Agnogenic myeloid metaplasia: role of splenectomy

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Summary
The splenomegaly associated with myelofibrosis and agnogenic myeloid metaplasia should not be considered a manifestation of the fundamental proliferative process, nor should it be considered as necessarily compensatory for reduced marrow haematopoiesis.

In deserving cases splenectomy may cause an improvement in the patient's general and haematopoietic status. Removal of the source of functional hypersplenism, causing haemolytic episodes and thrombocytopenia, results in marked amelioration in the clinical condition with reduction in the magnitude and frequency of replacement blood transfusion.

The massive size of the spleen associated with this condition may not only cause local pain and discomfort but may lead to traumatic or spontaneous rupture.

Consideration of two cases studied by the authors indicates that marked clinical improvement may be associated with splenectomy in selected cases of agnogenic myeloid metaplasia.

Introduction
The term agnogenic myeloid metaplasia of the spleen was first used by Jackson, Barker & Lemon (1940), in describing a condition in which the spleen becomes the site of extramedullary haematopoiesis. This extramedullary haematopoiesis, which involves the whole reticulo-endothelial system, is maximal in the spleen and results clinically in varying degrees of hepatomegaly and gross splenomegaly, and had been considered compensatory to failure of the bone marrow to carry out its haematopoietic function.

Bone marrow changes in these patients will vary from hyperplastic to hypoplastic with varying degrees of fibrosis. Myelofibrosis reflects the final end-stage of this disease with complete replacement of bone marrow spaces by fibrous tissue. The peripheral blood may demonstrate anaemia with features of haemolysis or may present with the effects of hypersplenism, or it may show a pseudo-leukaemic picture which does not, however, demonstrate the neoplastic invasive properties of true leukaemia. The range of disorders in this broad syndrome may be represented by polycythaemia vera or erythraemic leukaemia, referred to as di Guglielmo's syndrome, or may finally become manifest with a true leukaemia. Synonyms for this condition include such items as leucoerythroblastic anaemia, non-leukaemic myelosis and myeloproliferative syndrome.

Hickling (1937) reviewed twenty-seven cases of this condition in the literature in 1937 and found that most of these patients had undergone splenectomy on the erroneous diagnosis of splenic anaemia. The myeloid hyperplasia of the spleen was discovered after splenectomy, and he noted that in this series eighteen post-operative deaths had occurred, reinforcing the belief that the spleen provided an essential haematopoietic compensatory function and that its removal would result in death. In emphasizing the high mortality rate for splenectomy in this condition, he remarked that twelve patients died within 4 days and fifteen were dead within 4 weeks.

Wyatt & Sommers (1950), in a study of chronic marrow failure associated with myelosclerosis and extramedullary haematopoiesis, indicated that fibrosis of the marrow could be induced by many agencies. Thus, toxic agents, hepatic dysfunction or haemolysis, as well as cardiovascular or endocrine disorders might stimulate the pluri-potential cells of the reticulo-endothelial system to revert to embryonic erythroblastic activity. It is, therefore, important to appreciate that myelofibrosis does not always precede splenomegaly or anaemia and that myeloid splenic metaplasia may occur without myelofibrosis. In considering the relationship of myeloid metaplasia and myelofibrosis, Vaughan & Harrison (1939) were probably close to the truth when they
postulated that myelofibrosis and extramedullary haematopoiesis may provide a concurrent response to a common, as yet undefined, stimulus. It, therefore, becomes necessary to differentiate a primary type of myelofibrosis from a secondary group of bone marrow hypoplasia and fibrosis due to endogenous chemical toxins or malignant marrow infiltration or tuberculosis of bone.

