short report
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IDIOPATHIC MYELOFIBROSIS WITH NEUTROPHIL MYELOPEROXIDASE DEFICIENCY: A CASE REPORT

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ABSTRACT

We describe a case of idiopathic myelofibrosis with total neutrophil myeloperoxidase deficiency. The combination of this enzymatic defect with myelofibrotic changes in the nuclear shape of neutrophils confers a peculiar appearance on leukograms produced by a Technicon H*1. The clinical course of the disease was shortened by recurrent infections that may be ascribed, at least in part, to reduced leukocyte microbicidal ability.

Key words: idiopathic myelofibrosis, myeloperoxidase deficiency, infection

Myeloperoxidase (MPO), located in the azurophilic granules of neutrophils and monocytes, is part of the microbicidal system.[1] The identification of MPO deficiency has been favored by the introduction of automated cytochemical analyzers, and the estimated prevalence of this defect in unselected patients is about 0.15%.[2]

Idiopathic myelofibrosis (IMF) is a myeloproliferative disorder characterized by bone marrow fibrosis, leukoerythroblastic anemia and hepatosplenic myeloid metaplasia.[3] In IMF, circulating immature neutrophils are usually present and functional defects of neutrophils, monocytes and platelets[4] have been demonstrated. Cases of Sweet's syndrome, a neutrophilic dermal inflammation characterized by fever, leukocytosis and tender erythematous plaques, have also been reported.[5] We describe a case of idiopathic myelofibrosis with a total neutrophil myeloperoxidase deficiency.

Case Report

The patient, a 63-year-old male Caucasian was referred to our institution in 1987 for hepatosplenomegaly. His past medical history included juvenile paludism and pleurisy. Six years earlier his CBC was normal, but during the last two years moderate anemia, thrombocytosis and leukocytosis had been discovered. At physical examination, the liver was found to be five centimeters enlarged and the spleen reached the umbilicus. Blood work, performed by a Technicon H*1, revealed Hb 10.1 g/dL, MCV 88 fL, WBC 8.1×10^9/L, neutrophils 40%, lymphocytes 23%, LUC 36%, platelets 575×10^9/L. The leukocyte peroxidase channel disclosed a MPO deficiency that was initially partial and subsequently complete (Figure 1, D), and the nuclear lobularity channel indicated a left shift (d).

The peripheral blood showed a leukoerythroblastic picture (lymphocytes 5%, monocytes 1%, myelocytes 18%, metamyelocytes 15%, segmented neutrophils 61%, several orthochromatic erythroblasts) with dacryocytes. Sudan B, MPO and alkaline phosphatase (AP) stains were negative on neutrophils and platelet serotonin content was decreased. Lactic dehydrogenase was increased (1749 U/L), without a significant isoenzymatic pattern. Sternal bone marrow aspirate was hypocellular, while iliac histology still showed discrete marrow cellularity with an evident increase of reticulin (Figure 2, A). Chromosome banding (Giemsa-trypsin) demonstrated karyotype mosaicism with 15% normal and 85% t(8;12) (p23;q15) metaphases. A chest X-ray revealed right fibrothorax, and abdominal ultrasound and CT scans detected homogeneous liver and spleen enlargement.

The clinical course was characterized by progressive hepatosplenomegaly and transfusional needs. A rapid drop in the hemoglobin caused difficulties in performing erythrokinetics but suggested reduced red cell survival and splenic myelopoiesis. Increasing axial fibrosis and cell depletion were documented by serial biopsies and ^{99m}Tc scintigraphy of bone marrow. In 1989 another karyotype analysis demonstrated 100% t(8;12) metaphases. At this time several echogenic nodular areas were detected in the spleen, and a laparoscopic liver biopsy and spleen aspirate confirmed myeloid

