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CASE REPORT

West Nile encephalitis, status epilepticus and West Nile pneumonia in a renal transplant patient

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Summary

West Nile neuroinvasive disease (WNND) represents a small fraction of cases of West Nile Virus (WNV) infection. Organ transplantation is associated with increased risk of acquiring WNND. We report a patient with living-related renal transplantation who developed unusual manifestations of WNND. First, fatal status epilepticus unresponsive to pentobarbital ensued. Status epilepticus from WNV has been described very rarely in the medical literature. Second, this patient grew WNV on broncho-alveolar lavage samples. To our knowledge, this is the first case of culture positive West Nile pneumonia. Third, the finding in cerebrospinal fluid (CSF) of a negative West Nile immunoglobulin M (IgM) and a positive West Nile polymerase chain reaction is striking. It is consistent with a high-viral burden and impaired immune response. This finding raises questions about the appropriateness of relying on CSF IgM assays to rapidly diagnose WNV encephalitis in organ transplant patients, as has been recommended.

Three thousand cases of human West Nile Virus (WNV) disease were reported to Centers for Disease Control and Prevention in 2005 [1]. West Nile Neuroinvasive Disease (WNND), defined as presence of encephalitis, meningitis or acute flaccid paralysis because of WNV infection, accounted for 43.1% of the total cases. Organ transplant patients are at increased risk of developing WNND [2,3].

We report a fatal case of West Nile status epilepticus and West Nile pneumonia in a renal transplant patient. West Nile immunoglobulin M (IgM) antibody was not detectable in this patient's cerebrospinal fluid (CSF); however, WNV was detectable by polymerase chain reaction (PCR). This scenario raises questions regarding the appropriateness of relying solely on CSF IgM assays for early diagnosis of WNND in immunocompromised patients, as is the current recommended practice [4].

Case

A 56-year-old Caucasian man had a history of living-related renal transplant in 1999 for end-stage renal disease because of focal segmental glomerulosclerosis. He presented in October, 2005 complaining of 2 weeks of nonbloody diarrhoea and 2 days of fever, nausea and vomiting. The patient had no complaints of focal weakness, headache, neck stiffness, photophobia, confusion or seizure-like activity. His past medical history included hypertension, hyperlipidaemia and gout. He received daclizumab (anti-interleukin 2 receptor antibody) for induction immunosuppression. His maintenance immunosuppression (at the time of admission) consisted of cyclosporin 100 mg once daily, mycophenolate mofetil 750 mg b.i.d. and prednisone 5 mg once daily. Cyclosporin trough level at the time of admission was 30 ng/ml. An admission chest X ray showed

a right lower lobe infiltrate. Bronchoscopy and computerized tomography (CT) of chest were performed (Fig. 1a). On day 3 of admission, the patient developed altered mental status. Subsequently, intensive care unit care and intubation for airway protection were required. Fevers to 104 °F ensued. Magnetic resonance imaging (MRI) of the brain was unremarkable. Lumbar puncture was performed (day 3 of admission) which showed WBC of 41/μl (53% lymphocytes, 29% neutrophils and 18% monocytes), glucose of 65 mg/dl, protein of 73 mg/dl and RBC 0/μl. CSF gram stain was negative. The patient's working diagnosis was viral meningoencephalitis. CSF PCR results for herpes simplex virus, cytomegalovirus, enterovirus, varicella zoster virus and JC/BK polyoma virus were negative. CSF was negative for Lyme antibody by Western blot, *Cryptococcus neoformans* antigen and lymphocytic choriomeningitis virus IgM/IgG antibody. Serum Toxoplasma IgM, rapid plasma reagen (RPR) and HIV ELISA were negative.

