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ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2026, 43(4):574–576

Hematology Quiz – Case 75

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A 62-year-old non-vegetarian woman with no significant medical history presented with a month-long history of weakness and progressive exertional dyspnea. She denied alcohol use and regular medication intake. On examination, she was hemodynamically stable, with marked pallor and bilateral leg edema.

Initial blood tests showed leukocytes at 4.5×10^9/L (neutrophils 2.6×10^9/L, lymphocytes 1.7×10^9/L), severe macrocytic anemia (hemoglobin 3.9 g/dL, hematocrit 11.5%, MCV 129.1 fL), and thrombocytopenia (platelet count 78×10^9/L). Absolute reticulocyte count was 22.2×10^9/L (reference range: 20.0–100.0$\times10^9$/L). Peripheral blood smear revealed marked anisopoikilocytosis with microcytes, macrocytes, tear-drop cells (++), ovalocytes (+), and 0.6% schistocytes (figures 1 to 5). Additional findings included basophilic stippling, Cabot rings, and nucleated red blood cells with nuclear atypia (figures 1 to 3). The granulocytic lineage demonstrated hypersegmented neutrophils, a left shift (myelocytes 4%), and increased cytoplasmic granulation (figures 1, 3 to 5). Platelets were reduced and anisomorphic. No red cell agglutination or rouleaux formation was observed. Biochemistry revealed markedly elevated lactate dehydrogenase (LDH: 3,417 U/L; reference range: 135–225 U/L) and increased indirect bilirubin (1.37 mg/dL; reference range: 0.2–0.8 mg/dL), with normal hepatic and renal function. Both direct and indirect Coombs tests were negative; inflammatory markers were within normal limits. Coagulation studies showed mildly prolonged prothrombin time (16.4 sec; reference range: 11–15 sec) and elevated D-dimers (1.22 μg/mL; reference range: <0.50 μg/mL), with normal activated partial thromboplastin time and fibrinogen. Abdominal ultrasound was unremarkable.

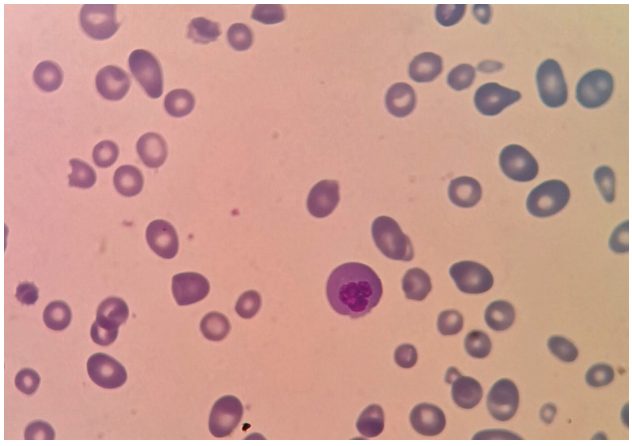

Figure 2

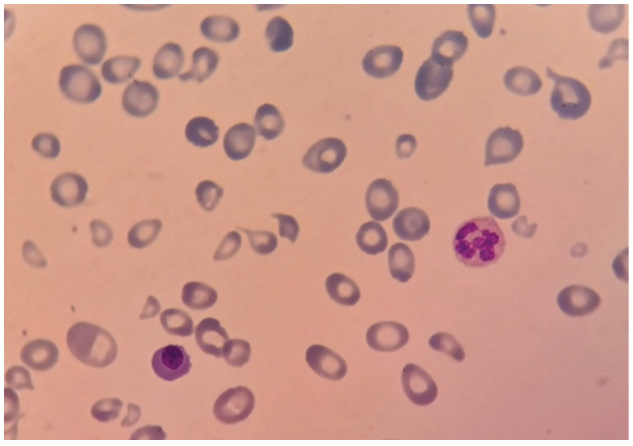

Figure 1.