Dameshek (1951) in speculating on the relationships of myelofibrosis, agnostic myeloid metaplasia, polycythaemia rubra vera, leucoerythroidic anaemia, erythroleukaemia and chronic myeloid leukaemia in the myeloproliferative syndromes, suggested that all these conditions represent variations in the broad spectrum of the myeloproliferative syndrome. Wasserman (1954), in his studies, tended to confirm this view and noted that 10–30% of patients with polycythaemia rubra vera would develop anaemia with myelofibrosis and myelometaplasia of the spleen and that the greater the splenic enlargement, the more likely the development of marrow and peripheral blood changes. Thus, some patients with polycythaemia rubra vera who develop agnostic myeloid metaplasia and myelofibrosis may finally terminate with chronic myeloid leukaemia. Hutt, Pinninger & Wetherby-Mein (1953), in further demonstrating the close relationship between polycythaemia rubra vera, leukaemia and other blood disorders, emphasized that the splenic enlargement should be considered a manifestation of the fundamental proliferative process and should not be considered as compensatory for reduced marrow haematopoiesis.

This view served as a spur to Green, Conley and their associates (1953) who studied five patients with agnostic myeloid metaplasia subjected to splenectomy. In contradistinction to the views of Hickling, they noted that splenectomy resulted in no deleterious effects in this series of five patients and that one patient was remarkably improved. In their series, four of the patients were demonstrated to have myelofibrosis and all had a leucoerythroidic peripheral blood pattern and myeloid metaplasia in the spleen or liver. In each of these cases, splenomegaly was the prominent feature leading to splenectomy. Similarly, Bukh & With (1945) studied a patient with chronic non-leukaemic myeloid splenomegaly associated with osteosclerosis in whom splenectomy was performed and collected fifty-four similar cases in whom splenectomy has not been shown to have a harmful effect, emphasizing that the occasional patient will have definite clinical and haematological improvement after operation.

Szur & Smith (1961) rationalized the indications for splenectomy in myelosclerosis and suggested that it was indicated if a markedly decreased red blood cell survival time was demonstrated with clear-cut evidence of splenic red blood cell destruction. Significant extramedullary haematopoiesis should not be present in the spleen or, if present, evidence of significant haematopoiesis in the liver or bone marrow should be manifest. Linman & Bethell (1957), in considering the natural history and present-day management of agnostic myeloid metaplasia, consider this disorder to be a progressively fatal disease in which splenectomy should be used as an adjunct in controlling the haemolymphic component of the disease without affecting the patient’s life-span.

Two patients with agnostic myeloid metaplasia and gross splenomegaly have been studied by the author and merit description in consideration of the benefits of splenectomy in this condition.

**Case 1**

This 62-year-old white female presented with a 5-month history of vague pains in the legs and non-descriptive weakness. A large spleen was noted by the physician she consulted. Apart from having undergone a thyroidectomy 26 years earlier and a cholecystectomy soon after this, followed by a vaginal hysterectomy, she had been in good health in the ensuing years with no history of allergy or hypersensitivity to past medications. Her blood pressure was noted to be 140/100 mmHg and the only other abnormality found was a mass extending for four fingers below the left costal margin to the umbilicus, moving with respiration, which was undoubtedly the spleen.

Investigations were all normal except that for a mild increase in the cephalin flocculation and thymol turbidity tests.

Peripheral blood examination: Hb 15.7 g/100 ml, PCV 52 and WBC 10,800 mm\(^3\) with 76% segmental forms, 8% stab, 10% lymphocytes, 3% mononuclear, 2% eosinophils and 1% metamyelocytes. Platelets were noted to be adequate. A repeat blood smear, performed on the 29 May 1965 showed: Hb of 17.2 g/100 ml, PCV 52, WBC 10,700 with 2% bands, 75% neutrophils, 22% lymphocytes and 1% monocytes. There was some poikilocytosis and anisocytosis of the red cell series which seemed out of keeping with the haemoglobin level. Beyond this, apart from some bizarre and abnormal sized platelet forms, the platelets were normal in number. Spherocytes were absent and there was no evidence of any haemolysis.

