Myelofibrosis complicated by intestinal extra-medullary haemopoiesis and acute small bowel obstruction

S MACKINNON,* AM McNICOL,† FD LEE,† GA McDONALD*

*From the Departments of *Haematology, and †Pathology, Royal Infirmary, Glasgow, Scotland*

SUMMARY A 78 year old woman with myelofibrosis presented with an acute small bowel obstruction. Pathology of the resected small bowel showed extramedullary haemopoiesis leading to acute small bowel obstruction. As far as we know this is the first such reported case.

Case history

In 1967 a 61 year old Scottish housewife presented with dizziness. She was otherwise asymptomatic. Clinical examination showed no abnormality. Haematological examination at that time gave the following values: haemoglobin 11.9 g/dl, platelets $639 \times 10^9/l$, white cells $8.6 \times 10^9/l$. Blood film showed normal morphology and a normal differential white cell count. Repeated platelet counts were consistently raised between 600 and $1000 \times 10^9/l$. Sternal marrow aspiration failed to show any marrow cells because of a dry tap. A trephine biopsy specimen showed a rather hypocellular marrow in which all haemopoietic elements were identified. There was a preponderance of megakaryocytes, some of which were larger than normal.

After other causes of thrombocytosis had been excluded essential thrombocythaemia was diagnosed. She was treated with 120 MBq of ^{32}P , and her platelet count returned to normal with a resolution of her symptoms. Between 1969 and 1975 the patient received a further five doses of ^{32}P amounting to a total cumulative dose of 640 MBq. The platelet count remained within normal limits with no further treatment between 1975 and 1984. In 1977 the blood film became leucoerythroblastic, and it was thought that she may have been developing marrow fibrosis, but her haemoglobin remained between 9 and 11 g/dl until she presented for surgery at the age of 78.

At presentation she had had a five day history of generalised abdominal pain, diarrhoea that settled after the first two days, vomiting, and anorexia. Two days before admission she had noticed abdominal distension with complete constipation. Examination

showed that the abdomen was distended with no tenderness on palpation. The liver was palpable 5 cm below the right costal margin as was the tip of the spleen. Bowel sounds were hyperactive. Abdominal radiographs showed dilated loops of small bowel. Small bowel obstruction was diagnosed, and she underwent laparotomy. At operation the distal ileum was found to be thickened, and 400 mm was resected with an end to end anastomosis.

At this admission the blood values were: haemoglobin 8.5 g/dl, platelets $205 \times 10^9/l$, white cells $12.7 \times 10^9/l$ (differential neutrophils 74%, lymphocytes 19%, monocytes 3%, myelocytes 2%, and myeloblasts 2%). The blood film was leucoerythroblastic and numerous tear drop poikilocytes were seen. The leucocyte alkaline phosphatase score was 113 (normal range 20-100). A trephine biopsy of the iliac crest was performed and showed pronounced marrow fibrosis with a reduction in all haemopoietic elements; and this was consistent with a diagnosis of myelofibrosis.

She made a very slow postoperative recovery requiring frequent blood transfusions to maintain her haemoglobin. She was eventually discharged home three months after surgery but was readmitted shortly after with staphylococcal septicaemia. This was complicated by the development of acute renal failure resulting in her death. Permission to perform necropsy was refused.

PATHOLOGY

The 400 mm length of ileum had a purulent exudate on the serosal surface along the central 200 mm. When it was opened a single area of ulceration 8 mm long near the midpoint surrounded by an area of congestion could be seen. The remainder of the bowel

Fig. 1 Ileum: mucosal and submucosal thickening associated with diffuse infiltrate of granulocytes and granulocyte precursors. (Haematoxylin and eosin.) $\times 160$.

Fig. 2 Submucosa: infiltrate of myeloid precursors which are staining strongly positive. High numbers are seen in blood vessels. (Chloracetate esterase.) $\times 500$.

showed severe mucosal and submucosal thickening.

Histological examination confirmed the ulceration. Submucosal oedema with foci of necrosis or incipient necrosis was also seen at sites distant to this area (Fig. 1). In some of these areas vascular thrombosis was identified. A widespread infiltrate of haemopoietic cells was present, with preponderance of cells of the myeloid series; only a small number of erythroid precursors were identified and very few megakaryocytes.

Towards the mucosal surface the cells were mainly mature neutrophil polymorphs, whereas in the deep submucosal and serosal layers large numbers of myeloid precursors were present, some of which were in mitosis. Such cells were also seen in high numbers in serosal vascular channels (Fig. 2). Foamy histiocytes were also identified both in the submucosa and lamina propria, and some of these showed erythrophagocytosis.

