Idiopathic myelofibrosis without dacryocytes

Idiopathic myelofibrosis (IMF) typically presents with marrow fibrosis, splenomegaly, progressive anemia, and a leukoerythroblastic blood smear with dacryocytes. We present a patient with IMF who did not have dacryocytes.

Haematologica 2006; 91:(6)e83-e84

Case Report

A 65-year-old woman presented with fatigue, abdominal discomfort, and early satiety. She required blood transfusions every two weeks. She had no other complaints including erythromelalgia, excess bleeding, or thromboses. Her past medical history included presumed essential thrombocythemia treated with anagrelide and asymptomatic childhood anemia. Physical examination showed massive splenomegaly at 22 cm confirmed by CT scanning. Her leukocyte count was 33.15 $\times 10^3/\mu L$, hemoglobin 8.3 g/dl, and platelets $193 \times 10^3/\mu L$. The reticulocyte count was 9.0%, lactate dehydrogenase 1516 IU/l (normal 300-600 IU/l), total bilirubin 1.0 mg/dl, and direct Coombs test negative.

We suspected idiopathic myelofibrosis and examined the blood smear. Although nucleated erythrocytes and myelocytes were present, dacryocytes were strikingly absent and spherocytes were present (Figure 1a). The bone marrow aspirate was dry while the biopsy was fibrotic, hypercellular, and without blast forms (Figure 1b). The cytogenetic karyotype of the biopsy was normal. Peripheral blood CD34+ cell proportion was elevated at 1.42% (normal range 0.03-0.08%) and the absolute CD34+ count was 424.3 cells/μL.[1] The patient's platelets and neutrophils were clonal in origin based on X-chromosome transcriptional analysis.[2] These tests established the diagnosis of idiopathic myelofibrosis.

The absence of dacryocytes remained puzzling. The history of asymptomatic childhood anemia suggested hereditary spherocytosis. Osmotic fragility of the red blood cells was increased. Detailed membrane protein analysis of the red blood cells revealed decreased ankyrin content (75% of control), slightly decreased spectrin content (92% of control), and decreased band 6 (G3PD) (42% of control) (Figure 2). The 4.1a/b ratio was normal.

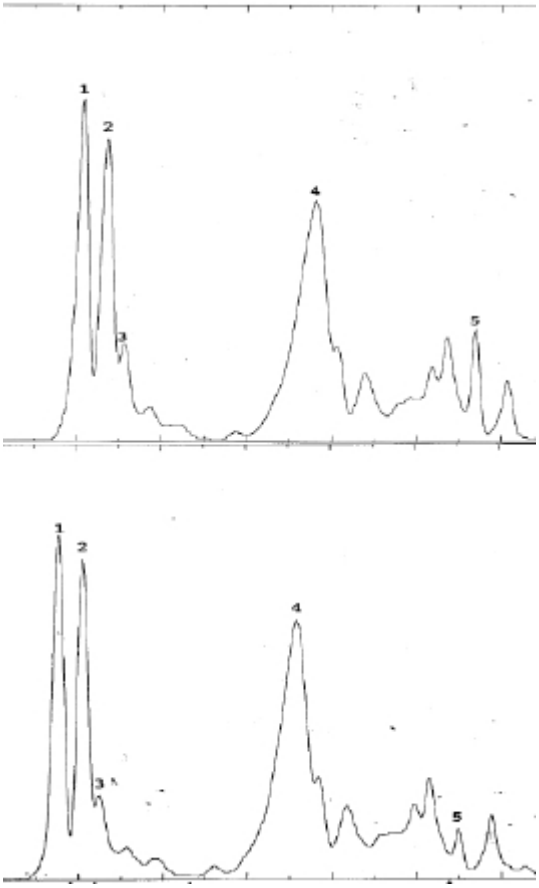

Figure 1. Peripheral blood smear and bone marrow core biopsy from a patient with myelofibrosis and hereditary spherocytosis. (A) Pre-splenectomy peripheral blood smear notable for the absence of dacryocytes (Wright stain, 1000x). (B) Bone marrow core biopsy showing extensive marrow fibrosis (reticulin stain, 400x). Photomicrographs were obtained at room temperature using an Olympus BX51 microscope equipped with UPlanFl 40x/0.75 dry and UPlanFl 100x/1.30 oil lenses and an Olympus DP70 digital camera. Olympus DP Controller software was used to acquire the images.

Figure 2. Quantification of red cell membrane proteins. Proteins (20 Ìg) were separated by sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS PAGE) on 3.5-17% exponential gradient Fairbanks gels and quantitated (n=4 for patient samples; n=10 for control samples) by densitometric scanning of the Coomassie Blue stained gels. Top panel: normal control; bottom panel: patient. Spectrin (peaks 1 and 2), ankyrin (peak 3), band 3 (peak 4), and G3PD (peak 5) are indicated.

Non-denaturing gels of spectrin extracts and SDS PAGE of the tryptic digests did not show any qualitative defects in the spectrin molecule.[3] These results confirmed hereditary spherocytosis and explained the patient's previous asymptomatic anemia and puzzling erythrocyte morphology.

Because of her severe disease, we proposed to treat the patient with submyeloablative allogeneic hematopoietic stem cell transplantation (HSCT). She opted instead for splenectomy. Since, she has been transfusion independent with an average hemoglobin concentration of 13.0 g/dl. She continues to have an elevated LDH, platelet count, and leukocyte count, and her blood smear still shows leukoerythroblastosis with spherocytes.

Discussion

Prognosis in IMF can be predicted with the Lille score which considers the degree of anemia (hemoglobin < 10 g/dL) and leukocytosis or leucopenia (WBC > 30000/μL or WBC < 4000/μL). Patients with both risk factors, one risk factor, or no risk factors survive for a median of 13, 26, and 93 months respectively.4 Prognosis dictates whether to proceed immediately with curative allogeneic HSCT or to palliate with splenectomy, chemotherapy, cytokines, or radiation. Because of her severe anemia and leukocytosis, our patient was classified as high risk and was offered allogeneic HSCT but chose splenectomy. Despite her risk factors, she responded remarkably well and was able to change risk categories. We suspect her excellent response stemmed from eliminating the significant anemia burden imposed by her hereditary spherocytosis. This insight would not have been possible without examining the blood smear and noting the absence of dacryocytes, illustrating the importance of analyzing incongruous clinical details. To do so may allow a less toxic therapy and prevent therapeutic misadventure.

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Acknowledgements: This work is supported by grant R01HL5007-11 NHLBI (JTP and EL) from the National Institute of Health and the National Research Foundation under GUN2051859 and the Medical Research Council of South Africa (TLC and KN).
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