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

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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)
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 autologous 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

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Table 1. Cytogenetic results.

| Analysis | Specimen | G banding | FISH ***(% +) |
|----------|----------|-----------|---------------|
| #1       | 08/05/10 | **BM      | del(5)(q12q33)[11]/46,XX[8] | -- |
| #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)[2q34;11.2],-22[3] | BCR/ABL1 +/(93%) Extra BCR/ABL1+ (3% metaphases) extra der(15)(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)[n15;19;22](q34;p10;q11.2),-22[5] | BCR/ABL1 + 100% Extra BCR/ABL1+/ (5.5%) [an extra der(15)(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)[9;15;22](q34;p10;q11.2),-22[1]/46,XX,t(9;15;22)(q34;p10;q11.2),+der(22)[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       | 04/24/15 | UB        | No chromosomes (no growth) | del(5)(q31)(0.5%) 3 copies of ABL1(16%) 1 copy BCR/ABL1(7.5%) |
| #7       | 07/16/15 | 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)[(5?),(p15?);,-7,-9, t(2;22)(q34;11.2),-15, der(22)[9;22](q34; q11.2) t(15;22)(q23;11.2)[cp9] //46,XX[11] | XX (56%), del(5)(q31) (1%) BCR/ABL1 (22.5%) der(22)[15;22](q23;11) (100%) XX (44%) |
| #9       | 01/27/16 | BM        | 45~46,XX,der(5)[(5?),(p15?),(q11.2), t(9;22)(q34;11.2),15,der(22)[9;22](q34; q11.2)(q23;11.2)[cp2] //46,XX[14] | XX (69%), del(5)(q31) (1.5%) BCR/ABL1 (1.5%) XX (30.5%) Normal 8 (100%) |

*# – Number; **BM – Bone Marrow; ***% + – Percent Positive; ****UB – Unstimulated Blood
• – Patient karyotype and FISH; •• – Donor karyotype and FISH
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 FACS Calibur 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. In August 2010 at our institution, morphologic evaluation of the BM was consistent with MDS and G-banded chromosome analysis revealed a deletion of 5q- syndrome.

| 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       |

Table 2. Hematology results.

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.
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). 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) was present in 8/20 metaphase cells and a der(22)t(9;22)(q34;q11.2) was present in 1/20 metaphase cells.

Twelve weeks later in November 2014, cytogenetic and FISH analysis of the remission BM revealed the same clones 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),-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/ABL1p210 transcript level of >10% and p190 not detected. See Table 3 for details.

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% | -- |
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).

In December 2015, she developed a rash and was diagnosed with Graft-versus-Host Disease (GVHD) treated with photopheresis. 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;q11.2),-15,der(22)(q9;22) (q34;q11.2)(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).

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.

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