Bone marrow study carried out at this time showed that the marrow cavity had been entered and demonstrated granulocytic and erythroid precursors along with masses of platelets. The thyroid series were noted to be normal, but there were too few cellular elements to make any
definitive statement on the basis of this bone marrow. Because of the large size of the spleen and the possibility that splenectomy might be helpful in what was thought to be early myelofibrosis with agnogenic myeloid metaplasia, splenectomy was carried out on 1 June 1965.

Operation

Splenectomy was performed through a long left upper paramedian incision and, on opening the peritoneal cavity, there was no obvious abnormality in the liver or any other evidence of disease apart from a massively enlarged spleen. The gastrectopic omentum was severally divided, thereby gaining entrance to the lesser sac, and the splenic artery was dissected out and ligated in continuity. The spleen was then mobilized and removed. Gross examination demonstrated a grossly lobulated spleen weighing approximately 850 g. It measured $27 \times 14 \times 9$ cm and, on cut section, revealed a dark red meaty pulp.

Microscopic examination of the spleen demonstrated accentuation of the splenic sinusoids and residua of the widely separated germinal centres about splenic arterioles. The splenomegaly was due to a marked increase in the red pulp with evidence of fibrosis and thickening of the splenic cords. Abnormal cells which were muti-nucleated and extremely large were noted and thought to be megakaryocytes. Evidence of erythropoietic activity was also represented by normoblastic activity.

Biopsy of the liver was also performed and histological study demonstrated a normal architecture with no discernible abnormality apart from an increase in the amount of pigment within the Kupffer cells.

Progress

Post-splenectomy study of the peripheral blood smear demonstrated remarkable, sudden and striking changes in the peripheral blood. The white cell count rose to 40,800 with 12% bands, 75% neutrophils, 7% lymphocytes and 1% myelocytes with discernible nucleated red cells. Platelets increased to 758,000, Hb to 14.3 g/100 ml, PCV 45; there was moderate poikilocytosis and anisocytosis. Fragmented megakaryocytes were noted in the peripheral blood. This marked thrombocytosis was more than could be part of a post-splenectomy thrombocytosis. Repeat peripheral blood examination 4 days later showed that the platelet count had become massive and was of the order of 2,452,000, the Hb 12.1 g/100 ml, PCV 40 and WBC 433,200 with 1% bands, 71% neutrophils, 12% lymphocytes, 8% eosinophils, 1% basophils, 2% metamyelocytes and 1% myelocytes. There were four nucleated red cells per 100 nucleated cells.

A bone marrow study carried out on the 7th post-operative day resulted in the first tap being a true dry tap. The sternum was subsequently entered successfully and an aspirate was obtained. A study of the marrow revealed whole fields and sheets of platelets and yet a strange lack of megakaryocytes. The granulocytic series appeared normal. There was a normoblastic erythropoiesis and the lymphocytic elements were normal. A study of the leucocyte alkaline phosphatase carried out on the bone marrow and the peripheral blood demonstrated a marked increase over normal controls indicating that the high white count was consistent with leukaemoid reaction rather than leukaemia.

Conclusion

There seems little doubt that a haematological diagnosis of the myeloproliferative syndrome may be made associated with agnogenic myeloid metaplasia of the spleen. In view of the marked post-operative thrombocytosis and elevated white cell count, busulphan was administered, 2 mg three times a day with gradual reduction of the leucocyte counts to 10,000 and the platelets to under 300,000. The dosage was gradually reduced and the drug ultimately stopped. Repeat peripheral blood counts over the ensuing 2 years have demonstrated a normal peripheral blood picture.

Case 2

This patient was a 62-year-old white male who presented for evaluation of splenomegaly. The patient had no complaints or associated symptoms. He had been followed in the medical clinics for the previous 3 years with a history of ready bruising over the chest.

