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CASE AND RESEARCH LETTERS

Zika Virus Infection: An Emerging Disease the Dermatologist Must Know About☆

Infección por virus del Zika: una enfermedad emergente que el dermatólogo debe conocer

Dear Editor:

In contrast to infection by other arboviruses such as dengue virus, which can cause potentially severe disease in humans, infection by Zika virus (ZIKV) is generally benign and self-limiting, with mainly asymptomatic episodes. Recent epidemiological shifts in the geographic distribution of ZIKV, however, have raised health care alarms around the world because of the possible association between ZIKV infection and congenital malformations, particularly microcephaly, and neurologic disorders, including Guillain-Barré syndrome. Although the discovery of the virus in the Zika forest in Uganda dates back to 1947, fewer than 20 cases of ZIKV infection had been reported in humans up to 2007. Preceded by the outbreaks on the island of Yap in Micronesia in 2007 and in French Polynesia in 2013, the epidemic that started in May 2015 in Latin America continues to expand uncontrolled. On February 1, 2016, the World Health Organization declared ZIKV infection a Public Health Emergency of International Concern. One week later, the Centers for Disease Control and Prevention upgraded its response to the outbreak to Level 1 activation, the agency's highest level. We present the case of a patient diagnosed with ZIKV infection in our center. Our aim is to increase awareness of this emerging arbovirus among dermatologists. Given the mainly cutaneous symptoms of the infection and the intensity of travel and migratory flows from Latin America, it seems highly likely that we will be diagnosing ZIKV in the coming months.

A 25-year-old woman from the Dominican Republic with no personal history of interest who had been living in Spain for 8 years was referred to the dermatology emergency department for assessment of a pruriginous exanthem that had started 48 hours previously and was extending down her body. She also had intense asthenia, sensation of poor temperature regulation, mild joint and muscle pain, headache, and ocular pruritus. Physical examination revealed bilateral malar erythema and edema, together with marked conjunctival injection (Figures 1 and 2) and subtle generalized micropapular exanthema with follicular accentuation (Figure 3). The blood workup revealed only slightly altered cytolysis in the liver. The fact that she had spent a month in her home country and arrived in Spain 12 hours before the onset of symptoms led us to suspect ZIKV infection. Therefore, we ordered serology tests and nucleic acid testing in serum and urine using reverse transcriptase polymerase chain reaction (RT-PCR) to detect ZIKV. We also requested a workup for dengue virus and chikungunya virus and the usual protocol for exanthematous viruses. The result of the pregnancy test was negative. Histopathology of the skin revealed a mild superficial perivascular lymphocytic infiltrate. The symptoms resolved completely 6 days after onset. RT-PCR in urine and serum was positive for ZIKV in samples collected at 48 hours from onset. The results of serology testing were negative.

ZIKV is a single-stranded RNA virus belonging to the genus *Flavivirus* of the Flaviviridae family. It is transmitted mainly by bites from mosquitos of the *Aedes* genus, in most cases *A aegypti* (although it is also carried by other species, including *A albopictus*). As with other arboviruses, vector-independent routes of transmission have been identified (eg, vertical and transfusional).[1] Remarkably, in contrast with other arboviruses, sexual transmission has also been documented.[2] It remains to be determined whether there is a risk of transmission via other fluids where viral RNA has been detected, such as saliva or breastmilk.[3,4]

It is estimated that only 1 in 5 infected persons develops clinical manifestations, which are generally mild and self-limiting. After an incubation period lasting between 3 and 12 days, the typical manifestations are pruriginous maculopapular rash that extends down the body, mild fever, mild pain affecting mainly the small joints of the hands and feet, and nonpurulent conjunctivitis. The manifestations last 2 to 7 days.[5] Although the clinical picture coincides with that of other viruses transmitted by the same vector, such as dengue or chikungunya, certain characteristics can orient us toward the causative agent, namely, predominance of rash with little involvement of the patient's general status in ZIKV infection, persistent joint pain in chikungunya infection, and

