1040

Severe Hemolysis in patient with known G6PD deficiency treated with Macitentan and Riociguat

Scott RL, Cerise MK, Renszel KM, Yael K, Shiue HJ, Leffler KE, Cartin-Ceba R
Mayo Clinic AZ, Phoenix, AZ

Background: We describe a 74 year old woman with Who Group 1 Functional Class III PAH who was on monotherapy for PAH with Bosentan since 2007. The patient was known to require blood transfusions every 2-3 months which was felt to be related to her known G6PD deficiency. Both she and her husband had noted a progressive decline in her level of function and quality of life over the past 3-4 months. We assumed her care and reassessed her functional status and PH severity.
Past medical history: Group 1 PAH on monotherapy with Bosentan. G6PD deficiency with associated hemolytic anemia requiring blood transfusions every 3-4 months. Rheumatic heart disease status post mitral valve replacement with a Saint Jude's #33 valve in 2005. Atrial fibrillation/flutter on chronic anticoagulation. Osteoporosis and GERD.
Physical Exam: Afebrile pulse 108 blood pressure 108/78 respirations 15
Well-developed cachectic appearing woman in no distress.
HEENT: Sclera mildly icteric pupil reactive
Cardiac: S1-S2 tachycardic regular rhythm regular rhythm. Jugular venous distention increased to 10 cm. Could not appreciate cyanosis or clubbing. Plus one to 2 lower extremity edema . 2/6 systolic murmur heard best at left lower sternal border. Loud P2.
Remainder of exam unremarkable.
Labs: Hb 8.5 HCT 27.5 Plat 118 Na 140 Cr 1.7 Bun 100 glucose 168 Tbilirubin 2.5 AST 33 ALT 14 MCV 126

Methods: Right heart catheterization done to assess reasons for worsening functional status:
RA 11 RV 53 PA 58/13 mean PA 30 PCWP 15 TPG 15 mmHg Fick CO/CI 5.0/3.0 TD CO/CI 4.9/2.9 PVR 3 Wood Units
Due to the right heart catheterization findings and worsening clinical status she was taken off of Bosentan and started on combination therapy with Macitentan 10 mg daily and Riociguat 0.5 mg TID.

Results: Patient feeling markedly fatigued dyspneic with reduced level of consciousness and hypotension. Patient admitted for further evaluation. Admitting labs notable for profound anemia likely secondary to hemolysis. Shortly after admission developed profound thrombocytopenia and became anuric requiring continuous renal replacement therapy and subsequently hemodialysis.

Renal biopsy: Pigment induced nephropathy
Bone Marrow Biopsy: Hypercellular marrow with dyserythropoietic changes felt consistent with hemolysis secondary to G6PD deficiency.
Clinic visit Labs 4/8/19 (2 weeks after starting Macitentan/Riociguat)
Na 138 Cr 2.1 Bun 208.9 Hb 4.8 Hct 15.1 Plat 148 INR >20
Pharmacogenetic testing confirmed that the patient was a CYP 2C19 and CYP1A2 rapid metabolizer.
Macitentan is primarily metabolized to its active metabolite by 3A4 (major). However, 2C19 also metabolizes it but in a minor role. Since she is a 2C19 rapid metabolizer, theoretically she could have increased levels of active metabolite. .
Also, macitentan has a sulfate moiety as a side group. Riociguat is metabolized primarily by 1A1 to its active metabolite but her rapid metabolizer enzyme is 1A2.

Presented at the 2019 Pulmonary Hypertension Association (PHA) Pulmonary Hypertension Professional Network (PHPN) Symposium.

Conclusions: Patient's with G6PD deficiency are prone to hemolysis. In this instance, the fact that she is a rapid metabolizer may have further predispose her to a profound hemolytic reaction resulting in hemodynamic compromise leading to both renal failure as well as a coagulopathy. Patients with G6PD deficiency with a need for pulmonary hypertension pharmacotherapy in select situations should be screen for the presence of pharmacogenetic abnormalities.