British Journal of Haematology, 2002, 118, 1187–1189

SHORT REPORT

Life-threatening human parvovirus B19 infection transmitted by intravenous immune globulin

FUMIHIKO HAYAKAWA,[1] KAZUMI IMADA,[2] MASAYUKI TOWATARI[1] AND HIDEHIKO SAITO[1] [1]*First Department of Internal Medicine, Nagoya University School of Medicine, Nagoya, and* [2]*Toyota Medical Corporation Kariya General Hospital, Kariya, Japan*

Received 3 December 2001; accepted for publication 4 April 2002

Summary. Infection of human parvovirus B19 (B19) is usually a self-limiting febrile illness, but can sometimes be life-threatening under certain circumstances, such as aplastic crisis in patients with haemolytic anaemia, hydrops fetalis in pregnant women and fulminant hepatitis. B19 can be transmitted through respiratory secretions, transplacentally and by transfusion of blood or blood products. In the present case, administration of intravenous immune globulin (i.v.Ig) transmitted B19 infection and consequently caused pure red cell aplasia and aggravation of hepatitis to fulminant hepatitis. Our case may raise important questions as to the safety of i.v.Ig and possible contamination by B19.

Keywords: parvovirus B19, intravenous immune globulin, fulminant hepatitis.

Infection by human parvovirus B19 (B19) is usually a self-limiting febrile illness and causes asymptomatic transient pure red cell aplasia in the bone marrow (Prowse *et al*, 1997). However, under certain circumstance the infection can be severe and life-threatening. For example, patients with chronic haemolytic anaemia can suffer transient aplastic crisis due to the combined effects of the short life span of the red blood cells and the erythroblastopenia in the bone marrow (Pattison *et al*, 1981). In immunodeficient patients, B19 infection may persist and cause severe and long-lasting red cell aplasia (Kurtzman *et al*, 1987). Fetuses can be infected during B19 infection of pregnant women, resulting in hydrops fetalis and fetal death (Brown *et al*, 1984). Even in healthy individuals, B19 infection occasionally causes fulminant hepatitis (Langnas *et al*, 1995). B19 can be transmitted through respiratory secretions, transplacentally and by transfusion of blood or blood products (Prowse *et al*, 1997). We report here a patient whose B19 infection was acquired from intravenous immune globulin (i.v.Ig).

CASE REPORT

The patient was a 19-year-old woman under hospitalization for fever of unknown origin since January 4 2000. She suffered from acute aggravation of hepatic dysfunction on January 24 [serum asparate aminotransferase (AST) 1322 IU/l, alanine aminotransferase (ALT) 1031 IU/l, bilirubin 15·4 μmol/l]. All bacteriological examinations and virological examinations for hepatitis A, B or C, cytomegalovirus or Epstein–Barr virus were negative. In addition, all tests for autoimmunity were normal. Administration of all drugs except liver hydrolysate and ursodeoxycholic acid had been stopped on January 13 when mild hepatic dysfunction was detected. Then 230 mg/kg/d of intravenous immune globulin were administered between January 27 and January 31 as treatment for a possible infectious disease of unknown origin. Hepatic function appeared to improve on February 4 (AST 680 IU/l, ALT 583 IU/l), but a skin rash and a body temperature of 40°C developed. On February 7, hepatic function began to deteriorate again, and abnormal coagulation and pancytopenia were observed [AST 1263 IU/l, ALT 681 IU/l, bilirubin 157·3 μmol/l, prothrombin time 32 s (normal control, 12 s), activated partial thromboplastin time 200 s (normal control, 32 s), fibrinogen 1·19 g/l, white blood cells 17×10^9/l, haemoglobin 9·6 g/dl, platelets 330×10^9/l]. The patient became drowsy and her blood ammonia level rose to 62 μmol/l. Bone marrow examination showed erythroid specific aplasia with a few giant proerythroblasts, suggesting human parvovirus B19 infection. We performed bone marrow examination also on January 24 as a result of mild thrombocytopenia (platelets 940×10^9/l) and found normal haematopoiesis. After treatment with steroid pulse and plasma exchange therapy, hepatic

Correspondence: Fumihiko Hayakawa, Section of Microbiology, Division of Biological Sciences, University of California at Davis, One Shields Avenue, Davis, CA 95616, USA. E-mail: fhayakawa@ucdavis.edu

