Review article

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Cutaneous features of Zika virus infection: a clinicopathological overview

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Summary

Zika virus (ZIKV) is an emerging mosquito-borne flavivirus transmitted mainly by *Aedes* species of mosquitos. Although the infection is usually mild and self-limiting, it is emerging as a public health challenge in tropical and subtropical countries owing to its unprecedented pathogenicity and increased risk for fetal malformations and neurological symptoms. Cutaneous manifestations as for other mosquito-borne viruses remain a hallmark of the disease. This article provides a detailed overview on ZIKV infection, including its varied cutaneous clinical manifestations and diagnostic aspects, and also provides detailed insights into its pathogenesis in human skin.

Introduction

Zika virus (ZIKV) is a mosquito-borne flavivirus, which was first isolated in nonhuman primates and mosquitos in 1947–1948 in the Zika forest (Uganda).[1] ZIKV has emerged over recent years in Africa and Asia, with the first major outbreaks in the western Pacific reported in 2007, and in French-Polynesia through 2013–2014.[2] In 2014, ZIKV reached the Americas,[3] causing great concern because of its unprecedented pathogenicity. Even though ZIKV infections are usually mild or remain clinically unapparent,[2] cutaneous manifestations remain a hallmark of the disease as for other mosquito-borne viruses.[4–6] We review the cutaneous clinical spectrum of ZIKV infection, and describe several aspects of its interaction with human skin cells.

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Clinical presentation

ZIKV infections in humans are usually asymptomatic. The disease was first reported in 1956 after experimental inoculation in a healthy volunteer, who developed symptoms without cutaneous manifestations.[6] In 1964, the disease was reported in another individual, who exhibited a characteristic maculopapular rash 24 h after the onset of headaches and other nonspecific symptoms.[7] However, it was not until the 2007 outbreaks in Yap State and French Polynesia that the classic combination of fever, rash, arthritis and/or arthralgia, conjunctivitis, and fatigue, would come to define the most common clinical picture of the disease.[8]

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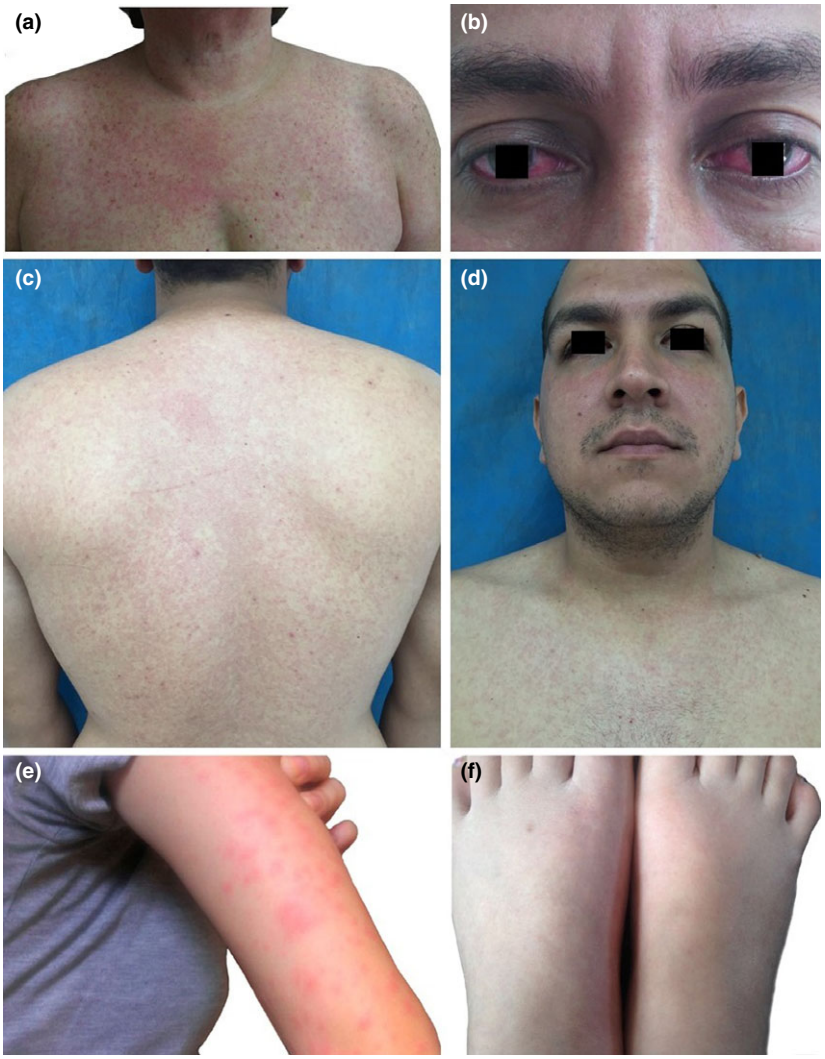

