Hematology and Leukemia
ISSN 2052-434X | Volume 4 | Article 2

HOAJ
Herbert Open Access Journals

Case report Open Access

Transformation of myelodysplastic syndrome with isolated 5q-syndrome to chronic myelogenous leukemia with a novel complex BCR/ABL1 translocation with rapid progression to blast crisis

Ann-Leslie Zaslav[1*], Rajarsi Gupta[1], Bruce T. Burks[2], Michael Schuster[3], Bita Jalilizeinali[3], Erin Knorr[1], Dan Tully[1], Paula Fernicola[1], Theresa Mercado[1], Silvia Spitzer[1], Marc Golightly[1], Yupo Ma[1] and Tahmeena Ahmed[1]

*Correspondence: ann-leslie.zaslav@stonybrookmedicine.edu

[1]Department of Pathology, Stony Brook University Medical Center, Stony Brook, NY, USA.
[2]Department of Pathology, St. Catherine of Siena Medical Center, Smithtown, NY, USA.
[3]Department of Medicine, Stony Brook University Medical Center, Stony Brook, NY, USA.

Abstract

We report a case of a 72 year old female who was referred to our institution in August 2010 for Myelodysplastic syndrome (MDS) with a deletion of part of the long arm of chromosome 5 [i.e., del(5)(q12q33)]. In June 2014, she transformed to Chronic Myelogenous Leukemia (CML), where cytogenetic and FISH analysis of the bone marrow (BM) revealed the del(5q) in 1.5% of nuclei and a complex BCR/ABL1 translocation [i.e., 45,XX,t(9;15;22)(q34;p10;q11.2),-22]. Six weeks later, in July 2014, she transformed to an Acute Myelogenous Leukemia (AML) blast crisis. RT-PCR was positive for BCR/ABL1 transcript. The patient was treated with a tyrosine kinase inhibitor, Nilotinib, then had a haploidentical allogeneic bone marrow transplant from her son, and was in remission after treatment. However, throughout the course of nine subsequent cytogenetic analyses, the patient continued to undergo clonal chromosome evolution, even during remission. Transformation from MDS del(5q) to CML with rapid progression to blast crisis has rarely been reported. To our knowledge, transformation with this complex translocation has never been described. Here we describe these rare cytogenetic findings and discuss possible mechanisms involved in the persistent and evolving clonal cytogenetic abnormalities seen during the clinical course of the disease.

Keywords: Chromosomal abnormality, complex BCR-ABL1 translocation, 5q-syndrome, clonal chromosomal evolution

Introduction

Myelodysplastic syndrome (MDS) is a group of clonal hematopoietic stem cell disorders that are characterized by peripheral blood cytopenias, dysplastic morphology, and clonal cytogenetic abnormalities. The majority of clonal cytogenetic abnormalities reported in 30% to 50% of MDS are monosomy 7, loss of Y, del(5q), del(7q), del(20q) and trisomy 8.

MDS with isolated 5q- syndrome is characterized by anemia, with or without other cytopenias, and a deletion of part of the long arm of chromosome 5. Patients with MDS with 5q-syndrome have a good prognosis and are usually monitored without treatment [1,2].

Multiple genetic abnormalities occur during the evolution of MDS. BCR/ABL1 rearrangements occur with a frequency of 1% (5). To our knowledge, this complex BCR/ABL1 translocation has never been reported. We present a case of MDS transforming to CML with a complex BCR/ABL1 translocation followed by rapid progression to an AML blast crisis.

Case presentation

A 72 year old female presented to an outside institution in 2007 and was diagnosed with MDS with isolated del(5q). Her care was transferred to our institution in August 2010, where G-banded chromosome analysis of the bone marrow (BM)

 doi: 10.7243/2052-434X-4-2

revealed a deletion of part of the long arm of chromosome 5 [i.e., del(5)(q12q33)] in 11/20 metaphase cells and was confirmed by FISH (**Table 1**). The complete blood count (CBC) of the peripheral blood showed anemia (**Table 2**).

In June 2014, she presented with worsening anemia, leukocytosis, and thrombocytosis (**Table 2**). Bone marrow evaluation showed a hypercellular marrow with left-shifted granulocytic and megakaryocytic hyperplasia, consistent with transformation of MDS to chronic phase Chronic Myelogenous Leukemia (CML). Cytogenetic and FISH analyses of the BM revealed del (5q) in 1.5% of nuclei and a complex BCR/ABL1 translocation [i.e., 45,XX,t(9;15;22)(q34;p10;q11.2),-22]. RT-PCR was positive for BCR/ABL1 transcript.

