Extensive bone marrow infarction followed by myelofibrosis in a patient with Ph⁺ positive chronic granulocytic leukaemia

BARBARA BAIN

From the Department of Haematology, Princess Alexandra Hospital, Brisbane, Australia

SUMMARY A 28-year-old man with Philadelphia chromosome positive chronic granulocytic leukaemia developed extensive bone marrow and bone infarction which was associated with anaemia and thrombocytopenia. He survived 20 months from the first symptoms of bone marrow infarction; during this time he developed myelofibrosis and osteosclerosis followed by blastic transformation. Extensive bone marrow infarction is a possible pathogenetic mechanism when chronic granulocytic leukaemia is followed by myelofibrosis.

Bone marrow infarction has been reported only rarely in chronic granulocytic leukaemia and there has been little opportunity for the progress of the disease to be followed thereafter. The patient here reported suffered from Ph⁺ positive chronic granulocytic leukaemia and was followed from the onset of bone marrow infarction to his death 20 months later.

Case history

A 28-year-old man presented in September 1975 with a one-month history of lethargy, weight loss, fever, and night sweats. He was pale with massive splenomegaly. Peripheral blood and bone marrow findings were typical of chronic granulocytic leukaemia. The haemoglobin (Hb) was 8 g/dl. The white cell count (WCC) was $270 \times 10^9/l$ with 36% neutrophils, 12% metamyelocytes, 17% neutrophil myelocytes, 5% promyelocytes, 4% blasts, 4% eosinophils, 3% eosinophil myelocytes, 15% basophils, 1% basophil myelocytes, and 3% lymphocytes. There were three nucleated red blood cells (NRBC)/100 white blood cells and the platelet count was $800 \times 10^9/l$. The bone marrow aspirate was intensely hypercellular with a myeloid: erythroid ratio of 20:1 and increased megakaryocytes. The Philadelphia chromosome was present. The bone marrow trephine confirmed granulocytic and megakaryocytic hyperplasia and showed occasional fibroblasts and a modest increase of reticulin.

Neutrophil alkaline phosphatase was 5 units, serum B₁₂ 1000 ng/l, and unsaturated B₁₂ binding capacity 4390 ng/l (NR 700-2000 ng/l).

The patient was treated with allopurinol followed by busulphan in a dose of 4 mg daily for seven months, with satisfactory disease control (Fig. 1). An elective splenectomy was performed in April 1976, a 500 g spleen being removed. Two months after splenectomy the WCC and platelet count had risen and the Hb concentration had fallen. Megakaryocyte fragments and large numbers of NRBC had appeared in the peripheral blood and remained a feature until preterminally; the NRBC count frequently exceeded the WCC. Busulphan was resumed and was continued until January 1977 when bone pain was first experienced. At this time the disease was well controlled with Hb 13 g/dl, WCC $16.0 \times 10^9/l$, and platelet count $380 \times 10^9/l$. At onset the pain was in the sacrum and both iliac crests. Subsequently it also involved the jaw, shoulders, knees, lumbar spine, and ribs. The pain continued with remissions and exacerbations for the next five months. There was an associated fall of Hb concentration and platelet count and so busulphan treatment was stopped. Bone marrow aspirates from the left iliac crest on 4 May 1977 and from the right iliac crest one week later yielded opaque white material which microscopy showed to be necrotic marrow (Fig. 2). No aspirate could be obtained from the sternum. Bone marrow trephine biopsy showed both bone marrow and bone infarction; there was death of osteocytes, osteoblasts, and osteoclasts. Blood vessels showed no organised thrombus or

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Fig. 1 Haematological values and therapy given. WBC = white blood cell count; NRBC = nucleated red blood cell count; bp = bone pain; busulphan, dosage between 4 and 8 mg; hydroxyurea, dosage between $\frac{1}{2}$ and $1\frac{1}{2}$ g; prednisone, dosage between 10 and 75 mg; $\downarrow$ vincristine 2 mg; $\blacklozenge$ bone marrow aspirate; $\circ$ blood transfusion; $\dagger$ death.

Fig. 2 Bone marrow aspirate showing necrotic cells; May-Grünwald-Giemsa $\times 120$.

Fig. 3 Histological section of skull showing myelofibrosis and formation of new bone around spicules of acellular, previously infarcted bone. H and E $\times 20$.

vessel wall infiltration. A ^{99m}Tc bone scan was normal. A ^{99m}Tc -sulphur colloid bone marrow showed bone marrow extending to the femora, tibiae, and fibulae, with no failure of uptake in bones normally containing haemopoietic marrow. A radiological skeletal survey was normal.

