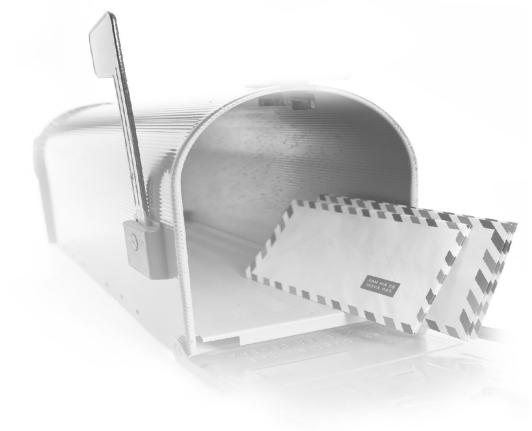

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Letters to the Editor

Long-term hematological response in a patient with 5q- syndrome after suspension of lenalidomide therapy and further improvement with deferasirox therapy

TO THE EDITOR: Anemia and its related clinical effects, including dependence on red blood cells (RBC) transfusions, are common findings in patients affected by myelodysplastic syndromes (MDS) with isolated chromosome 5q deletion (5q-). However, in recent years, the use of lenalidomide in the management of anemia related to 5q- syndrome has significantly changed the clinical scenario in this specific setting [1]. Several reports have described durable erythroid responses and the achievement of transfusion independence in patients with 5q- syndrome who were treated with lenalidomide despite the discontinuation of this agent and the persistence of the underlying malignant clone [1-4]. In addition, both anemia and transfusion are paradoxically associated with organ injury [5], for which iron chelation therapy (ICT) plays an expanding role in the global management of transfusion-dependent patients with MDS. ICT with deferasirox has been associated with hematological improvement and achievement of transfusion independence in some patients with MDS [6, 7], and a potential synergistic effect between deferasirox and lenalidomide has been suggested [4]. Here we describe the unusual outcome of a patient with 5q- syndrome who experienced an early and long-lasting response to lenalidomide despite discontinuation of therapy; interestingly, the hematological and cytogenetic responses improved during treatment with deferasirox, which was given as a single agent on a long-term basis after the suspension of lenalidomide therapy.

Using the International Prognostic Scoring System [8], low-risk MDS typical of 5q- syndrome was diagnosed in a 69-year-old woman in July 2007. Apart from well-controlled arterial hypertension and mild kidney failure, the patient's previous pathological history was unremarkable. Complete blood cell count revealed severe macrocytic anemia (hemoglobin [Hb] level, 66 g/L; mean corpuscular volume, 121 fL; reticulocyte count, 0.2%) and thrombocytosis (platelet count, 681×10^9/L). Total and differential white blood cells (WBC) counts were within normal limits. All possible pathologies potentially mimicking this framework were ruled out. In particular, *JAK2* V617F mutation analysis was negative, and hepatic diseases, hypovitaminosis, and hemolytic disorders were excluded. The common parameters regarding iron metabolism were within normal limits; the baseline serum ferritin level was 137 mg/L. Examination of bone marrow (BM) showed prominent erythroid dysplasia and an increased number of hypolobular megakaryocytes without blasts. Cytogenetic analysis revealed isolated del [(5)(q13q33)] in 20 of 20 (100%) analyzed metaphases. The patient initially received packed RBC transfusions and soon after was started on erythropoietin stimulation; however, the latter treatment allowed for only a transient and partial response. After about 6 months, the patient's anemia worsened and she became severely transfusion dependent, regularly needing about 2 units of RBCs every 2 to 3 weeks, so treatment with erythropoietin was discontinued.

The patient began treatment with deferasirox in 2010 at an adjusted starting dose of 10 mg/kg and reached a maximum daily dose of 20 mg/kg because of her slightly reduced renal function (creatinine clearance, 60 mL/min); at that time, her serum ferritin level was 1,857 ng/mL. However, her compliance with treatment was low, and treatment was often discontinued. In addition, the patient was reluctant to initiate treatment with lenalidomide, which was repeatedly proposed. However, because of the increasing need for transfusions and the appearance of both neutropenia (neutrophil count, 0.5×10^9/L) and thrombocytopenia (platelet count, 83×10^9/L), the patient was reevaluated in August 2012. A comprehensive hematological workup showed 5% of myeloblasts in the BM; the same karyotype was confirmed by cytogenetic analysis, ruling out additional chromosomal abnormalities. At the time of reassessment, the patient had received 118 RBC units and her serum ferritin level was 2,100 ng/mL; her International Prognostic Scoring System and World Health Organization Classification-Based Prognostic Scoring System [9] scores were 1 (intermediate-1 risk) and 3 (high risk), respectively. After

