Bone marrow necrosis at transformation of chronic granulocytic leukaemia treated with interferon

J R Kendra, S Pickens, K Singh

Abstract
A patient with chronic myeloid leukaemia was treated with interferon without using conventional cytotoxic agents. Bone marrow necrosis developed at the onset of blast transformation.

It is suggested that cytotoxic drugs should be given before treatment with interferon for chronic myeloid leukaemia. Cytotoxic drugs may also be needed to prevent rapid bone marrow growth once interferon has been withdrawn.

Bone marrow necrosis is a rare complication of a wide variety of disorders including leukaemia.1 Of the leukaemias with this complication, acute lymphoblastic is the most common.2 Bone marrow necrosis is rare in chronic myeloid leukaemia and only 11 cases have been reported.3 To 5 Interferon (Intron-A) is a recent therapeutic addition in the treatment of chronic myeloid leukaemia and results show promise, with sustained cytogenetic remission in a small proportion of patients.6 To 9 Of the 11 previous case reports only one patient had received interferon, given in combination with busulphan.

Case report
A 58 year old caucasian man was referred for the investigation of dyspepsia. His spleen was palpable two finger breadths below the costal margin. Investigations showed a haemoglobin concentration of 13.4 g/dl, a white cell count of 58 x 10^9/l and a platelet count of 1697 x 10^9/l. The differential cell count showed 1% blasts, 5% promyelocytes, 15% myelocytes, 6% metamyelocytes, 66% neutrophils, 5% lymphocytes and 2% basophils. The leucocyte alkaline phosphatase score was 20. The bone marrow was hypercellular with the appearances of the chronic phase of chronic myeloid leukaemia. Cytogenetic analysis showed a Philadelphia chromosome. Endoscopic examination showed superficial gastric erosions. Treatment for chronic myeloid leukaemia was started with interferon (Intron-A)—5 million units subcutaneously, daily, with Paracetamol to alleviate febrile reactions and muscle aches. General malaise and muscular stiffness prevented an increase in dose. Splenomegaly resolved after two months and by the fourth month the white cell count was 5.8 x 10^9/l, platelet count 298 x 10^9/l, and the haemoglobin had risen to 14.0 g/dl. The blood counts remained within the normal range for the next four months. At this time the patient went abroad for three weeks and the frequency of interferon was reduced to three times a week. During the holiday, the patient complained of fevers, stiff muscles, and lethargy, which impaired his mobility. When he returned to the United Kingdom he was admitted as an emergency and found to be febrile, with a temperature of 40°C, and the spleen was three finger breadths palpable below the costal margin. The white cell count was 24 x 10^9/l with 2% blast cells, haemoglobin 11.1 g/dl, and platelets 364 x 10^9/l. Interferon was discontinued and intravenous antibiotics given. The fever resolved within 24 hours. Antibiotics were discontinued on the fifth day and no growth was noted in blood cultures. During this time the serum creatinine rose from 118 µmol/l on admission to 531 µmol/l. The white cell count was 38 x 10^9/l with 12% blast cells. A sternal marrow aspiration produced a dry tap; a sample from the posterior iliac crest was hypercellular with necrotic cells with ill defined margins in an amorphous background material. Bone marrow necrosis was diagnosed. Anuria developed and the patient was transferred for haemodialysis. The serum urate concentration was 0.9 mmol/l. Haemodialysis was attempted but cardiac dysrhythmias prevented prolonged treatment. Four days later the white cell count rose to 70 x 10^9/l with 25% blast cells. Further dialysis was not attempted and the patient died five days later. Subsequent cytogenetic analysis detected an isochromosome 17, in addition to the Philadelphia chromosome. Immunological markers showed the origin of the blast cells to be non-lymphoid.

Discussion
Interferon has recently been licensed for the treatment of chronic myeloid leukaemia. In this condition, interferon may achieve normalisation of the blood counts, regression of splenomegaly, and in a small proportion of patients a sustained loss of the Philadelphia chromosome.10 The response is slow and may take six months to achieve haematological remission, and cytogenetic changes may require 12 months' treatment. We elected to treat our patient solely with interferon and without prior cytoreductive chemotherapy because the presenting white cell count was not excessive.

The pathogenesis of bone marrow necrosis is probably multifactorial and the complication...
Bone marrow necrosis in CML may occur in a wide spectrum of diseases. It has been reported in chronic myeloid leukaemia during chronic phase and at blast transformation. As the marrow in chronic myeloid leukaemia is characteristically hypocellular, the rapid cell growth during clonal evolution to blast crisis could both infiltrate the vessel walls and compress the marrow blood supply, causing ischaemia of the marrow sinusoids.

