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Hematology Quiz – Case 15

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ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2009, 26(5):719–720

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A 27-year-old Greek male was presented to the outpatient department because of progressive weakness and fatigue, dyspnea on slight exertion and fever. Fever started seven days before, reached 38.5 °C, often peaking twice daily; there were also chills, sweating, and sometimes dry cough. The administration of ampicillin initially and cefuroxime afterwards had no effect. His past medical history was unremarkable. Physical examination on admission revealed only pallor without any sign of infection. There were no hepatosplenomegaly or lymphadenopathy. The body temperature was 37.6 °C, the pulse rate was 125/min and the blood pressure was 110/70 mmHg.

His hematological tests showed severe normochromic and normocytic anemia (Ht 19.8%, Hb 6.4 g/dL), leukopenia (white blood cells 1.2×10^9/L; differential count: neutrophils 18%, lymphocytes 76%, monocytes 5% and eosinophils 1%) and a mild thrombocytopenia with large platelets (78×10^9/L) although MPV was within normal range. There were no immature forms of red or white series in the blood smears. The reticulocyte count was 0.1%. Coombs reaction was negative and serum haptoglobin levels were normal as well as the coagulation parameters. The erythrocyte sedimentation rate was 38 mm/1 hr. Serum biochemistry was as follows: SGOT 50 IU/L, SGPT 52 IU/L, LDH 263 IU/L, γGT 29 IU/L, ALP 128 IU/L, bibirubin 1.12 mg/dL, Fe 180 μg/dL. Serum proteins, ferritin, B_{12} and folate levels, serum electrophoresis and quantitative analysis of immunoglobulins were within normal range. Chest X-rays revealed no abnormality. Blood and urine cultures were unable to detect a bacterial or fungus infection. IgM antibodies titres for EBV, HCV, HSV and VZV were not elevated while IgM antibodies for CMV were positive (titre: 1/480). The tests for rheumatoid factor, antinuclear antibodies, LE cells and cryoglobulins were negative. Antibodies against brucella were not detected. No malaria parasites were present in the peripheral blood smears. Tuberculin skin test was negative. Stool examination for ova and parasites was negative. The abdominal ultrasound was normal. The bone marrow aspirate showed a marked hypoplasia with erythroblastopenia and reduced number of myeloid elements while small foci of sparse cellularity composed mainly of mature lymphocytes were observed (figures 1, 2). A bone marrow biopsy was performed and showed only yellowish white material, consisting chiefly of fat, fibrous tissue and polyclonal lymphocytes. The detection of CD55 and CD59 red cell populations, using sephacryl gel test microtyping system, revealed a 10% CD55 erythrocytic negativity (fig. 3).

Although no bacteria were detected cefotaxime, gentamycin and metronidazole were administered and the fever was controlled after three days. Four units of packed erythrocytes were transfused for the correction of anemia. After the febrile episode the administration of the appropriate therapy for basic disorder was effective as the blood cell count was near normal values two months later and the clinical condition of the patient was excellent.

Comment

Acquired aplastic anemia (AA) is a rare stem cell disorder characterized by peripheral blood pancytopenia and hypocellular bone marrow having a strong relationship with paroxysmal nocturnal hemoglobinuria (PNH). The exact responsible pathogenetic mechanisms of AA are unknown, but the possible causes include a primary stem cell defect, immune inhibition of hemopoiesis and an abnormal bone marrow microenvironment. PNH is also an acquired clonal hemopoietic stem-cell disorder characterized by a decrease or absence of glycosylphosphatidylinositol (GPI)-anchored molecules such as CD55 and or CD59 from the surface of affected cells, resulting in chronic intravascular hemolysis, venous thrombosis, frequent episodes

