

Original Article

Transformation of the 5q- syndrome to acute lymphoblastic leukemia: a report of two cases and review of the literature

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Abstract: Myelodysplastic syndrome (MDS) with an isolated deletion of the long arm of chromosome 5 (5q- syndrome) is a distinct subtype of MDS with an indolent course that rarely transforms to acute leukemia. Deletion of the long arm of chromosome 5 has also been reported in rare cases of de novo B-lymphoblastic leukemia. We present two cases of 5q- syndrome with a similar and unusual course of transformation to lymphoblastic leukemia while on Lenalidomide. These two patients achieved an initial response; however, later acquired a second cytogenetic abnormality, became refractory to treatment and evolved into acute leukemia. At the time of transformation, both patients had recurrence of the 5q- abnormality. Review of the literature and the mechanisms of transformation of the 5q- syndrome into an acute leukemia are discussed. Although the relationship between the events in our cases remains unclear, the intriguing similarity between the two cases raises a question whether immune modulators can alter the natural course of MDS. To our knowledge, no similar cases were previously reported in the literature.

Keywords: Myelodysplastic, syndrome, acute lymphoblastic leukemia, lenalidomide, 5q- syndrome

Introduction

Myelodysplastic syndrome (MDS) is a clonal hematologic disorder characterized by one or more cytopenias, dysplasia in one or more myeloid cell lines, ineffective hematopoiesis, and increased risk of transformation to acute leukemia [1]. Although progression to acute leukemia is the natural course of the disease in many cases of MDS, the percentage of patients who progress varies substantially in the various subtypes of MDS. While patients with refractory anemia with excess blasts-2 (RAEB-2) or complex cytogenetic abnormalities have an estimated lifetime risk of leukemic transformation of more than 50%, less aggressive subtypes, such as refractory anemia with unilineage dysplasia, have a lifetime risk of less than 5% [2]. Myelodysplastic syndrome with an isolated deletion of the long arm of chromosome 5 (5q- syndrome) is recognized as a distinct entity by the WHO classification. The syndrome is characterized by macrocytic anemia and thrombocyto-

sis in 30-50% of patients. The clinical course is favorable with leukemic transformation occurring in less than 10% of patients [3]. Acute leukemia evolving from an underlying MDS is almost always of myeloid lineage. Rare cases of MDS transforming to lymphoblastic leukemia (ALL) have been reported and although the 5q- abnormality has been previously reported in de novo ALL [4-6], MDS with a 5q- cytogenetic abnormality transforming to B- lymphoblastic leukemia has never been reported. We present 2 patients with a 5q- syndrome transforming into a lymphoblastic lymphoma/leukemia. To our knowledge, these are the first two cases reported in the literature to date.

Case one

Patient A is a 68-year-old Caucasian male who presented in January of 2007 with macrocytic anemia and hemoglobin of 9.1 g/dL. His white blood cell count, differential, and platelets were all normal. Bone marrow studies were per-

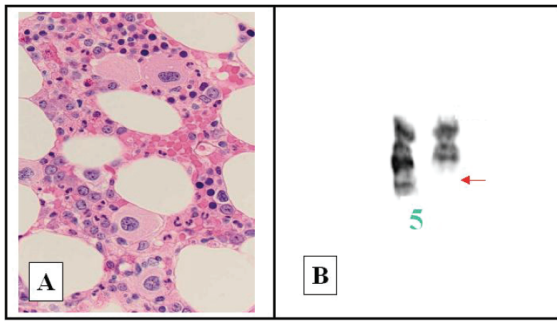


Figure 1. (A) Bone marrow core biopsy, 40X magnification, showing monolobated megakaryocytes; (B) Cytogenetics showing deletion of the long arm of chromosome 5.

formed and showed a cellular marrow with erythroid hyperplasia and frequent dysplastic small monolobated megakaryocytes (**Figure 1A**). Cytogenetics demonstrated an abnormal karyotype: 47,XY,+Y,del(5)(q13q33)[19]/47,XY,+Y[1]; with 5q- in 19 of 20 metaphases (**Figure 1B**). These findings were consistent with an MDS, 5q-syndrome. The patient was treated with le-

validomide, with a good response. His hemoglobin was maintained over 11 g/dL. In September of 2009, the patient developed pancytopenia with a hemoglobin of 7.2 g/dL, platelets of $35 \times 10^9/L$, and an absolute neutrophil count (ANC) of $0.5 \times 10^9/L$. Bone marrow studies were repeated and demonstrated sheets of medium size blasts with high N: C ratio, finely dispersed chromatin and inconspicuous nuclei that accounted for >90% of the total cellularity (**Figure 2A**). This blast population replaced background trilineage hematopoiesis and hence dysplastic changes were not appreciated on the examined smears. Flow cytometric studies demonstrated an expanded population of blasts (75% of the total events) with the following immunophenotype: CD19+, CD79a+, CD22+, CD10+ and TdT+ (**Figure 2C & D**). This blast population was negative for CD20, CD34 and all myeloid markers including myeloperoxidase confirming a diagnosis of B-lymphoblastic lymphoma/ leukemia. Cytogenetic studies at this time revealed a more complex karyotype in which all 20 metaphases were characterized by an extra copy of the Y chromosome. A second cell line had a deletion of long arm of chromosome 5 and a

