Concise report

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Generalized pustular psoriasis triggered by Zika virus infection

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Summary

Zika virus is an emerging arbovirus, which is expanding in epidemic proportions through tropical and subtropical areas of the world. Although Zika is linked to a number of congenital and neurological complications, there is scarce knowledge on the impact of ZIKV infection in human skin. We report the case of a 68-year old woman who presented with generalized pustular psoriasis after a preceding and otherwise uneventful episode of ZIKV infection. Based on recent experimental data on the biology of ZIKV infection in the cutaneous environment, we speculate that ZIKV may have directly triggered the development of generalized pustular psoriasis by stimulation of keratinocyte-derived mediators of inflammation and a polyfunctional T-cell driven immune reaction in the cutaneous milieu.

Zika virus (ZIKV) is an emerging arthropod-borne virus belonging to the Flaviviridae family,[1] which is expanding in epidemic proportions through tropical and subtropical areas around the world.[1] Transmission is predominantly vector-borne (mainly by *Aedes* mosquito species), although nonvectorial transmission (maternal–fetal, sexual, transfusion-related) has gained particular relevance during the pandemic.[1] The clinical presentation of ZIKV is nonspecific, and it is often misdiagnosed with other classic viral exanthems and arboviral infections such as Chikungunya (CHIKV), Dengue and Mayaro,[1,2] thus posing a challenge at the time of diagnosis. While ZIKV is mostly asymptomatic, the classic signs and symptoms of infection include mild fever, headaches, fatigue, rash, arthritis and/or arthralgia, myalgia, and conjunctivitis.[1,2] The emergence of ZIKV has been linked to the development of a number of clinical complications, mainly congenital and neurological,[1] yet, besides its self-limiting pruritic maculopapular rash, little is known about the biology and cutaneous manifestations of ZIKV disease.

Infections are among the well-known triggers of psoriasis.[3] We report an exceptionally interesting case of psoriasis presenting 3 weeks after an otherwise uneventful resolution of acute ZIKV infection.

Report

A 68-year-old woman with no personal or family history of psoriasis presented with a 10-day history of generalized erythema and sharply marginated scaly plaques of acute onset. She also reported general malaise, fever and localized tenderness. Three weeks previously, she had developed a pruritic maculopapular rash along with asthenia, small joint arthralgias and conjuctival hyperaemia, which resolved uneventfully after 5 days. At that time, full blood count (FBC) and blood chemistry results were unremarkable except

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for mild lymphocyte leucocytosis. Serological analyses using a commercial kit (Zika Virastripe® IgG/IgM test kit; Viramed®, Planegg, Germany) revealed positive IgM and negative IgG levels. Additional serological testing for DENV, CHIKV, EBV, CMV and parvovirus returned negative results. Reverse transcription PCR was negative for DENV and CHIKV but positive for ZIKV.

On physical examination, the patient was found to have extensive erythema and sharply demarcated,

