Medical Memoranda

Lymphosarcoma with a Positive Paul-Bunnell Test

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This case is reported because the findings of a positive Paul-Bunnell test delayed the relevant treatment for the patient's real illness. It also illustrates the point that a negative biopsy specimen from one area of the pathological tissue does not always exclude malignancy in other areas. On reviewing the literature we were unable to find previous reports of lymphosarcoma presenting with a positive Paul-Bunnell test.

Case Report

A 71-year-old woman originally presented at the outpatient department on 25 October 1967 with a six-weeks history of sore throat, general malaise, and cervical adenopathy. Examination showed enlarged, ulcerated tonsils and pharyngitis. Tonsillar biopsy showed no evidence of malignancy and a Paul-Bunnell test was positive (titres: unabsorbed serum 1/224, absorbed with guinea-pig kidney 1/224, absorbed with ox red cells 1/14). When seen again on 9 November she was subjectively much improved, but bilateral axillary nodes were noted. By 30 November she was much worse and gave a four-days history of pale stools, dark urine, and coffee-ground vomit. She was admitted for further investigation. On examination she was clinically jaundiced and dehydrated, with enlarged cervical, axillary, and groin nodes and a palpable liver.

Investigations.—Repeat Paul-Bunnell test negative (titres: unabsorbed 1/14, with guinea-pig kidney less than 1/71, with cells 1/14); alkaline phosphatase 68 units/100 ml.; serum alanine aminotransferase 64 milliunits/100 ml.; bilirubin: total 3-9 mg./100 ml., direct 3-4 mg./100 ml.; serum protein electrophoresis: reduced albumin, increased alpha-2 globulin; chest and skull x-ray examination showed nothing abnormal; haemoglobin 11.8 g./100 ml.; total white count 19,000/cu. mm., normal differential; E.S.R. 81 mm./hour; sternal marrow: atypical cells similar to those seen in virus infections, but multiple prominent nucleoli suggest reticulosarcoma cells; blood sugar 123 mg./100 ml.; protein-bound iodine 30 mcg./100 ml.; cholesterol 170 mg./100 ml.

The patient's clinical deterioration, together with the now negative Paul-Bunnell test and marrow appearances, threw suspicion on the diagnosis of infectious mononucleosis. She became worse over the next 48 hours, and in spite of treatment with intravenous fluids, chloramphenicol, steroids, and digoxin she died on 5 December.

At necropsy enlarged lymph nodes were present in the neck, the hilum of both lungs, the coeliac axis region, and in the abdominal para-aortic region. The nodes were soft and greyish and measured up to 3 cm. in diameter. The spleen was slightly enlarged (300 g.), and its cut surface displayed a uniform pink colour. Microscopical examination of the lymph nodes from the cervical, mediastinal, abdominal para-aortic, iliac, and inguinal groups showed complete destruction of the normal architecture and a replacement by diffusely arranged, poorly differentiated cells of the lymphocytic series. The appearances were those of a malignant lymphoma of poorly differentiated lymphocytic ("lymphoblastic") type. There was infiltration of the spleen by tumour cells, and deposits of tumour were also found in the lingual tonsils, in the bladder, in the portal tracts of the liver, and beneath the mucosa of the larynx, epiglottis, and stomach. The lungs showed bronchopneumonia, which was the immediate cause of her death.

Comment

A positive Paul-Bunnell test is widely assumed to be specific for glandular fever, though it can occur in Hodgkin's disease. This patient presented with cervical adenopathy, ulcerated tonsils, a negative tonsillar biopsy, hepatitis, and a positive Paul-Bunnell test. Even in retrospect a clinical diagnosis of infectious mononucleosis seems justified. Only when her clinical condition deteriorated was the diagnosis questioned. There are three possible explanations of the above facts. Firstly, the patient may have had true infectious mononucleosis coincidentally followed by lymphosarcoma. This is unlikely, because the lymph nodes, clinically swollen in the cervical region since the onset of the disease, were shown at necropsy to be due to lymphosarcoma. Secondly, the patient may simultaneously have had both glandular fever and lymphosarcoma. This possibility cannot be absolutely refuted, but with the above findings it seems extremely unlikely. Thirdly, this could have been a true lymphosarcoma presenting with a positive Paul-Bunnell test. It is submitted that this latter explanation is the most likely in this case.

We would like to thank Mr. H. J. Shaw and Dr. P. E. Thompson Hancock for permission to report this case, and Dr. Beryl Jameson for laboratory assistance. We are particularly indebted to Dr. Noel Gowing for his comments on the pathological aspects of this case.

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Ulcerative Colitis with Autoimmune Haemolytic Anaemia

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The association of autoimmune haemolytic anaemia with ulcerative colitis is uncommon, and only five cases, all female, have been reported in detail (Lorber, Schwartz, and Wasserman, 1955; Fong, Fudenberg, and Pearlman, 1963). Many of the complications of ulcerative colitis may be explained on an immunological basis (Anderson, Buchanan, and Goudie, 1967), and we have therefore studied a further case serologically in an attempt to establish a relation between the two conditions.

