West Nile virus encephalitis presenting with a vesicular dermatitis

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INTRODUCTION

West Nile virus (WNV) is a single-stranded RNA virus of the Flaviviridae family that is primarily transmitted by mosquitoes. WNV is a leading cause of viral encephalitis in the United States with up to 1% of infected individuals developing neuroinvasive disease. A nondiagnostic rash, frequently described as morbilliform, develops in up to half of patients with WNV fever. Although mouse models and cultured primary human keratinocytes have implicated the skin as a site of viral replication,[1] there has been no direct evidence for the presence of WNV proteins in the skin of patients. We report a case of neuroinvasive WNV in a 67-year-old male patient who presented with an unexpected vesicular rash in the skin. Immunohistochemistical (IHC) and immunofluorescence (IF) studies revealed WNV proteins to be present in the patient's affected skin lesions. This case expands the reported cutaneous manifestations of WNV infection. In addition, it raises the possibility that IF or IHC studies on skin biopsies could be used as an adjunct test patients suspected to have WNV infection, especially when serologic tests are delayed or unavailable. Finally, we review the diagnosis and clinical features of WNV and other neuroinvasive flaviviruses.

Abbreviations used:

CSF:	cerebral spinal fluid
IF:	immunofluorescence
IHC:	immunohistochemistical
PCR:	polymerase chain reaction
WNV:	West Nile virus

CASE REPORT

In the late fall, a 67-year-old man presented with 4 days of fever, malaise, and headache. He had no known immunosuppression and his past medical history was notable only for the successful surgical excision of prostate cancer and melanoma in situ. His only medication before admission was solifenacin for hyperactive bladder. He had traveled to California and South Carolina 1 week before presentation. No animal or arthropod exposures were reported, although the patient took daily walks in the woods near his home in north Texas. Upon admission, he was febrile to 39.5 °C, tachycardic to 102 beats/min, but was not hypotensive. The remainder of his physical examination, including neurologic, was unremarkable at presentation.

Initial blood count and metabolic panel were notable only for mild anemia (red blood cell count, 3.47 ($\times 10^6$/microL); hemoglobin, 10.6 (g/dL); and

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hematocrit, 31.3%). Urine and blood cultures showed no growth, and nasopharyngeal polymerase chain reaction (PCR) for influenza, respiratory syncytial virus, SARS-CoV-2 (COVID-19), parainfluenza, adenovirus, *Bordetella pertussis*, *Chlamydophila pneumoniae*, human metapneumovirus, rhinovirus, and enterovirus were negative. Serologic screens for HIV, *Cryptococcus neoformans*, *Rickettsia typhi*, *Rickettsia rickettsii*, *Mycobacterium tuberculosis*, and *Treponema pallidum* were negative. Chest X-ray, computed tomography imaging of the chest, abdomen, brain, and magnetic resonance imaging of the brain did not identify any acute processes or infection. Initial attempts at lumbar puncture were not successful and assistance from interventional radiology was requested. Given the concern for meningitis, the patient was started on empiric intravenous acyclovir, ampicillin, ceftriaxone, and vancomycin, with subsequent addition of oral doxycycline for coverage of rickettsial diseases. On day 3, tremulousness, hyperreflexia, and myoclonus developed in the patient. Cerebral spinal fluid (CSF) obtained via interventional radiology–assisted lumbar puncture revealed lymphocytic pleocytosis with 40 nucleated cells/mm^3, 14% neutrophils, 64% lymphocytes, and 20% monocytes. CSF total protein was elevated (50 [range, 15-45] mg/dL) and glucose was normal. CSF evaluation including bacterial culture, VDRL, herpes simplex virus-1/2, and enterovirus PCR and cryptococcal antigen testing were negative.

