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Reversal of bone marrow fibrosis in idiopathic myelofibrosis after treatment with α -interferon

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A 14-year-old boy presenting with primary myelofibrosis (MMM) was treated with α -interferon (IFN). After 6 months his spleen was no longer palpable and blood counts had returned to normal. A reversal of bone marrow fibrosis was histologically documented. Although improvement in symptoms and blood counts has been reported, this is only the second description of reversal of bone marrow fibrosis in MMM after treatment.

In vitro studies have shown that IFN can suppress proliferation of hemopoietic precursor cells, especially those of the megakaryocytic cell line.^{1,2} In addition, IFN can inhibit collagen synthesis by murine fibroblasts.³ IFN has been used successfully in chronic myeloid leukemia (CML) and may reduce platelet number in essential thrombocythemia.² In MMM, however, only half of the patients gain a significant reduction in spleen size as well as in platelet numbers.² Except for one case⁴ there is no reported evidence that IFN can reverse bone marrow fibrosis in MMM. We report the case of a young patient with MMM who got a clinical remission and normalization of reticulin fibers after IFN treatment.

Case report

A 14-year-old boy was referred to our hospital presenting with a 3-year history of transfusion-dependent anemia and hepatosplenomegaly. Liver 5 cm, spleen 13 cm; hemoglobin: 4.4 g, with anisocytosis, poikilo-

cytosis and dacrocytes. Leukocytes: $4.8 \times 10^9/L$; metamyelocytes: 4%, band forms: 2%, segmented neutrophils 54%, eosinophils 2% and basophils 1%. Platelets: $134 \times 10^9/L$. Coombs' test was negative.

Bone marrow aspiration yielded a dry tap. A trephine biopsy (Figure 1) showed a marked diffuse increase in reticulin fibers. Megakaryocytes were atypical and increased in number. Granulocytic precursors and erythroblasts were present. A liver biopsy showed myeloid metaplasia in the sinusoids. Inherited red cell abnormalities, autoimmune diseases, nutritional deficiencies and hepatitis were excluded. The karyotype was normal. Due to the severity of the anemia in an adult form of MMM and the absence of autoimmune phenomena, treatment with IFN, 3×10^6 U s.c. three times per week (body surface = 1.17 m^2) was attempted. No significant side effects were observed. Six months later, neither liver nor spleen was palpable. Hemoglobin = 15.2 g, leukocytes $6.7 \times 10^9/L$; 1% bands, 41% neutrophils, 2% eosinophils and 0% basophils; platelets: $193 \times 10^9/L$. A new bone marrow biopsy (Figure 2) showed normocellular hemopoiesis. Megakaryocytes had a normal morphology. Reticulin fibers were only slightly increased. The dose of IFN was then reduced to 2×10^6 U twice a week. The patient remains well, having normal blood counts 24 months after the start of treatment.

MMM is more frequent after the age of 50 although it may be seen at any age. In children, myelofibrosis is often secondary to another condition (vitamin D deficiency or autoimmunity). The rare cases of idiopathic myelofibrosis usually have a more aggressive form.⁵⁻⁷ Our patient had clinical and hematologic features of adult MMM with a chronic evolution in spite of his young age. This has been described rarely.

The patient was treated with IFN because of the latter's antiproliferative activity in myeloproliferative disorders. IFN has been useful in controlling thrombocytosis and reducing spleen size in almost 70 patients reported in the literature. The criteria for using IFN therapy varied between authors, but it was used in patients with a more proliferative form of disease. The dose schedule was also varied. An optimal response has been achieved with $3-5 \times 10^6$ U three times per week for 4-6 months.^{1,2,4} The dose used in our patient was in this range. After 6 months of treatment he had a complete clinical response and bone marrow biopsy showed an almost complete reversal of myelofibrosis. To our knowledge this is only the second case in which this event has been documented.⁴ Interestingly, together with normalization of the peripheral blood counts, hemopoietic cell morphology and marrow fiber content returned to normal, showing that the neoplastic clone was suppressed by IFN. This phenomenon has also been recently described in CML.⁸ The role of IFN in the treatment of bone marrow fibrosis in CML is controversial but it has recently been shown that after suppression of

