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REVIEW ARTICLE

The Emerging Zika Virus Threat: A Guide for Dermatologists

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Abstract We provide a guide for dermatologists to follow if they encounter patients with a rash and clinical history suspicious of Zika virus infection, including diagnostic testing and management options. We also provide an illustrative case report of a patient from Brazil who was diagnosed with Zika virus infection after presenting with a generalized pruritic rash. One of the most prominent symptoms of Zika virus infection is a cutaneous eruption. As such, it is especially necessary for dermatologists to understand this virus so that they may appropriately recognize this entity as a diagnostic consideration in the clinic. The rash associated with Zika virus infection is most commonly an erythematous maculopapular eruption that presents after an initial 3–4 days of fever, headache, and arthralgia or myalgia. The rash typically lasts for an average of 6 days, and can spread to involve any part of the body, including the face, torso, extremities, palms, and soles.

Key Points

The rash associated with Zika virus infection is most commonly a red rash that appears after an initial 3–4 days of fever, headache, and joint or muscle pains.

The rash typically lasts for an average of 6 days, and can spread to involve any part of the body, including the face, torso, extremities, palms, and soles.

Dermatologists should be alert to these features given the emerging Zika virus threat.

1 Introduction

The Zika virus is a flavivirus that is primarily transmitted to humans through the bite of *Aedes* mosquitoes [1]. It is closely related to the dengue virus, yellow fever virus, West Nile virus, and the Japanese encephalitis virus [2]. The Zika virus was first discovered in Uganda in 1947, and over the next few decades, only sporadic cases of human infections were reported [2]. In 2007, Zika virus presented as an outbreak for the first time outside its known endemic boundaries and caused an epidemic on Yap Island in the Federated States of Micronesia [3], and then another epidemic in 2013 in French Polynesia [4].

The recent outbreak of Zika virus in the Americas began in May 2015 in Brazil and has since spread to involve the USA, with over 3000 Zika virus cases reported in the USA as of September 2016, most of which were travel-related cases, except for the outbreak of cases identified in Florida

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[5]. The rapid spread of this virus is alarming, as the Centers for Disease Control and Prevention (CDC) announced that the Zika virus is spreading faster than anticipated. It is particularly necessary for dermatologists to understand this virus so that they may appropriately recognize this entity as a diagnostic consideration.

2 Case

A 54-year-old man presented to a dermatology clinic in Brazil with a generalized pruritic rash. The rash began acutely 3 days prior to his presentation to the clinic, and was localized initially to his head before spreading to the rest of his body. The patient also experienced photophobia, chills, and conjunctival erythema during this time. He recounts that 1 day prior to the onset of symptoms, he had a headache and diffuse myalgia. He denied fever, diaphoresis, bleeding symptoms, and comorbidities.

Detailed physical exam revealed edema and erythema of the malar region of the face and conjunctival injection (Fig. 1). There was a macular rash present on his trunk and abdomen (Fig. 2).

Blood counts, metabolic panels, and urine tests were all within normal limits. The patient reported having a neighbor who was ill with a similar presentation a few days before the patient became symptomatic. The patient resided in the metropolitan area of Rio de Janeiro, which is known to be endemic for dengue. He denied recent travel to other areas of the country. As part of the diagnostic work-up, serology tests were performed for dengue, cytomegalovirus, toxoplasmosis, mononucleosis, syphilis and HIV, which were all negative. Real-time polymerase chain reaction (PCR) for dengue and chikungunya also were negative. Due to the current outbreak of Zika virus in Brazil, specific reverse transcription PCR (RT-PCR) for detection of this virus' RNA was performed, which resulted positive for Zika virus.

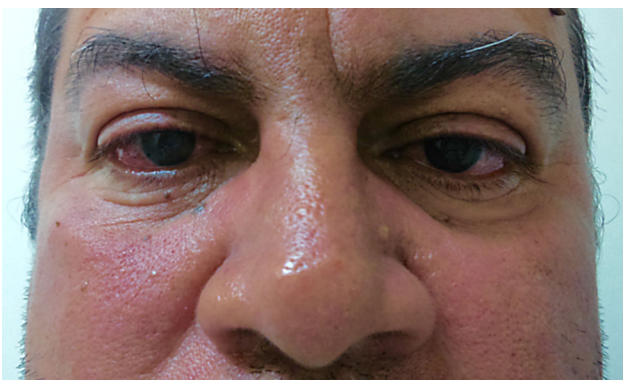

Fig. 1 Edema and erythema of the malar region of the face and conjunctival injection

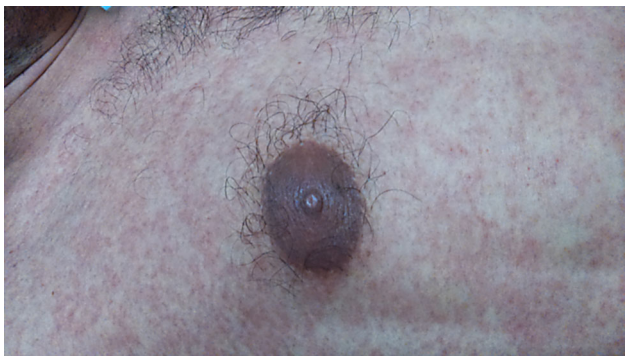

Fig. 2 Macular rash on the trunk

As there were no critically alarming clinical or laboratory signs, the patient was instructed to increase oral hydration and to return for re-evaluation. On reassessment 2 weeks later in the clinic, the patient reported that his symptoms completely resolved after the sixth day of his illness. The patient was asymptomatic and had no residual signs on examination.

