Medical Memoranda

Cytomegalic Inclusion-Body Disease Associated with Acquired Autoimmune Haemolytic Anaemia

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Cytomegalic inclusion-body disease is not uncommon in neonates and young children but has only occasionally been diagnosed in adults. The infection in children is usually restricted to the salivary glands, but may become generalized and lead to hepatosplenomegaly, thrombocytopenia, and jaundice, and, in those who survive, to microcephaly and mental retardation. In the adult the generalized disease has been reported principally as a terminal event in various debilitating conditions (Wong and Warner, 1962).

Recently, however, it has been suggested that an illness resembling infectious mononucleosis (Klemola and Kääriäinen, 1965), and also three cases of hepatitis (Lamb and Stern, 1966; Toghill *et al.*, 1967), all occurring in adults, may have been due to cytomegalovirus. In addition Zuelzer *et al.* (1966) have suggested that some cases of acquired haemolytic anaemia in children were due to cytomegalovirus. A case is here reported in which cytomegalic inclusion-body disease was associated with an acquired autoimmune haemolytic anaemia in an adult.

Case Report

A 45-year-old man was admitted to University College Hospital on 6 October 1967 from St. Albans City Hospital, where he had been admitted and treated for anaemia. On 13 April 1965 he had given a history of tiredness for a year, intermittent diarrhoea for four months, and slight jaundice for four days. There was no history of previous jaundice, injections, transfusions, or significant medication. On examination his liver edge was just palpable and his spleen was palpable two finger-breadths below the costal margin.

Investigations.—The haemoglobin, which had been 7.9 g./100 ml. on 8 April 1965, had fallen to 5.5 g./100 ml. on his admission five days later, and his reticulocyte count at that time was 1%. The anaemia was normocytic and normochromic. The erythrocyte sedimentation rate was 120 mm. in one hour (Westergren). Total serum bilirubin was 1.5 mg./100 ml., with a negative direct van den Bergh reaction. Other liver function tests were normal. Serum B_{12} and folate levels were normal and acid was present in an augmented test meal. The urine did not contain haemoglobin or urobilinogen and there was no occult blood in the faeces. The fat and urobilinogen content of the faeces was normal. The Paul–Bunnell, Coombs, and Schumm tests were all negative and no cold agglutinins or lupus erythematosus cells were detected in the blood. The sternal marrow was reported to show erythroid hyperplasia with a maturation arrest.

After transfusion with 7 pints (4 l.) of blood the patient's haemoglobin rose to 8.2 g./100 ml. with a reticulocyte count of 6.7%. As this level of haemoglobin was maintained he was discharged on 4 May feeling well and afebrile.

On 15 August 1967 he was readmitted to St. Albans City Hospital with a story of tiredness for three weeks and dark urine for one week. Four days before admission he had a febrile attack and had noticed that he was yellow. His liver was palpable at three finger-breadths below the costal margin and his spleen was just palpable.

Investigations.—Haemoglobin was 3.7 g./100 ml. with 2.8% reticulocytes on admission. Electrophoresis did not show any abnormal haemoglobin, and blood cultures remained sterile after three weeks' incubation. Total serum bilirubin was 5.2 mg./100 ml., of which 1.6 mg./100 ml. was conjugated. Other liver-function tests were again normal. Both bilirubin and urobilinogen were present in the urine. The patient's cells were positive to the direct Coombs test, reacting strongly with a broad-spectrum anti-human globulin but not with an anti-7S gammaglobulin reagent. The patient's serum was reported as containing a pan/autoagglutinin detectable at 37° C. by Coombs and enzyme techniques. The antibody could not be shown to have any specificity for the e or I antigens. Ham's acid serum test and the Wassermann reaction were negative.

Shortly after admission the patient was transfused and treatment was started with 40 mg. of prednisolone daily. The record of haemoglobin estimations and reticulocyte counts, together with transfusions required for haemolytic crises, are shown in Fig. 1. These transfusions included one of 2 pints (1,140 ml.) of fresh blood on 15 September to help correct a platelet deficiency, the platelet count having been 35,000/cu. mm. on 11 September. On 25 September there was clinical evidence of oropharyngeal moniliasis, and *Candida albicans* was isolated from later throat swabs. Despite treatment with nystatin this infection remained with the patient in varying degrees until his death five weeks later. On 6 October, after his haemoglobin had dropped from 11.8 g./100 ml. to 4.2 g./100 ml. in four days, he was transferred to University College Hospital.