Figure 1 (a) Classic pruritic maculopapular rash located in the chest and neckline of a 56-year-old woman. (b) Marked conjunctival hyperaemia. (c-d) Generalized rash with areas exhibiing a reticular 'net-shaped' appearance. (e) Exanthem-like eruption with predominance of confluent macules, plaques and patches recreating those seen in Chika virus infection. (f) Symmetrical periarticular oedema in small joints and ankles.

ZIKV infection usually produces an influenza-like illness that is difficult to differentiate from other arboviral or exanthematic viral diseases,[2] and when clinically apparent, often manfests as a mild form of the disease.[2] The incubation period usually ranges from 3 to 10 days and lasts about a week.[2] During the most recent epidemic, the Pan American Health Organization issued interim case definitions based on data obtained from the current epidemic in the Americas.[9] Thus, a suspected-case is a patient with a rash (usually pruritic and maculopapular) with two or more of the following signs or symptoms: elevated body temperature (~38.5 °C), arthralgia/myalgia, nonpurulent conjunctivitis or conjunctival hyperaemia (Fig. 1a), headache/malaise and periarticular oedema (Fig. 1b).[9] A confirmed case is a case with clinical suspicion and a positive laboratory confirmation of ZIKV.[9]

The cardinal cutaneous manifestation of ZIKV is the maculopapular rash and prurtitis (Fig. 1).[2,10–12] However, in our experience there is marked diversity in the characteristics of the rash and in the severity of the illness, ranging from a conspicuous, diffuse, mildly pruritic, maculopapular rash (Fig. 1c) to cases with nearly universal erythrodermia (Fig. 1d,e). In the middle of the disease spectrum are morbiliform-like rashes and exanthem-like eruptions with a predominance of macules, plaques and patches similar to those seen in Chikungunya virus (CHIKV) infection (Fig. 1f). In

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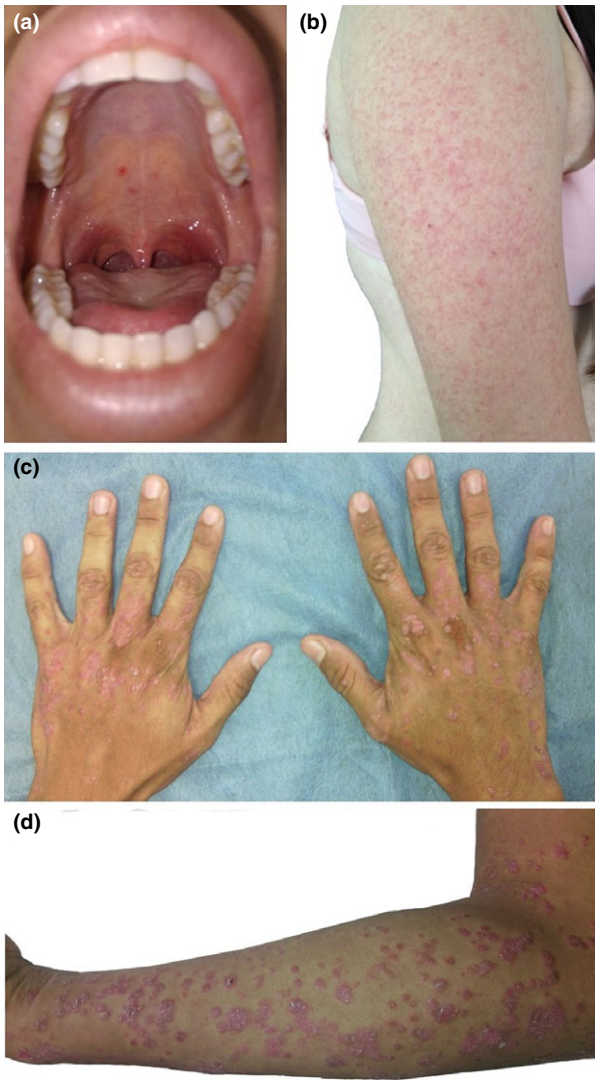