On day 4, an asymptomatic rash developed on the upper portion of the patient's back. The rash began as pink macules and papules that evolved into vesicles on the back, chest, and abdomen (Fig 1). The patient did not report any itching or symptoms from the rash and no topical therapies were required despite its evolution to vesicles. Swabs of the vesicles were negative for HSV-1/2 and varicella-zoster virus by PCR. There were no signs of skin pain, mucosal involvement, or other features suggestive of a severe drug reaction. The vesicles were biopsied, and microscopy revealed an intraepidermal vesicle with focal dyskeratosis and a mixed infiltrate in the papillary dermis (Fig 2). Direct IF studies did not reveal in situ deposits of IgG, IgA, IgM, C3c, and fibrinogen in the skin, making an autoimmune-mediated blistering dermatosis less likely. On day 6, both serum (WNV) IgM and IgG (drawn on day 2), and CSF WNV IgM (drawn on day 3) resulted as positive, rendering a diagnosis of WNV infection. The patient received supportive care and was hospitalized for 7 days with marked clinical improvement by discharge. His rash had largely resolved and only small areas corresponding to the healing vesicles were still visible.

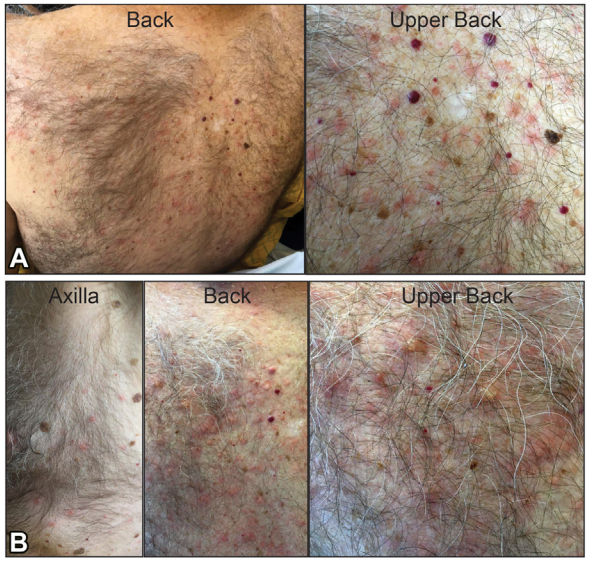

Fig 1. Clinical presentation of **(A)** initial day 4 and **(B)** evolving day 6 skin lesions in patient diagnosed with West Nile virus encephalitis. Early lesions were pink macules and papules on the back and chest. Late lesions included erythematous papules and vesicles on the back, chest, and extremities.

Studies on the skin biopsies revealed the presence of abundant WNV nonstructural glycoprotein (NS1) by IF and IHC (Fig 3). Biopsy from perilesional skin revealed intracellular and fibrillar IF, whereas normal tissue showed only nonspecific fluorescence of the corneal layer. IHC staining of WNV NS1 protein revealed strong intracellular staining of keratinocytes in a lesional biopsy from the patient, which was absent in normal-appearing skin.

DISCUSSION

The transmission cycle of WNV involves infected mosquitoes as vectors and birds as primary hosts. Humans are dead-end hosts. The vast majority of WNV infections in humans are secondary to bites from infected mosquitoes. Outbreaks of WNV infection initially presented as mild febrile illness, with rare reports of neurologic symptoms.[2] In 1996, a large WNV outbreak in Romania resulted in 352 cases of encephalitis and 17 deaths, and increased rates of neurologic disease have persisted.[3] First detected in New York City in 1999, WNV has expanded across North America and has the greatest geographic spread among arboviruses.[4]

Approximately 75% to 80% of WNV infections in humans are asymptomatic, whereas 20% to 25% experience West Nile fever.[5] Symptoms of West Nile fever are described as flu-like and typically include myalgia, headache, chills, vomiting, fatigue, and rash.[5] Fever may be absent in up to 40% of symptomatic