a frank discussion with the patient and her family regarding the need to adhere to proper treatment because of disease progression, the patient began treatment with lenalidomide (5 mg orally on days 1–21 of repeated 28-day cycles) at an adjusted starting dose because of her renal impairment [10] and concomitant treatment with deferasirox (20 mg/kg/day). Treatment with low-dose acetylsalicylic acid was also initiated for secondary antithrombotic prevention. The patient was more motivated than in 2010, resulting in good compliance with therapy. The hematological response was immediate, and no further transfusions have been required since the initiation of lenalidomide therapy. However, after the fourth cycle of lenalidomide therapy, an excessive erythroid response was observed; the patient's Hb values ranged from 14 to 16 g/dL without any clinical complications. Improvements in platelet and neutrophil counts were also observed. BM examination revealed full clearance of myeloblasts but the persistence of prominent erythroid dysplasia and an increased number of hypolobular megakaryocytes, although the latter was not increased; cytogenetic analysis showed 10 of 20 (50%) 5q- metaphases. Given the excessively high Hb levels, lenalidomide therapy was suspended and the patient continued treatment with deferasirox alone in January 2013. Treatment was well tolerated; except for 2 episodes of severe but uncomplicated neutropenia, the patient did not experience any adverse effects. In particular, renal function was preserved and no signs of renal tubulopathy or decreased creatinine clearance were recorded.

As of December 2013, 12 months after the discontinuation of lenalidomide therapy, the patient is well and has achieved near normalization of her hemogram (Hb, 13.1 g/L; mean corpuscular volume, 107 fL; reticulocyte count, 4%; platelet count, 182×10^9/L; normal total and differential WBC counts). Her last serum ferritin level was 482 ng/mL. Moreover, compared with previous BM examinations, a significantly less prominent erythrodysplasia and a reduced number of altered megakaryocytes were observed. In addition, no blasts were found. Cytogenetic analysis revealed the persistence of isolated 5q- alteration in 6 of 20 (30%) BM metaphases. The patient is regularly followed up and continues treatment with deferasirox alone at a reduced dose.

We have reported a case of long-term disease control in a patient with 5q- syndrome after suspension of lenalidomide therapy despite the persistence of the abnormal clone; at the same time, the patient's clinical course and hematological findings suggest that iron overload may have exerted a role in the progression of MDS. In this case, iron chelation therapy may have led to the improvement of erythroid dysplasia and the reduction of the cytogenetically abnormal clone that we observed during prolonged treatment with deferasirox by antioxidative mechanisms due to iron chelation itself and perhaps by other biological effects exerted by this agent. However, this case has only anecdotal value, and our interpretations of this unusual outcome are purely hypothetical and unproven by biological studies. Despite these limitations, we suggest that treatment with lenalidomide plus deferasirox should be explored in appropriately designated clinical trials in the setting of transfusion-dependent MDS.

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A case of myelodysplastic syndrome with a der(1;18)(q10;q10) translocation

TO THE EDITOR: Whole-arm translocations are relatively rare cytogenetic aberrations in hematologic malignancies [1]. Mostly, these translocations are unbalanced and accompanied by genomic imbalances, such as trisomy and monosomy of each whole-arm of the 2 involved chromosomes. Until now, approximately 11 different unbalanced whole-arm translocations have been reported as the sole recurrent abnormalities in hematologic malignancies: der(1;7)(q10;q10), der(1;14)(q10;q10), der(1;15)(q10;q10), der(1;18)(q10;q10), der(7;12)(q10;q10), der(13;14)(q10;q10), der(14;21)(q10;q10), der(17;18)(q10;q10), der(1;7)(q10;p10), der(1;7)(p10;q10), and der(9;18)(p10;q10) [1].

Particularly, the der(1;18)(q10;q10) translocation is very rare in hematologic malignancies. Only 3 cases of hematologic malignancy with der(1;18)(q10;q10) translocations have been reported since the translocation was first described by Wan *et al.*; each was a case of refractory anemia with excess blasts (RAEB), myeloproliferative disorder (MPD), and essential thrombocythemia (ET) [2, 3]. A few other cases including non-Hodgkin's lymphoma (NHL), polycythemia vera, and primary myelofibrosis had der(1;18)(q10;q10) translocations as a part of a more complex karyotype, but lacked detailed case descriptions [1, 4-6].

