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Case Report

Idiopathic myelofibrosis mimicking hemolytic anemia

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ABSTRACT

Idiopathic Myelofibrosis is an infrequent chronic myeloproliferative disorder characterized by varying degrees of bone marrow fibrosis and extra medullary hematopoiesis, with the fibrosis being a reactive phenomenon to a neoplastic proliferation of a pluripotent hematopoietic stem cell. Idiopathic Myelofibrosis is heterogeneous in presentation and clinical course, with anemia being one of the most important problems. We present a case of a 59 year old male who presented with severe anemia, the peripheral blood picture mimicking hemolysis with numerous schistocytes and teardrop cells.

INTRODUCTION

Bone marrow fibrosis is associated with numerous causes including myeloproliferative disease, other hematologic and nonhematologic malignant neoplasms, autoimmune disorders, and endocrine disorders.[1] Idiopathic Myelofibrosis (IMF) is an infrequent chronic myeloproliferative disorder characterized by varying degrees of bone marrow fibrosis and extra medullary hematopoiesis, with the fibrosis being a reactive phenomenon to a neoplastic proliferation of a pluripotent hematopoietic stem cell. IMF is heterogeneous in presentation and clinical course, with anemia being one of the most important problems. 20 to 25% of patients have anemic symptoms at presentation and 50% or more develop severe anemia during the evolution of the disease.[2,3] Myelofibrosis was first described in 1879 by Gustav Heuck.[4] There is stepwise evolution of the disease process with an intial prefibrotic stage that is characterized by hypercellular bone marrow (BM) with minimal reticulin fibrosis that merges into fibrotic stages which demonstrates marked reticulin or collagen fibrosis in bone marrow. A leukoerythroblastic blood smear with tear drop cells is characterstic findings in the fibrotic stage of IMF. Extramedullary hematopoiesis contributes to splenomegaly and hepatomegaly.

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CASE REPORT

A 59 year old male presented to the OPD with complaints of severe fatigue, slight dyspnea on exertion, mild swelling of the body and increasing pallor since last 8 months. He did not have any significant past history or family history. He gave history of smoking since last 10 years. He was diagnosed with anemia and treated with blood transfusion and haematinics. However, his symptoms were persistent and his health was deteriorating. On examination, his general condition was ill-looking with severe pallor, mild edema, no jaundice, cyanosis, lymph nodes or clubbing. He had mild tachycardia with heart rate of 98/minute. Mild hepatosplenomegaly was revealed. His hematological test showed markedly decreased hemoglobin level of 4 gm/dl, even after numerous blood transfusion, ESR was raised to 85 mm in the 1st hour. The RBC count was decreased to 2.1 million/cmm and the WBC count was slightly decreased to 3500/cumm with lymphocytosis. The peripheral blood

study showed predominantly normocytic normochromic RBC with severe anisopoikilocytosis (fig.1). Numerous Tear drop cells were seen along with occasional schistocytes. Morphology of platelets was normal except for occasional giant platelets. The Direct and Indirect Coombs tests were negative.

The biochemical tests for renal and liver functions were normal except for LDH which was significantly raised to 480 IU/L. The provisional diagnosis was hemolytic anemia. BM aspiration and biopsy was done to confirm the cause of anemia.

A bone marrow aspiration revealed hypocellular marrow and in biopsy severe myelofibrosis and increase megakaryocytes was observed. Reticulin stain was done to confirm the fibrosis which showed Grade 4 fibrosis (fig.2). The patient was finally diagnosed as a case of IMP.

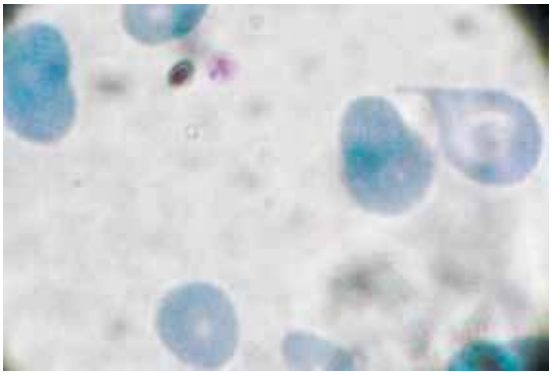

Figure 1: Peripheral blood smear showing teardrop cell, schistocytes, anisopoikilocytosis (Wrights Stain, X1000)

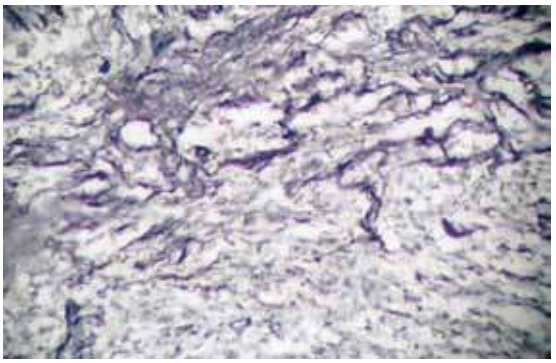

Figure 2: Grade 4 Reticulin deposition (Reticulin Stain, X400)

