CASE REPORT

Autoimmune Hemolytic Anemia in Chronic Granulocytic Leukemia

By NORMAN I. MALDONADO, JENARO HADDOCK AND ENRIQUE PÉREZ-SANTIAGO

AUTOIMMUNE HEMOLYTIC ANEMIA may complicate a wide variety of diseases, among which are infectious diseases, "collagen" diseases, benign tumors, malignant tumors, lymphomas and Hodgkin's disease.1,2 The lymphoproliferative disorders, especially chronic lymphatic leukemia, have often been associated with abnormal immunologic mechanisms. The myeloproliferative disorders are rarely associated with similar disorders, except perhaps in the Di Guglielmo syndrome, in which immunologic abnormalities have recently been described.3 The occurrence of autoimmune hemolytic anemia has been described in very few cases of chronic granulocytic leukemia.4,5 It is our purpose to report the occurrence of autoimmune hemolytic anemia with the presence of warm agglutinins in a patient with Ph1 positive chronic granulocytic leukemia.

CASE REPORT

J.L.S. was an 84-year-old white man seen at the O.P.D. of the University Hospital in April 1965; he complained of weakness, epigastric fullness and urinary symptoms. He was seen in the urology clinic and an intravenous pyelogram revealed a large spleen, for which he was referred to the hematology clinic. Hb was 8.2 Gm. per 100 ml. and the WBC count was 130,000 with 3 promyelocytes, 8 myelocytes, 26 juveniles, 30 stabs, 27 segmented, 3 lymphocytes, 2 eosinophils and 1 basophil. The platelet count was 92,000. Bone marrow examination showed striking granulocytic hyperplasia. The leukocyte alkaline phosphatase score was zero. The urinalysis revealed pyuria and microscopic hematuria. The fasting blood sugar and the blood urea nitrogen were normal. A chest x-ray was normal and an electrocardiogram showed a right bundle branch block.

The patient was placed on 8 mg. of busulfan (Myleran) daily and his symptoms improved. After 6 weeks the WBC count was 3900 and the medication was discontinued. Two months later the WBC count rose to 20,800; however, the hemoglobin was 7 Gm. per 100 ml. One unit of packed red cells was given and busulfan, 4 mg. daily, was resumed. After a few months gastrointestinal symptoms developed whenever the patient took busulfan, and the drug was discontinued. Ten months after diagnosis, the WBC count was 69,000, and 6 mg. of busulfan was given daily together with antiemetics and antispasmodics. During the next 2 months he improved and the WBC count dropped to 9200, following which all medication was discontinued. One month later, the WBC was 64,000 and busulfan was again administered for the fourth time. During the next week anorexia,
nausea, vomiting, weakness and icteric sclerae developed. When seen in the clinic he was jaundiced and had pale mucous membranes. The spleen was 8 cm. below the left costal margin and the liver, which had not been felt previously, was 5 cm. below the right costal margin.

The peripheral smear showed leukocytosis, thrombocytopenia, increase in atypical lymphocytes, spherocytosis and polychromatophilia. The hemoglobin was 7 Gm. per 100 ml. the platelets were 38,000, the reticulocyte count was 24 per cent, and the direct Coombs' test was positive. The patient was hospitalized. There was difficulty in cross matching, which was overcome when done at 37 C. When the hematocrit dropped to 15 per cent, he was given 500 cc. of packed cells and 100 mg. of hydrocortisone intravenously.

The laboratory studies prior to the transfusion revealed a total bilirubin of 2 mg. with 1.5 mg. indirect, the SCOT was 13.5 units, SGPT was 10 units, alkaline phosphatase was 22 K.A units, and uric acid was 8.7 mg. per cent. A repeat bone marrow showed granulocytic hyperplasia and the peripheral blood leukocyte alkaline phosphatase was again zero. Chromosome studies from a direct bone marrow preparation revealed a normal modal number of 46 chromosomes with a minute acrocentric Ph' chromosome in most metaphases studied. The direct and indirect Coombs' tests were positive. A cold hemagglutinin titer was 1:8 using the patient's own red cells. Elution of the antibody from the patient's red cells showed a warm nonspecific panagglutinin. A serum protein electrophoresis revealed 55.5 per cent albumin, 4.2 per cent alpha 1, 5.1 per cent alpha 2, 10.6 per cent beta, and 24.6 per cent gamma globulin. Quantitative immunoglobulin studies showed IgG 701 mg. per cent, IgA 260 mg. per cent, and IgM 145 mg. per cent.