Three years ago, a 73-year-old woman was admitted to our hospital because of pancytopenia. Her complete blood cell count (CBC) showed a hemoglobin (Hb) level of 7.7 g/dL with a mean corpuscular volume (MCV) of 105 fL (reference, 80–99 fL), a platelet count of 58×10^9/L, and a white blood cell (WBC) count of 2.29×10^9/L with 40% segmented neutrophils, 46% lymphocytes, 8% monocytes, and 3.9% eosinophils. The peripheral blood smear showed macrocytic erythrocytes without immature cells. At that time, a bone marrow (BM) biopsy was not performed. Theserum vitamin B_{12} level was 234 pg/mL (reference, 211–911 pg/mL) and the folate level was >20 ng/mL (reference, 4.2–19.9 ng/mL). Despite vitamin supplementation therapy for 3 years, her pancytopenia did not improve. However, her general health status was sustained at a tolerable state. Three months ago, the patient was diagnosed as having gastric adenocarcinoma and underwent a total gastrectomy. At that time, her CBC still showed pancytopenia with the following blood markers: Hb, 9.1 g/dL; WBC, 2.04×10^9/L (47.6% segmented neutrophils, 40.8% lymphocytes, 6.5% monocytes, and 1.3% eosinophils), and platelets, 58×10^9/L. The MCV was 102 fL and the serum vitamin B_{12} level was 1,180 pg/mL. The serum iron, total iron binding capacity, and ferritin levels were 114.1 μg/dL (reference, 29–164 μg/dL), 301 μg/dL (reference, 22–433 μg/dL) and 532.7 ng/mL (reference, 10–291 ng/mL), respectively. The reticulocyte level was 1.83% (reference, 0.5%–1.5%). The BM was hypocellular with 38.6% myeloid cells, 37.0% erythroid cells, and 20.7% lymphocytes. The erythroid series were slightly increased and a mild dyserythropoiesis (megaloblastic changes, binuclarity, and nuclear buddings) was observed (Fig. 1A). Myeloid cells and megakaryocytes were un-

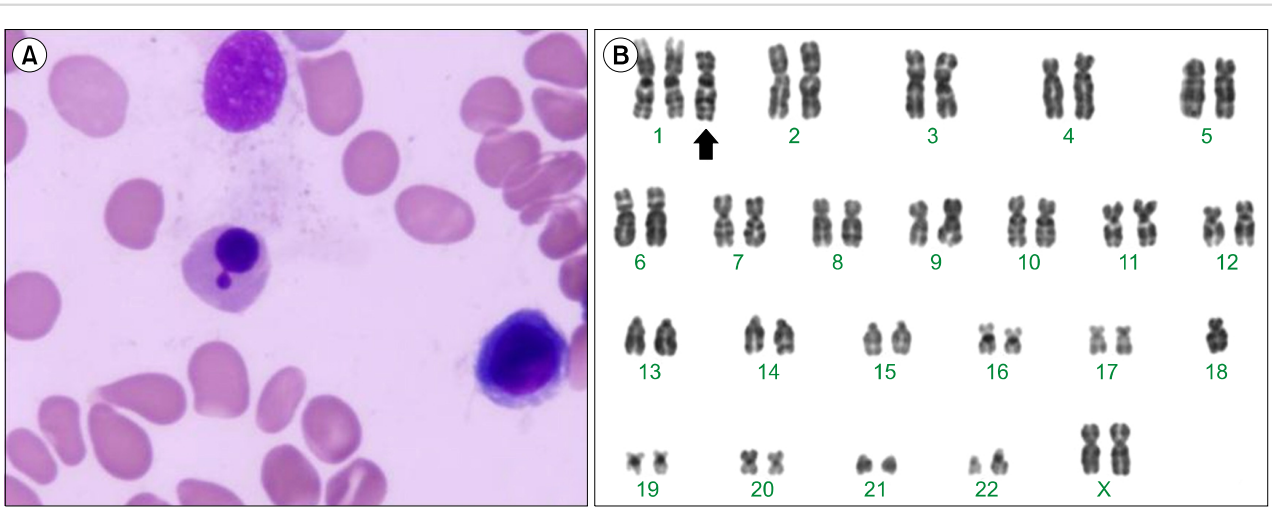

Fig. 1. **(A)** A nuclear-budding and megalocytic orthonormoblast representing dyserythropoiesis (Wright stain, ×1,000). **(B)** G-banded karyogram of bone marrow cells. The arrow indicates the der(1;18)(q10;q10) chromosome.