3 Discussion

Zika virus infection is characterized most commonly by an acute onset of fever, followed by headache, arthralgia, myalgia, and a generalized maculopapular eruption that can involve any area of the body [6–11]. It can be difficult to detect Zika virus clinically, as an estimated 80% of individuals infected with the virus are asymptomatic [6]. Even symptomatic disease is mild, non-specific, and can mimic multiple other diseases and infections, including dengue fever and chikungunya [6]. However, there are key distinguishing features of each disease that may aid in their diagnosis (Table 1).

The rash is a prominent feature of Zika virus infection, and has historically been reported to persist for an average of 6 days, as was the case in our patient [7, 10, 11]. The rash associated with the Zika virus has most often been described as an erythematous maculopapular (morbilliform or scarlatiniform) rash that usually presents towards the beginning of the infectious course [12, 13]. The rash can be pruritic [2, 8, 12, 14–25], descending [25], and/or blanching [26, 27].

The cutaneous symptoms usually present on day 3 or 4 of illness after an initial period of fever, headache, and arthralgia or myalgia, and lasts for an average of 6 days (range 2–14 days) [3, 7, 16, 17, 28–34]. However, some patients have noted the rash occurring earlier within 1 day after onset of other symptoms [8, 11, 26, 35–38], and even

Table 1 Clinical characteristics of similarly presenting febrile viral exanthems in travelers

	Zika	Chikungunya [53]	Dengue [54]	West Nile virus [55]
Severity	Majority asymptomatic (85%)	Majority symptomatic (70%)	Can cause asymptomatic (40–80%), mild, or serious illness	Majority asymptomatic (70–80%)
Illness course	Low-grade fever with headache and arthralgia or myalgia, followed by rash	Abrupt-onset fever, followed by debilitating arthralgia with associated symptoms	Initial abrupt-onset febrile phase, followed by critical phase and spontaneous recovery phase	Abrupt-onset fever, followed by associated symptoms
First symptoms/ phase	Low-grade fever (<38.5 °C)	Sudden-onset high fever (>39 °C)	Febrile phase: sudden-onset high fever (>39 °C); associated with headache, myalgia, retro-orbital pain, vomiting, macular rash, petechiae, and bruising	Sudden-onset fever
Second phase/ other major symptoms	Headache, mild joint pain, pruritus, conjunctivitis, fatigue	Intense and debilitating symmetric polyarthralgia localized to large joints of arms and legs; occurs soon after onset of fever; in regions where chikungunya virus circulates, the debilitating polyarthralgia has a positive predictive value of >80%	Critical phase: systemic vascular leak syndrome occurs in small proportion of patients; persistent vomiting, increasingly severe abdominal pain, tender hepatomegaly, mucosal bleeding, lethargy	Headache, backache, myalgia, anorexia, rash, generalized lymphadenopathy, vomiting, diarrhea
Rash details	Maculopapular rash begins on torso or neck, spreads throughout body; typically occurs after initial 3–4 days of fever, arthralgia/myalgia; can be pruritic	Maculopapular rash occurs within 48 h of symptom onset; primarily on trunk; can appear on face, extremities, palms and soles	Transient macular rash and petechiae in initial febrile phase; second rash may appear during recovery phase, which varies from mild maculopapular exanthem to severe, pruritic lesions	Roseolar or maculopapular rash on face and trunk
Distinguishing features	Low fever	High fever, debilitating polyarthralgia	High fever, myalgia, headache	High fever, severe fatigue

appearing first before all other symptoms [2, 12, 21]. While the rash often presents with concomitant fever, some patients may remain afebrile [30]. The rash may also persist after other symptoms of the illness have resolved [12, 35, 39]. The cutaneous eruption most commonly involves the patient's face, torso, arms, and legs, and can involve the palms and soles as well [11, 31, 35]. Several reports have described the rash as spreading, beginning on the torso or neck and spreading to involve the rest of the chest, back, and extremities [12, 13, 29, 30, 32].

The rash is such a prominent feature of Zika virus infection that a recent study enrolled all women who presented with a rash to an acute febrile illness clinic in Rio de Janeiro to test for Zika virus infection [25]. The study enrolled 88 women, of whom 82% had positive results for Zika virus on PCR in blood and/or urine [25]. They found that Zika virus-positive women were more likely to present with a maculopapular rash than Zika virus-negative women [25]. Interestingly, the study found that fever was not a prominent finding, occurring in just 28% of women, suggesting that the presence of a maculopapular rash is more sensitive for detecting Zika virus infections than the presence of a fever [25]. Similarly, other reports have found fever to be neither a reliable nor prominent symptom of Zika virus infection, and instead found pruritus to be a common symptom in infected patients [40].

