Punctate exanthem of West Nile Virus infection: Report of 3 cases

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The West Nile Virus (WNV) has rapidly emerged as an important etiology of meningoencephalitis in North America since 1999. Diagnosis of this infection on clinical grounds is difficult, as many signs and symptoms of infection are nonspecific. Although cutaneous manifestations are common in WNV-infected patients, these have not been described in detail nor are clinical images widely available. We describe 3 patients with WNV infections, two ambulatory, one hospitalized, who developed punctate erythematous, macular, and papular eruptions, most pronounced on the extremities. Histopathologic findings in one case showed a sparse superficial perivascular lymphocytic infiltrate, a feature commonly seen in viral exanthems but not previously reported with WNV infection. A literature review provides support that this punctate exanthem is a common cutaneous presentation of WNV infection. (J Am Acad Dermatol 2004;51:820-3.)

The West Nile Virus (WNV) is now a well-known cause of infectious meningoencephalitis throughout much of the world.1,2,3,4,5 It is a single-stranded RNA virus of the family Flaviviridae. In the United States in 2003 there were 9377 cases of WNV infection and 244 deaths reported to the Centers for Disease Control and Prevention (CDC).6 Birds are the natural reservoir for WNV, and infection has been documented in at least 138 bird species.7 Transmission of the virus occurs via Culex, Ochlerotatus, and Aedes mosquitoes.8,9,10 In temperate climates, most cases of WNV infection occur from late spring through early fall, during the period of active mosquito feeding. Recently, person-to-person transmission has been demonstrated to occur through blood product transfusion, solid organ transplantation, and possibly breastfeeding.11,12,13

Clinical severity of WNV infection is wide, ranging from total absence of symptoms to meningoencephalitis, coma, and death.14 Approximately 80% of infections are not clinically apparent. In patients with overt disease, common manifestations include sudden fever, malaise, anorexia, photophobia, myalgia, lymphadenopathy, arthralgia, and skin eruption. Less than 1% of infected patients develop severe neurological disease.15 In addition to meningoencephalitis, neurological complications include optic neuritis, chorioretinal lesions, ataxia, myelitis, and seizures.17,16 Diagnosis of WNV infection is established by IgM-capture enzyme-linked immunosorbent assay (ELISA) of serum; whereas central nervous system (CNS) infection is established by IgM-capture ELISA of cerebrospinal fluid.17

In a study of blood donors, multivariate analysis demonstrated that “new rash” and “painful eyes” were independently associated with recent WNV infection.11 In this study, the nature of the eye and skin complaints was not described further. “Rash” was described in approximately 20% of infected patients in recent WNV outbreaks in New York and Israel.5,18 A WNV-infected French patient had a pruritic macular and papular erythematous eruption following a trip to Senegal.19 Despite its potential utility as a diagnostic sign, the cutaneous manifestations of WNV infection are not well characterized in the dermatological literature. We describe 3 cases of WNV infection with punctate erythematous macules and papules concentrated on the extremities. One case had cutaneous histopathology, which has not been previously documented for WNV infection. A review of the literature suggests that this is a common cutaneous presentation of WNV infection.
CASE REPORTS

Case 1

A 40-year-old female was seen as an outpatient with a 1-week history of lethargy, and a 5-day history of an asymptomatic “rash” on the bilateral arms, legs, and trunk (Fig 1, A and B). The patient developed her illness in August and lived in the Chicago area. There was no reported history of mosquito exposure. The patient had previously been seen by a primary care physician who had diagnosed her with folliculitis. Physical examination showed numerous 1 mm-2 mm erythematous blanchable papules on the arms, legs, and trunk. Although the papules were not uniformly follicular, the overall appearance of the eruption was akin to a mild folliculitis. Serum ELISA was positive for anti-WNV IgM antibodies. The patient was not treated and the eruption resolved during the subsequent week.

Case 2

A 53-year-old female was seen as an outpatient with a 2-day history of an asymptomatic “rash” on the bilateral arms and legs, as well as the chest and back (Fig 1, C). This patient became ill in September and lived in the Chicago area. She felt vaguely ill during the preceding week. Two weeks before presentation, she attended an outdoor concert and was bitten by mosquitoes. Physical exam showed numerous 1 mm-4 mm erythematous blanchable papules on the arms, legs, chest, and back. Serum ELISA was positive for anti-WNV IgM antibodies. The patient was not treated and the eruption resolved during the next week.

Fig 1. Clinical images of WNV eruption. Erythematous papules on patient 1 (A, B) and patient 2 (C). Erythematous macules on patient 3 (D). Note the resemblance to folliculitis in all cases.

Fig 2. A sparse perivascular lymphocytic infiltrate in the superficial dermis consistent with viral exanthem (Patient 3). (Hematoxylin-eosin stain; original magnification: ×100.)
Case 3

A 66-year-old male with no significant past medical history was admitted for nausea, vomiting, headache, fever, “rash”, and new onset tremor. Five days before admission, the patient had abrupt-onset malaise and fatigue. Two days before admission, he developed an asymptomatic rash on his arms and legs. He was retired and lived in rural East Texas; he had no sick contacts, tick exposure, new medications, or recent travel. He had recently spent several hours in a wooded area searching for a lost dog. The month of presentation was July. Upon admission, the patient’s neurological status quickly deteriorated and he became obtunded. On physical examination, the patient was unconscious and had nuchal rigidity. There were numerous 1 mm-3 mm blanching erythematous macules on the plantar and lateral feet, lower legs (Fig 1, D), and to a lesser extent, on the volar wrists. On the legs, the macules appeared follicular (Fig 1, D). Examination of the mucous membranes was unremarkable. A punch biopsy from a leg macule showed a sparse peri-vascular lymphocytic infiltrate in the superficial dermis (Fig 2). The overlying epidermis appeared unremarkable.

