A rare case of myelodysplastic syndrome with refractory thrombocytopenia

Waqas Jehangir,1 John Webb,2 Shilpi Singh,3 Sabrina Arshed,1 Shuvendu Sen,1 Abdalla Youssi1

1Raritan Bay Medical Center, Perth Amboy, NJ, USA; 2Rosh University School of Medicine, Portsmouth, Dominica

Abstract

Myelodysplastic syndromes (MDS) represent a variety of clonal abnormalities, possibly preleukemic and display numerous phenotypic manifestations. Specific mutations carry high morbidity and mortality rates due to cell line dysplasia. MDS commonly presents with symptoms related to anemia, and approximately two-thirds will develop thrombocytopenia, a rare, but potentially lethal complication that increases complexity in treatment and morbidity, and may be due to unique genetic mutations leading to refractory thrombocytopenia, ultimately leading to an overall reduction in survival. Careful identification and monitoring of this patient subdivision can significantly reduce morbidity and mortality, and potential identification of specific gene mutations and advances in treatment options will hopefully provide guidance on detecting at-risk patients in the future. We present a case of a man with MDS-U (karyotype 46, XY, del (20) (q11.2q13.3) (20) with no detected JAK2 V617F mutation), who in despite of appropriate evidence based treatment, continued to exhibit refractory thrombocytopenia.

Case Report

A 71 year-old Caucasian male ex-smoker without any significant past medical history presented to the emergency department complaining of worsening redness and swelling in his left lower leg. He presented five days earlier and was given antibiotic treatment which did not resolve the problem. On physical exam Temp: 96.6°F, O2 saturation 96% on Room air. His left lower leg. He presented five days earlier. Considering pancytopenia as far as previous findings of thrombocytopenia as far as four years earlier. Considering pancytopenia an oncology consult was called who reviewed the peripheral smear which showed slight anisocytosis, monocytes with marked thrombocytopenia with some giant platelets, No pseudo-Pelger-Huet cells or circulating blasts were noted (Figure 1A). Given the laboratory findings, leukemia was considered as a differential and therefore a bone marrow biopsy was performed which showed the differential (Table 3) granulopoiesis, hypercellular marrow with increased myelomonocytic cells and megakaryocytogenesis (Figure 1B,C). Immunohistochemistry showed CD117: about 5-10% positive cells, consistent with immature cells/blasts, CD34. No increase in CD34 positive cells, CD163: Highlights predominantly monocytic component, CD123: Negative. Reticulin staining showed mild diffuse reticulin fibrosis. Immunophenotyping by flow cytometry analysis FLG13-859 shows mild myelomonocytic abnormalities. PCR study for JAK2 is negative. FISH was performed for BCR/ABL1 to detect the (9;22) translocation associated with CML and less commonly ALL or AML were normal. Cytogenetic testing demonstrated an abnormal karyotype 46, XY, del(20)(q11.2q13.3)(20) (Figure 2). Other 15 metaphase spreads examined showed a normal male karyotype, 46, XY. Patient was diagnosed with myelodysplastic syndrome, Unclassified (MDS-U) with refractory thrombocytopenia.

Discussion and Conclusions

MDS is a hematologic disorder that typically presents with one or more cytopenias. Anemia is ordinarily part of a bi- or pancytopenia, with independent neutropenia and thrombocytopenia cell lines being unusual. Refractory thrombocytopenia is a rare, but potentially lethal complication that increases complexity in treatment for the physician and increased...
morbidity for the patient. Genetic abnormalities are playing an expanded role in classifying prognosis and treatment, as well as the potential for MDS to transform into CML. This is especially true where there is a high proportion of cells in the G1 stage of the cell cycle.\(^5\)

One potential cytogenetic marker for clonal evolution is del(20), which was present in our patient. The del(20) is commonly found in patients with CML, but not in MDS, and agrees with previous reports.\(^5\)

Our patient had a del(20) with break points at 11.2 and 13.3. The 11.2 break point is the locus for the ASXL1 gene mutation. This particular mutation is found in approximately 21% of MDS cases and has been shown to be a non-favorable prognostic mutation. The ASXL1 (Additional Sex Combs Like 1) is implicated in chromatin remodeling and gene repression. It is believed to be responsible for repression of multiple transcription genes. The 13.3 break point correlates to the GNAS locus and is found in less than 1% of MDS diagnoses.\(^8\)