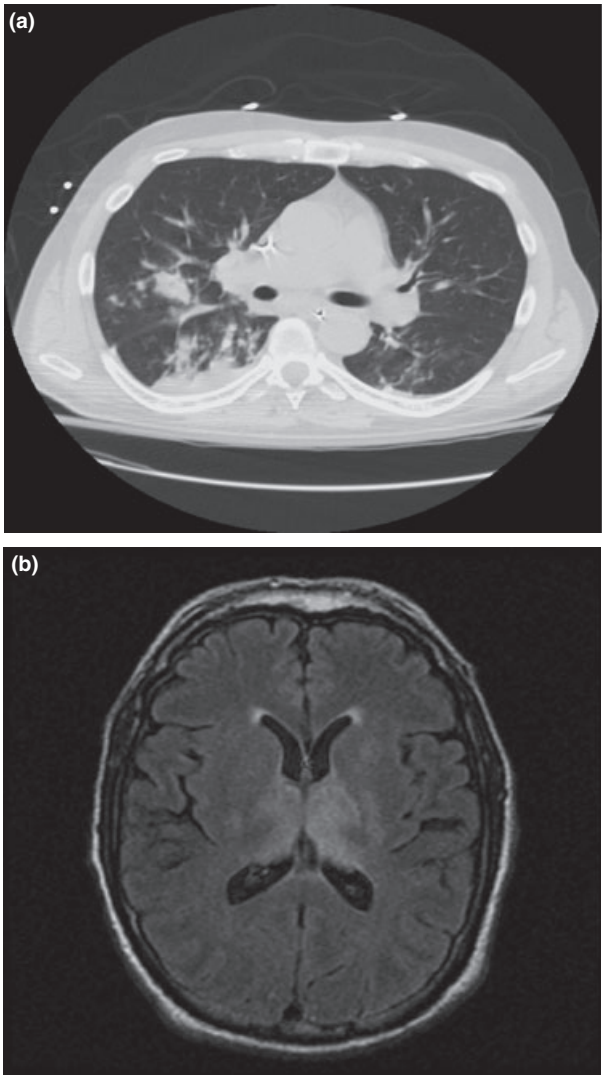

Figure 1 Computed tomography scan of the chest (a) showing infiltrates and magnetic resonance images of the brain (b) (fluid-attenuated inversion recovery, FLAIR signal) showing bilateral symmetrical involvement of thalami.

On day 8 of admission, the patient developed generalized tonic-clonic seizures and status epilepticus. Treatment with lorazepam and phenytoin was unsuccessful. Electroencephalogram (EEG) monitoring showed continuous epileptiform discharges and the patient was started on a pentobarbital drip for seizure control.

West Nile Virus testing is summarized in Fig. 2. West Nile Virus PCR from CSF specimen collected 3 days after admission was positive (Viromed laboratories, Minnetonka, MN, USA); IgM antibody detected by IgM capture enzyme immunoassay (EIA) from serum collected at the same time was negative. CSF viral culture collected at the same time was negative. Based on the positive PCR results, the patient was diagnosed with West Nile encephalitis and related status epilepticus. IgM capture EIA performed on serum collected 1 week later was positive. Cyclosporin was discontinued and the dose of mycophenolate mofetil was gradually tapered down to 250 mg orally twice daily. Treatment with Interferon alpha-2b was attempted for 2 weeks. Repeat MRI brain (with gadolinium) was performed on day 15 (Fig. 1b). Multiple attempts to wean off pentobarbital drip failed secondary to increased seizure-like activity on EEG. The family decided to withdraw ventilator support given the poor prognosis, and the patient expired on hospital day 29. An autopsy was declined. Subsequently, bronchial alveolar lavage (BAL) fluid from day 4 of admission grew WNV in viral culture in Rhesus Monkey Kidney Cells with identification by PCR (Bureau of Laboratories, City of Milwaukee Health Department, WI, USA).

Discussion

While seizures have been reported in 3–16% patients with WNND, status epilepticus because of WNND has been described very rarely in the medical literature [5,6]. To our knowledge, only two cases of status epilepticus because of WNND have been reported previously in organ transplant patients [7,8]. One additional case of status epilepticus because of WNND was reported in a nontransplant patient with refractory chronic lymphocytic leukaemia [9]. Of the four patients with WNV status epilepticus (including our patient), only one patient was alive at 6 months. Seventy-five per cent of patients reported, to date in the literature, therefore, have died when status epilepticus develops in the setting of West Nile infection. This pattern is consistent with more viral