The patient had an elevated white blood cell count of $13.8 \times 10^{9}/mm^3$, with 72% neutrophils. Cerebrospinal fluid (CSF) analysis showed normal glucose, total protein 121 mg/dL (normal <45 mg/dL), 253 white blood cells/mm$^3$, 31% lymphocytes and 64% neutrophils. CSF bacterial cultures, viral cultures, Venereal Disease Research Laboratory (VDRL) test, coccidioides titer, cryptococcus titer, human herpes simplex virus (HSV) 1, and HSV 2 polymerase chain reaction (PCR) were negative. Serum testing for syphilis, Rocky Mountain spotted fever (RMSF), leptospirosis, listeriosis, infectious mononucleosis, human immunodeficiency virus (HIV), hepatitis B virus, and hepatitis C virus were negative. Serum WNV IgM titer was >1:20 and CSF WNV IgM immunofluorescent antibody (IFA) was >1:2, both results were supportive of recent WNV infection.

The patient was initially treated with multiple antibiotics and supportive care. On hospital day 4, he regained consciousness and soon had baseline mental status. He was discharged on hospital day 6 with no residual neurological deficits. His skin eruption had rapidly faded and was absent at discharge.

DISCUSSION

With numerous nonspecific signs and symptoms and a wide spectrum of clinical severity, diagnosis of WNL infection is often difficult, ultimately requiring serological confirmation. Thus, any clinical clues available to trigger appropriate diagnostic testing are valuable to the treating physician. Skin manifestations of WNV infection are common and are readily apparent to both patients and practitioners alike. Here we attempt to refine the characteristics of the eruption associated with WNV infection.

We describe 3 patients with documented WNV infection who had similar eruptions: 1 mm-4 mm scattered erythematous blanchable macules and papules, mainly on the extremities. In all patients, the eruption was transient, asymptomatic, and bore a superficial resemblance to mild folliculitis. In addition, patient 3 had involvement of the soles of his feet.

<table>
<thead>
<tr>
<th>Location</th>
<th>Year</th>
<th>Description of eruption</th>
<th>Frequency of eruption</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Israel</td>
<td>1956</td>
<td>“Discreet pale roseolar spots, diffuse small spotted pale roseolar exanthema, mottling of skin consisting of pale roseolar maculae of varying size”</td>
<td>25/50 (50%)</td>
<td>1</td>
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<tr>
<td>Romania</td>
<td>1997-8</td>
<td>“Measles-like exanthema”</td>
<td>NR</td>
<td>21</td>
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<tr>
<td>Flushing, NY</td>
<td>1999</td>
<td>“Macular lesions on limbs, trunk and back”</td>
<td>1/8 (12%)</td>
<td>4</td>
</tr>
<tr>
<td>New York, NY</td>
<td>1999</td>
<td>“Erythematous macular, papular or morbilliform eruption on the neck, trunk, arms and legs”</td>
<td>11/59 (19%)</td>
<td>5</td>
</tr>
<tr>
<td>Israel</td>
<td>2000</td>
<td>“New rash”</td>
<td>4/21 (19%)</td>
<td>18</td>
</tr>
<tr>
<td>France (Senegal)</td>
<td>2001</td>
<td>Discreet macular-papular exanthema</td>
<td>Single case report</td>
<td>19</td>
</tr>
<tr>
<td>Cleveland, OH</td>
<td>2002</td>
<td>“Nonpruritic, maculopapular, erythematous rash”</td>
<td>6/26 (23%)</td>
<td>20</td>
</tr>
<tr>
<td>North America*</td>
<td>2002</td>
<td>“New rash”</td>
<td>4/14 (29%)</td>
<td>11</td>
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NR, Not reported.
*Blood donors.
To further characterize the cutaneous manifestations of WNV infection, we examined previous clinical and epidemiological reports of WNV-infected patients (Table 1). Two reports noted only the presence or absence of an eruption but did not describe it further.\textsuperscript{11,18} However, 5 studies noted the presence of spots of macular or papular erythema on the extremities.\textsuperscript{1,4,5,19,20} In addition, the eruption of WNV infection was commonly described as morbilliform.\textsuperscript{5,21} Although usually asymptomatic, pruritus was noted in one patient.\textsuperscript{19} To our knowledge, there are no reports of non-blanching (petechial) eruptions with this disease. In patients with overt WNV infection, the frequency of an eruption varied from 12% to 50%, with most reporting about 20%. A study of Israeli infections in the early 1950s noted that the eruption typically follows the onset of fever by 3 to 5 days, and rapidly wanes as the fever subsides.\textsuperscript{1} Confirmation of this timecourse will require additional clinical experience. There is no evidence that the extent of skin involvement correlates with severity of neurological disease.\textsuperscript{20}

The differential diagnosis for febrile patients with a new erythematous macular and/or papular eruption on the extremities includes RMSF, leptospirosis, atypical measles, meningococcemia, and other viral exanthems.\textsuperscript{22} Unlike RMSF and meningococcemia, the macular erythema of WNV infection does not evolve into petechia, although these entities may be clinically indistinguishable in early stages. In a patient suspected of having WNV meningoencephalitis, it is important to begin broad-spectrum antibiotic therapy until other infectious etiologies are excluded.

We describe 3 cases of WNV infection with multiple punctate blanching erythematous macules and/or papules on the extremities and trunk, with involvement of the soles of one patient. A review of the literature provides support that this punctate exanthem is a common cutaneous manifestation of WNV infection, affecting approximately 20% of overtly infected patients. WNV infection should be included in the differential diagnosis of an acutely febrile patient with an abrupt-onset macular and/or papular punctate erythematous eruption.

REFERENCES