This marker does not necessarily indicate a worse case scenario of CML clonal divergence or disease progression and only 1.7% of people with MDS exhibit this alteration. From a prognostic standpoint, this clonal abnormality is considered good with a median survival of 4.8 years and a progression to AML median time at 9.4 years.\(^7\)

Treatments continue to be reasonably general in patients with MDS. Cytotoxic agents, antibodies or immunosuppression treatments, allogeneic stem cell transplantation, and blood products to correct hypocellularity have been the mainstay of most regimens. Multiple therapies are introduced as a result of the theory that different cell lines are arrested and/or deranged in various stages of the cell cycle.\(^3\) Because of the preleukemic and potential myeloblastic nature of MDS, dozens of cytotoxic agents have been utilized to combat cell abnormal cell differentiation, but have had varied success to date. The outcomes of these treatments are very dependent on which somatic gene mutation(s) are present and whether or not they are responsive to the chemotherapeutic agent used. Allogeneic stem cell transplantation is usually limited to younger high-risk patients and rarely in very healthy older patients. As of date, this is the only curative treatment of higher-risk myelodysplastic syndromes, with prolonged disease-free survival of 35-50%.\(^1\) Immune mediated hematopoietic apoptosis caused by cytotoxic T-Cells, IFN-\(\gamma\) producing CD4+ cells, and Th17 cells is reduced by administering immune modulators. This has shown to not only help increase the reduced cell lines, but gives patients a more robust immune response which is crucial to reducing their morbidity and mortality. Specific and standard therapeutic approaches are made to increasing single or multiple cell line deficiencies. The goal in these treatments is to correct the cytopenias(s) involved as with any related reduction of the hematopoietic cell lines.

### Table 1. Complete blood count.

|                          | Patient's value | Normal range          |
|--------------------------|-----------------|-----------------------|
| White blood cells        | 7.3             | 3.6-11.0 K/uL         |
| Red blood cells          | 5.17            | 3.80-5.60 M/mL        |
| Hemoglobin               | 12.2            | 11.6-16.8 g/dL        |
| Hematocrit               | 37.8            | 35.1-50.0%           |
| Mean corpuscular volume  | 73.2            | 73.5-96.5 fL          |
| Mean corpuscular hemoglobin | 23.7         | 23.9-33.6 pg         |
| Mean corpuscular hemoglobin concentration | 32.3 | 32.35-35 g/dL |
| Red cell distribution width | 20.0          | 12.1-16.5%           |
| Platelets                | 37.0            | 150-375 K/uL         |

### Table 2. Peripheral blood differential count.

|                          | Patient's value | Normal range, %       |
|--------------------------|-----------------|-----------------------|
| Neutrophils              | 29              | 43-76                 |
| Bands                    | 1               | 0-10                  |
| Lymphocytes              | 20              | 17-45                 |
| Atypical lymphocytes     | 7               | 0-6                   |
| Monocytes                | 18              | 5-12                  |
| Eosinophils              | 0               | 0-8                   |

### Table 3. Bone marrow differential count.

|                          | Patient's value, % |
|--------------------------|--------------------|
| Erythroblasts            | 22                 |
| Blasts                   | 5                  |
| Neutrophils/precursors   | 16                 |
| Eosinophils              | 0                  |
| Basophils                | 1                  |
| Lymphocytes              | 4                  |
| Monocytes                | 50                 |
| Plasma Cells             | 2                  |
| Promonocytes             | 1                  |

Figure 1. A) Peripheral smear showing slight anisocytosis, monocytosis with marked thrombocytopenia with some giant platelets; B, C) Bone marrow biopsy showing granulopoiesis, hypercellular marrow with increased myelomonocytic cells and megakaryocytogenes at lower (B) and higher (C) magnification.
most serious problems found in many patients with MDS, yet normally successfully treated. In few cases, due to potentially unique genetic mutations, platelet counts remain low despite evidenced based treatment. Careful identification and monitoring of this patient subdivision can significantly reduce morbidity and mortality. Identification of specific gene mutations and advances in treatment options will hopefully provide forthcoming guidance on detecting at-risk patients in the future.

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