On examination, at that time, he had been noted to have a markedly enlarged spleen and bilateral inguinal adenopathy. PCV 43, Hb 15 g/100 ml, WBC 4150 with a normal differential. The platelet count was not noted at that time. Formal bone marrow biopsy in the right iliac crest and a right inguinal lymph node biopsy were performed and the pathological report was that of myelofibrosis and chronic lymphadenitis.

Over the ensuing years, the patient had been noted to become progressively anaemic and at this examination he had a markedly enlarged spleen, occupying the left half of the abdomen, extending down to the left iliac crest. No lymphadenopathy was noted. All other systems were normal.

Investigations showed: PCV 35, RBC $3.8 \times 10^6$ with a marked increase in poikilocytes and marked anisocytosis. Several nucleated red blood cells were noted; WBC 8700 with 49% neutrophils, 7% lymphocytes, 27% bands, 12% lymphocytes, 4% basophils.
and 1% eosinophils. The platelet count was 66,000 and bleeding and clotting times were normal. Total proteins were 7.4 g/100 ml, albumin 4.7, alkaline phosphatase 1.68 Bodansky units, fasting blood sugar 72 mg/100 ml and BUN 7.6 mg/100 ml.

Bone marrow study carried out on 29 January 1968 revealed the presence of myelofibrosis. Haematopoietic activity was present, but it was noted that despite many megakaryocytes there was very little budding of platelets.

Operation

In view of the very large spleen and the fact that there was adequately functioning bone marrow with evidence of superposed hypersplenism as manifested by the low platelet count, it was decided to perform a splenectomy and, at this time, a large spleen, weighing 2750 g, with a splenic artery aneurysm, which had manifested with calcification on a plain film of the abdomen, was found (Fig. 1). A splenectomy was accordingly carried out after ligating the splenic artery, removing the spleen and the aneurysm (Fig. 2). No splenunculi were noted and a liver biopsy was performed. The patient made an uneventful recovery from his operation and on the 10th post-operative day haematological examination showed: PCV 37 with fifty-nine nucleated red blood cells, WBC 17,850/mm³ with 70% neutrophils, 3% myelocytes, 15% bands, 7% lymphocytes, 4% basophils and 1% eosinophils, platelet count 228,000/mm³. Over the ensuing 3 months, this patient's haematocrit and red blood cell picture has remained constant. A marked increase in the plate-
let count to over 300,000 has been maintained (Fig. 3) and a repeat examination of marrow has demonstrated a near normal appearance without any gross evidence of myelofibrosis.

Comment

The unsatisfactory results reported by Hickling led to a general disinclination to recommend splenectomy for agnogenic myeloid metaplasia. With the elaboration of the concept that splenic enlargement is not necessarily a manifestation of the fundamental proliferative process and is not compensatory for the reduced marrow haematopoiesis, a better climate has developed for consideration of this operation (Fishman & Ballinger, 1965). In considering the criteria for splenectomy in patients with myelofibrosis and agnogenic myeloid metaplasia, specific indications would include:

1. Clear-cut evidence of splenic red blood cell destruction associated with decreased red blood cell survival time.
2. Absence of significant extramedullary haematopoiesis in the spleen or evidence of significant haematopoiesis in the liver or bone marrow.

If frequent blood transfusions are required to keep up with the rate of splenic red blood cell destruction, it would be fair to recommend splenectomy without undue consideration of the presence of haemopoietic activity in the bone marrow or elsewhere in the reticulo-endothelial system. If the haemolysis is a manifestation of hypersplenism, splenectomy may provide great benefit from the removal of this large reticulo-endothelial reservoir of blood destruction.

The superposition of hypersplenism upon the defective bone marrow haematopoiesis fortifies the clinician in recommending splenectomy and the experience in the two cases strongly suggests that removal of the spleen may reverse the polarity that has developed between the bone marrow and the spleen with possible resumption of bone marrow activity and improvement in the myeloproliferative state. In addition, the removal of a very large spleen with its susceptibility to traumatic rupture, provides a further reason for considering splenectomy.

References


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