Seven weeks later, in July 2014, her CBC still showed anemia, leukocytosis, and thrombocytosis, but now there were 14% blasts in the peripheral blood and 18% blasts by flow cytometry of the BM. Her disease transformed from CML chronic phase into a myeloid blast crisis. This was a rare occurrence of rapid transformation from MDS to CML to blast crisis. The patient was treated with Nilotinib, a tyrosine kinase inhibitor. The patient had a haploidentical allogeneic bone marrow transplant from her son. After completing treatment, the patient was in morphologic remission, with normal marrow morphology and cellularity. However, she continued to undergo cytogenetic clonal chromosomal evolution (**Figure 1** and **Table 1**).

To our knowledge, this is the first report of MDS transformation to CML followed by rapid progression to an AML blast crisis with this complex BCR/ABL1 translocation.

Materials and methods

Cytogenetic G-band metaphase analysis and fluorescence in situ hybridization (FISH) were performed using standard cytogenetic techniques on bone marrow (BM) and unstimulated

Table 1. Cytogenetic results.

Analysis		Specimen	G banding	FISH ***(% +)
*#	Date	Type	(number of cells in brackets)	--
#1	08/05/10	**BM	46,XX, del(5)(q12q33)[11]/46 XX[8]	del(5)(q31)/(18.5%)
#2	06/06/14	****UB	45,XX,t(9;15;22)(q34;p10;q11.2),-22[20]	del(5)(q31)/(1.5%) BCR/ABL1 + (100% metaphases)
#3	07/11/14	UB	45,XX, t(9;15;22)(q34; p10; q11.2),-22[12] /46,XX,t(9;15;22)(q34; p10; q11.2),+der (15),t(9;22) (q34;q11.2),-22[3]	BCR/ABL1 +/(93%) Extra BCR/ABL1+ (3% metaphases) extra der(15)t(9;15;22)(q34; p10;q11.2) (30% metaphases)
#4	07/21/14	UB	45, XX, t(9;15;22)(q34;p10;q11.2),-22[15] /46,XX,t(9;15;22)(q34;p10;q11.2), +der(15)t(9;15;22)(q34;p10;q11.2),-22[5]	BCR/ABL1 + 100% Extra BCR/ABL1+/(5.5%) [an extra der(15)t(9;15;22)(q34;p10;q11.2)] (10% of metaphases)
#5	11/14/14	BM	45, XX, t(9;15;22)(q34;p10;q11.2),-22[6] /46,XX,t(9;15;22)(q34;p10;q11.2),+der(15) t(9;15;22)(q34;p10;q11.2),-22[1] /46,XX,t(9;15;22)(q34;p10;q11.2), der(22)t(9;22)(q34;q11.2)[1] /45,XX,del(5)(q12q33)[1] /46,XX[11]	del(5)(q31)(0.5%) BCR/ABL1 +/(41% metaphases)
#6	4/24/15	UB	No chromosomes (no growth)	del(5)(q31)(0.5%) 3 copies of ABL1(16%) 1 copy BCR/ABL1/(7.5%)
#7	7/22/15	BM	47,XX,+8[CP5]/46,XX[7]	+8(5%) +9(6%) Normal BCR/ABL1 and 5q
#8	11/16/15	BM	• 42~46,XX,der(5)t(5;?)(p15;?),-7,-9, t(9;22)(q34;q11.2),-15,der(22)t(9;22)(q34;q11.2) t(15;22)(q23;q11.2)[cp9] •• //46,XY[11]	• XX (56%), del(5)(q31) (1%) • BCR/ABL1 (22.5%) • der(22)t(15;22)(q23;q11) (100%) •• XY (44%)
#9	1/27/16	BM	•45~46,XX,der(5)t(5;?)(p15;?),t(9;22) (q34;q11.2),15,der(22)t(9;22)(q34;q11.2)t(15;22) (q23;q11.2)[cp2] /46,XX[14] •• //46,XY[4]	• XX (69%), del(5)(q31) (1.5%) • BCR/ABL1 (1.5%) •• XY (30.5%) Normal 8 (100%)

*# – Number; **BM – Bone Marrow; ***% + – Percent Positive; ****UB – Unstimulated Blood
• – Patient karyotype and FISH; •• – Donor karyotype and FISH

doi: 10.7243/2052-434X-4-2

Table 2. Hematology results.

