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Severe Coombs Negative Hemolytic Anemia in Hepatitis B

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ALTHOUGH 25 PERCENT of patients with viral hepatitis have a slightly shortened erythrocyte survival time, severe hemolytic anemia rarely complicates viral hepatitis in the absence of preexisting red cell defects or chronic liver disease. Only six such cases have been reported. The purpose of this report is to describe the clinical course and management of a patient with hepatitis B who did not have congenital red cell enzyme deficiency or a membrane defect but in whom severe Coomb's negative hemolytic anemia and renal dysfunction developed.

Report of a Case

A 17-year-old white girl was transferred to the University of California, Los Angeles, Center for Health Sciences (UCLA-CHS) because of intense jaundice, severe pruritus and a profound hemolytic anemia. She had been well until five weeks before admission when an urticarial rash developed. Fourteen days later she had been admitted to another hospital because of jaundice, fever, chills, nausea and vomiting. The patient was known to use intravenous narcotics and hallucinogenic drugs, but had been receiving no other medications.

On physical examination, the patient was seen to be jaundiced. The liver was tender and had a span of 15 cm in the right midclavicular line. Laboratory studies showed the following values: serum glutamic oxaloacetic transaminase (SGOT), 8,320 international units (IU) (N=20-55); alkaline phosphatase, 290 IU (N=45-105); total bilirubin, 9.6 mg per dl (N <1.2)—direct fraction 8.0 mg per dl (N <0.35), and positive hepatitis B surface antigen (HBsAg) by radioimmunoassay. The patient was discharged after six days when nausea and vomiting stopped.

Three days after discharge the patient was readmitted because of increasing jaundice. Liver function studies showed the following values: SGOT, 678 IU; serum glutamic oxalic transaminase (SGPT), 780 IU (N=10-40); total bilirubin, 21.4 mg per deciliter; direct bilirubin, 11.4 mg per dl; prothrombin time, 100 percent of control. The hematocrit reading was 29 percent; leukocyte count was 4,900 per cu mm. Results of examination of a percutaneous liver biopsy specimen showed a mononuclear cell infiltrate in the portal tracts, lobular disarray, and some peripheral collapse. The next day the hematocrit reading decreased to 17.5 percent, the bilirubin value increased to 49 mg per dl and SGOT decreased to 113 IU. Other study findings included direct and indirect Coombs test, negative; glucose-6-phosphate dehydrogenase (G6PD), level normal, and reticulocyte count, 0.6 percent. Eight units of packed cells were transfused during the next 12 days to prevent severe anemia.

On physical examination after transfer to UCLA-CHS, the patient was found to be depressed and deeply jaundiced. A macular rash was noted on one arm. The abdomen was soft and not tender, the liver span measured 15 cm at the right midclavicular line and the tip of the spleen was palpable. Laboratory studies showed the following values: total bilirubin, 29.0 mg per dl—direct fraction 21.0 mg per dl; SGOT, 185 IU per liter; SGPT, 160 IU per liter; alkaline phosphatase, 280 IU per liter; total protein, 7.0 grams per dl; albumin, 4.2 grams per dl; prothrombin time, 11.5 seconds—control 11.6 seconds; HBsAg positive by radioimmunoassay; hemoglobin, 9.9 mg per dl; hematocrit, 28.4 percent; reticulocyte count, 0.4 percent; a leukocyte count of 5,400, 59 percent segmented cells, 7 percent band cells, 4 percent eosinophils, 16 percent lymphocytes, 9 percent monocytes and 5 percent metamyelocytes; a platelet count of 410,000; results of direct and indirect Coombs' tests, negative by standard clinical laboratory techniques; serum haptoglobin, 0 (N=20-200); plasma hemoglobin, 14.9 mg per dl (N <0.9); G6PD spot test, normal; monospot test, negative; serum iron, 137 micrograms (μg) per dl (N=65-175); total iron binding capacity, 318 μg per dl (N=250-400); serum

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folate, 19 ng per ml (N=5.6-21); serum vitamin B_{12}, 747 pg per ml (N=330-1,025); BUN 43 mg per dl (N=9-20); creatinine, 2.3 mg per dl (N=0.7-1.3); creatinine clearance, 35 ml per minute.

Dipstick examination of the urine for hemoglobin (Bibilastix®, Ames Co., Eckhart, Indiana) indicated the presence of a large amount. Examination of bone marrow aspirate showed notably increased erythroid elements. Examination of peripheral blood smears showed polychromasia and basophilic stippling of red blood cells, lymphocytes appeared normal. Sucrose hemolysis screen was negative. Red cell half life was 10 to 12 days determined by ^{51}Cr tagging technique.

Although reticulocytosis appeared on the patient's third hospital day, the hematocrit reading decreased from 28 to 16 percent during the first week and then began to increase; transfusion was not carried out. The reticulocyte count increased from 0.7 to 24 percent. Renal tubular dysfunction due to hemoglobinuria was treated with 3,000 ml per m^2 of surface area per day of intravenously given 5 percent solution of dextrose in water containing 50 milliequivalents per liter of sodium bicarbonate ($NaHCO_3$) to alkalinize the urine.

Eighteen days after admission, repeat studies gave the following values: SGOT, 65 IU per liter; total bilirubin, 5.0 mg per dl—direct bilirubin, 4.0 mg per dl; hemoglobin, 8.1 grams per dl; hematocrit reading 23.4 percent; serum hemoglobin, 0, blood urea nitrogen (BUN), 19 mg per dl, and creatinine, 1.6 mg per dl.