Discussion

Essential thrombocythaemia is regarded as one of the myeloproliferative disorders.¹ It is a clonal disorder of the haemopoietic stem cell,² which leads to an increase in platelet production. The natural history of the disease may lead to marrow fibrosis, which can occur acutely and be rapidly progressive, but which more usually pursues a slowly progressive course.³ The aetiology of marrow fibrosis is not due to a primary defect in the fibroblast, which is of mesenchymal origin, and is not part of the abnormal haemopoietic clone.^{4,5} Thus bone marrow fibroblast proliferation is a reactive phenomenon, possibly due to intramedullary release of platelet derived growth factor from the alpha granules of platelets.^{6,7} This polypeptide stimulates replication of target mesenchymal cells and can increase their collagen synthesis.^{7,8} It may be important in the genesis of myelofibrosis in the myeloproliferative disorders. The contribution that ³²P made in our patient to the marrow fibrosis is debatable. ³²P does have a preferential medullary action, and the marrow has a limited response to injury—that is, fibrosis.

Although the predominant differentiation to the myeloid series is rather unusual, the presence of small numbers of erythroid precursors and occasional megakaryocytes would categorise the ileal infiltrate as extramedullary haemopoiesis. Another point of interest is the presence of large numbers of early myeloid precursors in the serosal vessels, although the peripheral blast cell count was only 2%.

Extramedullary haemopoiesis is common in myelofibrosis.^{9–11} This often occurs in the liver and spleen, but has also been documented in kidney, adrenal gland, lymph node, lung, pleura, retroperitoneal fat, mesentery, skin, breast, dura mater, ovary, and thymus.^{11,12} The common factor in all these tissues is that they all contain elements of mesenchymal origin. The gastrointestinal tract also contains mesenchyme but is an unusual site of extramedullary haemopoiesis. Disease affecting the gastrointestinal tract has been described on only one occasion.¹² That case differs

from ours in that there was a three year period during which the patient had intermittent diarrhoea and ascites, whereas our patient presented with abdominal symptoms of less than one week's duration. In the previous case the small bowel obstruction developed secondary to extensive mesenteric and intestinal extramedullary haemopoiesis with associated fibrosis, whereas in our patient intestinal extramedullary haemopoiesis with no evidence of mesenteric fibrosis had occurred.

References

- 1 Dameshek W. Some speculations on the myeloproliferative syndromes. *Blood* 1951;6:372–5.
- 2 Fialkow PJ, Faguet GB, Jacobson RJ, Vaidya K, Murphy S. Evidence that essential thrombocythaemia is a clonal disorder with origin in a multipotent stem cell. *Blood* 1981;58:916–9.
- 3 Silverstein MN, Linmon JW. Causes of death in agnogenic myeloid metaplasia. *Mayo Clin Proc* 1969;44:36–9.
- 4 Van Slyck EJ, Weiss L, Duthy M. Chromosomal evidence for the secondary role of fibroblastic proliferation in acute myelofibrosis. *Blood* 1970;36:729–35.
- 5 Jacobson RJ, Salo A, Fialkow PJ. Agnogenic myeloid metaplasia, a clonal proliferation of haemopoietic stem cells with secondary myelofibrosis. *Blood* 1978;51:189–94.
- 6 Groopman JE. The pathogenesis of myelofibrosis in myeloproliferative disorders. *Ann Intern Med* 1980;92:857–8.
- 7 Burstein SA, Malpass TW, Yee E, *et al*. Platelet factor-4 excretion in myeloproliferative disease: implications for the aetiology of myelofibrosis. *Br J Haematol* 1984;57:383–92.
- 8 Scher CD, Shepard RC, Antoniades HN, Stiles CD. Platelet derived growth factor and the regulation of the mammalian fibroblast cell cycle. *Biochim Biophys Acta* 1979;50:217–41.
- 9 Reubner B. Myelosclerosis with serosal myeloid metaplasia and fatal liver involvement. *Ann Intern Med* 1960;53:1075–88.
- 10 Lieberman PH, Rosvoldi RV, Ley AB. Extramedullary myeloid tumors in primary myelofibrosis. *Cancer* 1965;18:727–36.
- 11 Ward HP, Block MH. The natural history of agnogenic myeloid metaplasia (AMM) and a critical evaluation of its relationship with the myeloproliferative syndrome. *Medicine* 1971;50:357–420.
- 12 Glew RH, Haese WH, McIntyre PA. Myeloid metaplasia with myelofibrosis: the clinical spectrum of extramedullary haemopoiesis and tumor formation. *Johns Hopkins Medical Journal* 1973;132:253–60.

Requests for reprints to: Dr GA McDonald, Department of Haematology, Royal Infirmary, Glasgow G4 0SF, Scotland.