Date	White Blood Cells (k/μL)	Hemoglobin (g/dL)	Platelets (k/μL)	Blast (%)
8/5/2010	4.2	11.9	271	2.0
7/18/2014	93.8	8.3	887	14.0
7/25/2014	47.4	7.2	1232	8.0
7/29/2014	59.39	7.2	1416	5.0
11/14/2014	CBC not performed	CBC not performed	CBC not performed	CBC not performed
4/24/2015	CBC not performed	CBC not performed	CBC not performed	CBC not performed
7/22/2015	1.32	10.2	137	0.0
11/16/2015	CBC not performed	CBC not performed	CBC not performed	CBC not performed
12/02/2015	10.21	3.12	294	0.0
01/27/2016	2.95	3.57	11	0.0

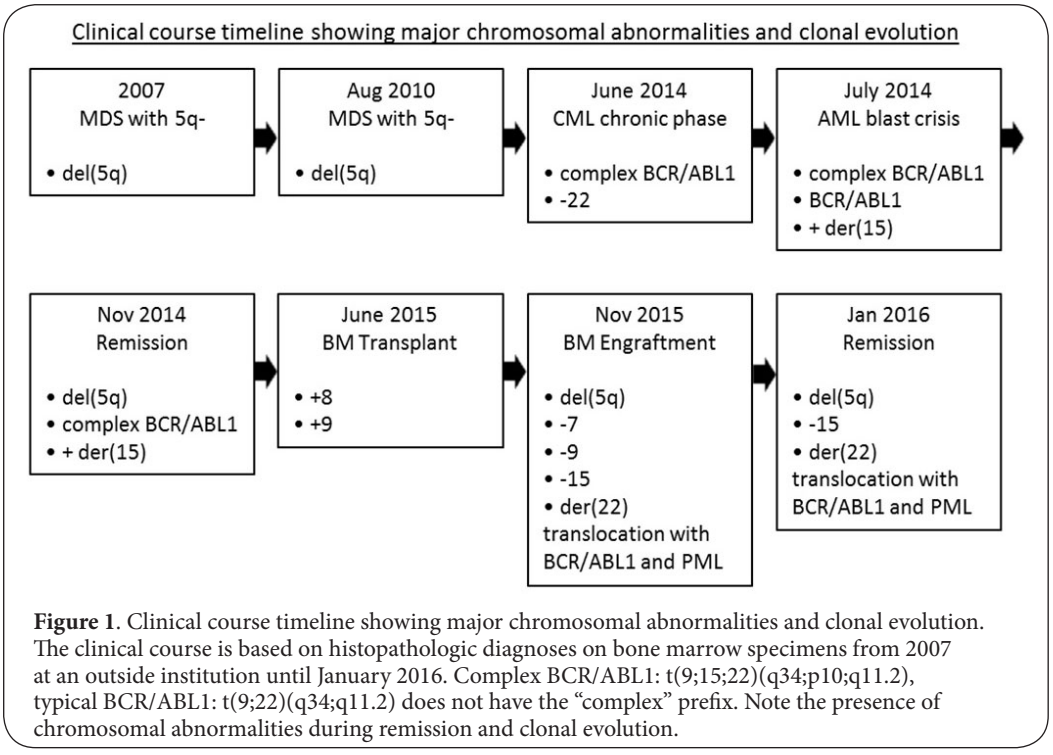

Figure 1. Clinical course timeline showing major chromosomal abnormalities and clonal evolution. The clinical course is based on histopathologic diagnoses on bone marrow specimens from 2007 at an outside institution until January 2016. Complex BCR/ABL1: t(9;15;22)(q34;p10;q11.2), typical BCR/ABL1: t(9;22)(q34;q11.2) does not have the "complex" prefix. Note the presence of chromosomal abnormalities during remission and clonal evolution.

blood (UB). Analyses were performed nine different times. G-banding was performed on 15 to 20 metaphase cells per analyses. FISH analysis was performed on 200 nuclei and/or 10 metaphase cells.

