlo B, Sambani C, Hagemeijer A, Marynen P, Delsol G, Dastugue N, Mecucci C, Brousset P. Myeloid cell differentiation arrest by miR-125b-1 in myelodysplastic syndrome and acute myeloid leukemia with the t(2;11)(p21;q23) translocation. J Exp Med. 2008 Oct 27;205(11):2499-506

Dvorak P, Lysak D, Vokurka S, Michalova K, Sarova I, Jonasova A, Hruba M, Rykovska A, Subrt I. The translocation t(2;11)(p21;q23) without MLL gene rearrangement--a possible marker of good prognosis in myelodysplastic syndrome patients. Hematol Oncol. 2014 Jun;32(2):82-6

Fleischman EW, Reshmi S, Frenkel MA, Konovalova WI, Guleva GP, Kulagina OE, Konstantinova LN, Tupitsyn NN, Rowley JD. MLL is involved in a t(2;11)(p21;q23) in a patient with acute myeloblastic leukemia. Genes Chromosomes Cancer. 1999 Feb;24(2):151-5

Gozzetti A, Tozzuoli D, Crupi R, Raspadori D, Fabbri A, Lauria F. A case of acute myelogenous leukemia: myelodysplastic syndrome with t(2;11)(p21;q23) without MLL rearrangement. Cancer Genet Cytogenet. 2003 Jul 15;144(2):177-8

Harrison CJ, Cuneo A, Clark R, Johansson B, Lafage-Pochitaloff M, Mugneret F, Moorman AV, Secker-Walker LM. Ten novel 11q23 chromosomal partner sites. European 11q23 Workshop participants. Leukemia. 1998 May;12(5):811-22

McCormick SR, Higgins RR, Grutkoski PS, Bousquet M, Quelen C, Bartholomaus LM, Brousset P. Myeloid neoplasm with translocation t(2;11)(p21;q23-24), elevated microRNA 125b-1, and JAK2 exon 12 mutation. Br J Haematol. 2015 Apr;169(2):290-3

Royer-Pokora B, Hildebrandt B, Redmann A, Herold C, Kronenwett R, Haas R, Drechsler M, Wieland C. Simultaneous occurrence of a t(9;22) (Ph) with a t(2;11) in a patient with CML and emergence of a new clone with the t(2;11) alone after imatinib mesylate treatment. Leukemia. 2003 Apr;17(4):807-10

This article should be referenced as such:

Ruano AL, Shetty S. t(2;11)(p21;q23) without KMT2A (MLL) rearrangement. Atlas Genet Cytogenet Oncol Haematol. 2017; 21(6):210-214.