Figure 2 (a) Petechial lesions on the hard palate of a female patient with acute Zika virus (ZIKV) infection. (b) Accentuation of the lesions in the proximal areas of the arms (a common feature seen in most Venezuelan patients). (c,d) Typical generalized salmon-pink papules and scaling psoriatic-like plaques that mimic those of eruptive 'guttate' psoriasis in two patients soon after the resolution of ZIKV symptoms.

contrast to CHIKV and dengue virus (DENV) infections, in which the rash occurs generally after the fourth day of onset of symptoms, the cutaneous manifestations of ZIKV commonly (in over 90% of the cases) occur within the first 24–48 h after the onset of symptoms.[13]

Individual lesions are usually macules, papules and/or plaques that can even appear as weals. They are usually erythematous and round to oval in shape, and are arranged in combination patterns (maculopapular most commonly)[2,9] (Fig. 1) or exhibit a reticular (linear and net-shaped) appearance[12] with blanching on palpation.[11] Lesions are usually generalized, following a symmetrical pattern that commonly involves the face, neck, trunk, palms and soles (Fig. 1).[2] In Venezuela, however (data not published), a distinct pattern characterized by accentuation of the lesions in proximal areas of the arms and legs (Fig. 2a), neckline (Fig. 1c), and abdomen has been observed. Painful periarticular oedema of the joints is also a distinctive sign,[11] occurring most commonly in the small joints[9,12] of wrists and ankles, often in a symmetrical fashion (Fig. 1b).

Atypical cutaneous manifestations include subcutaneous haematomas due to ZIKV immune-mediated thrombocytopenia,[13] petechiae[14] (Fig. 2b), ecchymosis, aphthous and ulcerous lesions of the oral mucosa,[15,16] and jaundice.[17] Conjunctivitis is considered one of the most common ZIKV signs[2,9] (Fig. 1a); it is often non-purulent and frequently described as conjunctival hyperaemia.[2,9]

In addition, the occurrence of psoriatic-like lesions (Fig. 2c,d) weeks after acute ZIKV infection in patients with no personal or family history of psoriasis has been described.[18] It is possible that genetic changes in ZIKV could be responsible for phenotypic changes influencing virulence and the clinical outcome of some of these patients, as noted previously for other arboviruses.

Pathogenesis

Because skin cells are the first to encounter arboviruses after their inoculation into the host, the identification of susceptible cell types is of pivotal importance for

Table 1 Clinicohistopathological correlation across the spectrum of ZIKV cutaneous lesions.

Lesion type	Histopathological findings
Classic erythematous maculopapular rash (Fig. 1c,d)	Non-specific lymphocytic dermal infiltrate, often perivascular and superficial (Fig. 3a,b)
Macular and patch-like lesions (Fig. 1a)	Slight acanthosis, focal spongiosis (Fig. 3c,d), erythrocyte extravasation and slight papillary dermal oedema (Fig. 3d)
Confluent macular lesions (mimicking those observed in CHIKV) (Fig. 1e)	Variable degree of spongiosis, focal exocytosis of lymphocytes into the epidermis and focal dyskeratosis (Fig. 3c)
Post-ZIKV psoriatic-like lesions (Fig. 2c,d)	Psoriasiform hyperplasia with regular acanthosis, focal parakeratosis, and a dense perivascular and interface lymphocytic infiltrate was a consistent finding (Fig. 3e,f)

