Acquired Platelet Dysfunction Secondary to Myelodysplastic Syndrome: Successful Resolution with Syndrome-Directed Therapy

A.Hockman[1], G. Medawar[1], L. Guo[1], E. Rinker[1], P. Baratam[1]
1. Medical University of South Carolina, Charleston, South Carolina

MUSC Health
Medical University of South Carolina
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Introduction

- **Acquired platelet disorders** have been reported to arise secondary to hematologic malignancies and underlying bone marrow dysfunction [1,2,3,4].
- Acquired platelet dysfunction is an increasingly recognized complication of hematologic malignancies such as **myelodysplastic syndrome (MDS)** [5].
- MDS is a clonal disorder characterized by ineffective hematopoiesis and dysplastic bone marrow morphology [6].
- These acquired bleeding disorders pose a significant challenge in treatment as the underlying etiology is complex and multifaceted.

Case

- 68-year-old female with a past medical history GERD, right eye wet macular degeneration and pre-diabetes presented in May 2023 for easy bruising on trunk, legs and arms with increased frequency over time
- Denied any mucosal bleeding, including epistaxis, oral bleeding, gastrointestinal bleeding, or hematuria.
- No personal history of excessive bleeding with tooth extraction and she had two vaginal deliveries with no excessive bleeding and no other surgical history.
- Her family history was unremarkable for diagnosed bleeding disorders
- The only medication she was taking on presentation was bevacizumab (intravitreal injection) which was started one year prior for macular degeneration, and she noted that her frequent body bruising was already present. She denied any recent or prolonged NSAID use, aspirin use or other medications or supplements.

Diagnostic course

- Initial laboratory testing in May 2022: platelet count of 111 K/cumm, normal PT/PTT, SPEP , Von Willebrand factor antigen, negative autoimmune workup and negative HIV and hepatitis C testing.
- Genetic testing for this disorder was negative (ITGA2B, ITGB3 gene tested negative) and the platelet glycoprotein flow cytometry was normal.
- Platelet transmission electron microscopy (PTEM) studies showed a significant decrease in alpha granules, decreased alpha granules and increased canalicular system, consistent with an ultra-structural abnormality.

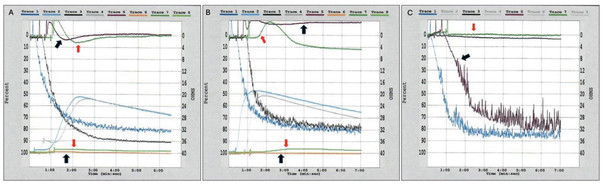


Figure 1. Platelet aggregation testing. This shows a marked defect in platelet function, with reduced to absent aggregation in response to ADP (5 uM and 10 uM), collagen, and arachidonic acid, while aggregation in response to ristocetin was preserved.

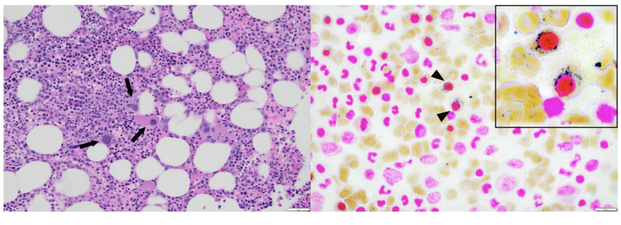


Figure 2. Histopathologic images from diagnostic bone marrow biopsy. Image on left: Bone marrow core biopsy, H&E stain: hypercellular marrow with dysplastic megakaryocytes (arrows). Image on right: Bone marrow aspirate smear, iron stain: right sideroblasts (arrow heads and inset)

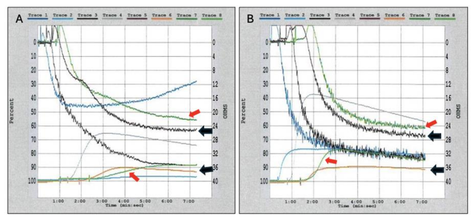
Diagnosis

- NGS was positive for SF3B1 K666N with variant allelic frequency (VAF) of 24%.
- Chromosomal microarray showed loss of 20q as the sole aberration.
- Based on IPSS-M, diagnosis of very-low risk MDS was established.
- The patient's bleeding diathesis was attributed to her MDS.

Treatment Course

- She began treatment with weekly **Decitabine** 0.2 mg/kg SQ on days 2, 9, 16, 23 with **Venetoclax** (400 mg once weekly) as a low dose non-cytotoxic regimen based on the Levitz et al. protocol.
- Cycle 1 was complicated by prolonged neutropenia (~3-4 weeks), which resulted in delay in starting cycle 2.
- Cycle 2 was started on May 2024 with 50% dose reduction, which was continued for the rest of the cycles. She completed a total of six cycles in October 2024.

Clinical Outcome



- In June 2024 platelet aggregation/ATP release study showed significant improvement in her platelet function with only mildly decreased platelet aggregation/ATP release in response to ADP, and normal platelet aggregation/ATP release in response to thrombin, arachidonic acid, collagen, and ristocetin
- 64% aggregation in response to 5 um ADP and 56% aggregation for 10 um ADP, 70% aggregation to AA and 64% aggregation to collagen.
- Bone marrow deferred and CBC showed WBC count of 6.53 K/cumm, Hemoglobin 13.9 gm/dL and platelet count of 228K/cumm.
- Clinically, bruising was resolved and there was no other mucocutaneous bleeding.
- She remains under close monitoring currently.

Treatment Strategy

- The qualitative platelet defects can lead to clinically significant bleeding which are attributed to dysmegakaryopoiesis and aberrant platelet granule content and surface receptor expression [1-3].
- Hypomethylating agents have shown normalization of platelet ultrastructure and adhesion in ex vivo testing, suggesting that disease-modifying therapy can reverse some of the intrinsic platelet defects induced by the dysplastic marrow environment [7].
- Hypomethylating agents can improve the overall hematopoiesis which translates into better platelet function [8].
- The desired outcome was to improve the bleeding diathesis by treating the underlying cause.
- This regimen uses the minimum dose required to suppress the myeloid clone while preserving functional hematopoietic cells which allows for an expedited blood count recovery.

Key Points

- Treatment of this patient's underlying MDS ultimately successfully managed their acquired alpha storage disease.
- Optimizing MDS therapy can impact platelet function.
- This outcome highlights the importance of treating the underlying hematologic disorder to address secondary platelet dysfunctions
- There is need for further research to refine treatment strategies, particularly in lower-risk MDS patients, to improve patient outcomes with MDS-associated platelet disorders.

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