West Nile Virus Meningoencephalitis and Acute Flaccid Paralysis After Infliximab Treatment

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ABSTRACT. West Nile virus (WNV) can cause severe central nervous system (CNS) illnesses including meningoencephalitis (MNE) and acute flaccid paralysis (AFP). Risk factors include advanced age, immunosuppression, cancer, and diabetes. In vitro studies show that tumor necrosis factor (TNF) has anti-WNV activity and is protective against WNV infection. Anti-TNF-α monoclonal antibodies may increase susceptibility to WNV by inhibiting an adequate TNF-α response, leading to prolonged viremia, viral penetration into the CNS, and fulminant WNV-CNS disease. We describe a fatal case of WNV with MNE and AFP after infliximab therapy. During WNV outbreaks, clinicians should encourage patients receiving anti-TNF-α drugs to take appropriate preventive measures because of the risk of severe WNV-CNS disease. (J Rheumatol 2006;33:191–2; First Release Dec 1, 2005)

Key Indexing Terms: WEST NILE VIRUS ACUTE FLACCID PARALYSIS INFLIXIMAB MENINGOENCEPHALITIS TUMOR NECROSIS FACTOR

West Nile virus (WNV) is a single-stranded RNA virus of the Flaviviridae family. Isolated in 1937 from a resident of the West Nile district of Uganda1, 2 WNV lineages exist. Lineage 1 is associated with human disease, while lineage 2 consists of African isolates maintained in enzootic cycles. Passerine birds (sparrows) are the primary amplifying hosts and WNV can be isolated from their fecal and oral secretions. Mosquitoes from the genus Culex are the principal vectors. Horses and humans are incidental hosts2-4.

WNV was first reported in the US with the 1999 New York outbreak. Coincident with the peak transmission within the bird→mosquito→bird cycle, about 85% of human infections occur in August and September. However, human cases have been reported in the United States from May to December. Most human infections are due to mosquito bites. Other documented transmission modalities are blood transfusion, organ transplantation, breast-feeding, and transplacental2-4.

The incubation period ranges from 2 to 15 days (usual 2–6 days). Most human infections are subclinical. One out of 5 persons with WNV infection develop West Nile fever. This typically lasts for 3–6 days and is characterized by fever, headache, eye pain, backache, myalgias, anorexia, nausea, and vomiting. Rhinorrhea, cough, sore throat, and generalized lymphadenopathy can occur. About 50% of patients have a rash (erythematous macular, papular, or morbilliform) that can involve the entire body2-4.

One out of 150 persons with WNV infection develop central nervous system (CNS) infection2-6. Meningoencephalitis (MNE), the most common presentation of CNS disease, may progress into acute flaccid paralysis (AFP) in a small percentage of patients. These patients have the greatest morbidity and highest case-fatality rates (9%)2-6. Advanced age is a significant risk factor for the development of severe WNV neurologic disease. Other risk factors include immunosuppression, cancer, and diabetes2,6.

Infliximab is a monoclonal antibody that inhibits tumor necrosis factor-alpha (TNF-α). Its therapeutic indications include the treatment of Crohn’s disease7,8 and rheumatoid arthritis (RA)9. Although infrequent, several infectious complications, especially the reactivation of tuberculosis, have occurred in patients receiving infliximab10. Other reported infections include common viral infections, bacteremia, Pneumocystis jirovecii, Candidiasis, herpetic reactivation (cytomegalovirus, herpes zoster, herpes simplex virus 1 and 2), and invasive fungal infections (aspergillosis)10-14.

The pathophysiologic role of TNF-α in WNV infection is still being elucidated. WNV-infected murine embryo fibroblasts show upregulated TNF mRNA transcription and secretion of soluble TNF. In vitro studies show that TNF has anti-WNV activity and is protective against WNV infection15. Potential mechanisms of action include TNF enhancement of interferon synthesis and TNF inhibition of viral replication by disrupting the viral life cycle, including viral entry16. In murine models, WNV entry into the brain is mediated by Toll-like receptor 3 (TLR3), where infection induces a TLR3-dependent inflammatory response that is
involved in viral penetration across the blood–brain barrier into the CNS with subsequent neuronal damage17.