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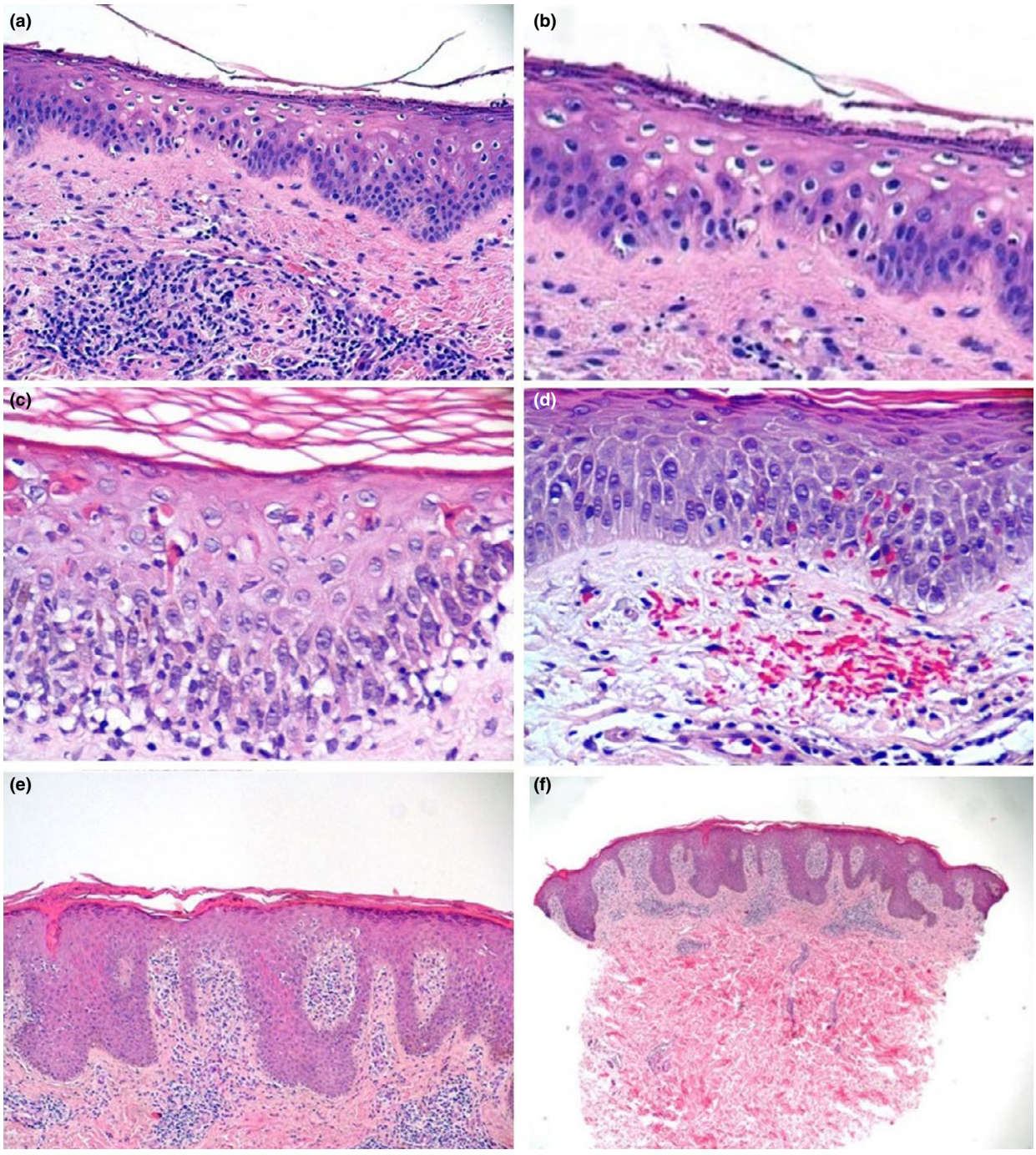

Figure 3 (a,b) Cytoplasmic keratinocyte vacuolation with presence of pyknotic nuclei as described by Hamel *et al.* experimentally. (c) Vacuolar degeneration of the basal cell layer, with presence of necrotic keratinocytes and a lymphocyte-predominant interface infiltrate. (d) Erythrocyte extravasation and slight papillary dermal oedema. (e,f) Psoriasiform hyperplasia with regular acanthosis, focal parakeratosis, and a dense perivascular and interface lymphocytic infiltrate. Haematoxylin and eosin, original magnification (a,e) × 100; (b,c) × 400; (d) × 200; (f) × 20.

elucidating the pathogenic aspects of ZIKV infection. As with other mosquito-borne viruses, ZIKV infection is initiated by a blood-feeding female mosquito[2] injecting the virus into the skin. The virus infects and replicates in skin-resident cells such as dermal macrophages and skin fibroblasts.[19] within which an initial immune

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response is triggered, as observed with other mosquito-borne viruses.[20,21] The concurrent delivery of several well-known constituents of mosquito saliva aids and potentiates the capacity of arboviruses such as ZIKV to replicate at the site of inoculation,[22–24] leading to an increased viraemic phase in the vertebrate host[25] and its dissemination to other tissues, causing acute viral symptoms.[22,26]

Epidermal keratinocytes, immature dendritic cells (DCs) and dermal fibroblasts are permissive to infection by ZIKV,[19] with over a dozen receptors and attachment factors playing a role in the entry of flaviviruses into mammalian cells.[19] ZIKV also infects and replicates in other cells of the cutaneous milieu that exhibit a selective tropism-based receptor-expression profile.[19,21] Human keratinocytes are permissive to ZIKV replication,[19] as suggested by the cytopathic effects observed in experimentally infected cells.[19] In addition, apoptotic blebs serve as shelter for the virus, allowing it to evade the host's cellular and humoral immune response.[27]

