A case report of AML with myelodysplasia-related changes with aggressive course in association with t(3;8)(q26;q24)

Olga V. Danilova · Norman B. Levy · Prabhjot Kaur

Received: 3 February 2013 / Accepted: 21 May 2013 / Published online: 4 June 2013
© Springer-Verlag Berlin Heidelberg 2013

Abstract Myelodysplastic syndrome (MDS) is frequently associated with clonal cytogenetic abnormalities which are major predictors of the disease outcome. t(3;8)(q26;q24) was reported as a rare recurrent cytogenetic abnormality in MDS/acute myeloid leukemia (AML) with poor prognosis. Here, we present a case of MDS which rapidly advanced to AML with t(3;8)(q26;q24) in an elderly patient. Anemia and prominent megakaryocytic dysplasia in the absence of marked thrombocytopenia were distinct morphologic features. Patient progressed to leukemia and succumbed to the disease within 7 months from the initial diagnosis. Morphologic and clinical features in this patient resembled “3q21q26 syndrome” which is also associated with poor prognosis. Reports of unfavorable outcome in the patients with t(3;8)(q26;q24) highlight the probable significance of this cytogenetic abnormality for risk stratification in MDS/AML.

Keywords t(3;8)(q26;q24) · MDS · AML · Transformation

Introduction

Myelodysplastic syndromes (MDSs) are a group of clonal hematopoietic stem cell diseases characterized by cytopenia(s),

dysplasia, and impaired hematopoiesis [1, 2]. Primary MDS occurs principally in elderly adults with a median age of 70 years old.

Clonal cytogenetic abnormalities are observed in ~50 % of MDS cases. The most common abnormalities are complex karyotype, del(5q), trisomy 8, and del(20q) [2–4]. Other recurring abnormalities include abnormalities in chromosome 7 and balanced translocations involving chromosomes 11, 16, 3, and 21, such as t(11;16)(q23;p13.3), t(3;21)(q26.2;p22.1), t(1;3)(p36.3;q21.2), t(2;11)(p21;q23), t(6;9)(p23;q34), and inv(3)(q21q26.2) [2].

Cytogenetic and molecular studies have a major prognostic significance in MDS and are predictive of disease progression and survival. They have been incorporated in the IPSS score which is commonly used to estimate survival of patients with MDS [2]. The prognostic significance of less common chromosomal abnormalities is not well determined due to the paucity of reported cases.

Recently, t(3;8)(q26;q24) was reported as a rare recurrent cytogenetic abnormality in MDS/acute myeloid leukemia (AML) associated with poor prognosis [5]. Here, we present a case of an 84-year-old patient with MDS/AML with t(3;8)(q26;q24), who manifested an aggressive disease course.

Materials and methods

Wright–Giemsa-stained peripheral blood and bone marrow aspirate smears and hematoxylin and eosin (H&E)-stained core biopsy specimens were reviewed. Immunohistochemical stains were performed as per manufacturer's instructions on the Leica Bond III autostainer (Leica Microsystems, Newcastle, UK), using the Bond Polymer Refine Detection System (DS9800, Newcastle, UK) on 4-μm-thick formalin-fixed, paraffin-embedded

The case was presented at the European Association for Hematopathology workshop, 2010 EAHP Meeting, Uppsala, Sweden.

O. V. Danilova (✉) · N. B. Levy · P. Kaur
Department of Pathology, Dartmouth-Hitchcock Medical Center,
Lebanon, NH 03756, USA
e-mail: olga.v.danilova@hitchcock.org

N. B. Levy · P. Kaur
Geisel School of Medicine at Dartmouth, Hanover, NH, USA

N. B. Levy · P. Kaur
Norris Cotton Cancer Center, Lebanon, NH, USA

Fig. 1 **a** Bone marrow aspirate on presentation showed dysplastic megakaryocytes and increased blasts. **b** Blood smear from October 2009. Megakaryocytic nuclear fragments are seen

Fig. 2 H&E section (a) shows normocellular marrow ($\times 400$). Myeloperoxidase (b) and CD117 (d) show left-shifted granulopoiesis. CD34 (c) is negative in immature precursors. CD61 (e) immunostaining shows increased dysplastic mononuclear megakaryocytes

sections. Antibodies to CD34, CD117, myeloperoxidase, and CD61 (all from Leica Microsystems, Newcastle, UK) were used as per manufacturer's instructions.