FISH probes: LSI 5q EGR1/D5S23 (5q31/5p15.2), LSI CEP8 (8p11.1-q11.1)(D8Z2), LSI BCR/ABL1 DFDC (22q11/9q34) and LSI SNRPN (15q11.2,CEP15,PML[15q22-q24]). (All probes were supplied by Abbott Molecular, Des Plaines, IL, USA). Flow cytometry was performed using a Becton Dickinson FACSCalibur using BD anti-CD33 (340679) and anti-CD34 (340667). Blood counts were performed using a Sysmex XN-10. BCR/ABL1 (p210) fusion transcript was quantified by RT-qPCR utilizing the Xpert BCR-ABL monitor kit, Cepheid, San Jose, CA. RNA was extracted from the patient's peripheral blood with the QIAamp RNA blood minikit, Qiagen, Germany. The RNA was reverse transcribed and then amplified by realtime-PCR with the Light-Cycler. BCR/ABL1 was quantified by using the t(9;22) quantification kit from Roche Molecular Systems Inc, Branchburg, NJ (this kit does not distinguish between p210 and p190).

Results

In 2007, the patient presented with MDS with 5q- syndrome at an outside institution. In August 2010 at our institution, morphologic evaluation of the BM was consistent with MDS and G-banded chromosome analysis revealed a deletion of

 doi: 10.7243/2052-434X-4-2

part of the long arm of chromosome 5 [i.e., del(5)(q12q33)] in 11/20 metaphase cells and confirmed by FISH (all cytogenetic results are summarized in **Table 1**).

In June 2014, bone marrow biopsy showed a hypercellular marrow with left-shifted granulocytic and megakaryocytic hyperplasia, consistent with transformation to CML in chronic phase (**Figure 2**). Cytogenetic and FISH analyses of the BM revealed the del(5q) in 1.5% of nuclei and a complex BCR/ABL1 translocation: 45,XX,t(9;15;22)(q34;p10;q11.2),-22 in all metaphase FISH cells (**Figure 3**, **Table 1**).

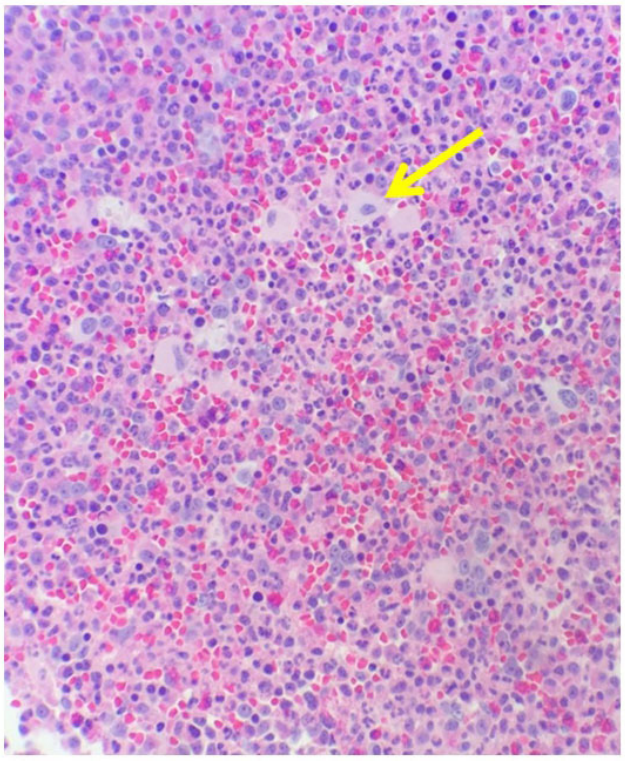

Figure 2. CML, chronic phase.
Histologic examination of the bone marrow with hematoxylin-eosin staining reveals hypercellular marrow space with left-shifted myeloid hyperplasia and dwarf megakaryocytes. Arrow indicates a dwarf megakaryocyte.

Seven weeks later in July 2014, she was in blast crisis with 14% blasts in the peripheral blood (PB) and 18% blasts by flow cytometry of the BM. G-banding and FISH of unstimulated blood (UB) revealed both the complex translocation and further clonal evolution. An additional der(15)t(9;15;22)(q34;p10;q11.2) in 5/20 metaphase cells was observed. RT-PCR molecular testing showed a p210 BCR/ABL1 transcript level of >10% (**Table 3**). The del(5q) was not present in this analysis. The patient transformed from CML to myeloid blast crisis in less than a month.

