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Paroxysmal Nocturnal Hemoglobinuria (PNH) is not a Cause for Anemia in Patients with Myelofibrosis

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To the editor

Paroxysmal nocturnal hemoglobinuria (PNH) is a disease characterized by the expansion of a nonmalignant hematopoietic stem cell clone harboring a somatic mutation in the *PIGA* gene, which is required for the biosynthesis of the glycosylphosphatidylinositol (GPI) moiety that anchors proteins to cell membranes [1,2]. Erythrocytes and granulocytes derived from this mutant clone are deficient in several GPI-anchored membrane proteins, two of which are necessary for activation of the complement system (CD55 [decay-accelerating factor (DAF)] and CD59 (membrane inhibitor of reactive lysis) [3]. Symptomatic patients generally present with intravascular hemolysis, hemoglobinuria and thrombophilia [4]. PNH has also been shown to be closely associated with other bone-marrow disorders such as aplastic anemia (AA) and myelodysplastic syndromes (MDS) [5-8]. Approximately 50-60% of patients with AA and 15-20% of patients with low-risk MDS that clinicopathologically mimics AA have a detectable population of GPI-AP deficient erythrocytes and granulocytes [4-7]. However, in 90% of these cases, the PNH clone represents less than 25% of the total neutrophil population [8], with no clinical evidence of hemolysis, and therefore does not require treatment. More importantly, the subclinical presence of the PNH clone among patients with low-risk MDS and AA has been associated with a benign disease course and predicts a favorable response to immunosuppressive therapy [6]. A few case reports of PNH associated with myelofibrosis (MF), have been reported [9,10]. However, the actual incidence of PNH among patients with MF is unknown, despite the fact that patients with MF commonly have high lactate dehydrogenase, low haptoglobin, and sometimes elevated indirect bilirubin, all possibly indicative of intravascular hemolysis.

We retrospectively searched clinical records of patients with MF seen at The University of Texas MD Anderson Cancer Center over last 5 years, in whom treating physicians ordered testing for PNH to determine whether PNH was a reason for significant anemia patients had. The study was based on a retrospective chart review protocol approved by the Institutional Review Board at MD Anderson. Testing for PNH, therefore, was solely based on a clinical suspicion of a treating physician; i.e. testing was done as a part of standard practice based on the involved physician's medical judgment. Although more than a thousand patients with MF were seen during that period of time, and great majority had clinically relevant anemia, only

62 patients with MF and significant anemia (hemoglobin <10 g/dL) were identified in whom testing for PNH was done: 41 with primary MF, 13 with MF secondary to polycythemia vera, and 8 with MF secondary to essential thrombocythosis. Both peripheral blood red cells and granulocytes were the primary cell populations used to identify cells with the PNH phenotype, deficient in GPI-APs (test sensitivity of 5%) by four-color flow cytometry immunophenotypic analysis [5].

Interestingly, none of the 62 patients evaluated were found to have a concomitant PNH clone. In trying to understand what might have prompted treating physicians to order testing for PNH in these patients, we identified that all of them had significantly elevated lactate dehydrogenase, all but 5 had significantly lower than normal haptoglobin, but only 4 had a major thrombotic event (e.g. portal vein or renal artery thrombosis). In another study of 136 patients with hematologic malignancies, including 5 with primary MF, none had peripheral blood granulocytes harboring the PNH phenotype [5]. Although the number of MF patients in that study was very small, the result correlates with our findings. In conclusion, our study suggests that the presence of granulocytes with the PNH phenotype in general is not present in patients with MF and significant anemia. PNH is likely an extremely rare complication in MF patients and it is appropriate to look for PNH only in those with unexplained serious thrombosis and/or significant intravascular hemolysis. Routine screening for PNH in this patient population to explain anemia is not recommended; other causes of anemia should be investigated in patients with MF.

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