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ΣΥΝΕΧΙΖΟΜΕΝΗ ΙΑΤΡΙΚΗ ΕΚΠΑΙΔΕΥΣΗ

Hematology Quiz – Case 36

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ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2013, 30(5):636–637

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A 34-year-old man was admitted to the hospital because of severe abdominal pain. The pain was continuous and started one day before admission, causing no changes in the stool and accompanied with nausea and vomiting. The patient had also complained about progressive weakness, fatigue, dyspnoea on slight exertion, dizziness, headache and arthralgias for the last 4 months. His past medical and family history was unremarkable.

On admission the physical examination revealed jaundice and a generalized sensitivity in the examination of the abdomen with signs of peritoneal reaction in the upper abdomen. The patient's temperature was 37.8 °C, the blood pressure was 145/95 mmHg and the pulse rate was 102/min. The liver was enlarged, 3 cm below the costal margin, and very sensitive. The spleen was also palpable (2 cm below costal margin), but not painful while there was no peripheral lymphadenopathy.

His hematological profile was as follows: WBC 1.9×10^9/L (differential count: Neutrophils 27%, lymphocytes 62%, monocytes 11%), Hb 8.2 g/dL, Ht 26.8%, and platelet count 94×10^9/L. The reticulocyte count was 0.2% and ESR was 62 mm/1 hour. The peripheral blood smears morphology is shown in figure 1. Serum biochemistry was as follows: Urea 72 mg/dL, creatinine 2.1 mg/dL, Na^+ 138 mEq/L, K^+ 5.4 mEq/L, Ca^{++} 4.9 mEq/L , SGOT 178 IU/L, SGPT 345 IU/L, γGT 181 IU/L, alkaline phosphatase 622 IU/L, bilirubin 4.2 mg/dL (conjugated 2.9 mg/dL) and LDH 340 IU/L. A mild prolongation in bleeding time (INR 2.1, aPTT 62 sec) was also observed while the fibrinogen degradation products were slightly increased. Chest X-rays and the ECG were normal. The ultrasonography of the abdomen revealed hepatomegaly, hepatic vein thrombosis with moderate ascites. The appropriate anti-coagulant medication was administered and the symptoms were vanished three weeks after the initiation of the treatment. Bone marrow aspiration findings are shown in figures 2 and 3; trephine biopsies were performed and were diagnostic. The osmotic fragility and the autohemolysis tests were within normal limits. The leukocyte alkaline phosphatase was almost absent. Caryotype was normal. The detection for CD55 and/or CD59 deficient red cell population in the peripheral blood, using the sephacryl gel microtyping system, revealed a 75% reduction of both antigens from the membrane surface (fig. 4).

The diagnosis was established and the disease had a chronic course despite the appropriate treatment.