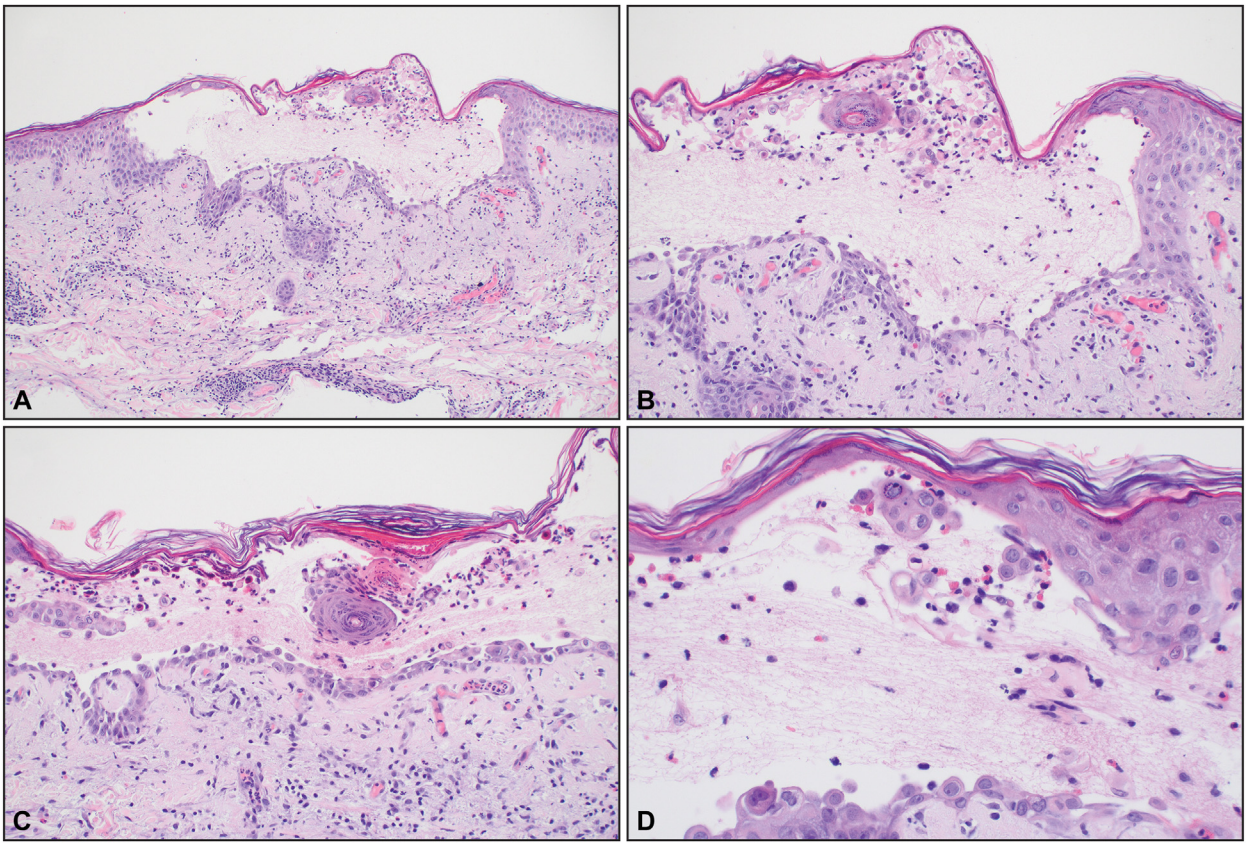

Fig 2. Biopsy revealed an acantholytic intraepidermal vesicle with focal dyskeratosis and a mixed infiltrate in the papillary dermis. (Original magnifications: **A,** ×100; **B,** ×200; **C,** ×200; **D,** ×400).

