Pure Red Cell Aplasia and Carcinoma

By A. B. S. Mitchell, G. Pinn and G. D. Pegrum

A patient presented with pure red cell aplasia, which responded to corticosteroids. Thirteen months later, a malignant pleural effusion developed, with subsequent death from adenocarcinomatosis. The reports of cases in which pure red cell aplasia has been associated with carcinomata are reviewed. An autoimmune mechanism can be postulated in these circumstances, and the complete response to corticosteroids in the present case would support this hypothesis.

A 69-YEAR-OLD MAN presented in January 1968 with a 3-week history of dizziness, lassitude, and increasing dyspnea. Previously he had been healthy except for paratyphoid fever in 1942 and osteoarthrosis of the spine, confirmed radiologically in 1966. He had not taken any drugs. He had worked in the office of a brewery for 30 years but was not in the habit of consuming large quantities of alcohol and did not smoke. On examination he was overweight but there were no abnormal physical signs other than pallor.

CASE REPORT

Investigations. Tests revealed the hemoglobin to be 7.6 g/100 ml and a packed cell volume of (PCV) 21 per cent. Red blood cells showed anisocytosis, poikilocytosis, slight polychromasia, and macrocytosis. The reticulocyte count was 0.6 per cent and the white blood cell count was 7600/cu mm, with a normal differential count. The Westergren erythrocyte sedimentation rate (ESR) was 55 mm in the first hour.

A bone marrow aspirate showed slightly reduced nuclear cellularity. Erythropoiesis was markedly reduced, but normoblastic, with adequate hemoglobinization; the stainable iron was increased in the developing erythroblasts. Granulopoiesis and megakaryocytes were normal. No malignant cells or acid fast bacilli were discovered.

No abnormalities were detected in the following tests: direct antihuman globulin, serum bilirubin, other liver function tests, serum haptoglobin, urinary urobilinogen and hemosiderin, Ham’s test, serum vitamin B₁₂ and folate, serum iron, stool occult blood, chest X ray, barium meal and enema, blood urea, serum electrolytes, creatinine clearance, urine chemistry and microscopy, white blood cell urinary excretion rate, intravenous pyelogram, antinuclear factor, rheumatoid factor, serum proteins, calcium, and acid phosphatase.

Radioactive-iron studies showed a striking retention of injected radioiron in the plasma. Plasma radioactivity declined slowly with a half-life of 334 minutes (normal range 60-140 minutes). There was no measurable uptake by the bone marrow as recorded over the sacrum. Radioiron accumulated in the liver and slightly in the spleen, and remained there throughout the 11 days of the test. The half-life of ⁵¹Cr in the blood was slightly reduced, being 20.5 days (normal 25-32 days).

Progress. The course of the illness is shown in Fig. 1. A variety of hematinics were given, including pyridoxine, vitamin B₁₂, and folic acid. A slight unsustained reticulocytosis followed the administration of pyridoxine.
Because of increasing transfusion requirements prednisolone was given. After 10 weeks there was evidence of bone marrow regeneration with a reticulocytosis, active erythropoiesis in marrow smears, and a rise in the hemoglobin concentration to normal levels. The dose of prednisolone was reduced in stages to 15 mg per day, and the hemoglobin concentration settled to 11 g/100 ml.

In February 1969, over a year after initial presentation, the patient developed a large pleural effusion. Pleural biopsy revealed tissue containing adenocarcinoma cells. Intrathoracic cyclophosphamide, then radioactive gold, had no effect on the reaccumulation of fluid. During this time the hemoglobin concentration rose to 13 g/100 ml. The patient died in May 1969.

Autopsy. The autopsy revealed a malignant left pleural effusion with deposits in the right lung, liver, pancreas, posterior pituitary and vertebrae. Sections showed a tubular, columnar celed carcinoma, the primary site of which could not be determined. The spleen was normal. The thymus was replaced by fatty tissue. Erythropoiesis was present in the marrow.

**Comment**

Pure red cell aplasia was indicated by the severe anemia, with a decrease of reticulocytes in the peripheral blood and no changes in the white blood cells or platelets, together with a marked reduction of erythropoietic activity in the bone marrow showing normal white blood cell and platelet precursors. This was confirmed by the lack of iron utilization by the marrow.

There have been few reports of cases associated with carcinomata, and these are listed in Table 1. It is unlikely that this association could have been fortuitous in all these cases.

Pure red cell aplasia may be produced by a factor which is active against either erythropoietin or erythroblasts, probably an immunoglobulin. A possible
Table 1.—Summary of Case Histories in Which Pure Red Cell Aplasia Has Been Associated With a Carcinoma

<table>
<thead>
<tr>
<th>Age at Death</th>
<th>Sex</th>
<th>Length of History</th>
<th>Response to Therapy</th>
<th>Carcinoma</th>
<th>Interval between Onset of Aemia and Discovery of Carcinoma</th>
<th>Additional Findings</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>F</td>
<td>3 years</td>
<td>Nil</td>
<td>Gastric</td>
<td>3 years</td>
<td>—</td>
<td>5</td>
</tr>
<tr>
<td>67</td>
<td>M</td>
<td>3 years</td>
<td>Nil to corticotrophin, cortisone, splenectomy; subsequent good response to corticotrophin</td>
<td>Bronchial, squamous</td>
<td>3 years</td>
<td>—</td>
<td>3</td>
</tr>
<tr>
<td>78</td>
<td>F</td>
<td>1 year</td>
<td>Nil</td>
<td>Breast</td>
<td>3 months</td>
<td>Benign thymoma found at autopsy</td>
<td>6</td>
</tr>
<tr>
<td>57 *</td>
<td>F</td>
<td>4½ years</td>
<td>Nil to prednisolone, corticotrophin, radical mastectomy</td>
<td>Breast</td>
<td>1 year</td>
<td>Benign thymoma removed 3 years before anemia developed</td>
<td>7</td>
</tr>
<tr>
<td>68</td>
<td>M</td>
<td>2 years</td>
<td>Nil to radiotherapy</td>
<td>Bronchial, anaplastic</td>
<td>19 months</td>
<td>Erythropoietic inhibiting factor demonstrable before, but not after, radiotherapy</td>
<td>2</td>
</tr>
<tr>
<td>76</td>
<td>F</td>
<td>6 weeks</td>
<td>Nil</td>
<td>Bronchial, squamous, sometimes anaplastic</td>
<td>6 weeks</td>
<td>Thrombocytopenia</td>
<td>8</td>
</tr>
<tr>
<td>70</td>
<td>M</td>
<td>16 months</td>
<td>Good response to prednisolone</td>
<td>Adenocarcinoma, primary undecided</td>
<td>13 months</td>
<td>—</td>
<td>Present case</td>
</tr>
</tbody>
</table>

* Alive and anemic at time of report.
link with carcinomata was provided by Entwhistle, Fentem and Jacobs (1964) when they found in their patient’s serum a factor that inhibited erythropoiesis in rabbits, which was no longer demonstrable after radiotherapy to the carcinoma. From the hematological response to prednisolone in our patient and to corticotrophin in that of Tsai and Levin (1957), an autoimmune mechanism can be inferred. This suggests that there is a relationship between pure red cell aplasia and carcinomata. A favorable hematological response to corticosteroids does not exclude underlying malignant disease, which may remain undetected for some time. When pure red cell aplasia complicates malignant disease, corticosteroids should be used in treatment.

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REFERENCES

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