Twelve weeks later in November 2014, cytogenetic and FISH analysis of the remission BM revealed the same clones

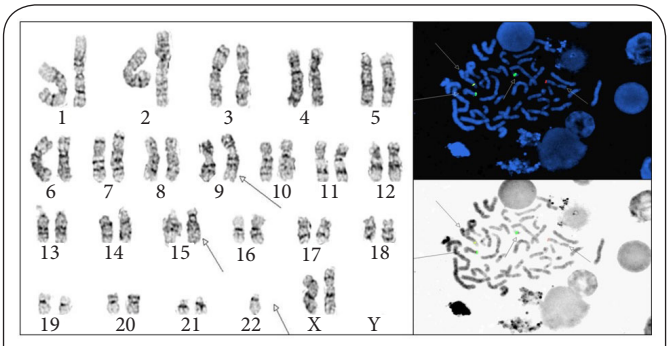

Figure 3. G-banded metaphase from analysis #2: 45,XX,t(9;15;22)(q34;p10;q11.2),-22.
Arrows indicate the derivative chromosomes (left panel). FISH-DAPI (top right panel) and Reverse-DAPI (bottom right panel), where arrows indicate the normal chromosome 9 (red), normal chromosome 22 (green), der(9) (yellow), and der(15) (yellow).

Table 3. BCR/ABL1 transcript results.

Specimen	Date	BCR/ABL1p210	BCR/ABL1p210 and p190
blood	7/15/2014	>10%	--
blood	8/12/2015	--	not detected
blood	12/11/2015	>10%	--
blood	12/21/2015	>10%	--
blood	1/12/2016	>10%	--
blood	1/23/2016	1.8%	--

present in July 2014 and the del(5q) in 1/20 metaphase cells and in 1/200 nuclei of FISH analyses. In addition to the del(5q), a der(15)t(9;15;22)(q34;p10;11.2) was present in 8/20 metaphase cells and a der(22)t(9;22)(q34;q11.2) was present in 1/20 metaphase cells.

Twenty-one weeks later in April 2015, nuclear FISH of PB revealed del(5q) in 1/200 nuclei, a variant BCR/ABL1 translocation in 6/200 nuclei, and three copies of ABL1 [i.e., trisomy 9] in 32/200 nuclei.

In June 2015, the patient had a haploidentical allogeneic bone marrow transplant from her son. The bone marrow biopsy at the end of June 2015 showed normal marrow morphology, cellularity and normal flow cytometry findings proving she was in morphologic and immunophenotypic remission. However, chromosome analysis and FISH of the BM showed +8 in 10/200 nuclei and +9 in 12/200 nuclei. The variant BCR/ABL1 and del(5q) were not detected.

In November 2015, post-transplant evaluation of the BM revealed normal marrow morphology and cellularity, normal blood counts, and normal flow cytometry. Cytogenetic and FISH analyses revealed a mixture of male and female cells. All of the female cells were abnormal [i.e., 42~46,XX,der(5)t(5;?),-7,-9,t(9;22)(q34;q11.2),-15,der(22)t(9;22)(q34;q11.2)t(15;22)(q23;q11.2)[cp9]. In this clone, the der(22) had BCR/

doi: 10.7243/2052-434X-4-2

ABL1 translocated to the long arm of the der(22) and PML (15q23) translocated to the short arm of the der(22) (**Figure 4**). FISH showed the reappearance of the BCR/ABL1 translocation in 45/200 nuclei and del(5q) in 2/200 nuclei. FISH also showed a normal signal pattern for chromosome 8. RT-PCR molecular testing for the p210 BCR/ABL1 transcript was positive >10% (**Table 3**).

