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Splenectomy as therapeutic approach in idiopathic myelofibrosis

KEYWORDS: Myelofibrosis; Splenectomy

INTRODUCTION

Idiopathic myelofibrosis (IMF) is a chronic myeloproliferative disorder characterized by splenomegaly, immature granulocytes and erythroblasts in the blood, distorted teardrop-shaped red cells and bone marrow fibrosis. The aim of this study was to explore indications for splenectomy and frequency of splenectomy in the therapy of IMF. Between 1995 and 2002, 44 patients with idiopathic myelofibrosis were examined at the Clinic of Hematology Niš. Sex distributions were 16 female and 28 males and the mean age at the time of splenectomy for the entire group was 57 years. The diagnosis of IMF was established in each patient by the following criteria: 1. the presence of splenomegaly, 2. a leukoerythroblastic blood picture, 3. significant teardrop poikilocytosis on peripheral blood smear and 4. some degree of demonstrable fibrosis on bone marrow biopsy. Therapeutic approach was: transfusion of deplasmic erythrocytes, corticosteroid and androgen therapy, chemotherapy (Busulfan, Hydroxyurea), splenic irradiation and finally splenectomy. From the total number of 44 patients six were splenectomized. Indications for splenectomy were: 1. painful enlarged spleen (4 patients), 2. excessive transfusions and refractory hemolytic anemia (1 patient), 3. refractory thrombocytopenia (1 patient). Spleens were measured and histopathologically examined. The patients were followed after splenectomy. One patient from these six cases died on the second day after splenectomy. The death was caused by massive pulmonary emboly in spite of administrated anticoagulant therapy. Second patient died six years after splenectomy because of extramedullary hemopoietic tumor. Other patients are still followed. Splenectomy can be recommended only in urgent indications or in selective cases. The utilities of splenectomy are higher quality of the life, loosing of the symptoms, which were caused by splenomegaly and increase of blood cells. Idiopathic myelofibrosis (IMF) is a clonal myeloproliferative disorder characterized by progressive bone marrow fibrosis and extramedullary

hematopoiesis in the spleen and in multiple organs (1). The primary pathogenetic mechanism is a clonal stem-cell disorder that leads to ineffective erythropoiesis, dysplastic-megakaryocyte hyperplasia and an increase in the ratio of immature granulocytes to total granulocytes (2,3). The diagnosis is often suspected when teardrop-shaped red cells and myeloid precursors are detected in the peripheral blood. The typical clinical features include marked splenomegaly, progressive anemia and constitutional symptoms (3). Splenomegaly is one of the characteristics of IMF. If spleen enlargement is massive, patients may be severely symptomatic with abdominal pain, early satiety and other manifestation. Because of the lack of curative options, treatment is mostly palliative and is essentially aimed at improving severe cytopenia and at relieving symptomatic organomegaly. In a substantial number of patients this can only be achieved with splenectomy (4-6).

The aim of this study was to explore indications for splenectomy and frequency of splenectomy in the therapy of IMF because informative data on the significance of splenectomy and histopathology of spleen in these patients were not provided.

MATERIAL AND METHODS

Between 1995 and 2002, 44 patients with IMF were examined at the Clinic of Hematology- Nis. The diagnosis of IMF was established in each patient by the following criteria: 1. the presence of splenomegaly, 2. a leukoerythroblastic blood picture, 3. significant teardrop poikilocytosis on peripheral blood smear and 4. some degree of demonstrable fibrosis on bone marrow biopsy.

There were 16 female and 28 males. The mean age at the time of splenectomy for the entire group was 57 years. The range of ages at which the procedure was carried out was 45-70 yr.

All the patients were examined: clinical (anamnesis, objective status, laboratory features); hematological (peripheral blood smear, bone marrow biopsy and smear stained by May Grunwald Giemsa). In splenectomized cases histological examination of the spleen sections were examined after specific staining: Jones silver stain, Spicer method for mast cells, Giemsa and Hematoxylin Eosin routine staining.

Therapeutic approach was: transfusion of deplasmic erythrocytes, corticosteroid and androgen therapy, chemotherapy (Busulfan, Hydroxyurea), splenic irradiation and splenectomy (2,4).

RESULTS

From the total number of 44 patients, 6 (13,64%) patients were splenectomized. The mean age of splenectomized patients was 66 yrs. Median time from diagnosis to splenectomy was 4 years (range, 2 to 8 years). Indications for splenectomy were: painful enlarged spleen (4 patients) excessive transfusion requirements and refractory hemolytic anemia (1 patient) and refractory thrombocytopenia (1 patient). If the indication for splenectomy was painful splenomegaly, the pain disappeared. If the indication for splenectomy was refractory thrombocytopenia, the platelet count rose above $100 \times 10^9/L$ and there was complete disappearance of bleeding. If the indication for splenectomy was refractory hemolytic anemia, the hemoglobin rose above 12g/dl and remained such without ancillary transfusion. Spleens were measured after splenectomy and average spleen weight was 4000g (range, 3000 to 5700 grams).

In all splenectomized cases, histological examination of the spleen sections showed atrophy of white pulp and trilineage hematopoiesis with the significant predominance of myeloid cells, marked myeloid metaplasia in sinusoids of red pulp of the spleen. In the red pulp fields of initial fibrosis have been seen. Hyperplasia of megakaryocytes and islands of erythroid precursors were visible. Mast cells, which are normally rare cell population in the spleen, were identified in a large number in the red pulp of splenectomized patients. The dilatation of red pulp sinusoids and intravascular hematopoiesis were identified by silver impregnation of Jones. Reticular glycoprotein coating of stromal

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The manuscript was received: 15. 02. 2004.
Provisionally accepted: 15.03.2004.
Accepted for publication: 23.03.2004.

cells were stained dark brown. Complications immediately following surgery were: that one patient died on the second day after splenectomy. The death was caused by massive pulmonary emboly in spite of anticoagulant therapy. Second patient died six years after splenectomy because of extramedullary hemopoietic tumor. At the time of the last follow -up, other patients were in good condition.

DISCUSSION

Scattered series relating to splenectomy in IMF have been published (5,7). Our present data demonstrate 25 month survival for the patients in whom splenectomy were performed which correspond to other published data. Splenectomy is effective in relieving symptoms, but surgical mortality is in the range of 9%-31% (6). There is concern about postsplenectomy associated complications and some reports have suggested an increased probability of leukemic transformation (6,8). In our examined patients we did not have this complication even mortality was high (33,3%). The present data suggest that any patient with huge painful spleen who has no significant coagulation problems can be splenectomized and have benefit in life quality (5,9). The proliferation rate of splenic hematopoietic cells was found suggesting that splenectomy was required. This accelerated phase of extramedullary myeloid proliferation was responsible for the symptom escalation that leads to splenectomy. Histological examination of the spleen sections showed trilineage hematopoiesis with significant hyperplasia of mast cells. As mast cells have a role in chronic inflammation , allergic and tumor processes, their number can be explained as a clonal expansion of their lineage in IMF. It has been assumed that the stromal reaction of the bone marrow and spleen is reactive process mediated by cytokines that are produced by megakaryocytes, monocytes and mast cells (3,10).

CONCLUSION

Splenectomy can be recommended only in urgent indications or in selective cases (symptomatic splenomegaly- mechanical discomfort, refractory thrombocytopenia, hypercatabolic symptoms, portal hypertension). The utilities of splenectomy are higher quality of the life, loosing of the symptoms, which are caused by splenomegaly and increase of blood cells, especially erythrocytes and platelets.

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