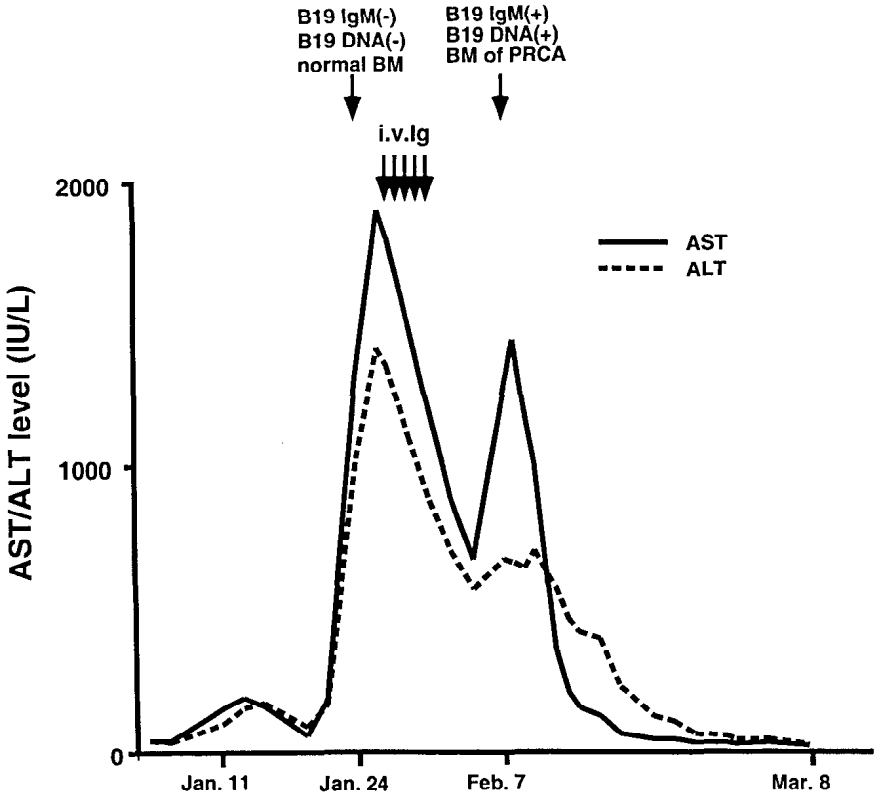

Fig 1. Clinical course of the patient. The unbroken line represents time-course of AST level and the broken line indicates that of ALT level. i.v.Ig, BM and PRCA refer to intravenous immune globulin, bone marrow and pure red cell aplasia respectively.

function recovered and pancytopenia disappeared within 1 month.

A serum sample obtained on February 7 was positive for B19 IgM antibody by enzyme-linked immunosorbent assay (ELISA) and B19 DNA by polymerase chain reaction (PCR), but a stored serum sample taken on January 24 was negative for both B19 IgM antibody and B19 DNA. The batches of immune globulin product administered to the patient on January 27 and 28 were positive for B19 DNA as revealed by PCR. Further virological examinations showed a significant increase in antibody titres against coxsackie B4 virus using paired patient sera obtained on January 11 and March 8. A diagram of the clinical course is shown (Fig 1).

DISCUSSION

In this case, fulminant hepatitis seems to have been caused by B19 infection following pre-existing coxsackie B4 infection. Coxsackie B4 virus infection usually causes asymptomatic or self-limiting febrile illness but occasionally causes myocarditis, meningitis, hepatitis and fever of unknown origin (Lau, 1983). Experimental intranasal B19 infection in adult volunteers has confirmed that viraemia appears from 7 to 10 d after infection and continues for another 7 d (Anderson *et al*, 1985), indicating that the B19 infection in this case may have occurred during the last 10 d of January. The patient was hospitalized in a private room and only a few medical staff and immediate family were in contact with her. There was very little possibility that B19 infection had occurred from accidental contact with a latent carrier whose frequency was about 0·03–0·6% (Prowse *et al*, 1997). She had not received any blood products except i.v.Ig. Virological examinations for B19 became positive after the administration of i.v.Ig, which later proved to be contaminated with B19. These findings strongly suggest that the B19 infection in this case was transmitted by the i.v.Ig. B19 has been reported to be transmitted by transfusion of red blood cells, platelets, fibrin sealant and clotting factor concentrate (Mortimer *et al*, 1983; Prowse *et al*, 1997; Hino *et al*, 2000). There is one report of 'possible' transmission of B19 by administration of i.v.Ig (Erdman *et al*, 1997). In that case, the possibility of B19 transmission from i.v.Ig was suggested by an abrupt change of B19 genotype after administration of i.v.Ig to a patient already displaying chronic B19 infection. However, the authors failed to show a correlation between the B19 genotype in the serum sample of the patient and that in the i.v.Ig administered to the patient. In addition, the second genotypic change of B19 occurred without administration of i.v.Ig. Thus, our case is the first report to clearly show B19 transmission from i.v.Ig. Although the manufacture of the i.v.Ig in this case uses pasteurization (60°C for 10 h), treatment with polyethyleneglycol, ethanol fractionation, and nanofiltration for viral inactivation and removal, B19 is highly resistant to all viricidal and removal methods at present commonly employed because of its small size and ability to withstand heat and detergent treatments (Prowse *et al*, 1997). The frequency of B19 contamination in blood donations has been estimated at about 0·03–0·6% and most plasma pools are prepared from a large number (> 5000) of donations (Prowse *et al*, 1997). As a result, it has been reported that 85% of start pools and 20% of i.v.Ig are