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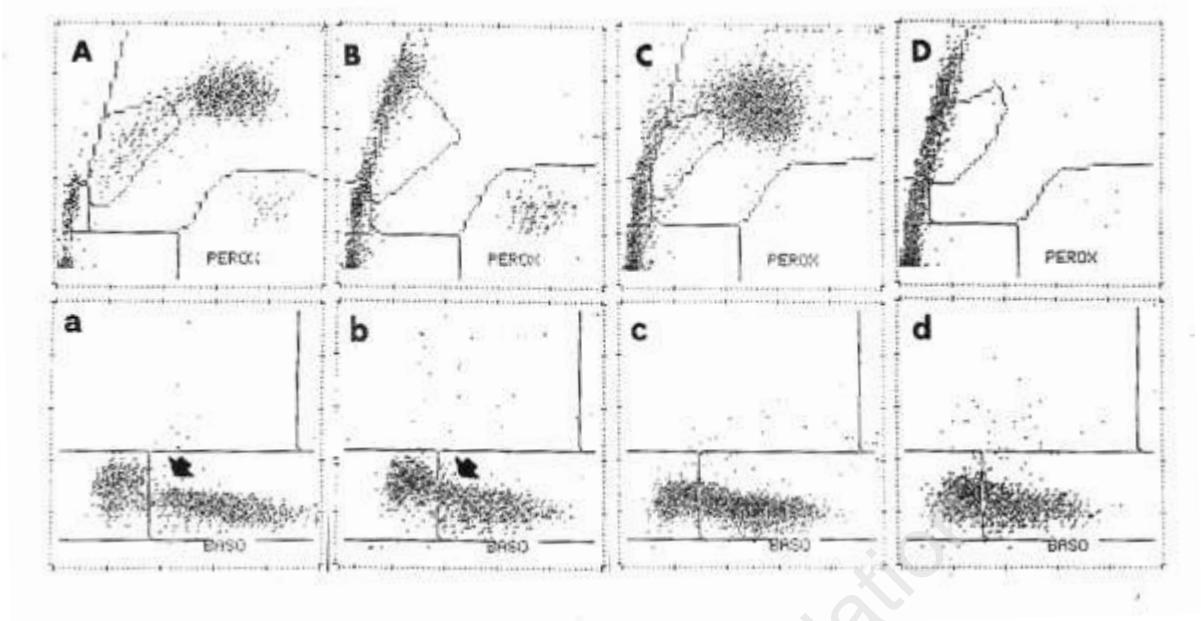

Figure 1. Myeloperoxidase (capitals) and nuclear lobularity (small letters) cytograms from a normal subject (A,a), a case of hereditary MPO deficiency (B,b), a control IMF patient (C,c), and the patient described in this report (D,d).

metaplasia (Figure 2, B and C). Despite therapy (including transfusions, prednisone, androgens, hydroxyurea, 1,25-dihydroxyvitamin D, α-interferon, spleen irradiation) the patient experienced progressive disease complicated by recurrent oral candidiasis and febrile episodes and died at the age of 67 of sepsis from *Pseudomonas aeruginosa*, without evidence of blast transformation.

Discussion

We describe a case of IMF with confirmed clonal myelopoiesis and agnogenic myeloid metaplasia, in which a total MPO deficiency was also present. These two disorders confer a particular appearance on neutrophil MPO and lobularity leukograms (Figure 1; D, d). In comparison, cytograms from a normal subject (A, a) and a child with hereditary