On admission the patient had no lymphadenopathy and his liver was no longer palpable, but his spleen was still enlarged. Treatment was begun with 100 units of A.C.T.H. given intramuscularly twice daily, in addition to 40 mg. of prednisolone daily. He responded temporarily to transfusions, but between 9 and 10 October his haemoglobin fell from 7.3 g./100 ml. to 4.0 g./100 ml. overnight. The total serum bilirubin was 9.6 mg./100 ml., and 5.9 mg./100 ml. was conjugated. The reticulocyte count was zero and the half-life of transfused donor cells tagged with ^{51}Cr was about three days, with radioactivity accumulating excessively in the spleen. An emergency splenectomy was performed.

The excised spleen weighed 1,175 g. and showed extramedullary haemopoiesis and iron deposition but no intranuclear inclusion bodies. A bone biopsy, performed at the same time, was reported to show bony spicules, fatty marrow, and much blood, but no blood-forming elements. With immediate postoperative transfusions the haemoglobin rose to 9.8 g./100 ml. and was maintained at about 10 g./100 ml. without further transfusion.

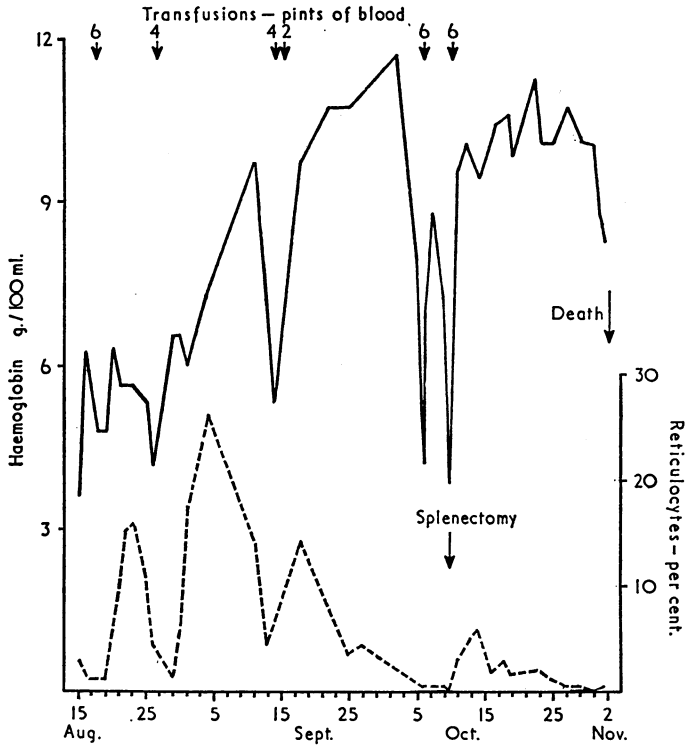

FIG. 1.—Haemoglobin (upper graph) and reticulocytes (lower graph).

The direct Coombs test, which on 6 October had been positive in antihuman globulin diluted to 1 in 32, had by 12 October become negative at all dilutions between 1 in 1 and 1 in 1,024. The haemoglobin level was maintained, but about two weeks after splenectomy the patient developed pyrexia, a cough, and respiratory distress. A purulent bronchitis was treated at first with ampicillin and cloxacillin, with improvement, and later, on deterioration, with gentamicin, benzylpenicillin, and cephaloridine. On 28 October the blood Po_2 fell to 28 mm. Hg, the Pco_2 was 48 mm. Hg, the tidal volume was 800 ml., and the minute-volume was 11 litres. Artificial ventilation was administered after a tracheostomy, but the patient died on the following day, 2 November.

Post-mortem Findings.—The right lung weighed 1,880 g. and the left 1,650 g.; both showed very severe oedema in all lobes, producing a picture of partial consolidation with a partly reddish grey, partly pinkish grey cut surface. Microscopical examination confirmed that very extensive oedema and patches of acute inflammatory infiltrate with numerous hyaline membranes were present in sections of all lobes. In sections from one lobe fungal hyphae which had the appearance of *C. albicans* were seen, but a much more widely disseminated pathogen was the virus of cytomegalic inclusion-body disease. Inclusion bodies were found in all the sections of the lungs that were examined, and "owl's eye" nuclei, typical of cytomegalic inclusion-body disease, were identified (Symmers, 1960). They were mainly intranuclear, but a few were in the cytoplasm. The intranuclear inclusion bodies were amphophilic and were found in cells of the alveolar walls but not in bronchial mucous glands. Similar inclusion bodies were found in the stomach adjacent to an area of ulceration about 2 cm. in diameter, and here they were present in vascular endothelium (Fig. 2).

