CASE REPORT
A SEVERE CASE OF HEMORRHAGIC FEVER WITH RENAL SYNDROME IN SINGAPORE

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Abstract. The incidence of human hantavirus infection in Singapore is low. Hitherto, only 2 cases of hemorrhagic fever with renal syndrome (HFRS) have been reported. A third case is reported here of a ragman who had the classical manifestations of HFRS, confirmed by serology. In addition, his condition was complicated by liver dysfunction and neurological disturbance. After a protracted stay, the patient was finally discharged from hospital 5 months after the onset of his severe illness.

Although hemorrhagic fever with renal syndrome (HFRS) is endemic only in some countries, there is serological evidence of hantavirus infections in rats and humans worldwide (Lee, 1988). In Singapore, Wong *et al* (1989) found a seropositivity rate of 26% for hantavirus infection in commensal rats, whereas the rates for patients with acute nephritis, suspected leptospirosis, suspected dengue hemorrhagic fever and non-A, non-B hepatitis were low at 2.0%, 2.7%, 8.0% and 8.0%, respectively. To date, only 2 HFRS cases in Singapore have been reported (Wong *et al*, 1985; Chan *et al*, 1987). We report here a third case who had a severe disease with both neurological and liver involvement.

The patient was a 67-year-old ragman with a history of diabetes mellitus and hypertension of more than 10 years' duration, for which he was treated with oral medications and followed up at a primary health care clinic. He was admitted to a general hospital on 5 April 1992 following 4 days of fever with chills and rigors, lethargy, weakness and confusion. Physical examination revealed a drowsy man with a generalized erythematous flush. His temperature was 38.5°C, pulse rate 100/minute, and blood pressure (bp) 130/60 mmHg. He was not jaundiced and the liver, spleen and kidneys were not palpable. Total white cell count was 5.3×10^9/l with 90% polymorphs, 6% lymphocytes and 4% monocytes. Hemoglobin was 17.9 g/dl and the platelet count 30×10^9/l.

The following day, his bp dropped to 90/80 mmHg, necessitating resuscitation and management as for septicemic shock. The bp remained at approximately 100/60 mmHg for 2 days before recovering to 150/90 mmHg. His temperature continued to spike intermittently and did not settle until the end of May.

The day after the onset of shock, the patient developed rightsided hemiparesis. At this time too, urine microscopy showed 2-4 white blood cells, 8-10 red blood cells and 1-2 epithelial cells per high-power field, in addition to moderate albuminuria. Oliguria developed on the eighth day of illness, fluid intake and output for 24 hours being 2,980 and 250 ml, respectively. Although treated with oral frusemide, he did not diurese until the eleventh day of illness.

Meanwhile, the patient's urea and creatinine levels had been climbing, from 7.9 mmol/l (normal, 2.8-7.7 mmol/l) and 116 µmol/l (normal, 44-141 µmol/l) on admission to peak, respectively, at 37 mmol/l and 527 µmol/l on the tenth day of illness. His renal function then returned to normal after a month.

There was laboratory evidence of liver impairment with raised total bilirubin (45 µmol/l; normal, 3-24 µmol/l), alanine aminotransferase (111 U/l; normal, 7-36 U/l) and aspartate aminotransferase (AST) (256 U/l; normal, 15-33 U/l) on the second day of admission. These markers, apart from AST which was marginally elevated (37 U/l), resumed their normal levels subsequently.

Despite the severe thrombocytopenia, prolonged prothrombin time (15.5 seconds; normal, 11-14

seconds; control, 12.5 seconds) and activated partial thromboplastin time (41.4 seconds; normal, 20-38 seconds; control, 27.5 seconds), no hemorrhagic episodes were witnessed except for microscopic hematuria. Ten days after admission, the platelet count and coagulation times returned to normal.

Of the investigations carried out on the cerebrospinal fluid, microscopic and biochemical analyses were normal except glucose which was raised (10.6 mmol/l; normal, 2.5-5.5 mmol/l). No microorganisms, including acid-fast bacilli and fungi, were seen or cultured. Complement fixing antibodies to herpes simplex, measles, mumps and Japanese encephalitis viruses were not detectable.

A computerised axial tomographic (CT) scan of the brain on 6 April was normal. When repeated after 12 days, an infarct of the left lentiform nucleus was revealed.

Total antibodies to Hantaan virus were present at a titer of 1:1,000 by immunofluorescent assay (IFA) (PROGEN, PROGEN Biotechnik GmbH, Germany) in a blood specimen collected on 7 April (5 days after onset of fever). The antibody titer rose to ≥ 1:800017 days later. The presence of anti-Hantaan IgM antibodies was also demonstrated in the paired sera by a modification of the test. IgG antibodies in the patient's sera were absorbed with caprine anti-human IgG antibodies (GullSORB Reagent, Gull Laboratories, USA) and the resulting 1:10 diluted sera tested for virus-specific IgM antibodies by PROGEN IFA using fluorescein conjugated sheep antihuman IgM (Wellcome Diagnostics, UK).

Other possible etiologies for the infection, *viz* dengue, typhoid fever, rickettsial infection, malaria and leptospirosis, were investigated and excluded. Cultures of blood and urine for bacteria were negative.

When the patient was able to ambulate with a walking frame and feed himself in late September 1992, he was discharged from hospital.

The diagnosis of HFRS in this patient was serologically confirmed by the presence of IgM antibodies and significant antibody rises to hanta virus in the acute and convalescent sera. He displayed the febrile, hypotensive, oliguric, diuretic and convalescent phases of the classical form of the disease. In addition, he presented with confusion and drowsiness. The altered mental state of the patient on admission could have been part of the manifestations of HFRS because hemiparesis developed only after the period of shock when his neurological state was further compromised by an infarction of the lentiform nucleus, probably consequent to marked hypotension in a previously hypertensive patient. Central nervous system manifestations of hantavirus infection including confusion, lethargy, convulsions, coma and meningismus had previously been described by Cohen *et al* (1983) and were suggested to indicate a grave prognosis.

Liver dysfunction, not often seen in classical HFRS, was first reported in two Malaysian patients by Chan *et al* (1987) and Lim *et al* (1987). This patient also had impaired liver function, suggesting that liver involvement in HFRS is not infrequent, at least in Southeast Asian patients.

The source of infection is unknown. This ragman lived in a flat on the fourteenth floor in a public housing estate. His junk, kept at the foot of his block of flats, could have been contaminated by rat excrement as rat droppings and burrows were found in the vicinity (Heng, personal communication). On the other hand, he had visited Johor Bahru across the causeway in Malaysia on multiple occasions prior to his illness. He could have been infected there although it is uncertain if any of his visits fell within the incubation period of his illness.

The incidence of human hantavirus infection in Singapore is low. In a serosurvey of the healthy population as well as among workers in the zoo, sewage and engineering departments in 1993, only 17 out of 1,164 people tested (1.5%) had anti-hantan IFA antibody titers ≥ 1:32 (Heng, personal communication). Therefore, without a high index of suspicion, the few HFRS cases that occur will remain unrecognized.

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