Flow cytometry immunophenotypic analysis was performed on a peripheral blood specimen. The panel of monoclonal antibodies included reagents specific for CD3 [fluorescein isothiocyanate (FITC)], CD7 (FITC), CD10 (FITC), CD11b [allophycocyanin (APC)], CD13 [phycoerythrin (PE)], CD14 (APC), CD16 (FITC), CD19 (APC), CD20 (FITC), CD33 (APC), CD34 (PE), CD38 (APC), CD42b (PE), CD45 (peridin-chlorophyll-a-protein), CD56 (PE), CD61 (FITC), CD64 (FITC), CD117 (PE), and HLA-DR (PE).

All antibodies were purchased from BD Biosciences (San Jose, CA, USA), and the analyses were performed using the BD FACSCanto II (BD Biosciences). For each antibody,

negative staining levels were set by comparison with an isotype-matched control.

Conventional cytogenetic analysis was performed on metaphase cells from BM aspirate cultured for 24 h without mitogens using standard techniques. Giemsa-banded metaphases were analyzed, and the results were reported using the International System for Human Cytogenetic Nomenclature, 2005.

Results/case report

Initial presentation

An 84-year-old Caucasian male presented in May 2009 with macrocytic anemia, thrombocytopenia, and fatigue for 7 months.

Fig. 3 **a** Peripheral blood immunophenotyping (October 2009) showed abnormal population of megakaryocytes. **b** Karyotyping results

Complete blood count revealed white blood cell (WBC) count $4.4 \times 10^9/\text{l}$, hemoglobin (Hgb) 8.8 g/dL, platelet count $138 \times 10^9/\text{l}$, MCV 97.5 fL, LDH 322 units/l, and negative direct antiglobulin test. Cytogenetic evaluation showed 15/20 cells with an extra copy of chromosome 14. Twelve of 15 cells demonstrated an additional material of unknown origin on the long arm of chromosome 8—47,XY+14[3]/47, add [8](q24)[12]/46,XY[5].

Peripheral smear showed anisocytosis, dysplastic neutrophils with pseudo-Pelger-Huet anomaly, circulating megakaryocytic remnants, and hypogranular platelets.

Bone marrow aspirate demonstrated normocellular marrow (30–40 %) with trilineage maturation, hematopoiesis with granulocytic left shift, dysplastic mononuclear megakaryocytes, and increased myeloid blasts (7 %) (Fig. 1a).

Bone marrow biopsy showed a normocellular marrow with trilineage maturation but decreased granulocyte-to-erythroid ratio, left-shifted granulopoiesis, and increased dysplastic mononuclear megakaryocytes (Fig. 2). Diagnosis of myelodysplasia—refractory anemia with excess blasts (RAEB1)—was made.

Transformation to acute leukemia

In October 2009, the patient had increased fatigue, and his transfusion requirements increased to 6 units of red blood cells per month. At that time, complete blood count showed WBC $6.7 \times 10^9/\text{l}$, Hgb 8.7 g/dL, MCV 92.2 fL, and

platelet count $121 \times 10^9/\text{l}$. Immunophenotyping of peripheral blood by flow cytometry identified abnormal $\text{CD45}^-/\text{CD42b}^+/\text{CD61}^+$ megakaryocytic precursor population (50 % of the sample) that was negative for CD34, CD45, CD117, and all other myeloid and lymphoid antigens tested (CD3, CD13, CD14, CD19, and CD56) (Fig. 3a). Cytogenetic evaluation showed an abnormal clone with an apparent translocation between the long arm of chromosome 3 and the long arm of chromosome 8 and an additional copy of chromosome 14. Of note, a clone with +14 and added material on 8q was seen in the first bone marrow preparation, but structural changes on chromosome 3 were not seen (Fig. 3b).

Significant numbers of small megakaryocytic nuclear fragments were detected (Fig. 1b), and red cell anisopoikilocytosis with increased ovalocytes, acanthocytes, and schistocytes was seen in the peripheral smear.

Bone marrow aspirate and biopsy were repeated, giving suspicion for disease progression. The aspirate was a particulate and hemodiluted. The biopsy showed increased marrow cellularity ranging from 40 to 90 % with fibrosis, decreased erythropoiesis, left-shifted granulopoiesis with atypically localized immature precursors, and increased small dysplastic mononuclear megakaryocytes.

The immunostaining revealed that a significant portion of the immature precursors were myeloperoxidase-positive (Fig. 4), and a subset also expressed CD117. There was a minimal expression of CD34. CD61 stain confirmed the increased numbers of dysplastic mononuclear megakaryocytes.