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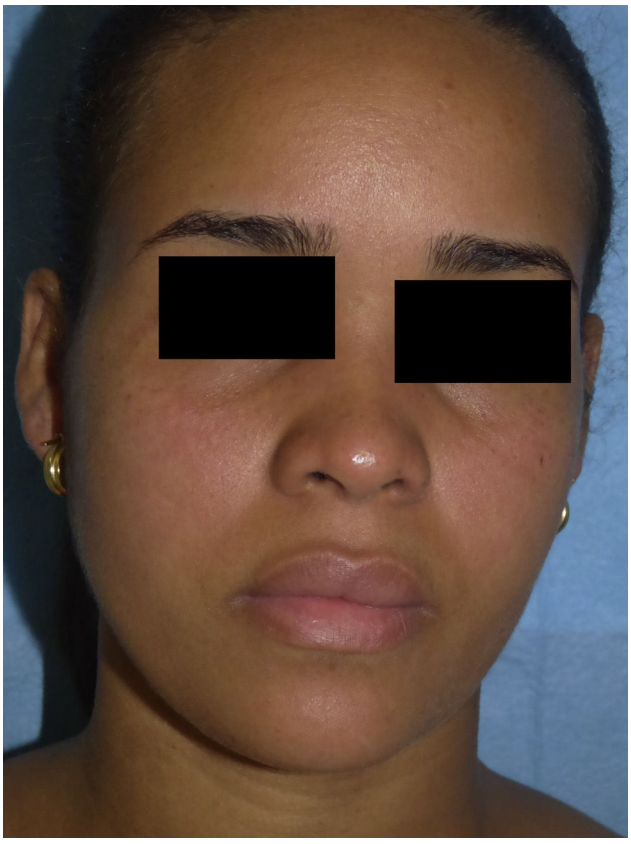

Figure 1 Bilateral malar erythema and edema and conjunctival injection.

the classic picture of rash respecting specific areas of skin, thrombocytopenia, and bleeding complications in dengue. The absence of pathognomonic findings, however, necessitates a microbiologic diagnosis based on the detection of viral RNA using RT-PCR assay in serum during the first 5 days with symptoms or in urine for up to 10-15 days. This study can be extended to cerebrospinal fluid in patients with neurological symptoms.[6] RT-PCR assay is followed by serology testing. This approach is of particular interest in pregnant

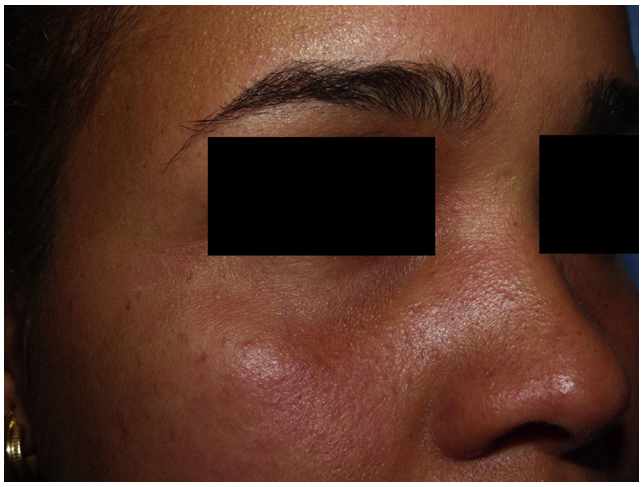

Figure 2 Detailed image of marked conjunctival injection.

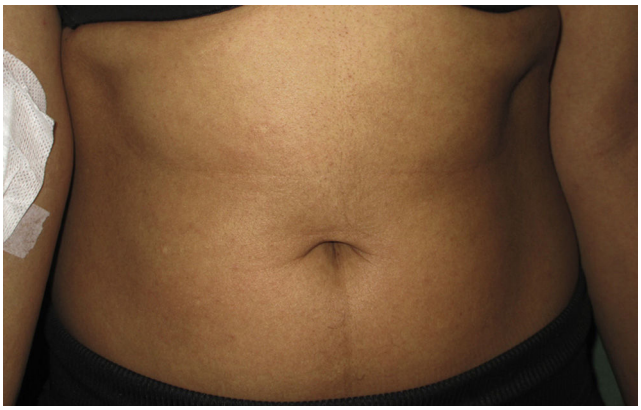

Figure 3 Subtle rash comprising micropapules on a background of generalized erythema.

women, although it is limited because of cross-reactivity with other flaviviruses. Available evidence indicates that ZIKV infection can confer prolonged immunity.