third line had deletion of the long arm of chromosome 20 (**Figure 2B, II**). The composite karyotype was: 47,XY,+Y[16]/47,idem,del(5)(q13q31)[2]/47,XY,+Y,del(20)(q11.2q13)[cp2]. FISH (Fluorescent in-situ hybridization) studies confirmed the 5q- abnormality in 62% of the cells (**Figure 2B, I**), however were negative for 20q deletion, monosomy 7, trisomy 6, 8, 21, MLL and BCR/ABL gene rearrangements. Treatment with 5-azacytadine was anticipated at this point. Unfortunately, the patient had persistent oozing arteriovenous malformations that precluded therapy. The patient's condition continued to decline and he expired soon thereafter.

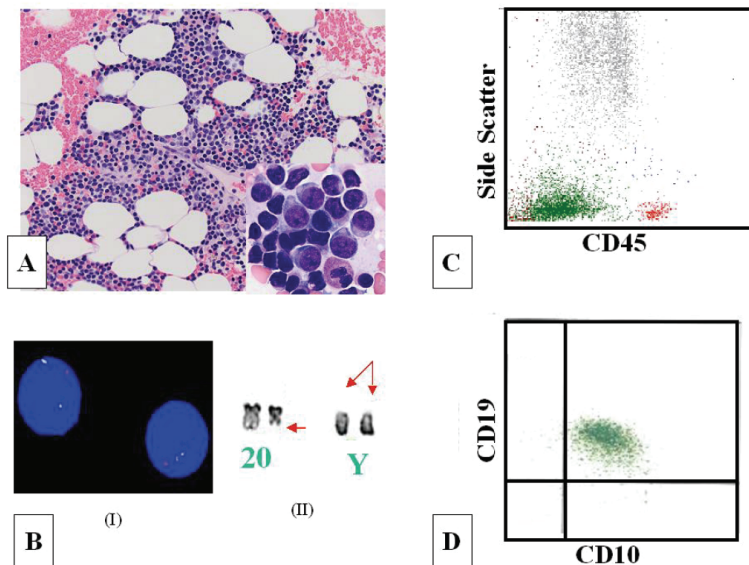


Figure 2. (A) Bone marrow core biopsy, 40 X magnification. Inset represent aspirate smear (100 X magnification). (B, I) FISH study showing 2 cells each with two green signals corresponding to internal signals probes (5p15.2) and only one red signal indicating loss of long arm of 5 (EGFR1). (B, II) Cytogenetics showing loss of the long arm of chromosome 20 and an extra Y. (C & D) Flow cytometry showing a CD45-, CD19+, CD10+ lymphoblast population.

Case two

Patient B is an 83-year-old female who presented in

2003 at an outside hospital with an acute myocardial infarction. A CBC was done and showed hemoglobin of 9.6 g/dL, WBC of $11.4 \times 10^9/L$ and a platelet count of $1214 \times 10^9/L$. Bone marrow studies were performed and demonstrated a slightly hypercellular marrow with prominent megakaryocytic hyperplasia and erythroid hypoplasia. Cytogenetic studies revealed an abnormal karyotype with partial deletion of the long arm of chromosome 5 in all 20 metaphase: 46, XX, del (5) (q13q33) [20]. These results supported a diagnosis of MDS, 5q- syndrome. The patient was placed on lenalidomide 5mg daily in the setting of a clinical trial. One year later, the patient was transfusion independent. Bone marrow studies in 2004 and 2005 demonstrated a normocellular marrow with trilineage hematopoiesis. Cytogenetics at both times confirmed a molecular remission with a normal karyotype: 46, XX [20]. FISH testing was also negative for deletion of 5q31. In 2007, the patient was referred to our institution for follow-up. Her blood counts remained stable until late 2008, when she developed anemia requiring erythropoietin treatment. In late 2009, she was admitted to the hospital with chest pain and shortness of breath. A CBC done at this time showed hemoglobin of 6.1 g/dL, platelet count of $65 \times 10^9/L$ and a WBC of $2.4 \times 10^9/L$. This was her first need for transfusion support since she had been started on lenalidomide six years earlier. Bone marrow studies were done and demonstrated an expanded population of blasts that accounted for 90% of the total cellularity. Flow cytometry showed the blasts to be CD10+, CD19+, CD34+, TdT+, CD117- and MPO-, confirming a B-lymphoblastic lymphoma/leukemia. Cytogenetics showed an abnormal karyotype: 46,XX,del(5)(q13q33) [18]/46,XX[2]/46,XX,del(5)(q13q33),del(20)(q11.2q13.1)[1].

