Lenalidomide induced durable remission in a patient with MDS/MPN-with ring sideroblasts and thrombocytosis with associated 5q- syndrome

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ABSTRACT

We describe a patient with MDS/MPN with ring sideroblasts and thrombocytosis who had deletions of long arm of chromosome 5 (5q-) and chromosome 20 (20q-). Molecular studies showed an exon 9, frame shift mutation in the calreticulin (CALR) gene, and absence of mutations in JAK2, MPL, SETBP1 or SF3B1.

Treatment with lenalidomide resulted in durable clinical remission which has lasted 2 years.

1. Introduction

Refractory anemia with ringed sideroblasts and thrombocytosis (RARS-t) was a provisional entity under myelodysplastic/myeloproliferative neoplasms (MDS/MPN) unclassifiable in the 4th edition of the WHO classification of myeloid malignancies [1]. Based upon a better understanding of the underlying molecular pathogenesis, the recent 2016 update of the 4th edition include RARS-t as a MDS/MPN overlap subtype, now called MDS/MPN with ringed sideroblasts and thrombocytosis (MDS/MPN-RS-T) [2]. Mutations in the spliceosome gene, SF3B1, occurs in up to 80% of these patients and co-exists with mutations in JAK2 (∼50%), TET2 (∼25%), ASXL-1 (20%), DNMT3A (∼15%) and CALR (0–12.5%) [3].

We describe a patient with features of MDS/MPN-RS-T, who was found to have a deletion in the long arm of chromosome 5 and chromosome 20. Molecular studies showed a frame shift mutation in the calreticulin (CALR) gene. Treatment with lenalidomide led to rapid normalization of peripheral blood abnormalities which have been durable for 2 years.

2. Case report

An 84-year-old white male was referred to us for anemia and thrombocytosis. He had a history of hypertension and dyslipidemia, for which he took enalapril and lovastatin. He lived and worked on a ranch in far west Texas. He had been fatigued for a few months. Physical exam showed mild conjunctival pallor. Liver and spleen were not palpable. Rest of the physical exam was unremarkable. Complete blood count (CBC) showed a white blood cell count of 9600/µl (4000–10,000) with a normal differential, hemoglobin of 9.9 g/dl (13.5–17.5) with MCV (mean corpuscular volume) of 108 fl (80–95). Platelet count was 986,000/µl (150,000–450,000). Peripheral blood smear showed macrocytosis, moderate anisopoikilocytosis and marked increase in platelets. Prothrombin time and activated partial thromboplastin time were normal. He then underwent a bone marrow biopsy and aspirate. This showed a cellularity of 50%. Megakaryocytes were increased (Fig. 1). Myeloid erythroid ratio was normal. There was no increase in fibrosis. Blasts were 1–2%. Iron stain showed 15–20% ring sideroblasts (Fig. 2).

Cytogenetic studies showed a deletion of the long arm of chromosome 5 and chromosome 20 in all twenty metaphases analyzed. Eleven of those cells also had a deletion of the long arm of chromosome 5 in all twenty metaphases analyzed. Eleven of those cells also had a deletion of the long arm of chromosome 20 (Fig. 3). Molecular studies did not show JAK2 mutation or BCR/ABL rearrangement. A CALR exon 9, frame shift mutation (c1103_1130del37) was detected.

No mutations were detected in CSF3R, SRTBP1, MPL or SF3B genes. Patient was initially started on hydroxyurea for cytoreduction. Once the results of cytogenetic studies became available, hydroxurea was discontinued and lenalidomide (10 mg) was initiated. After a transient period of worsening anemia, his CBC improved and by 3 months his peripheral blood counts were normal (Fig. 4). Fluorescent in situ hybridization and PCR studies on peripheral blood, performed 6 months after diagnosis, did not detect 5q deletion, 20q deletion or CALR mutation, suggesting molecular remission. At last follow up at 2 years, patient has continued to stay on lenalidomide and has a normal CBC.

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Disease's with features of both MDS and MPN have been termed MDS/MPN overlap syndrome. Amongst the overlap syndrome, Refractory anemia with ringed sideroblasts and thrombocytosis (RARS-T) was initially included as a provisional entity by WHO in 2001. It was felt to have features of the MDS, refractory anemia with ringed sideroblasts and the MPN, essential thrombocytosis. The pathological hallmark of dysplasia was the presence of ringed sideroblasts detected by Prussian blue staining, in 15% or more of the erythroid progenitors. However, presence of ringed sideroblasts do not signify clonality, is sometimes reversible, and the percentage of RS do not correlate with prognosis. In addition RS can sometimes be seen in other myeloid disorders, including MPNs [4,5].