Bone pain remitted spontaneously, and the patient remained stable on therapy for seven months.

He then decided to stop treatment. A skeletal survey at that time showed marked sclerosis of the pelvis and discrete sclerotic areas in the humeri, upper femora, and sternum. He remained well for two months but from March 1979 gradually entered a blastic transformation with progressive enlargement of the liver and subsequently generalised lymphadenopathy. Severe pain in the lumbar spine

Fig. 4 Histological section of vertebra showing recent necrosis of partly fibrotic bone marrow in an area of previous bone infarction with new bone formation. H and E $\times 20$.

recurred in August 1979. Further x-rays showed that the sclerotic process had progressed. There was a generalised increase of bone density in the pelvis, lumbar vertebrae, and bony thorax. The patient died later that month.

Postmortem examination confirmed massive leukaemic infiltration of most organs. Examination of the sternum, ribs, pelvis, and entire vertebral column showed that the bone marrow had been replaced by dense fibrous tissue and proliferating bone. Histological sections showed both myelofibrosis, osteosclerosis, and recent infarction of both cellular and bony tissue (Figs 3 and 4).

Discussion

A young man with well-controlled chronic granulocytic leukaemia suffered recurrent bone marrow necrosis and bone infarction over a five-month period. Subsequently, myelofibrosis and osteosclerosis developed. Bone marrow and bone infarction recurred preterminally when he had passed into a phase of acute transformation. Bone marrow necrosis is not infrequent in acute lymphoblastic leukaemia but is uncommon in acute myeloid leukaemia,^{1,2} and is rare in chronic granulocytic leukaemia. Two of the five patients previously reported developed bone marrow necrosis when the leukaemia was uncontrolled, white cell counts being 140 and $200 \times 10^9/l$ respectively.³ One of these patients had myelofibrosis before the occurrence of bone marrow infarction. No follow-up was reported. The series of 368 patients reported by Norgaard *et al.*⁴ included two patients with chronic granulocytic leukaemia; in both, the area of bone marrow necrosis was small. In the patient recently reported by Lee and Morris,⁵ extensive bone marrow necrosis occurred as the disease underwent metamorphosis. There was also necrosis of extramedullary myeloid proliferations. Death occurred soon afterwards. In the patient reported here, features suggesting metamorphosis (the appearance of numerous NRBC and megakaryocyte fragments) preceded bone marrow necrosis, but despite this the patient survived for another 18 months.

Bone marrow necrosis appears to be more common than is usually appreciated. Until the recent report of Norgaard *et al.*⁴ only 38 cases had been reported in life. Norgaard found necrosis to be present in one-third of bone marrow specimens but its presence had usually been overlooked in the initial examination.

The occurrence of bone marrow infarction may be related to increased metabolic demands in view of its occurrence in acute leukaemias, in megaloblastic anaemia, and in febrile, infected patients.^{3,6}

Microvascular failure is a likely mechanism, as indicated by its occurrence in sickle cell anaemia³ and disseminated intravascular coagulation.^{6,7} Microvascular failure may also be a pathogenetic mechanism when patients with leukaemia suffer bone marrow infarction. Intensely cellular bone marrow may have vessels compressed by proliferating cells; vessel walls may be infiltrated, and vessel lumina may be obstructed by leukaemic cells.⁸ In the patient of Lee and Morris,⁵ the vessels within the necrotic extramedullary myeloid tissue were also compromised by leukaemic infiltration. Bernard⁹ has observed destruction of the microvasculature in a patient with acute myelomonocytic leukaemia who died eight days after observation of bone marrow necrosis. The patient reported here was in a well-controlled chronic phase of the disease so that increased metabolic demands are unlikely to be a factor. Cytotoxic therapy has been suspected of causing bone marrow necrosis but Norgaard *et al.*⁴ found no evidence to support this.

Myelofibrosis and osteosclerosis may be present at presentation in chronic granulocytic leukaemia or may develop during its course.¹⁰ The production of bone marrow infarction is one of the mechanisms by which myelofibrosis may be induced experimentally. This case suggests that it may also be a mechanism of development of myelofibrosis in patients with chronic granulocytic leukaemia. Similarly, bone infarction, which often occurs with bone marrow necrosis, may lead to osteosclerosis. Microvascular failure is suspected as the underlying mechanism of bone marrow and bone infarction.

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Requests for reprints to: Dr Barbara Bain, Haematology Division, Pathology Department, Princess Alexandra Hospital, Ipswich Road, Woolloongabba, Brisbane, Queensland, Australia 4102