Systemic use of anti-TNF-α antibodies has recently been suggested as a risk factor for WNV infection16. The potential effect of infliximab on the clinical course of WNV-CNS disease needs further investigation. With WNV infection, it could be postulated that infliximab-mediated inhibition of TNF-α may allow viral penetration into the CNS, with resultant severe disease. We describe the first case of WNV-MNE-AFP developing after infliximab therapy.

CASE REPORT
In August 2003, a 66-year-old man with RA presented to a Maryland hospital with a 2-day history of fever, headache, confusion, agitation, nausea, malaise, myalgias, gait instability, and rapidly worsening lower extremity weakness. He had received infliximab 3 weeks prior to symptom onset. His only other medications were methotrexate (15 mg/wk) and amlodipine (5 mg/day).

His initial examination found a temperature of 40°C, blood pressure of 100/50 mm Hg, heart rate of 100 beats/minute, respiratory rate of 24/minute, and oxygen saturation 90% on room air. He was intubated due to increasing hypoxia, confusion, and agitation. Physical examination revealed marked meningismus, diffuse asymmetrical weakness, and diffuse areflexia. White blood cell count was 9,400/mm3 (neutrophils 80%, lymphocytes 11%, monocytes 9%), hemoglobin 13.3 g/dl, platelets 135,000/mm3. The results of other routine laboratory tests, including blood and urine cultures, were negative. Magnetic resonance imaging of the brain revealed increased signal intensity in the subcortical white matter. Cerebrospinal fluid (CSF) examination showed protein 58 mg/dl (normal 15–40 mg/dl), glucose 60 mg/dl (normal 40–70 mg/dl), and 104 white blood cells/mm3 (normal 0–5 cells/mm3) with 5% neutrophils and 95% lymphocytes. He received ceftriaxone, vancomycin, doxycycline, ampicillin, and acyclovir. WNV infection was confirmed with CSF positive for WNV IgM antibodies by ELISA capture technique. All other CSF studies (including Lyme-ELISA, VDRL, cryptococcus antigen, bacterial, viral, fungal, and mycobacterial cultures) were negative. The time interval between symptom onset and final laboratory diagnosis was 14 days. The family elected for comfort measures and the patient eventually died due to WNV infection. No autopsy was performed.

DISCUSSION
This is the first reported case of a patient developing WNV-MNE-AFP after treatment of RA with anti-TNF-α monoclonal antibodies. Infliximab may have increased his susceptibility to WNV by inhibiting an adequate TNF-α response, leading to prolonged viremia, viral penetration into the CNS, and subsequent fulminant WNV-CNS disease3–6. Patients with WNV-MNE-AFP have severe morbidity and high fatality rates3–6. In patients with an appropriate exposure history and risk factors, a clinical syndrome of fever, mental status changes, and asymmetrical weakness should alert physicians to consider WNV-MNE-AFP in the differential diagnosis. There are multiple criteria for diagnosis: WNV IgM-positive CSF is part of the Centers for Disease Control criteria for confirmed case of WNV-MNE19. With 3 US Food and Drug Administration-approved, randomized clinical trials (interferon-α-2b, intravenous immunoglobulin G, 3rd generation anti-sense) currently under way, rapid diagnosis is crucial so that these potential treatments may be expediently offered in addition to standard supportive measures19.

During WNV outbreaks, clinicians should encourage patients receiving anti-TNF-α drugs to take appropriate preventive barrier measures because of the potential risk for severe WNV-CNS disease. Prevention is 2-fold. Personal interventions include using DEET-containing insect repellent and permethrin clothing spray, minimizing outdoor activities from dusk to dawn, wearing appropriate clothing outdoors, and using window and door screens. Vector control focuses on eliminating sources of standing water and spraying for adult mosquitoes or applying larvicides to water collections19.

REFERENCES