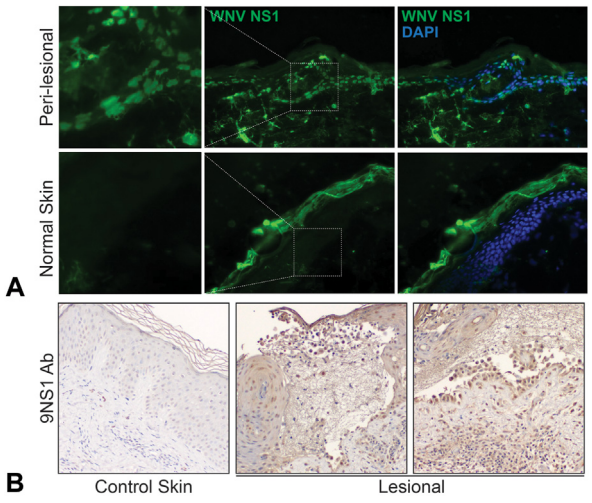

Fig 3. Immunofluorescence and immunohistochemical (IHC) staining for West Nile virus (WNV) NS1 glycoprotein. **A,** Biopsies were incubated with an antibody against WNV nonstructural glycoprotein NS1 (9NS1) and 4′,6-diamidino-2-phenylindole (DAPI), which highlights nuclei. Biopsy from perilesional skin from a vesicle revealed a intracellular and fibrillar staining pattern from patient with WNV which was absent in normal-appearing skin obtained from a tissue repository. **B,** IHC staining of WNV NS1 protein revealed robust intracellular staining of keratinocytes in lesional biopsy from patient with WNV which was absent in normal-appearing skin obtained from a tissue repository.

cases.[6] Full recovery is typical, but fatigue and muscle weakness may persist.[7] Less than 1% of WNV infections progress to severe neuroinvasive disease.[5] The common manifestations of WNV neuroinvasive disease are encephalitis, meningitis, or acute flaccid paralysis. WNV neuroinvasive disease is associated with symptoms of headache, neck stiffness, seizures, tremors, paralysis, and confusion.[5] Advanced age and immunosuppression are associated with increased risk of neuroinvasive disease.[8]

Suggestive clinical symptoms and confirmatory laboratory testing are necessary to diagnose WNV infection. Presentation of symptoms during mosquito season and travel to known areas of transmission should increase suspicion for WNV. Clinical symptoms and routine blood tests do not offer specific signs of WNV infection. Computed tomography imaging is often normal, but magnetic resonance imaging may show abnormalities in approximately one-third of WNV encephalitis cases. WNV infection is diagnosed by the presence of WNV-specific IgM antibodies in the serum or CSF. Detection of WNV IgM in the CSF indicates central nervous system involvement. CSF analysis may also show increased protein levels, normal glucose, and lymphocytic pleocytosis. Detection of WNV antigen in formalin-fixed central nervous system tissues by immunohistochemistry or

Table I. Flavivirus-induced neurotropic disease and possible cutaneous manifestations

