Pyrazinamide-induced sideroblastic anemia

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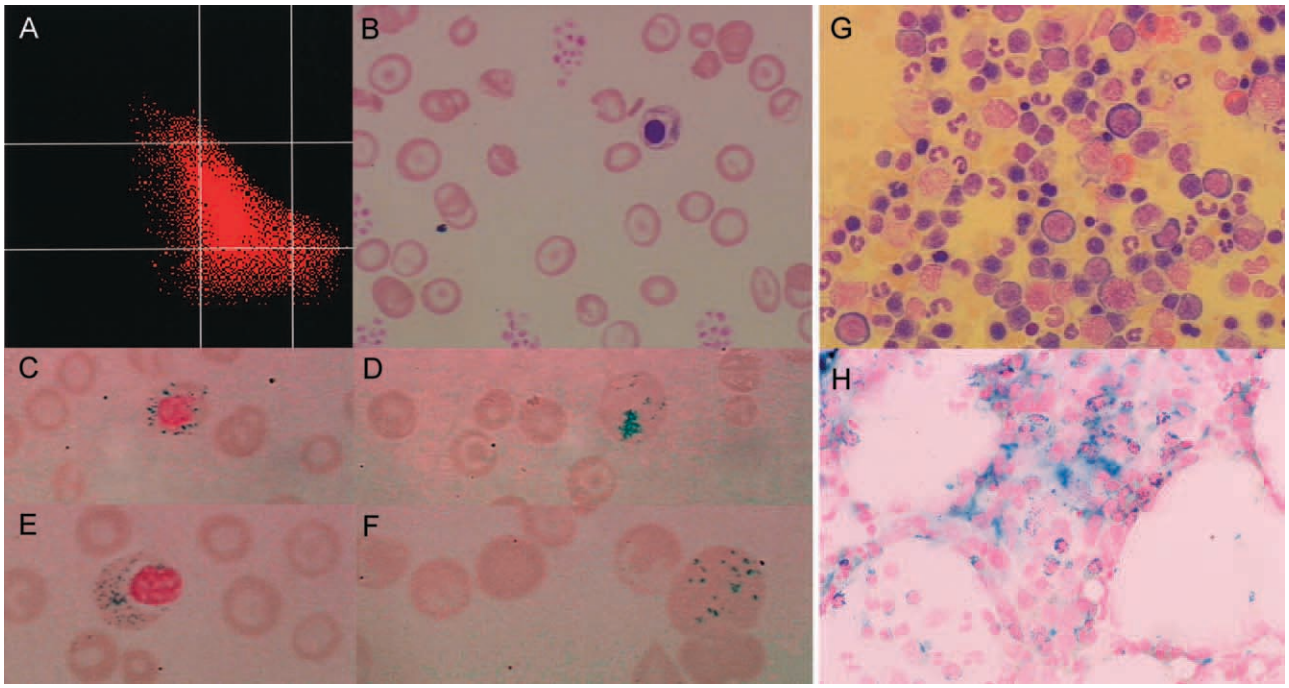

Image 1. Morphological features suggestive for sideroblastic anemia. A: ADVIA 120-erythrogram showing a broad scatter distribution of the red cells. B: Peripheral blood smear with target cells and one normoblast (×100). C–F: Perls' stain of peripheral blood showing one ring sideroblast, one sideroblast and two siderocytes (×100). G–H: Bone marrow aspirate smear illustrate dyserythropoiesis (Pappenheim, ×63), and ring sideroblasts (Perls' stain, ×63).

A 54-year-old African woman with heterozygous α-thalassemia (hemoglobin concentration, 141 g/l; mean corpuscular volume, 78 fl; mean corpuscular hemoglobin, 26 pg; red cell distribution width [RDW], 14.8%) was hospitalized because of peritonitis caused by *Mycobacterium tuberculosis*. The bone marrow aspirate showed normal hematopoiesis with absent storage iron and negative cultures for *M. tuberculosis.* She was treated with isoniazid, rifampicin, pyrazinamide, and ethambutol. Isoniazid had to be changed to moxifloxacin early in the course of therapy because of hepatotoxicity. Hemoglobin dropped progressively to 53 g/l (reticulocytes, 66 × 10^9/l) over 6 weeks despite intravenous iron substitution.

Mild hemolysis was present with a negative Coombs test and without hemosiderin in the urine. In the peripheral blood smear, increasing anisocytosis (RDW, 22.8%), poikilocytosis, polychromasia, target cells, and basophilic stippling were noted, as well as very few normoblasts (Image 1B), but no Heinz bodies were found after staining with vital dye. The pattern of the ADVIA 120-erythrogram showed an unusually broad scatter distribution of the red cells over eight of the nine areas of the scattergram (except the macrocytic hyperchromic [upper-right] field) (Image 1A). The erythrogram was suggestive for sideroblastic changes in the bone marrow (sideroachresia) [1]. Indeed, Perls' stain revealed several siderocytes, sideroblasts with even a few ring sideroblasts in the peripheral blood (Image 1C–F). Bone marrow aspiration was repeated and showed pronounced dyserythropoiesis (Image 1G) and heavily increased iron stores with numerous ring sideroblasts (Image 1H), confirming sideroachresia. Pyrazinamide-induced sideroblastic anemia with intramedullary hemolysis corresponding to ineffective erythropoiesis was suspected. The compound was stopped and pyridoxine was given, with normalization of hemoglobin and erythrocyte morphology within 3 months.

Sideroblastic anemia is a well-known side effect of tuberculostatic therapy. Both isoniazid and pyrazinamide are potentially responsible agents and pyridoxine should be given routinely as a prophylaxis. Both drugs inhibit the enzyme 5-aminolevulinic acid synthase-2 (ALAS-2), catalyzing the first step of hem biosynthesis. If ALAS is blocked, iron accumulates within the mitochondrial matrix bound to mitochondrial ferritin and is detectable by light microscopy as granules surrounding the nuclei of normoblasts. In severe cases of sideroachresia, nucleated red blood cells containing iron granules may be present even in the peripheral blood, as in this case.

Reference

1. Rovo A, Stussi G, Meyer-Monard S, et al. Sideroblastic changes of the bone marrow can be predicted by the erythrogram of peripheral blood. Int J Lab Hematol 2010;32:329–335.

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Conflict of interest: The authors declare no conflict of interest.

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