Primary acquired sideroblastic erythropoiesis in non-anaemic and minimally anaemic subjects

D T Bowen, A Jacobs

From the Department of Haematology, University of Wales College of Medicine, Heath Park, Cardiff

SUMMARY Six patients had primary sideroblastic erythropoiesis together with a haemoglobin concentration of 12.0 g/dl or higher. In four cases this was associated with macrocytosis. Other abnormalities included failure of erythroid progenitor growth from peripheral blood in three cases and occasional dysplastic appearances in neutrophils and megakaryocytes. Sideroblastic erythropoiesis seems to be an early manifestation of the myelodysplastic syndrome and may present clinically at a pre-anaemic stage.

The clinical syndrome of primary acquired sideroblastic anaemia (PASA) with its striking bone marrow morphological detail has been recognised for many years, and, more recently, the condition has been included among the myelodysplastic syndromes by the French-American-British (FAB) cooperative group. It is now generally accepted that this disorder results from the clonal proliferation of abnormal haemopoietic stem cells that have undergone premalignant transformation. Although the FAB group do not define anaemia in relation to the diagnosis of myelodysplastic syndrome, patients with PASA usually seem to have decreased haemoglobin concentrations and in many cases are dependent on transfusion. Jacobs and Clark suggested that PASA, with its accompanying erythroid hyperplasia in bone marrow, may represent an early stage in a progressive preleukaemic evolution of the haemopoietic stem cell, and this is in keeping with the relatively good prognosis in this group of patients. We describe six non-anaemic or minimally anaemic subjects in whom erythropoiesis was dominated by the presence of ring sideroblasts in the bone marrow. The gross disturbances of erythropoiesis found in these patients in the presence of a relatively normal haemoglobin concentration, leucocyte count, and platelet count add weight to the suggestion that sideroblastic change represents an early manifestation of the preleukaemic process.

Case reports

Case 1
A 68 year old retired engineer with a medical history of chronic obstructive airways disease, pneumonia in 1943, and an “ulcer” operation in 1972, was referred to the University Hospital of Wales after admission elsewhere for investigation of possible gastrointestinal bleeding. He had been a non-smoker for 20 years and drank little alcohol. Bone marrow aspiration carried out at the referring hospital showed sideroblastic haemopoiesis. On admission, direct questioning indicated symptoms of angina but there were no abnormal physical signs.

On admission to this hospital in July 1987, his haemoglobin concentration was 12.0 g/dl. The blood film showed some anisocytosis and macrocytes together with occasional hypogranular and bilobed neutrophils. Review of previous blood counts showed that he had been intermittently anaemic since 1984 with a haemoglobin concentration varying between 9.6-12.4 g/dl and a mean cell volume varying from 79 to 96 fl. Serum ferritin concentration was 343 µg/l, serum vitamin B12 573 ng/l, serum folate 55 µg/l, and red cell folate 1278 µg/l. Blood urea, electrolytes, and liver functions tests yielded normal results.

A bone marrow aspirate was hypercellular with plentiful megakaryocytes and occasional micro-megakaryocytes. There were some dyserythropoietic changes. Other haematological variables are shown in the table. The bone marrow karyotype was 46XY, though one cell with 46XY del(7) (q32-qter) was found. A two week course of folic acid (5 mg daily) and pyridoxine hydrochloride (200 mg daily), together with an injection of hydroxocobalamin (1000 µg) failed to produce any haematological change.

Case 2
A 65 year old housewife was referred for investigation of persistent macrocytosis found on routine examination. She neither smoked nor drank alcohol and had
Sideroblastic erythropoiesis in subjects with minimal or no anaemia