In addition to the 5q-, a deletion of the long arm of chromosome 20 was also found in one metaphase. FISH studies also confirmed deletion of 20q in 48.7% of the examined nuclei. The patient was treated with lenalidomide and supportive care, however, despite treatment; she rapidly deteriorated and died on hospice.

Discussion

Myelodysplastic syndromes associated with deletion of the long arm of chromosome 5 represent a distinct entity with an indolent course

that rarely transform into an acute leukemia [3]. In a study by Patnaik and colleagues, 80 patients with 5q- MDS were enrolled from 1989-2009 and only five patients were reported to have a leukemic transformation. The specific type of transformation was not reported in these cases [7]. MDS evolving into acute myeloid leukemia (AML) has been observed in patients with the 5q- syndrome when clonal evolution occurs with a more complex karyotype. Gohring and colleagues performed a long term follow up analysis of 42 patients with low or intermediate risk MDS including 19 patients with 5q- deletion as the sole abnormality who were treated with lenalidomide. Seven of those patients transformed to AML with 4 patients having complex cytogenetics at the time of transformation. The specific abnormalities were not stated, and the transformation occurred over an average of 53 months after diagnosis [8]. Cases of MDS in which the 5q- is not the sole abnormality are more likely not to achieve a complete cytogenetic response and tend to progress to acute leukemia. Jadersten and colleagues reported a case of a 76 year old woman with 5q- and a mutated clone of TP53 at diagnosis. The patient was treated with lenalidomide and had a partial cytogenetic response. This patient's MDS evolved into an AML. Cytogenetics at the time of progression showed an expansion of the TP53 mutated clone at 17p13, and a gain of the MLL and retinoblastoma-1 (RB1) locus as well [9]. Another report by Eclache et al. described the 5q- syndrome in a patient who had resistance to lenalidomide. This patient developed highly complex cytogenetics after being treated with lenalidomide for eight months [10]. These studies therefore indicate that MDS with 5q- treated with lenalidomide can evolve into an acute myeloid leukemia under three circumstances: (1) failure to achieve a complete cytogenetic response during treatment, (2) the presence of a complex karyotype in addition to the 5q- at presentation, (3) primary resistance to lenalidomide. The mechanism of transformation in these cases is thought to be due to clonal expansion from an abnormal pluripotent stem cell as most of these patients acquired additional chromosomal aberrations in addition to the 5q- during leukaemogenesis.

We present two cases of 5q- syndrome with a similar and unusual course of transformation to lymphoblastic leukemia while on Lenalidomide. These two patients achieved an initial response;

however, later on (32 months in patient A, approx. 72 months in patient B) acquired a second cytogenetic abnormality, became refractory to treatment and evolved into acute leukemia. At the time of transformation, both patients had recurrence of the 5q- (as evident by FISH in patient A and by karyotype in patient B). The additional cytogenetic abnormality in both patients at the time of their disease evolution was a 20q-. Deletion of chromosome 20 is a common cytogenetic abnormality seen in MDS and in AML evolving from MDS. It is usually not seen in ALL and its presence in these cases most likely reflects the underlying myelodysplastic state. It is quite impossible (in the absence of cell sorting) to speculate which cell line harbors the 5q- or the 20q-.

Lenalidomide is a multifunctional inhibitor of angiogenesis and an immune modulator that has been shown to reduce transfusion requirements and reverse cytologic and cytogenetic abnormalities in patients with 5q- syndrome [11-13]. Although, its mechanism of action is not entirely understood, *in-vitro* studies had shown that it affects the expression of several important genes, including the tumor suppressor gene *SPARC*. The *SPARC* gene maps to 5q31-q32 and therefore, there is a deficiency of its expression in patients with the 5q- syndrome. Lenalidomide was shown to restore *SPARC* expression to normal levels in cultured bone marrow mononuclear cells [14]. It is also possible to speculate that lenalidomide could suppress an indolent clone and while prolonging the disease free survival period, can potentially allow for a more aggressive clone to expand and evolve to an acute leukemia.

The intriguing similarity between these two cases raises a question whether immune modulators can alter the natural course of MDS. Future studies are needed to fully elucidate the exact mechanism of action of lenalidomide. It is rather difficult at this time to conclude whether patients with 5q- syndrome that are refractory to lenalidomide tend to develop a lymphoblastic rather than a myeloid leukemia. Therefore, the relationship between the events in our report remains unclear. Nevertheless, we report these two cases to highlight the importance of immunophenotyping, karyotype and FISH analysis in cases of relapsed MDS/ evolving acute leukemia and to alert the oncologists and pathologists about this unusual clinical course.

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5q- syndrome to acute lymphoblastic leukemia

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