Flavivirus	Clinical presentation	Cutaneous presentation	Frequency of rash or cutaneous eruption	Insect vector	Geographic distribution	References
Japanese encephalitis virus	Fever, headache, acute encephalitis, aseptic encephalitis, seizures, acute flaccid paralysis	No known associated rash	Not applicable	Mosquito	Asia, Western Pacific, Australia	Solomon et al[15]
West Nile virus	Fever, fatigue, memory impairment, weakness, neuroinvasive disease, meningitis, encephalitis, acute flaccid paralysis	Typically erythematous and morbilliform	20%-50%	Mosquito	North America, Africa, Europe, Australia, Middle East	Watson et al[10]; Gorsche and Tilley[16]
Zika virus	Fever, conjunctivitis, congenital microcephaly, Guillain-Barré syndrome, encephalitis, myelitis	Pruritic morbilliform eruption	90%	Mosquito	South America, Central America, North America, Africa, Asia	de Oliveira et al[17]; Musso and Gubler[18]; Wolford and Schaefer[19]
Tick-borne encephalitis	Fever, headache, myalgia, arthralgia, fatigue, malaise, anorexia, nausea, meningitis, encephalitis, myelitis	Rash uncommon, 1 reported case	Unknown	Tick	Europe, Asia	Charrel et al[20]; Mease et al[21]; Bogovic and Strle[22]
Powassan virus	Fever, headache, vomiting, weakness, encephalitis, meningitis, confusion, loss of coordination, problems with speech, seizures	Rash, erythema migrans	3 of 18 cases (17%), 6 of 14 cases (43%)	Tick	North America, Eastern Europe	Piantadosi et al[23]; El Khoury et al[24]; Kemenesi and Bányai[25]
St. Louis Encephalitis virus	Often asymptomatic, fever, headache, meningitis, encephalitis	Rash uncommon, 1 reported case	Unknown	Mosquito	North America, South America	Brinker et al[26]; Venkat et al[27]; Simon et al[28]
Usutu virus	Fever, myalgia, headache, arthralgia, asthenia, encephalitis, meningitis, acute flaccid paralysis	Rash, not specific, jaundice	2 of 8 cases (25%)	Mosquito	Europe, Africa, Middle East	Pauli et al[29]; Nikolay et al[30]; Gaibani and Rossini[31]; Pacenti et al[32]
Ilheus virus	Fever, encephalitis	Rash, not specified, vesicular rash (1 case)	Unknown	Mosquito	Central America, South America	Johnson et al[33]; Milhim et al[34]; Venegas et al[35]
Rocio virus	Fever, encephalitis, headache, lower-extremity weakness, conjunctivitis, anorexia, nausea, vomiting, myalgia	No known associated rash	Not applicable	Mosquito	South America	Saivish et al[36]

reverse transcription-PCR has been reported as an adjunctive measure.[9]

Patients infected with WNV may present with a morbilliform eruption affecting the trunk and extremities, but reported rates are variable (25%-50%).[6,10] A vesicular eruption associated with WNV has not been previously reported. WNV-associated rash commonly appears 3 to 7 days after symptom onset and typically lasts up to 7 days. Rash onset frequently coincides with defervescence. WNV-associated rashes may be associated with tingling, burning, and pruritus.[11] Analysis of large-scale WNV outbreaks revealed an inverse association between rash and risk of encephalitis and death, after adjusting for age.[12] The pathomechanisms underlying the improved prognosis of patients with WNV-associated rash is unclear, but its presence may represent a stronger host immune response against the virus. Rare histologic characterizations of WNV-associated rash have reported histopathologic features similar to those seen in viral exanthem, including superficial perivascular lymphocytic infiltrate.[13] To the best of our knowledge, this is the first time WNV proteins have been sought by IHC and/or IF on a WNV related rash, and these studies revealed strong WNV NS1 intracellular staining in keratinocytes by both IF and IHC. The presence of WNV NS1 protein in lesional skin raises the possibility that that the cutaneous eruptions in WNV infections may be mediated by an immune response against viral proteins present in the skin.

Most patients infected with WNV recover without intervention. Supportive treatment for headaches, nausea, and vomiting may be helpful in severe cases. Broad-spectrum antimicrobial treatment should be initiated in suspected cases of WNV meningoencephalitis, until other infectious causes have been excluded. Although corticosteroids, ribavirin, interferon alfa, and intravenous immunoglobulin have been used to treat neuroinvasive WNV, the efficacy of these treatments has not been confirmed in clinical trials.[5] No vaccine candidates have reached the final stages of clinical development.[14] Current prevention methods are largely focused on mosquito control through the reduction of breeding areas and insecticide treatments and reducing exposure to infected mosquitoes.

Other neurotropic flaviviruses continue to pose a significant global health threat because of their potential to cause serious central nervous system injury and long-standing morbidity (Table I).[15-36] In addition to WNV, flavivirus-induced neurotropic disease is caused by Japanese encephalitis virus and tick-borne encephalitis virus. In addition to the classically neurotropic flaviviruses, emerging neurotropic viruses such as Zika, St. Louis encephalitis, Powassan, Usutu, Ilheus, and Rocio viruses are being recognized for their epidemic potential.

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Conflicts of interest

None disclosed.

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