Table  Haematological data from six patients with sideroblastic erythropoiesis

<table>
<thead>
<tr>
<th>Reference values</th>
<th>Case 1 (M)</th>
<th>Case 2 (F)</th>
<th>Case 3 (M)</th>
<th>Case 4 (M)</th>
<th>Case 5 (F)</th>
<th>Case 6 (M)</th>
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<tbody>
<tr>
<td>Peripheral blood:</td>
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<tr>
<td>Haemoglobin</td>
<td>Male 13-5–16-5 g/dl</td>
<td>12.0</td>
<td>12.0</td>
<td>12.0</td>
<td>14.0</td>
<td>12.1</td>
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<tr>
<td></td>
<td>Female 11-5–13-5 g/dl</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Mean cell volume</td>
<td>80-100 fl</td>
<td>96</td>
<td>106</td>
<td>114</td>
<td>99</td>
<td>102</td>
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<tr>
<td>White cells</td>
<td>4-10-5 × 10⁹/l</td>
<td>8.3</td>
<td>9.0</td>
<td>7.8</td>
<td>8.4</td>
<td>9.0</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>1-5-7-5 × 10⁹/l</td>
<td>4.0</td>
<td>5.5</td>
<td>3.3</td>
<td>3.4</td>
<td>6.3</td>
</tr>
<tr>
<td>Platelets</td>
<td>150-450 × 10⁹/l</td>
<td>177</td>
<td>247</td>
<td>466</td>
<td>390</td>
<td>655</td>
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<tr>
<td>BFU-E</td>
<td>35-400/ml blood</td>
<td>0</td>
<td>94</td>
<td>0</td>
<td>37</td>
<td>0</td>
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<tr>
<td>CFU-GM</td>
<td>5-308/ml blood</td>
<td>13</td>
<td>0</td>
<td>8</td>
<td>18</td>
<td>9</td>
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<tr>
<td>Marrow:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>% Erythroblasts</td>
<td>5–35</td>
<td>29</td>
<td>26</td>
<td>35</td>
<td>32</td>
<td>30</td>
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<tr>
<td>% Ring sideroblasts</td>
<td>Nil</td>
<td>45</td>
<td>80</td>
<td>52</td>
<td>78</td>
<td>53</td>
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<tr>
<td>% Blasts</td>
<td>0–3</td>
<td>&lt;1</td>
<td>2</td>
<td>2</td>
<td>&lt;1</td>
<td>2</td>
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<tr>
<td>Ferrokinetics</td>
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<td></td>
<td></td>
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<tr>
<td>Marrow iron turnover</td>
<td>75–160 μmol/l/d</td>
<td>155</td>
<td>142</td>
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<tr>
<td>% Ineffective erythropoiesis</td>
<td>10–30</td>
<td>37</td>
<td>68</td>
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</tbody>
</table>

no specific symptoms. No abnormalities were found on examination.

Her haemoglobin concentration was 12-0 g/dl. Serum vitamin B₁₂ concentration was 640 ng/l and serum folate was 4-2 μg/l. The bone marrow aspirate was hypercellular with plentiful megakaryocytes and occasional micromegakaryocytes. Other haematological variables are shown in the table.

CASE 3
A 59 year old builder had had transient attacks of cardiac ischaemia six years before being seen at this hospital. At that time he had been thought to be polycythaemic with a haemoglobin concentration of 20-2 g/dl and a mean cell volume of 119 fl. Red cell volume, however, had been 36-4 ml/kg body weight and plasma volume 32 ml/kg body weight: the bone marrow aspirate was said to have been megaloblastic at that time. He smoked 20 cigarettes daily. Treatment with vitamin B₁₂ and folic acid was accompanied by venesection on three occasions. He was reviewed regularly over the subsequent six years while his haemoglobin slowly fell, during which time he had stopped smoking.

On referral, his haemoglobin concentration was 12-0 g/dl, serum vitamin B₁₂ was 660 ng/l, serum folate 3-7 μg/l, and serum ferritin 480 μg/l. Bone marrow aspirate was cellular with morphologically normal megakaryocytes. Additional haematological data are shown in the table. Cytogenetic analysis indicated a constitutional karyotype abnormality (46XY, 16p +).

CASE 4
A 60 year old miner was referred for investigation of chest pain and breathlessness. He smoked moderately and had a history of excessive alcohol intake until six months previously. His recent alcohol consumption was two pints of beer weekly. No abnormality was found on physical examination. He had a haemoglobin concentration of 14-0 g/dl. Serum vitamin B₁₂ was 789 ng/ml, serum folate 2-8 μg/l, red cell folate 363 μg/l and serum ferritin 630 μg/l. Gamma glutamyl transferase was 21 IU/l.