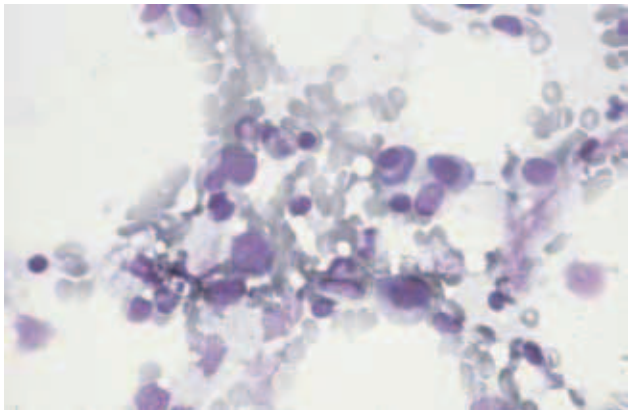

Figure 1

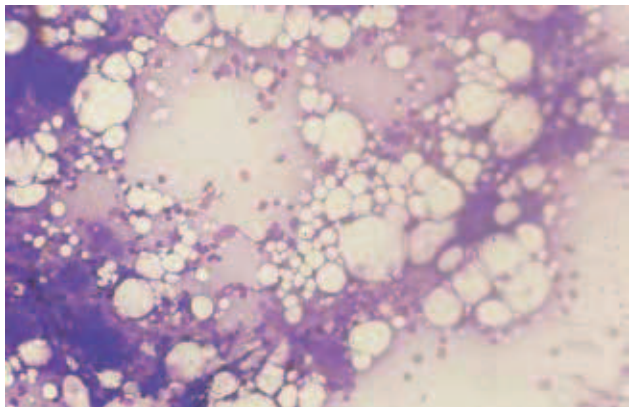

Figure 2

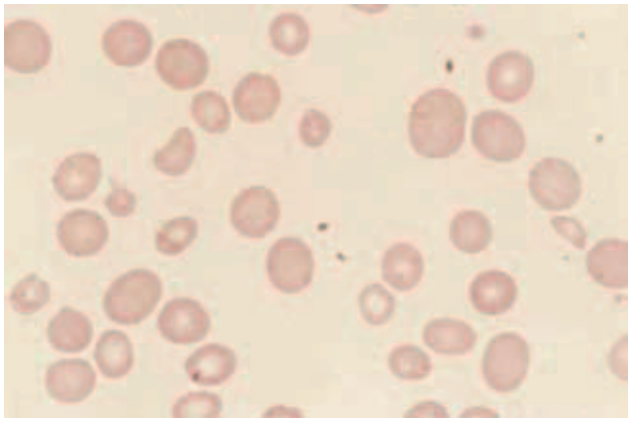

Figure 3

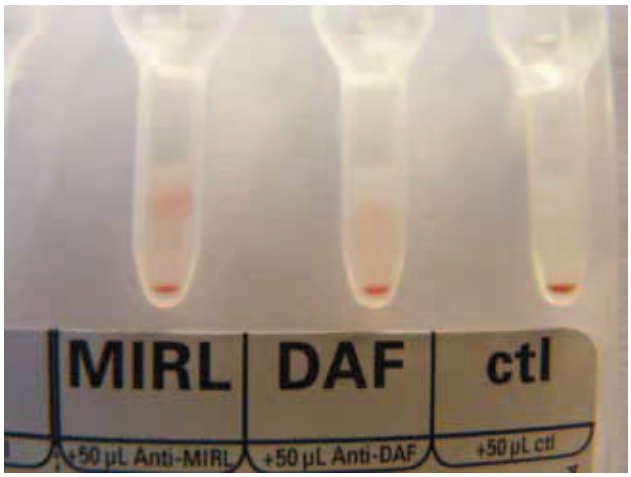

Figure 4

Comment

Acquired aplastic anemia (AA) is a rare clonal stem cell disorder characterized by severe bone marrow failure; blood cell counts are extremely low and the bone marrow appears empty. The pathophysiology of aplastic anemia is believed to be immune-mediated, with active destruction of blood-forming cells by T-cells. The aberrant immune response may be triggered by environmental exposures, such as to chemicals and drugs or viral infections and, perhaps, endogenous antigens generated by genetically altered bone marrow cells. There is a strong association between paroxysmal nocturnal hemoglobinuria (PNH) and AA. PNH patients may develop pancytopenia with hypoplastic or aplastic bone marrow and 10–25% of them will develop a secondary AA. Most of these patients present PIG-A mutations that are not observed at the beginning of AA. A minor population of blood cells deficient of GPI-anchored membrane proteins is often detected in patients with AA, at a proportion that varies among different studies between 10% and 55%. Patients with AA and PNH clones have repeatedly a negative Ham test and no sign of hemolysis. A very interesting finding is the absence of CD59 from erythrocytes of patients with AA, who do not present the same deficiency from their monocytes or neutrophils, indicating that a larger number of patients with AA may present PNH clones.

In this point, it should be mentioned that AA and PNH share a lot of common biological features. CD34 (+) cells from patients with AA and PNH produce significantly lower in vitro CFU-Meg formation compared with normal donors, and have the same apoptosis resistance. As PIG-A mutated cells have not a proliferative advantage in the normal bone marrow it can be supposed that the hypoplastic marrow of AA can offer a survival advantage to these cells resulting in their proliferation and detection. There is experimental evidence that cells lacking GPI-anchored surface proteins may be more resistant to attack by NK- and T-cells. It is well known that there is a greater suppressor lymphocytes number in both peripheral blood and bone marrow of AA patients. These activated T-cells can induce apoptosis of CD34+ cells leading to bone marrow failure. The detection of GPI-anchored protein-deficient clones in such a high proportion of AA patients strongly suggests that the PNH clones are linked to immunologically mediated forms of bone marrow failure. The higher T-cell receptor beta-variable chain repertoire that is present in PNH compared with controls supports a possible immune mechanism in PNH. Furthermore, AA patients with expanded PNH clones show more skewed variable region of beta-chain T-cell receptor repertoire than AA patients without a PNH clone. These data suggest common pathogenetic links between AA and PNH. In the future it may be possible to identify the precise target, which is responsible for a possible autoimmune attack on hematopoietic precursors inducing the development of AA, PNH or AA/PNH syndrome.

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Diagnosis: *Hepatic vein thrombosis in paroxysmal nocturnal hemoglobinuria with marrow hypoplasia*