The patient was seen one month after discharge. She was asymptomatic and findings on physical examination were normal. Finding from laboratory studies included: SGOT, 32 IU per liter; SGPT, 44 IU per liter; alkaline phosphatase, 122 IU per liter; total bilirubin, 1.0 mg per dl; hematocrit reading, 34.6 percent; haptoglobin, 121 mg per dl; reticulocyte count, 1.6 percent, and creatinine, 1.0 mg per dl.

Discussion

Acute severe hemolytic anemia is a very rare complication of acute viral hepatitis in the absence of chronic liver disease or preexisting hemolytic disorder. Oesman[1] reported the case of a 6-year-old child in whom the hemoglobin value decreased to 6.0 grams per dl with viral hepatitis. In this case the indirect Coombs' test gave positive findings and the marrow appeared hyperplastic. Raffensperger[2] reported three cases of viral hepatitis in which results of direct Coombs' tests were negative for hemolytic anemia. Two of the three patients were children and in one of them there was histologic evidence of chronic liver disease. Wagner[3] reported the case of an 18-year-old patient in whom results of direct Coombs' tests were hemolytic positive for hemolytic anemia and in whom a prolonged aplastic phase occurred which required multiple transfusions. Hansbarger[4] reported two cases, both with negative findings on Coombs' tests, in which the hemoglobin decreased to 5.0 and 5.9 grams respectively. Erythroid hyperplasia was observed on marrow aspiration.

Severe hemolytic anemia is a more frequent complication of viral hepatitis in patients with glucose-6-phosphate dehydrogenase deficiency, beta thalassemia and congenital nonspherocytic anemia.[5-7]

Subclinical hemolysis has been shown to occur in 25 to 50 percent of patients with uncomplicated viral hepatitis.[8] The hematocrit reading is often slightly decreased during the second and third weeks of jaundice.[9] Reticulocytosis follows the onset of the decreased hematocrit by approximately one week. This delay is due to marrow suppression caused by hepatitis. The cause of the hemolysis is unknown. It occurs with both homologous and autologous cells to the same degree, implicating an extracorpuscular factor. This could be due to circulating antibodies or to a direct effect of the virus upon the red cell. This phenomenon usually lasts for one to two months but may persist for up to two years.[7]

Our case is similar to the others in which severe hemolysis was present. The severity of the hemolysis was not related to the degree of hepatitis. Hemolysis persisted for six weeks before the hemoglobin and hematocrit values began to increase. The patient's complete recovery, with normal haptoglobin and reticulocyte count, is evidence against preexisting hemolytic disease. The contributions of marrow suppression to our patient's anemia is difficult to assess because bone marrow aspiration was carried out late in the course of her disease.

Hemolysis of transfused packed red blood cells may have temporarily worsened this patient's condition. Transfusion should be given in such patients only when symptoms develop due to the anemia because the increased hemolysis may result in hemoglobinura and renal failure. The decrease in creatinine clearance in our patient

most likely resulted from the hemoglobinuria. Generous hydration and alkalinization of the urine are then necessary to prevent precipitation of casts and resulting renal damage.

ADDENDUM: Additional follow-up studies could not be made in the case discussed because the patient was killed in an automobile accident one month after her last visit to the clinic.

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Mucocutaneous Lymph Node Syndrome with Encephalopathy in the Continental United States

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RECENTLY, three papers have appeared in the pediatric literature calling attention to acute febrile mucocutaneous lymph node syndrome (MLNS),[1-3] an illness that previously had been seen only in Japan and Hawaii. This illness is an acute febrile mucocutaneous condition accompanied by swelling of cervical lymph nodes. Fatalities were reported in 1 to 2 percent of cases.[1] In each instance, the cause of death was proved to be myocardial infarction secondary to coronary thromboarteritis. The findings were almost indistinguishable from those of infantile polyarteritis nodosa.[4] Fetterman and Hashida[5] commented, "Whether or not MLNS is a problem of any degree in the continental United States . . . should become apparent within the next year or so." Reported here is a case of MLNS that occurred in the San Francisco Bay Area in May 1975. The illness was consistent with that described by Kawasaki and colleagues[1] on the basis of their experience, their review of the Japanese literature, findings from a Japanese public health survey that included nearly 4,000 cases and their awareness of more than 6,000 cases reported up to 1973. An additional manifestation in the infant described here was focal encephalopathy.

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Report of a Case

An 8-month-old white girl was admitted to Kaiser Foundation Hospital, Santa Clara, California, on May 25, 1975 because of high fever, seizures, apnea, rash and diarrhea. On May 19 (four days before admission), ampicillin had been given for an ear infection. When the infant was seen as an outpatient on May 24 (one day before admission), fever, a macular rash on the arms and diaper area, and conjunctival injection were noted. Because measles was suspected, the ampicillin was discontinued. On May 25, before the patient was admitted to hospital, four generalized tonic-clonic seizures and a period of apnea necessitating resuscitation had occurred.

When admitted the patient was comatose and febrile, and a generalized macular morbilliform rash was seen to be present. Noted were conjunctival injection, erythema of the buccal and pharyngeal mucosa, swelling and prominence of the tongue papillae simulating strawberry tongue, and cervical lymphadenopathy. The liver edge was palpable 4 cm below the costal margin. The palms of the hands and soles of the feet were erythematous. The present illness was considered to have started May 22, the first day of fever. The clinical features and the duration of each are shown in Figure 1. Details not evident from the figure are given below.

From the 1st day of illness through the 18th,