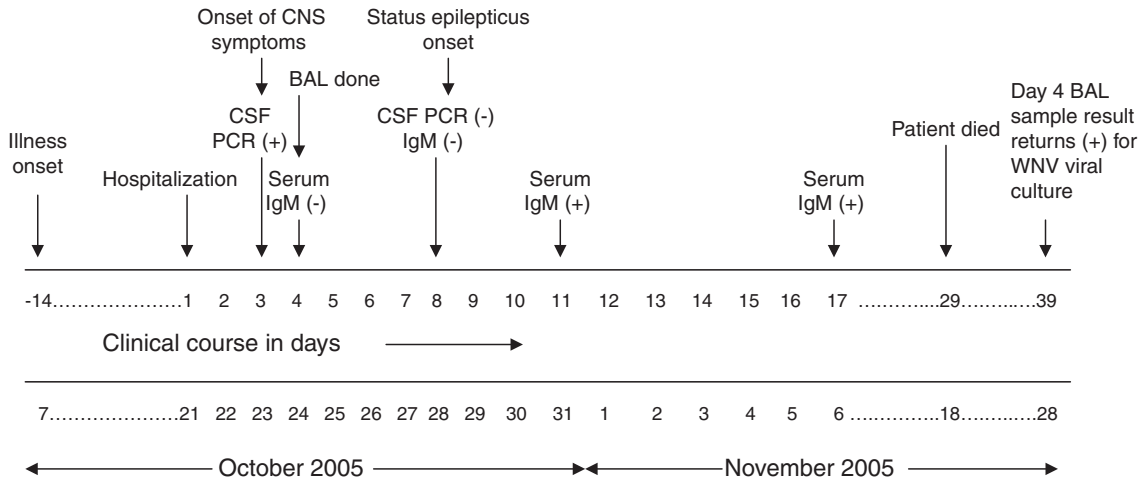

Figure 2 Timeline of events with West Nile virus test results.

damage to the CNS in the setting of compromised immunity.

The patient had a chest CT scan on day 3 of admission which showed features of bronchopneumonia. Bronchoscopy showed no evidence of bleeding. His BAL from day 4 grew WNV in culture without any other pathogens detected, despite extensive evaluation. This suggests our patient's immunocompromised condition led to high-grade viraemia that resulted in seeding of lung tissue. Recently, at autopsy, WNV antigens were detected in the lung tissue of a patient who developed fatal haemorrhagic fever because of WNV [10]. The finding of positive WNV culture as the sole pathogen from BAL fluid, presence of infiltrates on chest CT scan and absence of blood contamination of the BAL, is consistent with the diagnosis of WNV pneumonia. To our knowledge, our patient is the first reported case of West Nile pneumonia confirmed with ante-mortem testing and identified by viral culture.

Our patient initially complained of nausea, vomiting and diarrhoea and was thought to have gastroenteritis at the time of admission. Weiss *et al.* [6] reported that 58% of patients with WNND during the 2000 New York epidemic had at least one gastrointestinal symptom or had abnormal abdominal findings. They suggested that WNV should be considered in the differential diagnosis of patients with gastrointestinal prodromal symptoms, fever and neurologic symptoms during summer months in the areas of WNV transmission. A similar observation was made by Wadei *et al.* and DeSalvo *et al.* in renal transplant patients who developed WNND [7,11]. This case supports such an association.

The presence of IgM in CSF is the current accepted standard for diagnosis of WNND [4]. Our patient displayed unusual CSF diagnostic test results. His CSF PCR for WNV was positive on day 3 and negative on day 8 postadmission. He had negative CSF IgM on day 8. CSF IgM-negative, PCR-positive WNV infection cases have rarely been reported in the literature [12–15]. Importantly, all of these patients were immunocompromised, but none had received a solid organ transplant. Penn *et al.* [15] reported a patient with non-Hodgkin's lymphoma on chemotherapy who developed WNND. In this patient, CSF WNV PCR was positive for >60 days after hospitalization and CSF IgM tests were negative on multiple occasions. This indicates that WNV infection may persist for longer periods in immunocompromised patients. Potentially, these results occur because immunocompromised patients carry a greater viral burden and are less capable of mounting IgM and IgG responses to antigenic challenge. CSF PCR testing therefore may have greater utility for immunocompromised patients. Thus, both CSF PCR and CSF antibody testing should be considered for immunocompromised patients who are being evaluated for WNND. As neither CSF IgM nor PCR is 100% sensitive for WNV, repeat testing of both CSF and sera should be performed if clinical suspicion is high. Further studies clarifying the appropriate use of CSF IgM and PCR are indicated.