DISUCSSION

The designation 'idiopathic' myelofibrosis denotes a primary bone marrow disease in which the normal hematopoietic bone marrow cells for unknown reasons are progressively replaced by connective tissue. Several cases have been published in which bone marrow fibrosis and a clinical syndrome resembling IMF developed under the influence of various leukaemogenic agents, eg. Benzene, X-rays and, or thorotrast administration. An association with virus infection and the development of myelofibrosis has also been described, and in some patients immunological mechanisms maybe involved. The chronic form of IMF is marked by leuco-erythroblastic anaemia, anisopoikilocytosis with many tear drops, platelet polymorphism, a variable leucocyte count and a huge spleen owing to extra medullary hematopoiesis. A subset of patients with IMF presents with an acute variant of the disease marked by severe pancytopenia and constitutional symptoms although the spleen is not enlarges on clinical examination. The bone marrow is hypercellular with a predominance of dysplastic megakaryocytes and severe bone marrow fibrosis. This particular subtype of IMF has very poor prognosis, with death within a year from diagnosis in the large majority of patients.[5]

Pathogenesis of bone marrow fibrosis in Idiopathic Myelofibrosis

Current concepts implicate the megakaryocyte cell lineage as playing an important role in the pathogenesis of IMF. According to the hypothesis proposed by Castro-Malaspina[6], defective maturation of megakaryocytes results in the intramedullary death of large numbers of megakaryocytes with ensuing abnormal release of megakaryocyte components, including a growth factor similar to platelet derived growth factor (PDGF), and factor 4, which inhibits collagenase activity. The imbalance generated between increased collagen production and decreased collagen degradation accounts for an excessive accumulation of collagens within the marrow stroma.[7] Growth factors other than PDGF are contained in platelet granules, including epidermal growth factor and transforming growth factor-β, which may also be candidates for growth promoting activity in the bone marrow. Several observations support that release of mitogens from the megakaryocyte cell lineage may be involved in the development of myelofibrosis.[8] Thus, the accumulation of collagen fibers is usually closely associated with clusters of dysplastic megakaryocytes. In addition, the findings of decreased PDGF activity in circulating platelets or increased urinary platelet factor-4, reflecting a-granule release, are consistent with the idea that an abnormal release of PDGF occurs from platelets or megakaryocytes in the bone marrow microenvironment. Finally, the clinical observations of severe myelofibrosis in patients with acute megakaryoblastic leukaemia and in the gray-platelet syndrome, which is marked by excessive release of PDGF, are in line with this concept.[9] Most recently, bone marrow fibroblasts from patients with myeloproliferative disorders have been found to exhibit an increased sensitivity to various mitogens, which might further enhance fibroblast proliferation and the ultimate accumulation of collagen in the bone marrow.[7] Although the megakaryocyte may play a major role in the development of

bone marrow fibrosis in IMF, other cell lines and pathogenetic mechanisms should be considered. Circulating immune complexes have been demonstrated, but their pathogenetic significance is uncertain. However, autoimmune bone marrow damage may be incriminated in the pathogenesis in a subgroup of patients. Thus, in the early stage of IMF the myeloproliferation is often accompanied by immune activity in the bone marrow with a marked increase of lymphoid nodules. In addition, the clinical observations of a favourable outcome of immunosuppressive therapy in some MF patients with evidence of autoimmune activity support the idea that autoimmunity may be a main pathogenetic factor in a subset of patients.[10,11]

Collagen studies

Most histological studies of bone marrow from patients with IMF have emphasized the abundance of megakaryocytes, the topographic relationship between clusters of megakaryocytes and fibre formation, the intraluminal budding or location of this cell line and the marked endothelial proliferation with increased amounts of capillaries.[12] Principally, three stages of myelofibrosis have been described, implying that bone marrow fibrosis progresses from a stage with only slightly increased fiber network ("reticulin fibrosis") (stage 1) to a stage with pronounced haematopoietic hypocellularity and dense myelofibrosis ("collagen fibrosis") together with osteosclerosis.[13,14] However, this evolution has not been convincingly proved in larger sequential biopsy studies. Thus, a constant bone marrow pattern or regression of bone marrow fibrosis have been the most common findings, which might be explained by partial resolution of bone marrow fibrosis during cytotoxic or immunosuppressive treatment.[5]