Up to mid-March 2016, the Spanish National Microbiology Center had confirmed 43 cases of ZIKV infection in Spain, all of which were imported. However, the presence of *A albopictus* (commonly known as the tiger mosquito)[7] along the Mediterranean coast and in the Basque Country and Aragon enables autochthonous transmission of ZIKV in Spain, mainly during summer and winter, which is when vector activity is most intense and more people travel from epidemic areas.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

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Erythema Multiforme-Like Bullous Pemphigoid[☆]

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To the Editor:

Bullous pemphigoid (BP) is the most common chronic autoimmune subepidermal bullous dermatosis, occurring mainly in the elderly. It is characterized clinically by a pruritic polymorphous skin rash that typically arises on the abdomen, the flexor surfaces of the limbs, the neck, axillas, and groin. Initially the lesions are often excoriated, erythematous, eczematous, and/or urticarial. Blisters usually then develop on normal or erythematous skin, giving rise to crusted erosive areas that heal without scarring. The diagnosis is confirmed by the demonstration of deposits of immunoglobulin (Ig) G or of the C3 component of complement on the epidermal basement membrane, and the presence in the serum of circulating IgG antibasement membrane zone antibodies against antigens BP-180 and BP-230. Numerous variants of BP have been described, with a broad spectrum of clinical manifestations.[1–3]

A 32-year-old woman, with skin phototype VI, with no personal or family history of interest, was seen in dermatology outpatients for the appearance of a highly pruritic, widespread skin rash that had developed 3 weeks earlier. The patient was not taking any medication or using topical products, had not been sunbathing, and reported no associated systemic symptoms.

On physical examination, she presented a good general state of health. Examination of the skin revealed multiple well-defined, confluent, edematous erythematous plaques with centrifugal growth, with tense peripheral vesicles and blisters containing a clear fluid, producing a polycyclic, annular morphology (Fig. 1, A and B). The skin lesions affected the face, neck, trunk, and limbs, including the dorsum of the hands and feet. No lesions were observed on the palms, soles, mucosas, nails, or scalp. The Nikolsky and Asboe-Hansen signs were negative.

Laboratory tests including routine biochemistry, urinalysis, coagulation studies, antinuclear antibodies, antitransglutaminase antibodies, serum electrophoresis, and immunoglobulin and complement levels were normal or negative. The only findings of interest were a white cell count of 20 000 cells/μL with eosinophilia of 6000 cells/μl, and elevation of the erythrocyte sedimentation rate (35 mm in the first hour). Serology for syphilis, hepatitis B and C viruses, and HIV was negative. The Mantoux test was negative. Chest x-ray showed no significant changes of interest.

A skin biopsy taken from an urticarial plaque showed a lymphocytic and eosinophilic dermal infiltrate with focal changes at the dermoepidermal interface (Fig. 2A). A biopsy was also taken from a blister, revealing a subepidermal blister associated with a lymphocytic and eosinophilic dermal infiltrate (Fig. 2B). Direct immunofluorescence of healthy perilesional skin was positive, showing linear deposits of IgG and C3 at the dermoepidermal junction with a U-serrated pattern (Fig. 2C). Indirect immunofluorescence on 1 M sodium chloride-separated skin showed the presence of circulating antibasement membrane zone antibodies bound

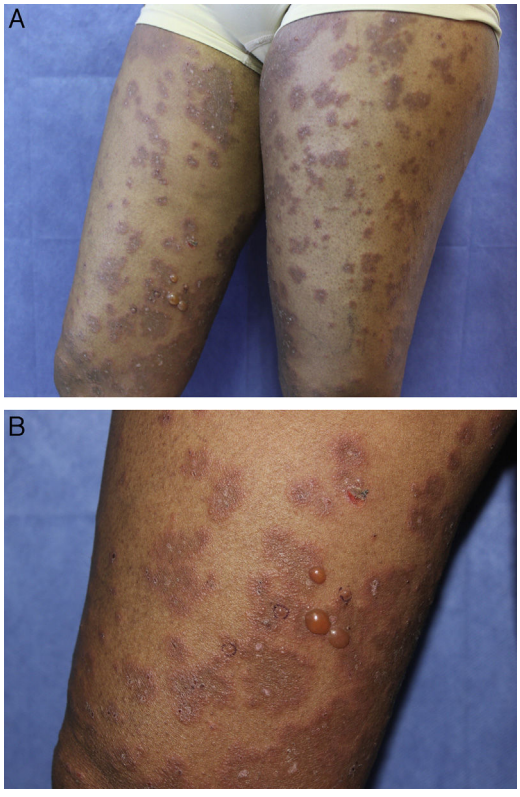

Figure 1 A, Annular and polycyclic erythematous plaques with tense peripheral blisters on both thighs. B, Detail of the same lesions.

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