Conclusions

Status epilepticus is a rare manifestation of WNV infection. West Nile pneumonia should be included in the differential diagnosis of immunocompromised patients with pneumonia and West Nile infection. CSF PCR along with CSF IgM antibody testing should be considered in all immunocompromised patients who are being evaluated for WNND.

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Authorship

NJ collected and analysed the findings, wrote the paper. DF collected and analysed the findings, wrote the paper. MS involved with the laboratory aspect of WNV and contributed to manuscript. KSK involved with the laboratory aspect of WNV and contributed to manuscript.

References

1. Centers for Disease Control Website. 2005 *West Nile Virus Activity in the United States*. Retrieved on July 18, 2006 from http://www.cdc.gov/ncidod/dvbid/westnile/surv&controlCaseCount05_detailed.htm.
2. Ravindra KV, Freifeld AG, Kalil AC, *et al.* West Nile virus-associated encephalitis in recipients of renal and pancreas transplants: case series and literature review. *Clin Infect Dis* 2004; **38**: 1257.
3. Kumar D, Drebot MA, Wong SJ, *et al.* A seroprevalence study of West Nile virus infection in solid organ transplant recipients. *Am J Transplant* 2004; **4**: 1883.
4. Hayes EB, Sejvar JJ, Zaki SR, Lanciotti RS, Bode AV, Campbell GL. Virology, pathology, and clinical manifestations of West Nile virus disease. *Emerg Infect Dis* 2005; **11**: 1174.
5. Nash D, Mostashari F, Fine A, *et al.* The outbreak of West Nile virus infection in the New York City area in 1999. *N Engl J Med* 2001; **344**: 1807.
6. Weiss D, Carr D, Kellachan J, *et al.* West Nile virus Outbreak Response Working Group. Clinical findings of West Nile virus infection in hospitalized patients, New York and New Jersey, 2000. *Emerg Infect Dis* 2001; **7**: 654.
7. Wadei H, Alangaden GJ, Sillix DH, *et al.* West Nile virus encephalitis: an emerging disease in renal transplant recipients. *Clin Transplant* 2004; **18**: 753.
8. Bosanko CM, Gilroy J, Wang AM, *et al.* West Nile virus encephalitis involving the substantia nigra: neuroimaging and pathologic findings with literature review. *Arch Neurol* 2003; **60**: 1448.
9. Gea-Banacloche J, Johnson RT, Bagic A, Butman JA, Murray PR, Agrawal AG. West Nile virus: pathogenesis and therapeutic options. *Ann Intern Med* 2004; **140**: 545.
10. Paddock CD, Nicholson WL, Bhatnagar J, *et al.* Fatal hemorrhagic fever caused by West Nile virus in the United States. *Clin Infect Dis* 2006; **42**: 1527.
11. De Salvo D, Roy-Chaudhury P, Peddi R, *et al.* West Nile encephalitis in organ transplant recipients: another high risk group for meningoencephalitis and death? *Transplantation* 2004; **77**: 466.
12. Mawhorter SD, Sierk A, Staugaitis SM, *et al.* Fatal West Nile virus infection after rituximab/fludarabine-induced remission for non-Hodgkin's lymphoma. *Clin Lymphoma Myeloma* 2005; **6**: 248.
13. Hiatt B, Des Jardin L, Carter T, Gingrich R, Thompson C, de Magalhaes-Silverman M. A fatal case of West Nile virus infection in a bone marrow transplant recipient. *Clin Infect Dis* 2003; **37**: e129.
14. Huang C, Slater B, Rudd R, *et al.* First Isolation of West Nile virus from a patient with encephalitis in the United States. *Emerg Infect Dis* 2002; **8**: 1367.
15. Penn RG, Guarner J, Sejvar JJ, *et al.* Persistent neuroinvasive West Nile virus infection in an immunocompromised patient. *Clin Infect Dis* 2006; **42**: 680.