In 2006, Szpurka et al. found that 67% of patients with RARS-t had mutations in the JAK2 gene [6]. In addition to JAK2, mutations on CALR (3/24) and MPL have been described and probably contribute to the proliferative phenotype of MDS/MPN-RA-t [7–9]. It is possible that cases of RARS can transform to MDS/MPN-RA-T after acquiring mutations in these genes.

Since 2011, with the advent of next-generation sequencing in clinical practice, it has become obvious that a large proportion of cases with RARS-T have mutations in the genes encoding mRNA splicing factors, predominantly in the SF3B1 gene [10]. The detection of spliceosome mutation correlates with the morphological presence of RS, however its contribution to prognosis is controversial. The 2016 WHO revision
listed the following criteria for the diagnosis of MDS/MPN-RA-T [2]:

a) Anemia associated with erythroid lineage dysplasia without multilineage dysplasia, ≥15% RS, <1% blasts in peripheral blood and <5% blasts in the bone marrow.

b) Persistent thrombocytosis with platelet count ≥450 × 10^9/L

c) Presence of SF3B1 mutation, or in the absence of SF3B1 mutation, no history of recent cytotoxic or growth factor therapy to account for the MDS/MPN features.

d) No BCR-ABL1 fusion gene, no rearrangement of PDGFRα, PDGFRβ or FGFR1; or PCM1-JAK2; no (3;3)(q21;q26), inv(3)(q21;q26) or del (5q)

e) No preceding history of MPN. MDS (except MDS-RS) or other type of MDS/MPN.

Intersitial deletion of the long arm of chromosome 5, del(5q), is one of the most commonly detected chromosomal aberration in MDS. Since its original description in 1974, patient with isolated 5q- deletion, thrombocytosis with small hypolobate megakaryocytes, erythroid hypoplasia and less than 5% myeloblasts were said to have the “5q-syndrome”. However, since not all patients have all of the above features and since lenalidomide works in the vast majority of the patients who have del(5q), with or without the whole syndrome, WHO now refers to this as MDS with isolated del(5q) and not as “5q syndrome”. Haplo-insufficiency of critical genes in the 5q region is believed to contribute to the pathogenesis of this subtype of MDS. Loss of one copy of RPS14 gene, a component of the 40s ribosomal subunit and increased activation of p53 contributes to erythroid hypoplasia while the loss of microRNAs (miRNAs), miR-145 and miR 146a, contribute to megakaryocytic dysplasia and increased platelets. Recently it has been noted that one additional chromosome abnormality in addition to del (5q) does not affect clinical presentation or prognosis and as such these patients can also be classified as MDS with isolated del(5q), as long as the additional chromosomal abnormality is not monosomy 7 or del(7q)

Although thrombocytosis can be seen in some patients with MDS with del(5q), ring sideroblast morphology is uncommon. MDS with del (5q) was first described 40 years ago. We queried the Mitelman database for 5q deletion and RARS morphology. Only 15 results were obtained describing RS morphology with 5q as sole abnormality [14]. This suggests that RS are distinctly unusual in this disease. In addition, although mutations in MPN driver genes (JAK2, MPL, CALR) are frequent in MDS/MPN-RA-T they are unusual in MDS with del(5q) [15].

Our patient had overlapping features of MDS/MPN-RS-T and MDS with 5q deletion. As is typical of patients with MDS with del(5q), our patient had a good response to lenalidomide. The disappearance of CALR mutants from the blood at the time of disappearance of 5q clone suggests that the 5q deletion may have been the early initiating event and CALR mutation to have developed as a clonal evolution.

On the other hand the presence of ringed sideroblasts and somatic mutation in calreticulin, one of the 3 driver genes of MPN suggests the diagnosis of MDS/MPN-RS-T. However, the 2016 WHO update specifically excludes cases with del(5q) from this diagnosis.

A PubMed search revealed one similar case published in 2010 which had overlapping features of MDS/MPN-RA-T and MDS with del(5q) and which also responded to lenalidomide [16]. Our case is unique in including the molecular results of CALR and SF3B mutations, clinical significance of which had not been recognized in 2010.

Taken together, the above two cases show that despite frequent updates in classification, hematological diseases which do not clearly fit any category continue to challenge practicing hematologists.

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