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MEDICAL MEMORANDA

Paroxysmal Nocturnal Haemoglobinuria-like Red Cell Abnormality in Patient with Lymphoproliferative Disease

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British Medical Journal, 1972, 4, 649-650

Paroxysmal nocturnal haemoglobinuria is diagnosed on the basis of a positive acidified serum lysis test. An association between the disease and aplastic anaemia is well established (Lewis and Dacie, 1967). The development of a paroxysmal nocturnal haemoglobinuria-like abnormality—that is, a positive acidified serum lysis test—has been seen in myelosclerosis (Lewis *et al.*, 1971) and, conversely, acute myeloblastic leukaemia has developed in at least six patients with pre-existing paroxysmal nocturnal haemoglobinuria. The patient reported here developed a positive acidified serum test during the course of a lymphoproliferative malignant disease. He had a concomitant autoimmune haemolytic anaemia and hypogammaglobulinaemia.

Case Report

A caucasian man, aged 59 years was admitted to Hammersmith Hospital in April 1969 with a six-week history of lymph node enlargement, sweating, and weight loss. On clinical examination he was apyrexial, not jaundiced, and had no petechiae or bruising. Large (2-4 cm) very firm anterior and posterior cervical nodes, and palpable auricular, submandibular, and submental nodes were present. There was a 20-cm splenomegaly and 6-cm hepatomegaly. Occasional haemorrhages were present in both fundi. The blood count gave the following results: haemoglobin 8.4 g/100 ml, reticulocytes 0.8%, platelets 107,000/mm³, W.B.C. 370,000/mm³ with 82% lymphocytes. The lymphocytes were predominantly small mature cells, but about 15% were larger nucleolated lymphoid cells showing varying degrees of immaturity. A direct antiglobulin test was strongly positive (IgG). The bone marrow was markedly hypercellular and infiltrated with predominantly small mature lymphocytes. Larger nucleolated lymphoid cells were present in

numbers comparable to those found in the peripheral blood. Uric acid was 9.1 mg/ml, bilirubin 0.4 mg/100 ml, alkaline phosphatase 19 K.A. units, serum albumin was 3.5 g/100 ml, and globulin was 2.1 g/100 ml. Immunoglobulins were: IgG 820, IgA 85, and IgM less than 10 mg/100 ml. No serum myeloma-like protein was present. However, Bence Jones protein, type k, was detected in a concentration of 4 mg/100 ml. A ⁵¹Cr red cell survival study was normal (T₅₀ 24 days). A chest x-ray film showed bilateral hilar lymphadenopathy, confirmed by tomography. A diagnosis of chronic lymphocytic leukemia was made, although the atypical blood and bone marrow morphology and strikingly firm lymphadenopathy on palpation raised the possibility of this being a variant of lymphocytic lymphoma.

The patient was treated with chlorambucil, 5 mg/day, allopurinol 400 mg/day, and prednisone 40 mg/day. He was discharged 16 days after admission on prednisone 40 mg/day and allopurinol 300 mg/day. He was then symptom-free and the lymphadenopathy was greatly reduced. The evolution of the disease is shown in the chart.

Between May and August 1969 he became progressively anaemic with increasing anorexia, fever, and sweats, despite receiving chlorambucil and prednisone. He was readmitted to hospital in August. Examination showed splenomegaly (6 cm), hepatomegaly (7 cm), and multiple very firm axillary, cervical, and inguinal nodes. Haemoglobin was 5.8 g/100 ml, reticulocytes were 22%, platelets were 88,000/mm³, and W.B.C. was 9,000/mm³ with 87% lymphocytes. The peripheral blood film showed spherocytes, polychromasia, and anisocytosis. A direct antiglobulin test was again strongly positive (IgG). In an auto-red cell survival study the ⁵¹Cr T₅₀ was eight days, and surface counting showed that the spleen was the principal site of red cell destruction. As the acute haemolysis did not respond to high doses of prednisone, splenectomy was performed. The spleen weighed 980 g; its sinuses were packed with red cells and widened splenic cords contained many lymphocytes, some mature and some poorly differentiated. Sections of a superficial lymph node removed at the time of surgery showed that the normal cellular architecture had been completely replaced by a uniform mass of rather poorly differentiated lymphocytes. Splenectomy was followed by a rapid improvement in the blood count, and the patient was discharged in October on prednisone, 5 mg/day (see chart). Haemoglobin was 11.5 g/100 ml, reticulocytes were 1.8%, W.B.C. was 16,000/mm³, and platelets were 454,000/mm³. A red cell survival study performed one month later was normal (T₅₀ 25 days).

