CLINICAL VIGNETTE

Unexplained Thrombocytosis with Microcytic Anemia and a Family History of Thalassemia: What's the Diagnosis?

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A 35-year-old female had been fully functional in good health. She had been told of anemia since childhood and of a family history of possible "thalassemia". Since adolescence she had been taking oral iron sporadically, and it is unclear if there had ever been any response. Over the last 3 years prior to presentation she had been taking iron more consistently. She a full-term pregnancy while taking iron with uncomplicated C-section delivery.

She was in her usual state of health without noticeable fatigue but wanted an updated internist evaluation. Labs including a complete blood count (CBC) revealed a microcytic anemia, with a hemoglobin (Hb) of 9.7 gm/dL and a mean corpuscular volume (MCV) of 70 fL with marked thrombocytosis with platelets = 1259 x 10-3/ uL. Her chemistry panel showed a mildly elevated total bilirubin, 1.3 mg/dL, and her serum iron was 190 mcg/dL and transferrin saturation of 69 % and a ferritin of 1184 ng/mL.

Initial hematology evaluation, included laboratory testing to evaluate for possible inherited hemolytic anemia with secondary iron overload. Her serum haptoglobin was undetectable, consistent with intravascular hemolysis, and her direct antiglobulin test (DAT) was negative, showing no evidence of autoimmune hemolysis. Her inherited hemoglobinopathy screen revealed a normal electrophoresis with a Hb A of 97.8 % and a Hb A2 of 2.2 % which was not consistent with beta thalassemia. Beta Thalassemia is associated with an elevated, generally twice normal Hb A2.[1] She also underwent alpha globin gene deletion testing, which screened for the most common genetic abnormality associated with alpha thalassemia,[1] which was negative.

Given a Coombs negative intravascular hemolytic anemia without peripheral blood smear evidence of microangiopathic hemolytic anemia (MAHA) and a personal history of longstanding anemia not requiring transfusion, she underwent additional testing for inherited hemolytic anemia. Her glucose 6 phosphate dehydrogenase (G6PD) and pyruvate kinase (PK) enzyme levels were elevated, 26 U/gm Hb (upper limit of normal (ULN) 16.0) and 19.5 U/ gm Hb (ULN 11.2), showing no common glycolysis enzyme deficiency. Her osmotic fragility test, to screen for red blood cell (RBC) membrane defects, was only mildly abnormal and more consistent with thalassemia than an inherited RBC membrane protein abnormality. Follow up alpha thalassemia gene sequencing revealed one deleterious heterozygous mutation and one likely deleterious mutation, consistent with her lifelong microcytic anemia and family history of thalassemia.

Her follow up iron profile off oral iron showed persistent elevated parameters, in particular a transferrin saturation of 82% and ferritin of 1688 ng/mL. Screening test for the most common hereditary hemochromatosis (HH), deleterious mutations in the HFE gene, was negative. While other causes of HH were possible, the most likely explanation was the increased iron absorption with chronic hemolytic anemia exacerbated by the multi-year administration of oral iron for her microcytic anemia.

Her persistent marked thrombocytosis was clearly not due to iron deficiency. Since she had a lifelong partially compensated hemolytic anemia, abdominal ultrasound was performed to rule out auto splenectomy from serial small splenic infarcts as is commonly seen in sickle cell anemia. This showed a mildly enlarged spleen. She subsequently underwent bone marrow aspirate and biopsy which revealed a mildly hypercellular marrow with erythroid and megakaryocytic dysplasia without increased fibrosis by reticulin stain or increased blasts by morphology or flow cytometry. Her cytogenetics were normal and her myeloproliferative neoplasm (MPN) panel was also negative, including JAK 2, CAL-R and MPL mutations. Her hematologic malignancy gene sequencing panel was negative for mutations, including in ATRX, which when mutated in myelodysplastic syndrome (MDS) causes an alpha thalassemia type defect.

Her evaluation clearly confirmed alpha thalassemia trait, secondary hemochromatosis and an underlying MPN bone marrow disorder.

Discussion

This case clearly illustrates the importance of confirming the underlying etiology of CBC abnormalities. She had a longstanding history of a microcytic anemia, which appropriately prompted the consideration of iron deficiency. However, particularly with a family history of thalassemia and no identified time when her anemia wasn't present, she merited additional testing with at least an iron profile to confirm or rule out iron

deficiency. Even though her alpha globin gene deletion screen was negative, her alpha thalassemia diagnosis merited the alpha globin gene sequencing which revealed a 2 of 4 gene mutation pattern which was consistent with her chronic moderate microcytic but not transfusion dependent anemia.[1]

Her secondary hemochromatosis was most likely primarily due to lifelong increased iron absorption from inherited hemolytic anemia. Her iron overload was worsened by oral iron advised by medical professionals. In addition, her thrombocytosis not explained by iron deficiency or being asplenic merited the bone marrow biopsy which confirmed an MPN, specifically ET (essential thrombocytosis).

If accurate, her MDS component currently has a low risk of progression to acute myelogenous leukemia (AML) with no excess blasts or high-risk molecular changes. MDS survival can be estimated by the Revised International Prognostic Scoring System (IPSS-R), which is based on blood count levels and cytogenetics and % blasts.[2] She had a low risk group on IPSS-R with a median survival of 5.3 years and a median time to 25% chance of evolution to AML of 10.8 years.[2] The only curative therapy would be an allogeneic bone marrow transplant. Her particular assessment is complicated by a histologic MDS diagnosis with alpha thalassemia so, given no separate molecular marker confirming MDS, the erythroid morphological abnormalities on her bone marrow might have been caused by lifelong moderate chronic hemolytic anemia.

Even without a molecular marker, her MPN diagnosis was convincing given bone marrow morphology and no plausible alternative explanation for her marked thrombocytosis. She merited treatment to reduce her platelets to 300-600 x 10-3/ uL which decreases the risk of stroke using either hydroxyurea or anagrelide.[3] Fortunately, younger women with ET rarely have complications even with platelets over 1000 x 10-3 /uL (3). ET survival is generally several decades.

Her secondary hemochromatosis with a ferritin > 1000 ng/dL merited aggressive efforts to lower body iron stores to avoid end organ injury, particularly to liver, heart, pancreatic islet cells and pituitary and to a lesser extent joints.[4] The most effective treatment is phlebotomy, however her multi factorial anemia would severely limit tolerance. If periodic phlebotomy wasn't tolerated, she would be a candidate for oral iron chelating agents like deferasirox.[4]

She was started on hydroxyurea for ET and judicious phlebotomy if her Hb > 8.4 gm/dL. If she were to decide to become pregnant, hydroxyurea would be potentially teratogenic. She could switch to pegylated alpha interferon which has been shown to be effective at lowering platelet counts and is generally well tolerated with mainly flu like symptoms and not associated with worse pregnancy outcomes.[5]

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