Of note, even though one of the most common symptoms of Zika virus infection is a cutaneous rash, there have been some reports of patients with Zika virus infection presenting without the characteristic rash [41–43].

For patients who present to a dermatology clinic with this type of generalized erythematous maculopapular rash, it is imperative that dermatologists perform a thorough review of systems and inquire about recent travel history. Travel to Central America, South America, the Caribbean, Pacific Islands, and Zika endemic regions of the USA, such as Florida, should be of particular concern. Patients with the rash who report concomitant acute onset fever, arthralgia, or non-purulent conjunctivitis during or within 2 weeks of travel to the aforementioned areas should be

tested for Zika virus infection [6]. These series of actions are especially important for pregnant women, as it is confirmed that Zika virus causes microcephaly and other brain anomalies in the fetus [44, 45].

Diagnosis of Zika virus infection is accomplished by laboratory testing, including serum or plasma tests to detect the virus, viral nucleic acid, or Zika virus immunoglobulin M or G and neutralizing antibodies [1]. Virus-specific antibody testing should occur at least 4 days after the onset of illness. RT-PCR on patient serum can usually detect the virus during the first week after symptom onset [1]. RT-PCR can also be performed on cerebrospinal fluid, urine, amniotic fluid, semen, and saliva [46]. The Zika IgM Antibody Capture Enzyme-Linked Immunosorbent Assay (Zika MAC-ELISA) is another diagnostic test that can detect the Zika virus in patients' blood [47]. Due to the potential for false positives, which can occur if the patient is infected with a similar virus, such as the dengue virus, it is important that positive and inconclusive results be followed up with additional testing by the CDC or CDC-authorized laboratories to confirm the presence of Zika virus antibodies [47]. Furthermore, as it routinely takes more than 24 h to obtain confirmatory results for RT-PCR, patients will often be discharged home, pending laboratory results. As such, it is critically important to advise the patient upon discharge to exercise precautions to avoid mosquito bites. If tests result positive, it remains important for the patient to avoid mosquito bites while symptomatic as well. These are necessary measures to help avoid local transmission of Zika virus.

There is no specific medication or vaccine to treat Zika infections [1]. Supportive therapies are recommended, such as acetaminophen to relieve fever and pain, fluids to prevent dehydration, and rest [1]. Aspirin and other non-steroidal anti-inflammatory drugs should be avoided until dengue infection can be ruled out in order to decrease the risk of hemorrhage [6].

The sedative effects of antihistamine therapies may be beneficial to patients, and topical corticosteroids should be avoided for now, as their efficacy on this type of rash is unknown [7].

As Zika virus infection is particularly of concern in pregnant women, the CDC has recommended strict precautions for pregnant women to prevent mosquito bites. These include wearing long-sleeved shirts and long pants and staying in places either with air conditioning or that use window and door screens to keep mosquitoes from entering the indoor area [48, 49]. The CDC has also recommended the use of Environmental Protection Agency (EPA)-registered insect repellents, which are proven safe for pregnant and breastfeeding women and have been confirmed by the EPA to be effective [48]. These repellents should contain one of the following active ingredients: DEET, IR3535, picaridin, oil of lemon eucalyptus, or para-menthane-diol [48]. Users should spray the repellent over clothing, not on the skin under clothing [48]. If using sunscreen, sunscreen should be applied before spraying the insect repellent [48].

Zika virus infection usually only causes a mild illness in adults. However, current research suggests that Guillain-Barré syndrome (GBS) is strongly associated with Zika infection, although only a small proportion of people infected with Zika get GBS [50, 51]. The most alarming consequence of Zika virus infection is in pregnant women. In April 2016, the CDC definitively confirmed that there is a causal relationship between prenatal Zika virus infection and microcephaly and other serious brain anomalies, collectively known as congenital Zika syndrome. Congenital Zika syndrome is distinguished by severe microcephaly (>3 standard deviations below the mean), with findings consistent with fetal brain disruption sequence; brain anomalies, including cerebral cortex thinning, abnormal gyral patterns, and increased fluid spaces; ocular abnormalities, including macular scarring and focal pigmentary retinal mottling; congenital contractures, such as clubfoot; and neurological impairments [52]. This indicates the first time that a mosquito has been found to cause congenital birth defects.

Zika virus is a nationally notifiable condition [1]. Confirmed cases of Zika virus infection should be reported to state or local health departments [1].

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Compliance with Ethical Standards

Informed consent was obtained from all individual participants included in the study.

Institutional review board status Approval not required.

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Conflict of interest Alice He, Patrícia Brasil, Andre M. Siqueira, Guilherme A. Calvet, and Shawn G. Kwatra declare that they have no conflicts of interest relevant to the content of this article.

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