From February to June 1971 superficial lymph nodes showed progressive enlargement despite continuing chemotherapy. In June of that year a five-week course of local radiotherapy was given to enlarging cervical and inguinal nodes, with subsequent shrinkage of the tumour masses. In August an inguinal node was also irradiated. From then until November the patient showed continuing clinical deterioration without evidence of further superficial node enlargement.

On his final admission in November he was sick, wasted, and pyrexial. The superficial nodes were not enlarged above 1.5 cm. A lymphangiogram, however, showed the presence of large abnormal para-aortic glands, and a chest radiograph showed the recurrence of bilateral hilar lymphadenopathy. Accordingly he was started on a course of radiotherapy to the para-aortic region (see

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chart). The bone marrow was then hypercellular and the pre dominant cell type was a large immature lymphocyte.

His clinical condition rapidly deteriorated, bilateral broncho-pneumonia, left ventricular failure, hyponatraemia, and renal failure occurred, and he died on 21 December. Permission for a postmortem examination was not obtained.

Investigation of the Abnormality.—In June 1970 the acidified serum lysis, cold antibody, and sucrose lysis tests were negative. No haemosiderin could be seen in the urinary deposit. In February 1971 the cold antibody lysis test became strongly positive (14%) and the sugar lysis screening test was also positive (1.3%). The acidified serum lysis test was negative. The cold antibody lysis test was again positive in November 1971, as was the sugar lysis test (2.2%), but on this occasion the acidified serum lysis was also positive (9%) (see chart). This test was positive, however, with some, but not all, of the sera tested, and it was negative with the patient's own serum.

The most unusual feature in the present patient was the development of a positive acidified serum lysis test. Less specific tests for paroxysmal nocturnal haemoglobinuria—namely, the sucrose and cold antibody lysis test—have been found to be positive in some patients with lymphoproliferative or myeloproliferative diseases (Catovsky *et al.*, 1971) but in none of these patients was the acidified serum lysis test positive, and we are not aware of any detailed reports of a positive acidified serum lysis test occurring in a patient with a lymphoproliferative disease.

It should be noted, however, that the positive acidified serum test was not characteristic of paroxysmal nocturnal haemoglobinuria in that it was negative with the patient's own serum. This suggests that the lysis is more likely to have been due at least in part to antibody sensitivity rather than

Haematological response of patient during course of disease. RT = Radiotherapy.

Comment

Three features of this case deserve special mention—namely, the autoimmune haemolytic anaemia, hypogammaglobulinaemia, and the development of a positive acidified serum test. Autoimmune haemolytic anaemia is well recognized in association with chronic lymphocytic leukaemia and other lymphoproliferative disorders (Dacie, 1967). The direct antiglobulin test remained strongly positive throughout the course of his illness and was not apparently altered by treatment or by clinical remission. Early in the course of the present patient's illness overt haemolysis developed which was unaffected by steroids and could be controlled only by splenectomy. Hypogammaglobulinaemia, which is frequently found in chronic lymphocytic leukaemia, is also a feature of some cases of "idiopathic" autoimmune haemolytic anaemia (Blajchman *et al.*, 1969).

The presence of two distinct lymphoid cell populations—one mature and one immature—in the peripheral blood, bone marrow, and lymph nodes suggests that more than one clone of leukaemic lymphocytes were present in this patient. The predominantly mature lymphocytic population decreased in number in peripheral blood and bone marrow as the disease progressed, perhaps as a response to treatment; then the poorly differentiated lymphoid cells became the predominant cell line.

to complement sensitivity. This is similar to the finding in congenital dyserythropoietic anaemia (Crookston *et al.*, 1969). The onset of a positive test, together with increased lysis by cold antibody and a positive sucrose lysis test, appeared to coincide with a change in the nature of the disease from a benign lymphoproliferative process to a more malignant drug-resistant one. A similar sequence of events has been seen in a patient who developed myelomonocytic leukaemia after chronic lymphocytic leukaemia (Catovsky *et al.*, 1971). The changing pattern of lysis supports the premise of the development of an abnormal clone of erythroid cells. This might be due to the disease itself or to bone marrow damage from alkylating agents or ionizing radiation (Dameshek, 1967), both of which the patient had received in the course of treatment.

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