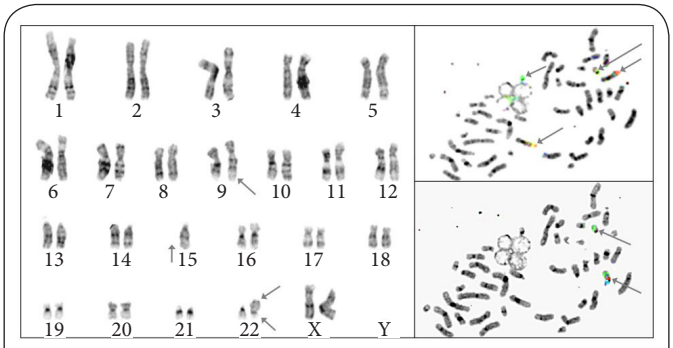

Figure 4. G-banded metaphase from analysis #8: 45,XX,der(5)t(5;?),t(9;22)(q34;q11.2),-15,der(22)t(9;22)(q34;q11.2)t(15;22)(q23;q11).
The der(22) has BCR/ABL1 translocated to the long arm of the der(22) and PML (15q23) translocated to the short arm of the der(22). The arrows indicate the derivative chromosomes 9 and 22 and the missing chromosome 15 homolog (left panel). Top right panel reverse-DAPI image demonstrates the BCR/ABL1 translocation on the long arm of the der(22). Arrows indicate the normal chromosome 9 (red), the normal chromosome 22 (green), the der(9) (yellow) and the der(22) (yellow). Bottom right panel reverse-DAPI image demonstrates PML (15q23) (green) on the short arm of the der(22). Arrows indicate the normal chromosome 15 and the der(22).

In December 2015, she developed a rash and was diagnosed with Graft-versus-Host Disease (GVHD) treated with photophoresis. Her most recent bone marrow biopsy from January 2016 showed trilineage engraftment and no morphologic and no immunophenotypic evidence of MDS, AML, or CML. However, BCR/ABL1 was present in the chromosomes FISH and by RT-PCR (**Tables 1** and **3**, **Figure 4**).

Discussion

The transformation from MDS to CML has rarely been reported [**6**]. To our knowledge, this is the first report of rapid progression to CML myeloid blast crisis with a complex BCR/ABL1 translocation [45,XX,t(9;15;22)(q34;p10;q11.2),-22] (**Figure 1**) in this clinical scenario. The patient had clonal cytogenetic evolution with chromosomal gains and losses of diverse cell populations during the various phases of therapy and during remission.

AML has been proposed to arise from Class I and Class II mutations. Class I mutations increase cell proliferation and survival, whereas Class II mutations suppress differentiation and apoptosis. BCR/ABL1 is a Class II mutation that impairs differentiation and apoptosis [**3**]. In AML, cooperation of Class II mutations suppressing differentiation with Class I mutations increasing cell proliferation are frequently seen with BCR/ABL1 positive subclones in patients with AML. This was reported in a small series of patients by Bacher et. al., 2011 [**4**]. These subclones occurred in various subtypes of AML and one patient had del(5q). It is possible that the BCR/ABL1 translocation could cooperate with different mutation types in AML as a Class I mutation promoting cell proliferation of the abnormal clones. As the BCR/ABL1 translocation only occurs in approximately 1% of patients with AML [**5**], this may be significant for cell proliferation.

Fukunaga [**6**] reported a case of MDS that initially presented with del(5q) and add(16q). After 18 months, the patient still had the del(5q), add (16q) clone, but also acquired a t(9;22)(q34;q11.2), an add(1)(q32), and a +8 clone. Our patient also acquired the complex BCR/ABL1 translocation and a +8 clone. After the appearance of the t(9;22)(q34;q11.2), the BM in both cases showed AML morphology.

The BCR/ABL1 translocation occurs in <1% of MDS patients [**5**]. The few reported cases support evidence that the process represents multistep leukemogenesis. The initial event may result from clonal proliferation of stem cells in the acquisition of the translocation existing in neoplastic cells [**6**]. Some patients with AML may acquire the translocation as an additional chromosome abnormality during the evolution of the disease or during relapse, as reported by Bacher [**4**] and seen in our patient. Three possible explanations for the late appearing BCR/ABL1 translocation are:

1. It may have been present during the course of the patients' disease, but the patient was not cytogenetically evaluated for four years.
2. It may represent evidence of a multistep process.
3. The translocation may represent a new clone in leukemic relapse [**6**-**9**].

These findings indicate that the translocation could have arisen during various times within the overall course of the disease. The patient went from MDS to CML to an AML-like blast crisis within one month. To our knowledge, this was the first report associated with this complex BCR/ABL1 translocation: 45,XX,t(9;15;22)(q34;p10;q11.2),-22 with rapid progression resulting in the loss and gain of diverse cell populations. This case illustrated the importance of careful patient monitoring to diagnose the nature of this disease and to accordingly modify the course of treatment. Additional cases of MDS with complex BCR/ABL1 translocations are needed to further determine the clinical significance of these findings.