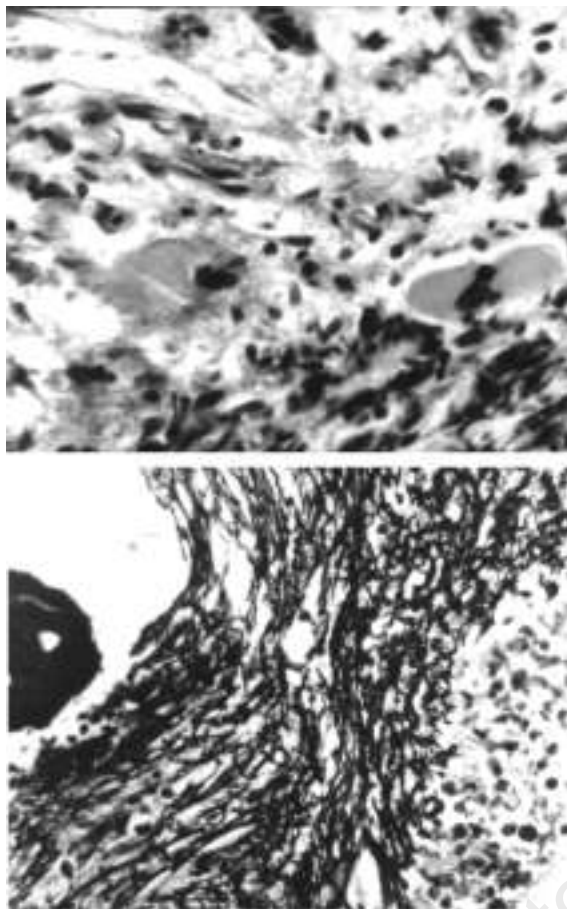


Figure 1. Bone marrow biopsy of the patient at diagnosis. Hemopoietic tissue with diffuse fibrosis (A). Two large atypical megakaryocytes can be seen. HE $\times 300$. Marked increase in coarse reticulin fibers (B). Gomori $\times 300$.

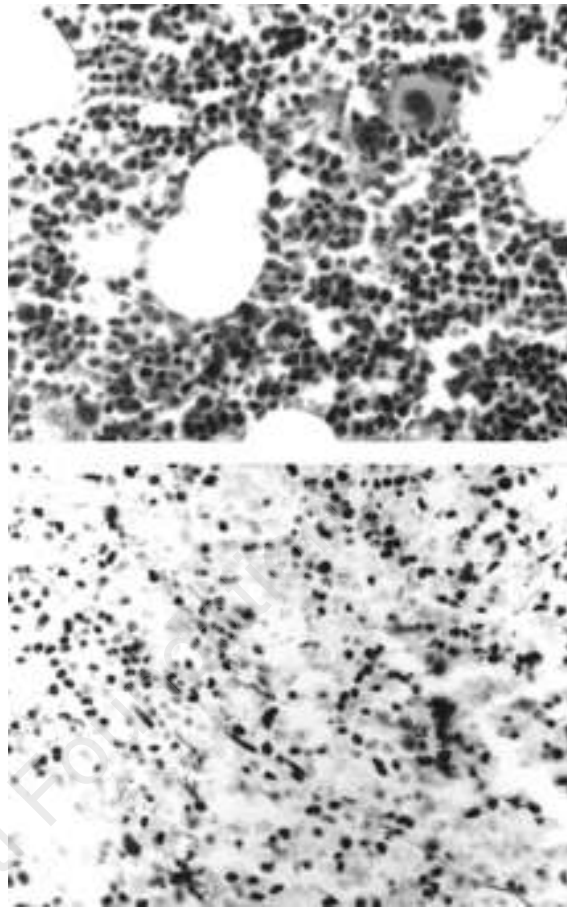


Figure 2. Bone marrow biopsy after 6 months treatment with IFN. Hemopoietic tissue with a normal architecture and presence of all 3 cell lines (A). Few reticulin fibers are present (B).

the Ph positive clone, the marrow content of fibers remains constant or is even reduced.^{8,9} The good response observed in our case may be due to the different behavior of MMM in young patients, but documents that IFN is able to reverse bone marrow fibrosis even in more advanced forms of MMM.

Key words

Myelofibrosis, children, interferon, treatment

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