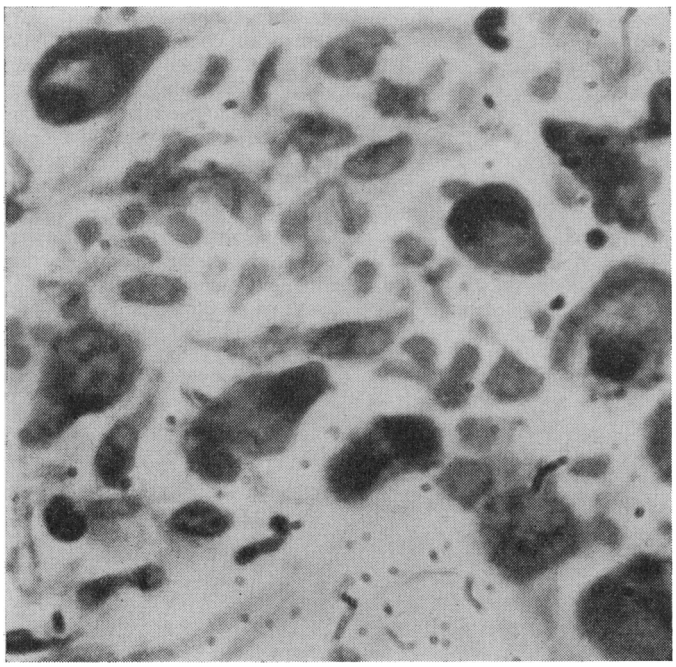

FIG. 2.—Inclusion bodies in vascular endothelium in the stomach. (H. and E. ×1,000.)

Small numbers of inclusion bodies were seen in the adrenals, which showed haemorrhage and congestion but no necrosis. A small number were present in the anterior pituitary. The liver weighed 2,600 g. and was fatty, with iron pigment present in Kupffer and parenchymal cells. The marrow of the femur was fatty throughout almost all of its extent and that of the vertebrae was hypoplastic.

COMMENT

The aetiology of autoimmune haemolytic anaemia is still obscure in many cases, but viral infections are well known to be associated with this type of anaemia and especially with the production of cold antibodies (Dacie, 1962). In the case of cytomegalic inclusion-body disease, Zuelzer *et al.* (1966) have suggested that the presence of viraemia or non-infective viral products in the circulation may be the true cause of the haemolytic process and that the immune phenomena may only be a secondary contributory factor. They describe an association between episodes of lymphadenitis, due to cytomegalovirus, and periods of haemolysis in 22 children with acquired haemolytic anaemia. The children ranged in age from birth to 12 years, and in 18 of them direct antiglobulin tests were positive.

Marked lymphadenopathy was never observed in the present patient and cytomegalovirus was found only after death. The possible correlation between viral activity and the attacks of haemolysis was therefore not investigated. In two adult cases of hepatitis due to cytomegalovirus, Toghill *et al.* (1967) observed episodes of haemolysis, one severe enough to require blood transfusion, but not associated with autoantibodies. In addition, Becker and Eddy (1964) have reported a case in which cytomegalic inclusion-body disease and a poorly differentiated lymphoma were found at the post-mortem examination of a 15-year-old boy with acquired haemolytic anaemia.

The association of cytomegalovirus and haemolytic anaemia in the present patient may, however, have been accidental. Like the *C. albicans*, the virus may have been active only in the terminal stages. It may not have been transmitted to the patient until late in his illness, in the fresh blood used for transfusion on 15 September. This mode of transmission has been suggested for the virus in similar cases (Kääriäinen *et al.*, 1966). On the other hand the cytomegalovirus, like other herpes viruses, is thought to be able to survive latent in the tissues for a considerable time, and latent virus may have been activated by the splenectomy or by the large doses of steroids, A.C.T.H., or antibiotics.

It remains possible that cytomegalovirus may have caused all the attacks of haemolysis in the present patient and cytomegalic inclusion-body disease may be added to the list of infections recognized as causing haemolytic anaemia in the adult. The significance of finding a red cell autoantibody in this disease is debatable. The haemolytic process might be attributed to the presence of this antibody, as has been suggested in the case of the autoimmune haemolytic anaemia complicating other virus infections. Nevertheless, the suggestion made by Zuelzer *et al.* (1966) that the antibody is only a secondary contributory factor in the process deserves further consideration.

My thanks are due to Professor T. A. J. Prankerd for suggesting that this case should be reported and for allowing me to present it. I am also grateful to Dr. E. D. H. Cowen, of St. Albans City Hospital, and to Professor J. F. Smith for the photomicrograph and for permitting me to quote his post-mortem findings.

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