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Acquired Hb H disease associated with elevated Hb F level in patient affected by primary myelofibrosis

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Dear Editor,

The hemoglobin H (Hb H) disease is an hereditary disorder characterized by the inactivation of three α -globin genes caused by large deletions (—MED—del; -20.5—del; -3.7; -4.2) and rarely by point mutations (NcoI; HphI), leading to an excess of β -chains within the erythrocytes that form β -tetramer, also known as hemoglobin H [1, 2]. Patients with Hb H disease usually have moderate anemia with marked microcytosis and hypochromia. We report the case of 37-year-old woman who received diagnosis of primary myelofibrosis (PMF) in early phase in March 2001. In 2005, because of a progressive increase in transfusion need, patient underwent splenectomy resulting in a rapid improvement of blood counts. ASO-PCR performed at this time on peripheral granulocytes and on DNA extracted from diagnosis—bone marrow biopsy did not reveal any *JAK2* or *MPL* mutations. After 3 years, in May 2008, patient was admitted in the hospital because of the sudden occurrence of severe anemia, with signs of acute hemolysis. At clinical examination, hepatomegaly and ascites were present, and the performance status was severely compromised. Abdominal ultrasound and MRI revealed extramedullary tissue in splenic lodge associated with portal vein thrombosis. Laboratory tests showed increased transaminases and LDH values but bilirubin in normal range. The peripheral blood

count confirmed a severe microcytic anemia (Hb=7 g/dL, MCV 63 fl), with normal reticulocytes, associated with leukocytosis (WBC=177,000/mm³, erythroblasts 60%, myelocytes and promyelocytes 40%) and normal PLT count. Morphology of peripheral blood smear showed severe anisopoikilocytosis with schistocytes, teardrop erythrocytes, and red cell inclusions. Blu cresile staining identified Heinz bodies usually suggestive for β and/or γ globin chains precipitation. To investigate a possible hemoglobinopathy, we performed high-performance liquid chromatography (HPLC) assay which demonstrated the presence of a significant Hb H level (23%) associated simultaneously to the elevation of fetal hemoglobin (Hb F) value (14.2%) comparing with normal Hb A2 (1.2%). Tris-EDTA-borate electrophoresis and agarose isoelectrofocusing confirmed the HPLC results. The molecular analysis by GAP-PCR [3] did not reveal any mutations in the α -locus and α -genes promoter. We concluded that an acquired Hb H disease is associated with compensative increase of Hb F in patients affected by PMF in myeloproliferative phase. Patient started treatment with hydroxyurea (2 g/die) and warfarin for thrombosis prophylaxis, experiencing a progressive improvement of general conditions and ascites reduction. After 2 weeks of therapy, we assisted to a decrease of WBC and peripheral erythroblast counts with a progressive elevation of Hb level. At this time, patient is still under cytoreductive treatment (hydroxyurea 1 g/die) with normal Hb value (last measure 12.9 g/dl). Interestingly, HPLC at this point found a significant reduction in Hb H level (7%) but the elevation of Hb F value (39%). Acquired Hb H disease has been well characterized and associated to several hematological malignancies (acute leukemia, myeloproliferative diseases (MPDs), and myelodysplastic syndromes) [4–8], but the mechanisms by which, in absence of mutations in globin genes, these patients develop a thalassemic phenotype are still unclear. It

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may be due to a posttranscriptional failure in the neoplastic clone. Here, we report the first case of acquired Hb H disease in MPD patient associated with another hemoglobinopathy. The Hb F increase could have been a compensative mechanism of the Hb H presence or an additional effect of posttranscriptional mistake. Hydroxyurea could have affected Hb level in this patient reducing the myeloproliferative clone but also stimulate directly the Hb F transcription as suggested by HPLC result, reinforcing the idea of compensative role of Hb F.

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