Fig. 4 H&E section (a) shows hypercellular bone marrow with atypically localized immature precursors and increased number of dysplastic mononuclear megakaryocytes ($\times 400$). Myeloperoxidase (b) and CD117 (d) immunostaining highlights immature precursors which are CD34-negative (c). CD61 (e) immunostaining highlights increased population of dysplastic mononuclear megakaryocytes

Table 1 Association of MDS and AML with cytogenetic aberration t(3;8)(q26;q24)

Reference	Patient number	Diagnosis	Age (years)/gender	Dysplasia	Karyotype	SLF/TLF(m)
[6]	1	t-AML (sarcoma)	46/F	Multilineage	46,XX,t(3;8)(q26;q24),-7,+mar	A (15)
[6]	2	t-AML (DLBCL)	68/F	Multilineage	46,XX,t(3;8)(q26;q24)/46,XX	A (1)
[6]	3	t-MDS (MCL)	57/M	Multilineage	45,XY,t(3;8)(q26;q24),-7	A (16)
[6]	4	AML	82/M	Multilineage (elevated platelets)	47,XY,t(3;8)(q26;q24),+13	D (6)
[6]	5	AMML	73/M	Multilineage	46,XY,t(3;8)(q26;q24)	A (2)
[10]	CR	MDS, progressed to AML	62/M	Multilineage (elevated platelets)	t(3;8)(q26;q24)	D (72)
[3]	905	MDS/AML	NI	NI	t(3;8)(q26;q23)	NI
[9]	CR	AML, NOS (HL)	58/F	NI	46,XX,t(3;8)(q26;q23),t(9p15q),+f	D (0)
[11]	CR	t-AML	28/M	Multilineage	t(3;8)(q26;q24), monosomy 7	A (3)
[12]	CR	CML, t(9;22)	47/F	One lineage	46,XX,t(3;8)(q26;q24),t(9;22)(q34;q11)/46, idem,t(4;5)(p16;q31)/46, idem,del(6)(q21q27)	D (23)
[14]	164	AML/MDS	NI	NI	45,XY,t(3;8)(q26;q24),-7	NI
[16]	39	AML/M5	66/F	NI	46,XX,t(3;8)(q26;q24),-7	NI
	40	AML/M2	69/F	NI	46,XX,t(3;8)(q26;q24),del(5)(q14q34),-7,-18	NI
[15]	16	AML	52/F	NI	45,XX,t(3;8)(q26;q24),-45, idem,inv(7)(q22q34)	NI
[17]	CR	MDS/CMML AML	65/F	Multilineage	46,XX,t(3;8)(q26;q24)/46, idem,t(8;21)(q13;q22)	D (84)
[18]	556_H042	AML, NOS	NI/M	NI	46,XY,t(3;8)(q26;q24)	NI
[13]	CR	Anaplastic large cell lymphoma	13/M	NI	46,XY,t(2;5)(p23;q35),t(3;8)(q26;q24)	D (6)
Current report	CR	AML with myelodysplasia-related changes	84/M	Multilineage	47,XY,t(3;8)(q26;q24),+14	D (7)

CR case report (single patient is reported), SLF/TLF(m) status at the last follow-up/time of the last follow-up in months, A alive, D deceased, NI no information available, AML, NOS acute myeloid leukemia, not otherwise specified, t-AML therapy-related AML, MCL mantle cell lymphoma, AMML acute myelomonocytic leukemia, HL Hodgkin lymphoma, CML chronic myelogenous leukemia, CMML chronic myelomonocytic leukemia, M male, F female

Final pathologic diagnosis of MDS with fibrosis and progression to acute myeloid leukemia was rendered (AML with myelodysplasia-related changes).

Following diagnosis, patient was started on lenalidomide and prednisone. Patient's hemoglobin increased to 8.3–9.0 g/dL, and platelet count returned to normal. This was accompanied by the disappearance of circulating blasts and megakaryocytic fragments and a 25 % decrease in transfusion requirement. In December 2009, patient developed fevers and myalgias and was admitted to the hospital with pancytopenia and sepsis. He elected to pursue comfort measures and died 7 months after the initial diagnosis of MDS.

Discussion

The reported case is of an 84-year-old patient who presented initially with macrocytic anemia, mild thrombocytopenia, and fatigue and was diagnosed with MDS/RAEB1. The patient quickly became transfusion-dependent, manifested progression to acute leukemia with extensive myelofibrosis and dysmegakaryopoiesis, and expired 7 months after initial diagnosis of MDS. Cytogenetic evaluation of bone marrow showed 47,XY,t(3:8)(q26;q24),+14[11] which was first detected at the time of the transformation.