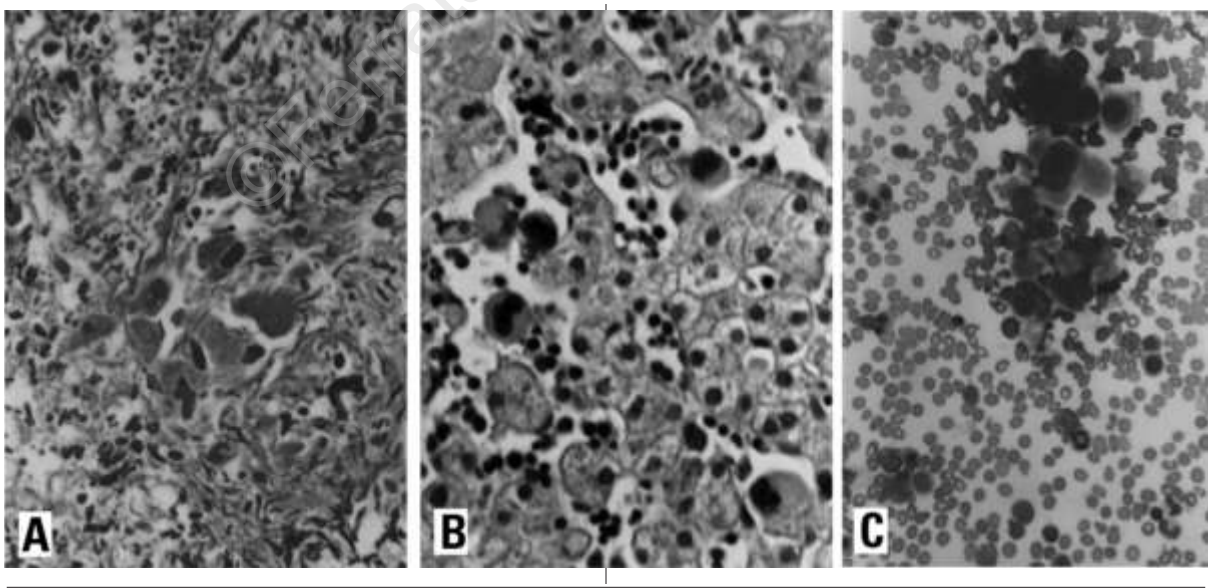

Figure 2. A) Marrow biopsy. Myelopoiesis is partially displaced by fibrous tissue mainly surrounding clusters of megakaryocytes (Silver imp., 312 x). B) Liver biopsy. Sinusoids contain several megakaryocytes and erythroblasts (H.& E. 312 x). C) Aspirate from a splenic node. All myelopoietic cells are represented in a marrow-like picture. Note teardrop erythrocytes. (Giemsa, 312 x).

MPO deficiency (B, b) show the normal valley between mononuclear and polymorphonuclear nuclei (arrows). This valley is absent, due to reduced nuclear segmentation, in the leukogram (c) from a control IMF patient whose MPO (C) is almost normal. The patient described in this report shared the MPO deficiency (D=B) and the nuclear pattern of myelofibrosis (d=c).

MPO deficiency may be inherited or acquired, and total or partial.[1] A partial deficiency may be expressed as reduced MPO activity in all neutrophils, or its absence in a portion of the cells. In the hereditary defect, which has no essential clinical importance and whose genetic base is still obscure,[6] MPO is absent from all or a part of the neutrophils but no additional granular defects have been described.[2] Conversely, acquired MPO deficiency is associated with susceptibility to infections, disturbed leukocyte maturation and chronic intravascular degranulation, and the defect, usually partial, may be accompanied by loss of other granular substances such as elastase-like protease and lactoferrin.[2,7] Acquired MPO deficiency has been described in myelodysplastic syndromes[8] and in acute and chronic myeloproliferative disorders.[1,9] Clonal defects of neutrophils, including MPO deficiency, have been reported in IMF.[10]

Our patient mimicked the inherited disorder in the total absence of the enzyme, and the acquired MPO deficiency in the presence of additional granular defects. This could be sustained by a clonal defect of metabolism or maturation of neutrophils, and even some loss of granular content in the abnormal reticuloendothelial system cannot be excluded. The presentation of the disease (cellular counts and *proliferative bearing*) suggested a more favorable prognosis than the patient actuallly experienced, probably because the infections that complicate IMF *per se* were additionally favored by the MPO deficiency. Nevertheless, the origin, incidence and prognostic relevance of MPO deficiency in IMF remain to be clarified.

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