Idiopathic acquired sideroblastic anaemia transforming to acute myelosclerosis

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SUMMARY A case of idiopathic acquired sideroblastic anaemia transforming to acute myelofibrosis is reported. The appearance of atypical megakaryocytic proliferation in idiopathic acquired sideroblastic anaemia may presage the development of an acute myelofibrotic phase of this usually chronic disease.

Idiopathic acquired sideroblastic anaemia is a disorder of haematopoietic stem cell differentiation and proliferation, probably representing the emergence of an abnormal haemopoietic clone.¹ While patients with this disease, usually elderly, often die of unrelated causes, this disease often undergoes transformation to acute leukaemia.²⁻⁷ Transformation to acute myelofibrosis, however, is rare.⁸⁻¹⁰

We report a patient with idiopathic acquired sideroblastic anaemia who developed acute myelofibrosis.¹¹ In addition to the characteristic ring sideroblasts and erythroid hyperplasia, this patient's bone marrow showed atypical megakaryocytic proliferation before progression to acute myelofibrosis.

Case report

A 68 year old white man presented in April 1981 with fatigue and a seven year history of insulin dependent diabetes mellitus. There was no history of other chronic disease, excessive use of alcohol, or exposure to lead or relevant drugs. Physical examination was unremarkable, without splenomegaly or lymphadenopathy. Peripheral blood findings were as follows: haemoglobin concentration 10.8 g/dl, white cell count $6.2 \times 10^9/l$ (normal differential), and platelet count $135 \times 10^9/l$. The blood film showed both hypochromic microcytic and normochromic normocytic red cells, with a few oval macrocytes. Serum iron concentration was 32 $\mu\text{mol/l}$ (normal range 13-30 $\mu\text{mol/l}$), total iron binding capacity was 38 $\mu\text{mol/l}$ (normal range 50-70 $\mu\text{mol/l}$), with a saturation of 0.84 (normal range 0.2-0.5). Serum vitamin B₁₂, red cell folate, and serum ferritin concentrations were within normal limits. The bone marrow

was hypercellular with hyperplastic erythropoiesis, mild dysplastic changes, and numerous ring sideroblasts (Fig. 1). Granulopoiesis was unremarkable. Megakaryocytes were clearly increased in number with more than normal variation in size, nuclear form, ploidy, and nuclear to cytoplasmic ratio. Idiopathic acquired sideroblastic anaemia was diagnosed.

The patient was given blood transfusion, but otherwise his clinical and laboratory findings did not change appreciably until October 1982, when neutropenia, increasing thrombocytopenia, and palpable splenomegaly were found. By January 1983, thrombocytopenia was severe (platelet count $20 \times 10^9/l$) and the blood film became leukoerythroblastic with the presence of myelocytes ($0.4 \times 10^9/l$) and occasional blast forms (haemoglobin concentration 7.7 g/dl, white cell count $2.6 \times 10^9/l$). Attempts at bone marrow aspiration yielded a "dry tap." Bone marrow biopsy showed a hypercellular marrow with, as before, atypical megakaryocytic proliferation now accompanied by increased reticulin and collagen fibres (Fig. 2). Erythroid and granulopoietic elements were present with evidence of differentiation. Acute myelofibrosis was diagnosed.

In March 1983 he became jaundiced. Liver function tests suggested hepatitis, but radioimmunoassay for hepatitis B surface antigen was negative. A provisional diagnosis of non-A, non-B hepatitis was suggested. In early April he developed bronchopneumonia. Sputum cytology showed malignant cells. A few days later he fell and suffered epidural and intracranial haematomas, and he died on 7 April.

Permission was obtained for a limited necropsy, which revealed the following: splenomegaly (0.5 kg), with extramedullary haematopoiesis;

Fig 1 Bone marrow film showing erythrocytes and erythroblasts containing Prussian blue positive granules (ring sideroblasts). Prussian blue reaction counterstained with 1% neutral red. Original magnification $\times 1800$.

Fig 2 Bone marrow biopsy sample showing atypical megakaryocytic proliferation accompanied by increased deposition of reticulin fibres. Silver impregnation, counterstained with iron haematoxylin. Original magnification $\times 775$.

myelofibrosis of the bone marrow with atypical megakaryocytic hyperplasia and increased reticulin fibres; haemosiderosis of the liver without evidence of parenchymal inflammation; and Kimmelstiel-Wilson diabetic glomerulonephropathy of the kidney. Adequate examination of the lungs and any examination of the brain and meninges were precluded by the limited nature of the necropsy.

Discussion

Idiopathic acquired sideroblastic anaemia usually occurs in older patients and is characterised by a chronic course. While death often occurs owing to intercurrent disease, it is not uncommon for the condition to undergo transformation to acute leukaemia.³⁻⁷ While acute lymphoblastic leukaemia has been reported,¹² acute myeloid leukaemia is the usual form. The cause of the predisposition is unclear, but evidence indicates that both acute myeloid leukaemia and idiopathic acquired sideroblastic anaemia may be clonal disorders originating in pluripotent stem cells.^{13 14} While erythroid,

granulocytic, monocytic, and platelet lineages derive from a common pluripotent stem cell, marrow fibroblasts are probably of separate origin.¹³

It is rare for idiopathic acquired sideroblastic anaemia to progress to acute or malignant myelofibrosis. Lewis and Szur first identified malignant myelofibrosis as a separate entity in 1963.¹¹ Yeung and Trowbridge¹⁰ described the first example of idiopathic acquired sideroblastic anaemia transforming to acute myelofibrosis in 1977. A further case was identified by Butler *et al*⁸ which showed atypical megakaryocytic proliferation, and Lukowicz *et al*⁹ reported two patients with idiopathic acquired sideroblastic anaemia who had thrombocytosis associated with myelofibrosis.

In five cases of de novo acute myelofibrosis blast cells in the peripheral blood were characterised as being of megakaryocytic origin using the platelet peroxidase reaction.^{15 16} Bain *et al*¹⁵ postulated that acute myelofibrosis is secondary to the megakaryocytic proliferation. In most cases of idiopathic acquired sideroblastic anaemia transforming to acute myelofibrosis there has been evidence of

megakaryocytic hyperplasia. Platelet derived growth factor has been suggested as having a role in the pathogenesis of myelofibrosis. Defective megakaryocytic maturation results in the intramedullary destruction of developing megakaryocytes, and it has been suggested that megakaryocytic cytoplasmic contents are released into the marrow, including megakaryocytic platelet derived growth factor and factor 4.⁵ Platelet derived growth factor stimulates fibroblasts to proliferate and secrete collagen. Factor 4, contained in platelet alpha granules, causes inhibition of granulocyte and fibroblast collagenase, which normally degrades bone marrow collagen and reticulin fibres.¹⁷ It is suggested that as a result of the action of these two factors, collagen and reticulin fibres are increased, resulting in acute myelofibrosis.¹⁷

The presence of megakaryocytic proliferation in sideroblastic anaemia may have prognostic potential, indicating the likelihood of subsequent transformation into acute myelofibrosis and therefore predicting a poor prognosis.

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