Clinical features

IMF is a disease of the elderly, most cases being diagnosed after the age of 60 year, although it has also been described in children and young adults.[2,5] The clinical spectrum is exceedingly broad, encompassing almost asymptomatic patients with a chronic stable disease for many years and patients with severe constitutional symptoms from the beginning and a rapidly fatal course within a few months.[9] In between these extremes are the large proportions of patients in whom most symptoms are explained by one or more of the following mechanisms: 1) bone marrow failure 2) hypermetabolism 3) splenic enlargement 4) thromboembolism and 5) autoimmune diseases. Splenic enlargement is the physical hallmark of classical IMF. A subgroup of patients is marked by no or minimal splenomegaly, pancytopenia, severe myelofibrosis and a rapidly fatal clinical course within a few months. Hepatomegaly is found in 40-80% of the patients at the time of diagnosis. In general, the occurrence of hepatomegaly is associated with very large spleens. Splenectomy may be accompanied by increasing liver size. Irrespective of the rate of growth of the liver, a rise in alkaline phosphatase activity in plasma is observed shortly after splenectomy. A minority of patients exhibits rapid liver enlargement, which may indicate an accelerated phase of the disease, imminent blastic transformation or the Budd-Chiari syndrome. Ascites is found in a few patients, most often as a terminal phenomenon, being related to the portal hypertension or peritoneal myeloid metaplasia. Cardiovascular diseases are common. Occasionally, pericardial tamponade due to myeloid metaplasia is the reason for the development of heart failure. The condition is easily relieved by pericardiocentesis and pericardiectomy, together with cytotoxic treatment, may prevent its recurrence for years.

Differential diagnosis

The diagnosis of IMF is easily made in patients who present with classical clinical and histopathological features, including leucoerythroblastic anaemia with tear-drop poikilocytosis, platelet polymorphism, a high leucocyte alkaline phosphatase score, huge splenomegaly and bone marrow fibrosis with striking megakaryocytic proliferation. Other conditions associated with bone marrow fibrosis may occasionally imitate IMF.[15]

Severe myelofibrosis and even osteomyelosclerosis may be seen in patients with chronic myelogenous leukemia (CML). This particular subtype of CML may only be distinguished from IMF by the presence of the Ph-chromosome, emphasizing the importance of a chromosome analysis in all patients with IMF. Other subgroups within the myeloproliferative syndrome to be differentiated from IMF include patients with a transitional myeloproliferative disorder between polycythemia rubra vera (PV) and IMF and patients with postpolycythaemic myelofibrosis, since the latter condition appears to carry a worse prognosis than classical IMF. Patients with classical hairy-cell leukaemia (HCL) and IMF have certain features in common, including splenomegaly, bone marrow fibrosis, platelet polymorphism and an elevated alkaline phosphatase score. However, in HCL-patients without circulating hairy cells the highly characteristic bone marrow appearance is diagnostic. When malignant lymphoma presents with pancytopenia and severe myelofibrosis without splenic enlargement, leucoerythroblastosis and red cell polymorphism, the disorder may resemble patients with acute myelofibrosis. Systemic mast cell disease occasionally presents with osteosclerotic lesions and bone marrow fibrosis. The differential diagnosis may be difficult since an increase in the number of mast cells is also frequently observed in IMF.

Laboratory Finding

The large majority of patients have anaemia at the time of diagnosis.[5,10] The anaemia is usually normochromic, normocytic. Megaloblastic anaemia due to folate and/or vitamin B-12 deficiency is rare, whereas iron deficiency due

to gastrointestinal blood loss is commonly seen.[5] Ineffective erythropoiesis, haemodilution and haemolysis are major mechanisms contributing to the anaemia. Ineffective erythropoiesis is a feature of both extramedullary and medullary erythropoiesis in IMF, being most pronounced in extramedullary. Haemodilution is due to an expanded plasma volume consequent to enlargement of the spleen. Red cell destruction in the enlarged spleen appears to be the most important factor for the hyperhaemolysis. In addition, intrinsic red cell abnormalities may give rise to enhanced red cell destruction. A paroxysmal nocturnal haemoglobinuria (PNH)-like defect has been demonstrated. Immune haemolysis may sometimes contribute to the anaemia. At the time of diagnosis the leucocyte count displays a wide range. During the course of the disease, stable, highly variable or steadily increasing values have been recorded. In most patients the platelet count is either normal or decreased. Platelet counts below 100 x 109/l are mainly seen in patients with a syndrome of AMF or huge splenomegaly. In the majority of patients the platelet count declines during the course of the disease, this being partly explained by ineffective megakaryopoiesis, platelet pooling and sequestration in the enlarged spleen. Immunological mechanisms may also play a role in the decreased platelet count. The platelet life-span is shortened. Functional platelet defects have been found, but no uniform platelet dysfunction has been observed. There is no relationship between the occurrence of platelet dysfunction and thrombohaemorrhagic complications. The most consistent abnormality of routine liver function tests has been raised alkaline phosphatase activity in plasma. Elevated plasma LDH values are seen in the large majority of patients and appear primarily to reflect the activity of the clonal myeloproliferation rather than being a marker of liver damage or haemolysis. High plasma alkaline phosphatase activity is associated with widening of liver sinusoids rather than myeloid metaplasia.

Corresponding criteria have already been regarded by the newly introduced so-called Cologne Classification, in particular to avoid a confusion of essential thrombocythemia and thrombocythemias occurring in early-hypercellular stages of IMF.[16]

CONCLUSION

In conclusion, the dynamics of the disease process in IMF are characterized by evolving MF in the BM and closely associated changes of relevant hematological findings. The prognosis of idiopathic myelofibrosis, when compared with other myeloproliferative disorders, remains poor and has not changed significantly during the past 20 years. It is to be hoped, therefore, that the recent advances in this once neglected disease will eventually lead to effective therapeutic measures.

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