Competing interests

The authors declare that they have no competing interests.

Publication history

Editors: Pedro C. Redondo, University of Extremadura, Spain.
Tarek M. A. Owaidah, Al Faisal University, Saudi Arabia.
Received: 04-Apr-2016 Final Revised: 09-May-2016
Accepted: 23-May-2016 Published: 02-Jun-2016

Authors' contributions

Authors' contributions	ALZ	RG	BB	MS	BJ	EK	DT	PF	TM	SS	MG	YM	TA
Research concept and design	✓	--	--	--	--	--	--	--	--	--	--	--	✓
Collection and/or assembly of data	✓	✓	✓	✓	✓	✓	✓	✓	--	✓	✓	✓	✓
Data analysis and interpretation	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Writing the article	✓	--	--	--	--	--	--	--	--	--	--	--	✓
Critical revision of the article	✓	✓	--	--	--	--	--	--	--	--	--	--	✓
Final approval of article	✓	--	--	--	--	--	--	--	--	--	--	✓	✓
Statistical analysis	✓	✓	--	--	--	--	--	--	--	--	--	--	✓

References

1. McPherson R and Pincus M. **Henry's clinical diagnosis and management by laboratory methods.** Philadelphia, PA: Elsevier Saunders.
2. Campo E, Swerdlow SH, Harris NL, Pileri S, Stein H and Jaffe ES. **The 2008 WHO classification of lymphoid neoplasms and beyond: evolving concepts and practical applications**. *Blood*. 2011; **117**:5019-32. | Article | PubMed Abstract | PubMed FullText
3. Specht A, Bernard P, Goeldner M and Peng L. **Mutually induced formation of host-guest complexes between p-sulfonated calix[8]arene and photolabile cholinergic ligands**. *Angew Chem Int Ed Engl*. 2002; **114**:4900-4902. | Article | PubMed
4. Bacher U, Haferlach T, Alpermann T, Zenger M, Hochhaus A, Beelen DW, Uppenkamp M, Rummel M, Kern W, Schnittger S and Haferlach C. **Subclones with the t(9;22)/BCR-ABL1 rearrangement occur in AML and seem to cooperate with distinct genetic alterations**. *Br J Haematol*. 2011; **152**:713-20. | Article | PubMed
5. Keung YK, Beaty M, Powell BL, Molnar I, Buss D and Pettenati M. **Philadelphia chromosome positive myelodysplastic syndrome and acute myeloid leukemia-retrospective study and review of literature**. *Leuk Res*. 2004; **28**:579-86. | Article | PubMed
6. Fukunaga A, Sakoda H, Iwamoto Y, Inano S, Sueki Y, Yanagida S and Arima N. **Abrupt evolution of Philadelphia chromosome-positive acute myeloid leukemia in myelodysplastic syndrome**. *Eur J Haematol*. 2012; **90**:245-9. | Article | PubMed
7. Gilliland DG. **Hematologic malignancies**. *Curr Opin Hematol*. 2001; **8**:189-91. | PubMed
8. Ebert BL, Pretz J, Bosco J, Chang CY, Tamayo P, Galili N, Raza A, Root DE, Attar E, Ellis SR and Golub TR. **Identification of RPS14 as a 5q- syndrome gene by RNA interference screen**. *Nature*. 2008; **451**:335-9. | Article | PubMed Abstract | PubMed FullText
9. Jacobsen RJet. al. **Late appearance of Philadelphia Chromosome**. *British Journal of Haematology*. 2008; **63**:392-394.

Citation:
Zaslav A-L, Gupta R, Burks BT, Schuster M, Jalilizeinali B, Knorr E, Tully D, Fernicola P, Mercado T, Spitzer S, Golightly M, Ma Y and Ahmed T. **Transformation of myelodysplastic syndrome with isolated 5q-syndrome to chronic myelogenous leukemia with a novel complex BCR/ABL1 translocation with rapid progression to blast crisis**. *Hematol Leuk*. 2016; **4**:2.
http://dx.doi.org/10.7243/2052-434X-4-2