Cutaneous fibroblasts also allow active viral replication,[19] where ZIKV is able to trigger its replication by autophagy induction.[19] Langerhans cells and dermal/interstitial DCs have been shown to be permissive for the growth of DENV, thus providing a potential mechanism for transmission through the human skin.[28] Preliminary results from Hamel *et al.*[19] reveal that up to 50% of human *in vitro*-generated immature DCs challenged with ZIKV will express virus envelope proteins, suggesting a role for DCs as potential 'Trojan horses' for the propagation of the virus in human skin.[19]

Diagnosis

Considerations on the differential diagnostic approach, not only to ZIKV infection but other arboviruses, is challenging and must be based not only the type of cutaneous lesions but also on systemic signs and symptoms. In-depth understanding of the natural history and epidemiology of arboviral infections is pivotal, as the incubation period and onset of symptoms may differ widely or overlap in some circumstances.[4] For example, the incubation period for ZIKV, CHIKV and DENV may significantly overlap, with a time range of 5–10 days for each.[4] Other commonly considered differentials include Mayaro virus,[4] West Nile virus,[29] human herpesviruses (particularly HHV-6),[30] enteroviruses, rubella and measles, among others.[2,31] Parvovirus B19 may cause arthralgias akin to those caused by arthritogenic alphaviruses such as CHIKV.[31]

Histopathological findings are nonspecific, but vary according to lesion types (Table 1). Nucleic acid testing (NAT) of whole blood, serum or urine is the gold standard in patients presenting with symptom duration of ≤ 7 days.[9] Because Zika IgM can persist for months after infection, clinicians should no longer routinely recommend IgM testing unless a plaque reduction neutralization test is performed.[9]

Conclusions

Lessons learned from what has been observed in the recent outbreak in the Americas have been useful in guiding efforts to help recognize ZIKV disease and its potential complications from a clinical standpoint. Despite a significant clinical overlap with other viral exanthems, the skin still holds pathognomonic clues in recognizing cutaneous ZIKV disease.

Learning points

- ZIKV is a mosquito-borne flavivirus transmitted mainly by *Aedes* mosquito species.
- Infection usually presents as an influenza-like illness, which mimics other arboviral or exanthematic viral diseases (such as CHIKV, DENV and Mayaro virus, among others).
- Classic signs and symptoms include acute onset of fever and maculopapular rash with pruritus, arthralgia/myalgia and/or conjunctivitis.
- Human keratinocytes, DCs, dermal fibroblasts and endothelial cells have been shown to be permissive for ZIKV infection.
- Histopathological findings vary according to the nature of the cutaneous lesion.
- NAT of whole blood, serum or urine is the gold standard in patients presenting with symptom duration of ≤ 7 days.

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CPD questions

Learning objective

To gain up-to-date knowledge about the pathological features of Zika virus, general aspects about its biology and interaction with human skin cells, and its recognition throughout the disease spectrum.

Question 1

Which of the following virus types is Zika virus?

(a) Poxvirus.
(b) Herpesvirus.
(c) Flavivirus.
(d) Hantavirus.
(e) Togavirus.

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Question 2

Which of the following statements about the clinical features of Zika virus infection is true?

(a) ZIKV lesions present as generalized, sharply marginated, hypopigmented or hyperpigmented scaling macules.
(b) It usually exhibits a triad of pruritic rash, arthralgia/myalgias and conjunctivitis.
(c) Lesions usually appear as discrete, small vesicular lesions on the fingers, palms and feet.
(d) Lesions are tender.
(e) Lesions usually appear on the face and spread caudally.

Question 3

Which of the following cutaneous cell populations does the Zika virus affect?

(a) Dendritic cells.
(b) Cutaneous fibroblasts.
(c) Endothelial cells.
(d) Keratinocytes.
(e) All of the above.

Question 4

Which of the following pathological features is revealed by the histopathology of Zika virus?

(a) Perivascular lymphocytic dermal infiltrate and erythrocyte extravasation.
(b) Multinucleated keratinocytes with nuclear moulding.
(c) Focal spongiosis and dyskeratosis.
(d) Reticular degeneration and eosinophilic cytoplasmic inclusions.
(e) Both (a) and (c).

Question 5

Which of the following statements about diagnosis of Zika virus infection is true?

(a) Histopathological examination is the gold standard.
(b) Testing for Zika IgM is routine.
(c) IgM testing should be confirmed by a plaque reduction neutralization test).
(d) Nucleic acid testing remains positive for over 20 days.
(e) None of the above.

Instructions for answering questions

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