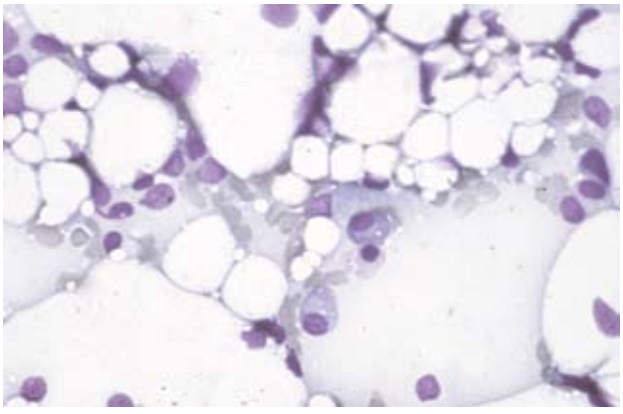

Figure 1

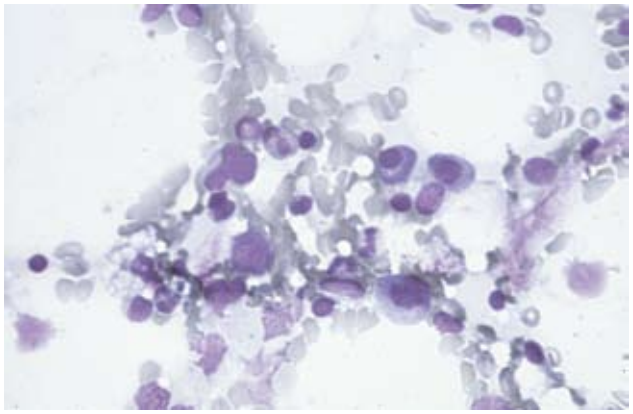

Figure 2

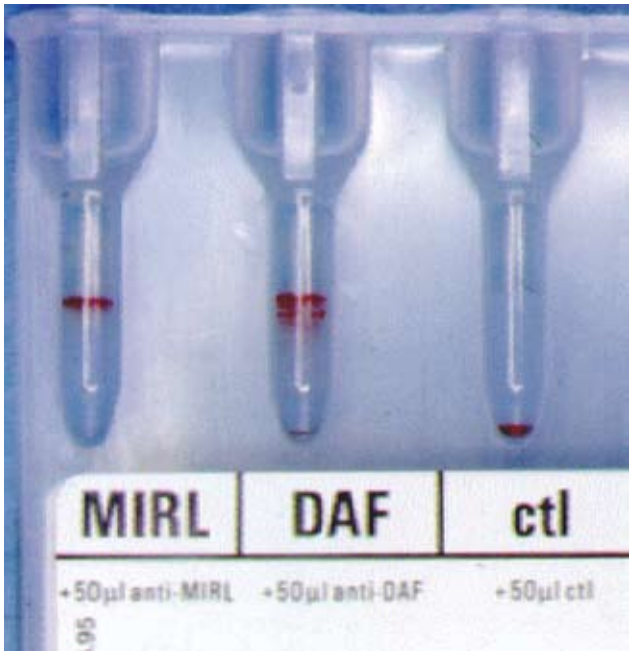

Figure 3

of infection and rarely leukemic conversion. PNH patients may also develop pancytopenia with hypoplastic or aplastic bone marrow and 10–25% of them will develop a secondary AA. PNH has been also considered as a late clonal hematopoietic complication of AA, despite the possible existence of the expanded PNH clones in AA at diagnosis. Deficient GPI-linked molecules cells are detectable in about 10–57% in AA patients, mainly after immunosuppressive treatment. Most of these patients present PIG-A mutations that are not observed at the beginning of AA. The "AA-PNH syndrome" was considered as a very rare AA variant few years ago when the detection of PNH cells was based only on Ham and sucrose lysis tests. Nowadays with flow cytometric analysis and other techniques, like the sephacryl gel test microtyping system, it can be declared that 20–25% of patients with AA as having the "AA-PNH syndrome". These patients have not a higher response rate using immunosuppressive therapy. However, the initial hematological improvement is so frequent in AA that rigorous demonstration of a higher rate of response in this subset of AA would require a great number of patients.

It is important to be mentioned that CD34+ cells from patients with AA and PNH produce significantly lower in vitro CFU-Meg formation compared with normal donors and that CD34+ cells of both AA and PNH has the same apoptosis resistance. Elevated levels of circulating microparticles, mostly stemmed from platelets, were detected in both de novo PNH patients and AA subjects with a PNH clone, but not in those with AA without a PNH clone. As PIG-A mutated cells have not a proliferative advantage in normal bone marrow, it can be supposed that the hypoplastic marrow of AA may 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 the immune system. 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 induce apoptosis of CD34+ cells leading to bone marrow failure. Thus, 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 β-variable chain repertoire that is present in PNH compared with controls supports a possible immune mechanism in PNH. These data suggest common pathogenetic links between AA and PNH and in the future it may be possible to identify the precise target GPI-anchored protein responsible for an autoimmune attack on hematopoietic precursors inducing the development of AA, PNH or AA-PNH syndrome.

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