Chronic lymphocytic leukaemia terminating in acute myelofibrosis

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SUMMARY Acute myelofibrosis developed in a patient with longstanding chronic lymphocytic leukaemia who had been treated with alkylating agents and total body irradiation. The case is discussed in the context of acute non-lymphoid leukaemias occurring in chronic lymphocytic leukaemia with special reference to megakaryoblastic variants.

Acute myelofibrosis was first described by Lewis and Szur in 1963.¹ It is a rare condition characterised by pancytopenia and diffuse marrow fibrosis, but the splenomegaly associated with classic myelofibrosis is lacking. Peripheral red blood cell morphology is unremarkable. Small numbers of circulating immature white cells are seen, and giant platelets or megakaryocytic fragments are common. The marrow is difficult or impossible to aspirate and the trephine biopsy is characteristically fibrotic with prominent numbers of normal or abnormal megakaryocytes. This presentation has been shown to occur in the acute myeloid^{2,3} and acute megakaryoblastic types of leukaemia.^{4,5}

Chronic lymphocytic leukaemia terminating in acute leukaemia has been reported previously in 34 patients, but none has presented with the syndrome of acute myelofibrosis.^{6,7} We describe a patient who developed acute myelofibrosis more than six years after the diagnosis of chronic lymphocytic leukaemia.

Case report

A 42 year old woman presented in August 1975 with weight loss, shortness of breath, increasing abdominal girth, and pain in the left flank. Examination showed peripheral lymphadenopathy, moderate hepatosplenomegaly and an epigastric mass of lymph nodes.

The haemoglobin concentration was 10.4 g/dl, the leucocyte count $26 \times 10^9/l$ with 85% small lymphocytes, and the platelet count was normal. Chronic lymphocytic leukaemia was diagnosed and treatment with chlorambucil and prednisone in conventional doses was started. The patient's condition

showed no improvement and treatment was changed to cyclophosphamide, vincristine, and prednisone, again without effect. Sixteen months after presentation she was given total body irradiation, 120 rads in eight fractions over 30 days. Radiotherapy was discontinued because of thrombocytopenia—platelet count $90 \times 10^9/l$.

After recovery of the platelet count the patient remained well with no evidence of disease for 4 years, when abdominal pain recurred. Ultrasound examination confirmed intra-abdominal nodes and ascites. After paracentesis, radiotherapy to the anterior and posterior abdomen at a dose of 750 rads in 15 fractions over nine days was administered, plus a single exposure of 15 rads to the whole body.

Six weeks later she was admitted with generalised lymphadenopathy, hepatosplenomegaly, and bilateral pleural effusions. Haemoglobin concentration was 8.3 g/dl, leucocyte count $2.2 \times 10^9/l$ (neutrophils 76%, lymphocytes 16%, monocytes 7%, eosinophils 1%), platelet count $70 \times 10^9/l$. Marrow aspirate was hypercellular with an increased number of megakaryocytes and an abnormal infiltrate of lymphoid cells. Trephine biopsy confirmed these findings.

Treatment on this occasion consisted of pleural aspirations, blood transfusion, chlorambucil, vincristine, and prednisone. After five courses of chemotherapy, there was no evidence of disease on clinical examination. Chemotherapy was discontinued in October 1981 because of pancytopenia. Since diagnosis she had received 1240 mg of chlorambucil and 1800 mg of cyclophosphamide.

In December 1981 her haemoglobin concentration was 6.7 g/dl, leucocyte count $1.8 \times 10^9/l$, and platelet count $7 \times 10^9/l$. Blood film showed nucleated red blood cells 15/100 white cells, myelocytes, occasional blast cells, giant platelets, and

- (a) Megakaryocytic fragments present in the peripheral blood. $\times 100$.
 (b) 2–3% blasts were seen in the peripheral blood. Insufficient numbers were obtained for accurate typing. $\times 100$.
 (c) Megathrombocytes with atypical vacuolation were present in the peripheral blood. Morphologically normal platelets were absent. $\times 100$.
 (d) Trephine biopsy from right iliac crest showed gross increase in reticulin. Megakaryocytic trapping was evident. $\times 25$.

megakaryocytic fragments (see Figure a, b, c). Marrow aspiration was unsuccessful in two sites. Trephine biopsy was hypercellular with increased numbers of megakaryocytes and a substantial increase in reticulin (Figure d). Acute myelofibrosis was diagnosed.

During the next months the clinical course was punctuated by admissions for treatment of infections and blood transfusions. No further chemotherapy was given. The white blood cell count remained low, though blast cells were more easily identified. During her final illness she developed progressive weakness of the lower limbs and died 81 months after initial diagnosis.

Postmortem examination showed splenomegaly (740 g); histological examination of sections of the spleen showed myeloid metaplasia and diffuse infiltration by large primitive cells. A similar infiltrate was found in sections of an abdominal lymph node, but there was no disturbance of nodal architecture.

Using the immunoperoxidase technique, these infiltrating cells were negative for muramidase and α_1 -antitrypsin, IgA, and IgM. They appeared to contain cytoplasmic IgG, but were positive for kappa and lambda and this probably represents passive absorption from the circulation rather than intracellular production. They were negative for chloracetate esterase and factor VIII related antigen, but the Unna-Pappenheim stain showed moderate cytoplasmic pyroninophilia.

Sections of vertebral bone marrow examined showed infiltrating cells similar to those seen in the spleen and nodes, but fibrosis in sections examined was less evident.

Discussion

Acute myelofibrosis is only one term used to describe the syndrome of pancytopenia, absence of hepatosplenomegaly, fibrosis of the marrow, and a variable number of peripheral blood blast cells. Other authors have used the terms acute myelofibrosis,² malignant myelofibrosis,^{3,8} acute megakaryoblastic leukaemia,^{4,5} and acute megakaryocytic myelofibrosis.⁹ This disorder is usually rapidly fatal with a mean survival of six months, although recently more optimistic reports have been published following the use of aggressive chemotherapy^{10,11} or bone marrow transplantation.^{12,13}

Thirty four cases of chronic lymphocytic leukaemia terminating in acute leukaemia have been reported. Most of the acute non-lymphocytic leukaemias have occurred in patients treated with radioactive phosphorous, chemotherapy, or

chemotherapy with radiotherapy. One case occurred in a patient treated only with total body irradiation,⁷ and one occurred in a previously untreated patient.¹⁴ Treatment in our patient included chlorambucil, cyclophosphamide, total body irradiation, and regional radiotherapy. All these treatments have been implicated as causes of secondary leukaemia.^{15,16}

Bain *et al*⁵ and Den Ottolander *et al*⁴ have postulated that in most cases acute myelofibrosis might be synonymous with acute megakaryoblastic leukaemia. Other workers^{2,3} have positively identified the blast cells in cases of acute myelofibrosis as myeloblasts, based on the presence of Auer rods or characteristic cytochemical reactions.

Absolute diagnosis is often difficult because of the small numbers of circulating blast cells and absence of marrow aspirate material for cytochemical staining or cell surface marker studies. Our patient never had more than $1.8 \times 10^9/l$ circulating white cells with 2–3% blast cells, and attempts at definitive cell typing were unsuccessful.

Nevertheless, clinical findings, peripheral blood film, and trephine biopsy confirmed the diagnosis of acute myelofibrosis, and we believe this to be the first reported case of this syndrome arising in a patient with chronic lymphocytic leukaemia.

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