Bone marrow aspiration showed a hypercellular marrow with morphologically normal megakaryocytes and no abnormality in the myeloid series. Additional haematological data are shown in the table. Treatment with pyridoxine (150 mg daily) and folic acid (5 mg daily) for three weeks, together with hydroxocobalamin (1000 μg) stat failed to change the peripheral blood count or bone marrow appearances.

CASE 5
A 72 year old woman was referred for investigation of persistent macrocytosis that was discovered following an attack of labyrinthitis. She already had diabetes mellitus and mild hypertension, neither of which required treatment. She smoked 20 cigarettes a day and drank little alcohol. There were no abnormal findings on physical examination.

At presentation her haemoglobin concentration was 12-1 g/dl. Serum B₁₂ concentration was 396 ng/l, serum folate 4-6 μg/l, and serum ferritin 334 μg/l. Bone marrow aspirate was hypercellular with many dysplastic megakaryocytes. Many cells showed dyserythropoiesis. Cytogenetic analysis from blood and bone marrow showed a normal female karyotype (table).

CASE 6
An 84 year old man returned from abroad for hip surgery. Macrocytosis was noted on a routine blood
count. He was fit and well and had no significant medical history. He denied excessive alcohol consumption, did not smoke, and took no medication. His haemoglobin concentration was 12-2 g/dl. Serum vitamin B_12_ was 428 ng/l and serum folate 19 nmol/l. Bone marrow karyotype was 46XO in all metaphases. A blood sample was not obtained for cytogenetic analysis of peripheral blood (table).

Discussion

Primary acquired sideroblastic erythropoiesis is usually associated with anaemia. Cheng et al found a mean haematocrit of 0-27 in the 268 cases they reviewed. The 23 patients described by May et al and the 37 patients described by Cazzola et al all had haemoglobin concentrations of less than 12-0 g/dl. We draw attention to the occurrence of sideroblastic erythropoiesis in patients with a haemoglobin concentration above this value. In four of our patients there was an unexplained macrocytosis resistant to treatment with vitamin B_12_ and folic acid and, in one case, examination of the peripheral blood showed dysplastic neutrophils despite a normal neutrophil count. In two patients the platelet count was above our normal reference range.

Further special investigations showed other haemopoietic abnormalities typical of patients with myelodysplastic syndromes. In three cases peripheral blood culture showed a failure of erythroid progenitors (BFU-E) to grow normally, and in one case there was a failure to grow granulocyte-macrophage colonies (CFU-GM) after 14 days' culture, despite apparently normal neutrophils in the peripheral blood. These findings are similar to those seen in cultures of bone marrow progenitors in myelodysplastic syndrome. In two cases where a ferrokinetic assessment of erythropoiesis was carried out the increased degree of ineffective erythropoiesis combined with a slight increase in total erythroid output was again typical of the findings in early myelodysplastic syndrome. Cyto genetic analysis of the bone marrow showed no clonal abnormalities in any case. Ras mutations in haemopoietic cells have been found in about 40% of patients with myelodysplastic syndrome. None was found in cases 1-4 in our group.

Five of our patients have been followed up. The longest follow up is four years with no haematological change. Case 2 has become anaemic after 18 months and case 3 dropped his haemoglobin concentration by 2 g/dl three months after referral.

Oscier has suggested that the incidence of myelodysplastic syndrome may be about 1 in 4250 a year but that in those above the age of 55 years there may be a prevalence of the order of 1 in 462. These figures suggest that myelodysplastic syndrome is more common than might have been imagined. We do not know how long sideroblastic change had been present in our patients but the cases presented here illustrate the need for a high degree of suspicion in making an early diagnosis. The early identification of these patients is important as they are at risk of eventual evolution into a more hazardous clinical state. Cheng et al found that acute leukaemia occurred in 10% of the 268 patients with sideroblastic anaemia, and Todd and Pierre show that the seven year survival compared with an age and sex matched population was only 37% that of the controls. Similar data have been published by Oguma et al. Erythroid abnormality associated with ring sideroblast formation seems to be an early manifestation of myelodysplastic syndrome.

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References


Requests for reprints to: Dr DT Bowen, Department of Haematology, University of Wales College of Medicine, Heath Park, Cardiff CF4, Wales.