Eleven cases of bone marrow necrosis and chronic myeloid leukaemia have been reported, but full documentation was not available for two reported by Brown,¹ nor the three reported by Norgard et al.⁹ Survival can be prolonged if necrosis occurs during stable chronic phase, as noted by Brown.⁶ Bain reported a 20 month survival from the onset of necrosis and subsequent development of myelofibrosis.⁷ Macheta et al described a survival of 12 months from necrosis in chronic phase.⁸

Three patients survived less than four weeks when necrosis occurred at the time of disease progression.⁵ ⁹ ¹⁰ However, Scudla et al.¹¹ reported a 14 week survival following bone marrow necrosis at blast crisis. This patient recovered focal areas of normal haemopoiesis after unspecified chemotherapy.

Our patient did not receive cytoreductive chemotherapy but was treated with interferon alone. Although this resulted in the normalisation of the peripheral blood and regression of splenomegaly, it did not prevent blast crisis and the subsequent development of bone marrow necrosis. We wonder, therefore, if despite the improvement in the peripheral blood the bone marrow remained hypocellular so that when blast transformation occurred, there was already a large residual cell mass in situ, thus increasing the risk of bone marrow necrosis by compression.

Interferon also has an inhibitory effect on bone marrow cells. The reduction in interferon and the subsequent abrupt withdrawal may have allowed rapid expansion of bone marrow cells.

Cytoreductive chemotherapy should be given before treatment with interferon for chronic myeloid leukaemia. There may also be a need to cover the withdrawal of interferon with conventional chemotherapeutic agents to prevent rapid bone marrow growth.

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CORRECTIONS

Our apologies to Dr A K Singh (Bone marrow necrosis at transformation of chronic granulocytic leukaemia treated with interferon) J Clin Pathol 1992;45:830-1. The first initial of his name was inadvertently omitted.

An error appeared in the article Modified latex agglutination test for antibodies to Toxoplasma gondii in eluates from Guthrie cards by Drs S P Parker and W D Cubitt (J Clin Pathol 1992;45:907-9). The legends to figures 2 and 3 were transposed.

Postgraduate course in gynecologic and obstetric pathology with clinical correlation
April 26–30, 1993
The Departments of Pathology, Massachusetts General Hospital and Brigham and Women's Hospital, Harvard Medical School, will present a postgraduate course in gynecologic and obstetric pathology. The course will be held at the Four Seasons Hotel, Boston. This course is designed for pathologists and obstetrician-gynecologists at resident and practitioner levels. It will provide an in-depth review of gynecologic and obstetric pathology with emphasis on morphologic diagnostic features and clinical-pathologic correlation including management. Special attention will be paid to recent advances and newly recognized entities. Instruction will be primarily by lecture, but will also include case presentations and discussion periods. Each participant will receive a comprehensive course syllabus.

The fee for the course is $695.00 (residents and fellows $550.00). For further information contact: Department of Continuing Education, Harvard Medical School, 25 Shattuck Street, Boston, MA 02115 (Telephone: 617-432-1525).

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British Lymphoma Pathology Group Tutorial
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Topics to include:
Techniques in lymphoma diagnosis; the borderline between Hodgkin’s and non-Hodgkin’s lymphoma; angiocentric immunoproliferative disorders; MALT lymphomas; monocytoid B cell lymphomas; diagnostic pitfalls in lymphoma pathology correlation
Guest lecturer: Dr Elaine Jaffe, National Cancer Institute, USA
Course fee: £300.00 (includes all accommodation costs and course slides).
For further information or application forms please contact: Dr A D Ramsay, BLPG Secretary, Department of Histopathology, Southampton General Hospital, Tremona Road, Southampton SO9 4XY. Tel: 0703-796447 Fax: 0703-705580.
(Closing date for application: 26 February 1993)

The following will be offered this Spring by
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Methods and applications
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For further information on any of the above courses, contact Roger K Cunningham, PhD, Director, The Ernest Wiesbey Center for Immunology, 442 Sherman Hall, University at Buffalo, 3455 Main Street, Buffalo, New York 14214. Phone: 716/829-2901 Fax: 716/829-2158. Because class size is limited in all courses, we recommend registrations be submitted at least one month prior to respective starting dates for best possibility of acceptance.

NOTICES

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July 5–8, 1993
Vienna, Austria
Local organizing committee: A Hansel, KL Resch, T Saradeth, Congress Secretariat, Dept Phys Med Rehab, University of Vienna (AKH), Währinger Gürtel 18–20, A-1097 Vienna, Austria. Tel: +43/1/40400-4330 Fax: +43/1/40400-5281

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