contaminated with B19 (Saldanha & Minor, 1996). Our results suggest that i.v.Ig can also be a serious source of B19 infection. There is one report which indicates that screening of plasma pools with a moderate-sensitive PCR results in the exclusion of highly contaminated donations and the reduction of B19 DNA to undetectable levels in the final product (Weimer *et al*, 2001). Such efforts to improve the virus safety margin for B19 in plasma products are desirable.

We could not confirm whether the B19 infection was solely responsible for the patient's fulminant hepatitis, however, this is the first case reporting that the contamination of B19 in an immune globulin product caused prominent B19 infection and worsened the patient's condition as a result. Our case may raise important questions as to the safety of i.v.Ig and possible contamination by B19.

REFERENCES

Anderson, M.J., Higgins, P.G., Davis, L.R., Willman, J.S., Jones, S.E., Kidd, I.M., Pattison, J.R. & Tyrrell, D.A. (1985) Experimental parvoviral infection in humans. *Journal of Infectious Diseases*, **152**, 257–265.

Brown, T., Anand, A., Ritchie, L.D., Clewley, J.P. & Reid, T.M. (1984) Intrauterine parvovirus infection associated with hydrops fetalis. *Lancet*, **2**, 1033–1034.

Erdman, D.D., Anderson, B.C., Torok, T.J., Finkel, T.H. & Anderson, L.J. (1997) Possible transmission of parvovirus B19 from intravenous immune globulin. *Journal of Medical Virology*, **53**, 233–236.

Hino, M., Ishiko, O., Honda, K.I., Yamane, T., Ohta, K., Takubo, T. & Tatsumi, N. (2000) Transmission of symptomatic parvovirus B19 infection by fibrin sealant used during surgery. *British Journal of Haematology*, **108**, 194–195.

Kurtzman, G.J., Ozawa, K., Cohen, B., Hanson, G., Oseas, R. & Young, N.S. (1987) Chronic bone marrow failure due to persistent B19 parvovirus infection. *New England Journal of Medicine*, **317**, 287–294.

Langnas, A.N., Markin, R.S., Cattral, M.S. & Naides, S.J. (1995) Parvovirus B19 as a possible causative agent of fulminant liver failure and associated aplastic anemia. *Hepatology*, **22**, 1661–1665.

Lau, R.C. (1983) Coxsackie B virus infections in New Zealand patients with cardiac and non-cardiac diseases. *Journal of Medical Virology*, **11**, 131–137.

Mortimer, P.P., Luban, N.L., Kelleher, J.F. & Cohen, B.J. (1983) Transmission of serum parvovirus-like virus by clotting-factor concentrates. *Lancet*, **2**, 482–484.

Pattison, J.R., Jones, S.E., Hodgson, J., Davis, L.R., White, J.M., Stroud, C.E. & Murtaza, L. (1981) Parvovirus infections and hypoplastic crisis in sickle-cell anaemia. *Lancet*, **1**, 664–665.

Prowse, C., Ludlam, C.A. & Yap, P.L. (1997) Human parvovirus B19 and blood products. *Vox Sanguinis*, **72**, 1–10.

Saldanha, J. & Minor, P. (1996) Detection of human parvovirus B19 DNA in plasma pools and blood products derived from these pools: implications for efficiency and consistency of removal of B19 DNA during manufacture. *British Journal of Haematology*, **93**, 714–719.

Weimer, T., Streichert, S., Watson, C. & Groner, A. (2001) High-titer screening PCR: a successful strategy for reducing the parvovirus B19 load in plasma pools for fractionation. *Transfusion*, **41**, 1500–1504.