A fatal case of Epstein-Barr virus infection with jaundice and renal failure

M. H. DAVIES
M.B., M.R.C.P.

P. MORGAN-CAPNER†
B.Sc., M.B.

B. PORTMANN
M.R.C.Path.

S. P. WILKINSON*
M.D., M.R.C.P.

R. WILLIAMS*
M.D., F.R.C.P.

*The *Liver Unit, and †Department of Microbiology, King's College Hospital,
Denmark Hill, London SE5 9RS*

Summary

A fatal case of Epstein-Barr virus infection in a 17-year-old male is described. The patient presented with an illness clinically typical of infectious mononucleosis but death followed development of renal failure, jaundice and pulmonary failure. There was no absolute lymphocytosis nor a significant number of atypical mononuclear cells in his peripheral blood. However, heterophile antibody and Epstein-Barr virus-specific IgM were present.

Introduction

A proliferation of T-lymphocytes, directed against virus-determined antigens on the surface of infected B-lymphocytes, is generally held to be responsible for the lymph-node hyperplasia, hepatosplenomegaly and typical blood picture which are found in infectious mononucleosis (Epstein and Achong, 1977). A fatal case of Epstein-Barr (EB) virus infection is described which was associated with jaundice and renal failure, but in which a significant atypical mononuclear cell response was not seen.

Case report

A previously healthy 17-year-old Caucasian male with no relevant family history, presented to his general practitioner with a 10-day history of lethargy, anorexia and sore throat. On examination, severe pharyngitis, palatal petechiae and mild cervical lymphadenopathy were noted. The total WCC was $2.4 \times 10^9/l$ but a differential count was not obtained. The 'Monospot' test was positive. During the next 10 days he became increasingly unwell with deepening jaundice and then oliguria with upper gastrointestinal bleeding. He was

initially admitted to his local hospital and 24 hr later transferred to King's College Hospital. Before hospital admission he had received 4 days' treatment with prednisone 20 mg/day. Prednisone was discontinued on admission and he received no more corticosteroids during his illness.

On admission, he was gravely ill with fever (38.5°C), marked jaundice, and had moderate hepatosplenomegaly. The maximal abnormalities of the liver function tests were: serum bilirubin $530 \mu\text{mol/l}$, alkaline phosphatase 385 i.u./l , aspartate aminotransferase 300 i.u./l and prolongation of the prothrombin time 5 sec. Tests for hepatitis B surface antigen and antibody (by radioimmunoassay) and hepatitis A antibody (by immune electronmicroscopy) were negative.

Oliguria continued with the plasma urea rising to 53.0 mmol/l and the creatinine to $555 \mu\text{mol/l}$ when continuous peritoneal dialysis was commenced. The biochemical findings in the urine were in keeping with acute tubular necrosis (urine sodium 68 mmol/l , urine/plasma osmolality ratio < 1.10).

He developed clinical and radiological evidence of pulmonary oedema, which became progressively more severe, leading to a complete 'white-out' of the lung fields on chest X-ray and to severe hypoxia (Po_2 6.0 kPa). For this he required ventilation which never adequately controlled the hypoxia and the illness culminated in a series of hypoxic cardiac arrests 10 days after admission.

Findings relating to underlying EB virus infection

The leucocyte count fluctuated between 5.8 and $11.1 \times 10^9/l$ but at no time was an absolute or relative lymphocytosis seen and atypical mononuclear cells were never present in a concentration greater than 2% of the total leucocyte count. Cold agglutinins were present in the serum during the first few days

Requests for reprints: Dr P. Morgan-Capner, Department of Microbiology, King's College Hospital, Denmark Hill, London SE5 9RS.

after admission. The 'Monospot' test remained consistently positive as did the Paul-Bunnell test (320, before and after absorption with guinea-pig antigen; 10, after absorption with ox red cell antigen). IgG antibodies to EB virus capsid antigen were positive to a titre of 512 and specific IgM was found to be present after density gradient fractionation. The complement fixation titre against cytomegalovirus (CMV) was 8 and culture of the urine for CMV was negative.

Post-mortem findings

The liver was markedly enlarged (4000 g). Immediate post-mortem needle liver biopsy showed preservation of the normal architecture with minimal hepatic cell necrosis although ballooning of many hepatocytes was present (Fig. 1). A prominent cellular infiltrate consisting of both mononuclear and polymorphonuclear leucocytes was present within the portal tracts and dilated sinusoids, but no atypical cells were seen. Moderate splenomegaly (750 g) and cervical and mediastinal lymphadenopathy were also found at post-mortem although severe autolytic changes prevented accurate histological categorization of the cellular infiltrates seen in these tissues and the interpretation of electron microscopy sections. The lungs were congested with patchy haemorrhages, focal pneumonia and extensive non-aerated areas. Histology showed intra-alveolar haemorrhages, fibrin, epithelial debris and a patchy, minimal infiltrate of mononuclear and polymorphonuclear leucocytes.

Fig. 1. Kupffer cell activation and prominent sinusoid mixed cell infiltrate in absence of significant liver cell damage (HE, $\times 250$).

Discussion

The virological studies in this case strongly suggest the cause of the illness to have been an EB virus infection. The factors that contributed to death were a combination of hepatic dysfunction, renal failure and severe pulmonary oedema. Minimal hepatic damage is common in infectious mononucleosis, although fatal hepatic necrosis is rare. In 2 of 3 previously reported cases of hepatic and renal failure associated with EB virus infection (Adkins and Steele, 1977; Chang and Campbell, 1975; Crawford *et al.*, 1979) the degree of hepatic necrosis appears to have been more severe than in this case.

An unusual feature of the present case of EB virus infection was the absence of an absolute lymphocytosis or a significant number of atypical mononuclear cells. Smith and Denman (1978) suggest that a failure to develop atypical mononuclear cells during EB virus infection indicates a defect in cell-mediated immunity. Unlike the case described by Smith and Denman, however, there was nothing in the medical history of this case to suggest a pre-existing immune defect. Whether or not the administration of steroids early in his illness altered his cell-mediated immune response is unknown. The importance of an impaired lymphocyte response in determining the outcome is also uncertain, although in one of the previously reported cases associated with hepatic and renal failure (Crawford *et al.*, 1979) a deficiency of peripheral blood T-cells was found, but in the others (Adkins and Steele, 1977; Chang and Campbell, 1975) this was apparently normal as indicated by the appearance of numerous atypical mononuclear cells.

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