The patient was placed on 50 mg. of prednisone, 6 mg. of Myleran, and 300 mg. of isoniazid. Because of gastrointestinal intolerance the Myleran was discontinued. The Hb increased to 8.9 Gm. per 100 ml. and the reticulocyte count dropped to 4 per cent during the next month. The spleen decreased in size and there was marked symptomatic improvement. A red blood cell survival with Cr6' was normal one month after the onset of the hemolytic anemia, with a T 1/2 of 32 days. The Coombs' test was still positive. The prednisone was tapered and he was discharged to be followed at the clinic. The leukocyte count remained about 69,000 during the prednisone therapy.

One month after discharge, the patient developed acute bronchitis and was given tetracycline and continued on 20 mg. of prednisone. He did not improve and became dyspneic and agitated. He was brought to the emergency room but died before treatment could be instituted. At autopsy he presented pulmonary fibrosis, acute bronchopneumonia, pulmonary edema, and extensive coronary arteriosclerosis with myocardial fibrosis. The liver and spleen were enlarged. The kidneys showed nephrosclerosis and amyloid degeneration. Diffuse petechial hemorrhages were present in the brain. Histologic examination confirmed the diagnosis of chronic granulocytic leukemia and failed to reveal any additional neoplasm.

**Comments**

The patient described had chronic granulocytic leukemia, as indicated by the history, physical findings, elevated leukocyte count with immature forms, a score of zero in the leukocyte alkaline phosphatase test, and a Ph1 chromosome. He developed severe gastrointestinal reactions with each course of busulfan administration. Eventually, following one of these reactions, the anemia became severe and was associated with a positive Coombs' antiglobulin test. There was no evidence of any viral illness when he developed the hemolytic anemia, and at autopsy a second neoplasm was not found.

The anemia in chronic granulocytic leukemia is usually associated with a slight decrease in red cell survival, generally in the presence of marked splenomegaly. The Coombs' test is almost invariably negative.

Autoimmune hemolytic anemia was reported by Videbaek in two patients.
among 27 cases of chronic granulocytic leukemia. His first patient had a moderately positive Coombs' test and his second case showed a weakly positive antiglobulin test. In both instances this complication developed when there was a transition of the chronic process to an acute one or shortly before it. Osgood reported one instance of AIHA among 48 patients with chronic myelogenous leukemia. In 18 patients, Finkel et al. found no erythrocyte autoantibodies. Dameshek has seen one instance of AIHA in chronic myelogenous leukemia.

The occurrence of paraproteinemia or monoclonal gammopathy in chronic granulocytic leukemia is also a rare occurrence, but a few such cases have been reported. Hypergammaglobulinemia is not such a rare finding. Although we can draw no conclusions from one isolated observation, it is our purpose to call attention to the fact that autoimmune phenomena may occur in another disease of the myeloproliferative group. In the present case, it may have been initiated by the chemotherapeutic agent busulfan, to which the patient showed unusual sensitivity. It also seems that prednisone was able to control the moderate hemolytic process without an adverse effect on the granulocytic proliferation.

**SUMMARY**

A patient with chronic granulocytic leukemia developed autoimmune hemolytic anemia. He was found to have a cold agglutinin and a nonspecific warm panagglutinin. Therapy with prednisone appeared to control the hemolytic crisis and did not affect the granulocytic process. The patient died of bronchopneumonia, and at autopsy no other neoplasm was found.

**SUMMARIO IN INTERLINGUA**

Un patiente con chronic leucemia granulocytic disveloppava autoimmun anemia hemolytic. Esseva constatate que ille possedeva un cryoagglutinin e un nonspecific thermopanagglutinin. Le administration therapeutic de prednisona pareva dominar le crises hemolytic e non afliceva le processo granulocytic. Le patiente moriva de bronchopneumonia. Al necropsia, nulle altre neoplasma esseva trovate.

**ACKNOWLEDGMENT**

The authors are grateful to Mrs. Jean Fradera and Dr. Antonio Barquet for the antibody studies and to Dr. William Dameshek for suggestions as to the management of this patient.

**REFERENCES**

AUTOIMMUNE HEMOLYTIC ANEMIA IN LEUKEMIA

Mechanisms of anemia in leukaemia.
Case Report: Autoimmune Hemolytic Anemia in Chronic Granulocytic Leukemia

NORMAN I. MALDONADO, JENARO HADDOCK and ENRIQUE PÉREZ-SANTIAGO