Case Report

A 23-year-old woman was admitted to hospital on 22 November 1967 with a one-week history of breathlessness, fainting, and headache. She was seven weeks postpartum and her haemoglobin at the end of pregnancy had been 10.5 g./100 ml. (72%). The delivery and puerperium were normal. In 1965 a diagnosis of ulcerative proctocolitis involving the rectum and sigmoid had been made and she had been treated with sulphasalazine and prednisolone enemas.
She discontinued treatment after a few weeks, though she continued to have mild intermittent rectal bleeding but no diarrhoea.

On admission she appeared severely anaemic and slightly icteric. The spleen was not palpable. The urine contained a marked excess of urobilinogen; bilirubin was absent. The haemoglobin was 4·4 g./100 ml. (30%) and the blood film showed marked polychromasia, numerous microspherocytes, and occasional nucleated red cells. The reticulocyte count was 52% and the serum bilirubin 3·7 mg./100 ml. The direct Coombs test was positive and the gammaglobulin neutralization test showed that the antibody on the cells was of the “warm” or gammaglobulin variety. The white cell count was 19,000/cu.mm. and the platelet count 235,000/cu.mm. The E.S.R. was 166 mm. in one hour. Repeated examinations for I.E. cells and for antinuclear factor were negative.

Shortly after admission she developed a rectal haemorrhage. Sigmoidoscopy and barium enema showed the changes of ulcerative proctocolitis as far as the sigmoid colon.

Treatment was started with systemic and rectal steroids and with blood transfusions. The clinical course is shown in the Fig. On discharge the reticulocyte count was 5%; the serum bilirubin was 0·3 mg./100 ml., and the direct Coombs test was weakly positive.

SEROLOGICAL INVESTIGATIONS

The patient's red cells were group A subgroup A1 Rh-positive (Rho positive). When her serum was tested against a comprehensive panel of red cells no reactions occurred at 10 or 15° C., but at 37° C. all the cells in the panel reacted positively by the papain and anti-globulin methods. The reactions were weaker with RbRs and Rb cells, suggesting a predominantly anti-D specificity. It was not possible to elute an antibody from the patient's red cells.

The rheumatoid arthritis latex fixation test was weakly positive and the Rose-Waaler test showed agglutination of sheep red cells sensitized with rabbit antibody at a titre of 1:512 and of unsensitized sheep red cells at a titre of at least 1:128; this result was interpreted as negative for rheumatoid factor. The agglutination of sheep red cells did not appear to be attributable to the heterophile antibody that is associated with infectious mononucleosis, as the screening test for this antibody, using formalized horse red cells, was negative.

Because the patient's serum agglutinated both human and sheep red cells cross-absorption studies were performed. They showed that the antibodies concerned were separate; absorption of the patient's serum with human e-positive cells did not alter its antibody titre against sheep red cells, and conversely absorption with sheep red cells did not alter its titre against human cells. In order to determine to which classes of immunoglobulins the two antibodies belonged the patient's serum was fractionated on Sephadex G 200. Agglutinating activity for sheep red cells was found only in the IgM fraction. When the various fractions were tested against human e-positive and e-negative papainized cells no agglutination was detected, but haemolysis localized to the IgM-containing region occurred while the test was standing overnight. On subsequent testing the whole serum gave no reaction with papainized cells, but it had by this time been frozen and thawed several times, a procedure which has been found particularly detrimental to IgM antibody activity in other systems. It was concluded that both antibodies were macroglobulins.

Fluorescent antibody tests for the presence of antibody to a variety of antigens were carried out on cryostat sections of snap-frozen tissues. These comprised rat colon, kidney, diaphragm, stomach, liver, and spleen, and calf and human thyroid. The patient's serum was tested at a dilution of 1:10 and the fluorescent conjugate used was specific for human IgG. All these tests were negative.

COMMENT

At least four possible mechanisms for autoimmune haemolysis in ulcerative colitis have been suggested: (1) Colitic bowel absorbs antigenic substances from the lumen that are not normally absorbed and that are similar to antigens on the red cells. These substances give rise to antibodies which react with the red cells (Lorber et al., 1955). (2) Colitic bowel contains an antigen or hapten which is also present on the patient's red cells. In ulcerative colitis autoantibodies are formed which react at both sites (Lorber et al., 1955). (3) Colitic bowel absorbs patient's blood from the lumen and this blood is altered in some way so as to become autoantigenic. The antibodies formed react with circulating red cells (Balint, Hammack, and Paton, 1962). (4) The bowel lesion in ulcerative colitis is only one expression of a basic immunological defect. Manifestations such as hepatitis, arthritis, spondylitis, iritis, erythema nodosum, and autoimmune haemolytic anaemia are other expressions of this defect (Fong et al., 1963).

Our findings are in accord with the first of these four propositions. It is known that certain antigens of colonic bacteria are shared with sheep red cells (Trentin, 1967), while others are shared with human red cells (Springer et al., 1961). A possible explanation for the presence of antibodies to human and sheep red cells in our case is that bacterial antigens were absorbed by colitic bowel.

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