Recurrent translocation or inversion between regions of 3q21 and 3q26, most commonly inv(3)(q21q26) and t(3:3)(q21;q26), gives rise to the so-called “3q21q26 syndrome.” Rearrangement of 3q26 has been described in 5 % of MDS cases and also noted in AML and chronic myeloid leukemia in blast crisis [6]. The distinctive clinical features are normal or elevated platelet count at the initial presentation, hyperplasia and dysplasia of megakaryocytes, and aggressive course with poor response to therapy.

Association of MDS and AML with cytogenetic aberration t(3:8)(q26;q24) has been described in a total of 14 patients [3, 7–18] (Table 1). Poor outcome was a characteristic of this group. Two patients also demonstrated marked thrombocytosis.

Low normal platelet count and dysmegakaryopoiesis with circulating megakaryoblasts were distinguishing features.

The 3q26.2 chromosome band contains *ectopic viral integration gene (EVII)* [19]. *EVII* is a proto-oncogene that is involved in the development of myeloid-type leukemia with poor prognosis [5, 20, 21]. The gene encodes a nuclear DNA-binding zinc finger protein [19]. It is aberrantly expressed in AML and MDS, which exhibit rearrangements of 3q26. In normal tissues, *EVII* is found in a longer variant, MDS-EVII, and encodes a protein that functions as a negative regulator of tumorigenesis. Breakpoints of various translocations are heterogeneous and are located both upstream and downstream of the *EVII* coding region, leading to inappropriate *EVII* activation under the putative promoters located on 3q21. Ribophorin I and GR6 were

implicated as fusion partners of *EVII*. In case of t(3;3), ribophorin I is translocated upstream, and in case of inv(3), it is translocated downstream of *EVII* [22].

Lennon and colleagues demonstrated that in AML with t(3:8)(q26;q24), the breakpoints are located at the *EVII*/MDS1 locus on chromosome 3 and are distal to plasmacytoma variant translocation 1 (PVT1) on chromosome 8 [5]. Overexpression of *EVII* protein and *PVT1* amplification ensue. PVT1 is an oncogene homolog that activates C-MYC which in turn enhances cell proliferation [23]. t(3:8)(q26;q24) typically involves aberrant overexpression of *EVII* regardless of the heterogeneous breakpoints and various fusion partners [5].

The translocation t(3:8)(q26;q24) was seen in association with monosomy of chromosome 7 in 6 of 14 reported patients. The loss of chromosome 7 is a frequent abnormality in MDS, AML, and “3q26 syndrome” and is part of the so-called “monosomal karyotype” indicating poor prognosis. Five of 16 patients had t(3:8)(q26;q24) as a sole genetic abnormality. Our patient showed a 47,XY karyotype with an additional copy of chromosome 14. One of five patients in Lin's study who presented with de novo AML and fatal outcome in 7 months also had a 47,XY karyotype with additional chromosome 13 [6].

The molecular (*EVII* expression) and clinicomorphological (dysmegakaryopoiesis with normal/high platelets and aggressive clinical course) features of cases with t(3:8)(q26;q24) resemble 3q21q26 syndrome which has poor prognosis. Our prior reports show that t(3:8)(q26;q24) in MDS/AML is also associated with unfavorable prognosis. In our case, the cytogenetic abnormality was first demonstrated at the time of transformation to AML. Additional cases may help to delineate t(3:8)(q26;q24) as a marker of aggressive disease with poor outcome in MDS/AML.

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Alvarez S, Cigudosa JC (2005) Gains, losses and complex karyotypes in myeloid disorders: a light at the end of the tunnel. *Hematol Oncol* 23(1):18–25
2. Swerdlow SHCE, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, Vardiman JW (2008) WHO classification of tumours of haematopoietic and lymphoid tissues, 4th edn. International Agency for Research on Cancer, Lyon
3. Olney HJ, Le Beau MM (2007) Evaluation of recurring cytogenetic abnormalities in the treatment of myelodysplastic syndromes. *Leuk Res* 31(4):427–434
4. Lai JL, Preudhomme C, Zandecki M, Flactif M, Vanrumbeke M, Lepelley P et al (1995) Myelodysplastic syndromes and acute