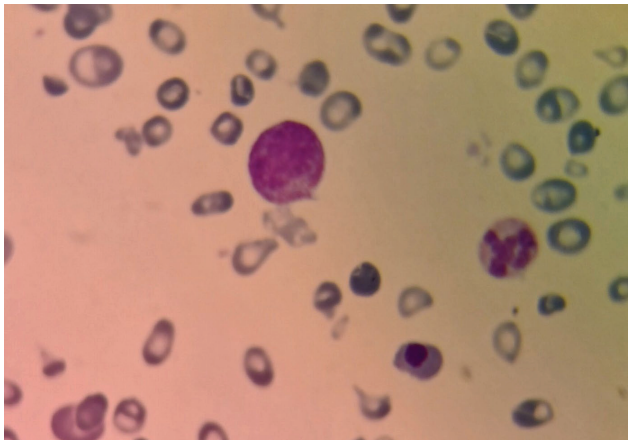

Figure 3

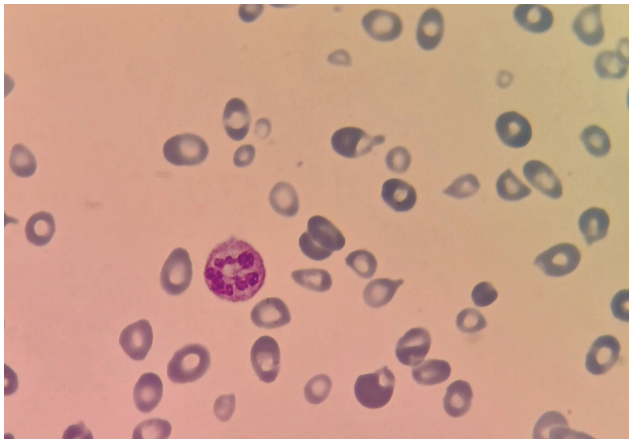

Figure 4

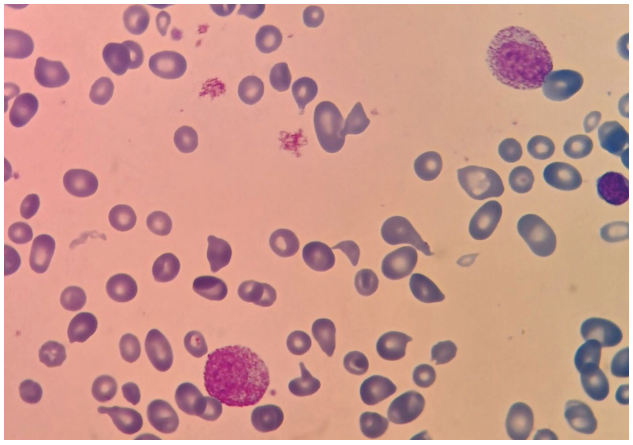

Figure 5

The patient received two units of packed red blood cells and parenteral hydroxocobalamin (1 mg daily intramuscularly for 5 days, then monthly). Serum vitamin B_{12} was found markedly low (<83 pg/mL; reference range: 187–833 pg/mL) within 24 hours of admission; with normal ferritin and folic acid levels. Autoimmune testing revealed positive anti-parietal cell antibodies (titer 1:80) and elevated anti-intrinsic factor antibodies (114.1 units; reference range: <20), confirming the diagnosis.

Comments

The leukoerythroblastic picture (fig. 3) initially raised suspicion for myelofibrosis; however, this did not explain the hemolysis. The absence of splenomegaly, lack of hemoglobinuria, and presence of hypersegmented neutrophils argued against this diagnosis. Myelodysplastic syndrome (MDS) with a possible paroxysmal nocturnal hemoglobinuria (PNH) clone was considered due to the combination of cytopenias, hemolytic markers, and dysplastic erythropoiesis.

The combination of anemia, thrombocytopenia, elevated D-dimers, and schistocytes raised suspicion for thrombotic microangiopathy (TMA). However, the absence of bleeding, low schistocyte count relative to anemia severity, and presence of reticulocytopenia –indicating impaired marrow response– argued against this diagnosis. No evidence of renal, neurologic, or gastrointestinal dysfunction was present. The PLASMIC score was 4, corresponding to a low probability (4.3%) of true thrombotic thrombocytopenic purpura (TTP). Disseminated intravascular coagulation, autoimmune hemolytic anemia, and G6PD deficiency were also excluded.

Megaloblastic anemia due to vitamin B_{12} or folate deficiency was strongly considered. An MCV >120 fL has 99% specificity for vitamin B_{12} deficiency, and combined macrocytosis with neutrophil hypersegmentation has 97% specificity. Severe vitamin B_{12} deficiency can mimic TTP ("pseudo-TTP") in 2.5% of cases, making early recognition crucial to prevent unnecessary and potentially harmful interventions.

Vitamin B_{12} deficiency can cause both intramedullary and, less commonly, extramedullary hemolysis. Intramedullary hemolysis results from ineffective erythropoiesis and typically lacks schistocytes. Bilirubin levels tend to be lower due to hemolysis of immature precursors, while LDH and platelet counts may be higher. Extramedullary hemolysis occurs through erythrocyte destruction in the reticuloendothelial system, driven by reduced red cell membrane flexibility and toxic effects of hyperhomocysteinemia on erythrocytes and endothelium.

Tear-drop cells are frequently seen in megaloblastic anemia. In a study of 50 patients with moderate to severe megaloblastic anemia and without splenomegaly or myelofibrosis, tear-drop cells were present in 40 cases, ranging from 1–10%. Their presence reflects altered erythrocyte passage through an active spleen. The leukoerythroblastic reaction, traditionally associated with malignant or metastatic neoplasms, can occur in vitamin B_{12} deficiency, often with pancytopenia and splenomegaly, reflecting marrow stress or extramedullary hematopoiesis. A systematic review reported that hemolytic disease accounts for 7.6% of leukoerythroblastic anemia cases, while infections, hemolytic, and nutritional anemias are commonly observed in Africa and Asia. In vitamin B_{12} deficiency, this reaction is usually moderate and of uncertain clinical significance.

Elevated homocysteine and methylmalonic acid levels serve as confirmatory markers in symptomatic patients with borderline vitamin B_{12} levels (200–300 pg/mL). In our patient, the very low vitamin B_{12} level made further confirmatory tests unnecessary. Following treatment, reticulocyte counts increased nearly 10-fold within 24 hours, reaching 13.31% (absolute reticulocyte count: 217.6×10^9/L). The patient had no systemic symptoms, and bone marrow biopsy was not performed, as it is not typically required in vitamin B_{12} deficiency. Typical bone marrow findings include hypercellularity, erythroid hyperplasia, and nuclear-cytoplasmic asynchrony, mimicking MDS or even leukemia.

Pernicious anemia, an autoimmune disorder primarily affecting individuals over 60, accounts for 20–50% of adult vitamin B_{12} deficiency. Intrinsic factor, secreted by gastric parietal cells, binds vitamin B_{12} for absorption in the terminal ileum. Anti-intrinsic factor antibodies have 40–60% sensitivity and nearly 100% specificity for diagnosis of pernicious anemia. Patients require lifelong vitamin

B_{12} therapy. This case highlights the importance of considering vitamin B_{12} deficiency in patients presenting with pancytopenia and hemolytic markers to avoid misdiagnosis and inappropriate treatment. Peripheral smear review and targeted laboratory testing are crucial to distinguish vitamin B_{12} deficiency from more severe hematologic disorders.

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