- myeloid leukemia with 17p deletion. An entity characterized by specific dysgranulopoiesis and a high incidence of P53 mutations. *Leukemia* 9(3):370–381
5. Lennon PA, Abruzzo LV, Medeiros LJ, Cromwell C, Zhang X, Yin CC et al (2007) Aberrant EVI1 expression in acute myeloid leukemias associated with the t(3;8)(q26;q24). *Cancer Genet Cytogenet* 177(1):37–42
 6. Lin P, Medeiros LJ, Yin CC, Abruzzo LV (2006) Translocation (3;8)(q26;q24): a recurrent chromosomal abnormality in myelodysplastic syndrome and acute myeloid leukemia. *Cancer Genet Cytogenet* 166(1):82–85
 7. Lin P. (2007) t(3;8)(q26;q24). In: Atlas of genetics and cytogenetics in oncology and haematology. <http://AtlasGeneticsOncology.org/Anomalies/t0308q26q24ID1463.html>. Accessed 12 Nov 2012
 8. Mitelman F et al. (2012) Mitelman database of chromosome aberrations and gene fusions in cancer. <http://cgap.nci.nih.gov/Chromosomes/Mitelman>. Accessed 12 Nov 2012
 9. Iurlo A, Mecucci C, Van Orshoven A, Michaux JL, Boogaerts M, Noens L et al (1989) Cytogenetic and clinical investigations in 76 cases with therapy-related leukemia and myelodysplastic syndrome. *Cancer Genet Cytogenet* 43(2):227–241
 10. Mertens F, Johansson B, Billstrom R, Engquist L, Mitelman F (1987) A case of myelodysplastic syndrome with high platelet counts and a t(3;8)(q26;q24). *Cancer Genet Cytogenet* 27(1):1–4
 11. Schroeder T, Hildebrandt B, Mayatepek E, Germing U, Haas R (2008) A patient with glycogen storage disease type Ib presenting with acute myeloid leukemia (AML) bearing monosomy 7 and translocation t(3;8)(q26;q24) after 14 years of treatment with granulocyte colony-stimulating factor (G-CSF): a case report. *J Med Case Rep* 2:319
 12. Lin P, Lennon PA, Yin CC, Abruzzo LV (2009) Chronic myeloid leukemia in blast phase associated with t(3;8)(q26;q24). *Cancer Genet Cytogenet* 193(2):119–122
 13. Monaco S, Tsao L, Murty VV, Nandula SV, Donovan V (2007) Oosterheld Jet al. Pediatric ALK⁺ anaplastic large cell lymphoma with t(3;8)(q26.2;q24) translocation and c-myc rearrangement terminating in a leukemic phase. *Am J Hematol* 82(1):59–64
 14. Andersen MK, Christiansen DH, Pedersen-Bjergard J (2005) Centromeric breakage and highly rearranged chromosome derivatives associated with mutations of TP53 are common in therapy-related MDS and AML after therapy with alkylating agents: an M-FISH study. *Gene Chromosome Cancer* 42(4):358–371
 15. Bobadilla D, Enriquez EL, Alvarez G, Gaytan P, Smith D, Slovak ML (2007) An interphase fluorescence in situ hybridization assay for detection of 3q26.2/EVI1 rearrangements in myeloid malignancies. *Br J Haematol* 136(6):806–813
 16. Charrin C, Belhabri A, Treille-Ritouet D, Theuil G, Maquaud JP, Fiere D, Thomas X (2002) Structural rearrangements of chromosome 3 in 57 patients with acute myeloid leukemia: clinical, hematological and cytogenetic features. *Hematol J* 3(1):21–31
 17. Isoda A, Sakurai A, Ogawa Y, Miyazawa Y, Saito A, Matsumoto M, Sawamura M (2009) Chronic inflammatory demyelinating polyneuropathy accompanied by chronic myelomonocytic leukemia: possible pathogenesis of autoimmunity in myelodysplastic syndrome. *Int J Hematol* 90(2):239–242
 18. Lugthart S, Groschel S, Beverloo HB, Kayser S, Valk PJ, van Zelderen-Bhola SL et al (2010) Clinical, molecular, and prognostic significance of WHO type inv(3)(q21q26.2)/t(3;3)(q21;q26.2) and various other 3q abnormalities in acute myeloid leukemia. *J Clin Oncol* 28(24):3890–3898
 19. Wieser R (2007) The oncogene and developmental regulator EVI1: expression, biochemical properties, and biological functions. *Gene* 396(2):346–357
 20. Buonamici S, Chakraborty S, Senyuk V, Nucifora G (2003) The role of EVI1 in normal and leukemic cells. *Blood Cells Mol Dis* 31(2):206–212
 21. Buonamici S, Li D, Chi Y, Zhao R, Wang X, Brace L et al (2004) EVI1 induces myelodysplastic syndrome in mice. *J Clin Invest* 114(5):713–719
 22. Martinelli G, Ottaviani E, Buonamici S, Isidori A, Borsaru G, Visani G et al (2003) Association of 3q21q26 syndrome with different RPN1/EVI1 fusion transcripts. *Haematologica* 88(11):1221–1228
 23. Nucifora G, Laricchia-Robbio L, Senyuk V (2006) EVI1 and hematopoietic disorders: history and perspectives. *Gene* 368:1–11