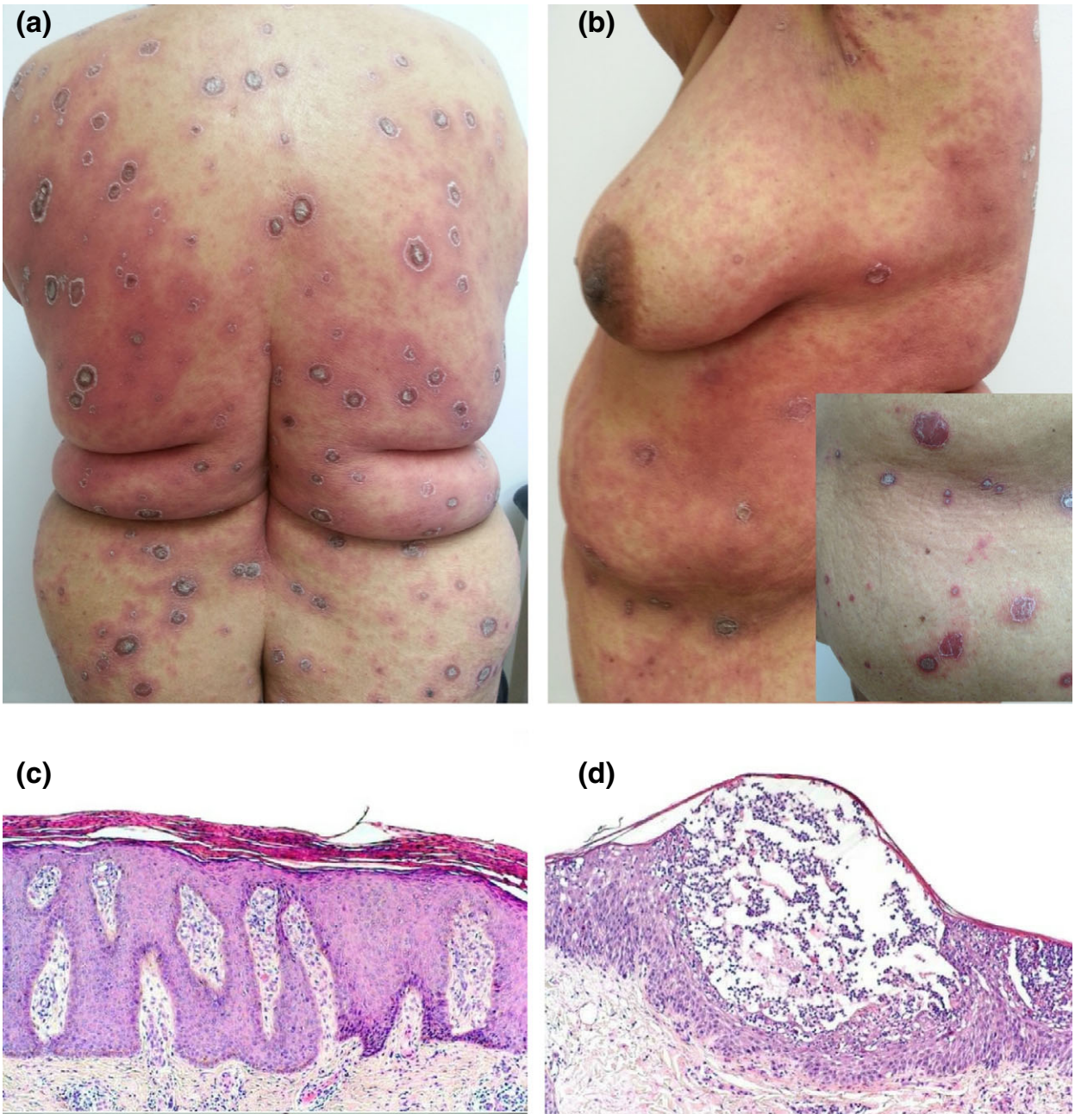

Figure 1 (a) Sharply demarcated erythematous scaly round to oval plaques with coalescing macroscopic pustules forming large central crusts. (b) A background of extensive erythorderma with sharply demarcated psoriatic plaques. Inset shows close-up of coalescing and individual dried pustules. (c) Psoriasiform hyperplasia with pronounced neutrophil exocytosis and parakeratosis; (d) subcorneal intraepidermal pustule with neighbouring spongiform changes and neutrophil exocytosis. Haematoxylin and eosin, original magnification (a,b) × 40.

erythematous, round to oval plaques with whitish central scales arranged in an arciform pattern. Most plaques harboured obvious coalescing, macroscopic, dried pustules forming large central crusts (Fig. 1a,b). Lesions started as erythematous macules, exhibiting abrupt centrifugal expansion in a period of hours. Interestingly, most lesions were localized to the trunk and proximal aspects of limbs, where the original ZIKV-associated rash was more pronounced.

Histological examination revealed psoriasiform epidermal hyperplasia with horizontally confluent parakeratosis and neutrophil exocytosis (Fig. 1c) at the lesion edges, along with intraepidermal (subcorneal) neutrophilic pustules towards the centre (Fig. 1d), and a mixed dermal lymphocytic and neutrophil infiltrate.

At admission, FBC, blood chemistry and hepatic transaminase tests were normal, while C-reactive protein was elevated (98 mg/L; normal < 10 mg/L). Screening for other infectious agents including hepatitis A, B and C, human immunodeficiency virus and syphilis was negative. Antistreptolysin O titre testing returned negative results as well.

The patient was started on intensive topical therapy with class 1 steroids (clobetasol propionate 0.05% twice daily) and methotrexate at a starting dose of 7.5 mg weekly. Her symptoms gradually resolved with persistence of a few large lesions that eventually faded after 15 weeks. She did not report any side effects, and laboratory values remained normal.

Psoriasis is a chronic skin disease that affects approximately 2% of the population.[4] There are many triggering factors, both external and systemic, capable of inducing the disease phenotype in susceptible individuals.[4] Compelling evidence suggests that many microorganisms may play a role in the onset or exacerbation of psoriasis.[3] Bacterial agents such as streptococci and staphylococci are considered the most common players implicated in the development of the disease, presumably through superantigen activation of skin-seeking T cells.[3]

Other agents linked to the pathogenesis of psoriasis include fungi such as *Malassezia* and *Candida* spp. Similar to pyogenic bacteria, these organisms may colonize the skin surface and elicit an upregulation of keratinocyte expression, promoting a hyperproliferative state and production of T cell-activating superantigenic factors.[3] In addition, infection with viral agents such as retroviruses,[3] Epstein–Barr virus[5], varicella zoster virus,[6] cytomegalovirus,[5] human papilloma virus[3] and herpes simplex virus[7] have also been reported as associated with the onset of psoriasis. Moreover, a recent study has suggested the potential role of CHIKV as a trigger for psoriasis.[8]

Although viral triggers have been implicated in the pathogenesis of psoriasis, the exact mechanisms driving its progression have not been well established, and the precise mechanism driving the pathogenesis of ZIKV at the cutaneous level remains unclear. However, recent evidence reveals that human keratinocytes are permissive to ZIKV replication in the early stages of infection, with notable cytopathic effects and induction of apoptosis.[9] This initial interplay between the virus and keratinocyte sets the scene for the development of the psoriatic plaque-initiating events, including activation and production of type 1 interferons (IFNs) via specific induction of pattern recognition receptors and upregulation of expression of IFN-stimulated genes (*OAS2*, *ISG15* and *MX1*) as well as chemokines (such as CXCL10, CXCL11 and CCL5) that promote T-cell attraction and direct receptor independent-like antimicrobial activity.[9]

In addition, polyfunctional T-cell activation [T helper (Th)1, Th2, Th9 and Th17 response] has been reported during the acute phase of ZIKV infection.[10] Recent evidence suggests that up to 50% of human *in vitro* generated immature dendritic cells (DCs) challenged with ZIKV express virus envelope proteins (favouring propagation of the virus in human skin).[9] Such evidence supports a role for aberrant activation of dermal DCs, leading to stimulation of autoreactive Th17 cells and cytokines, thus inducing keratinocyte activation and epidermal proliferation. In addition, ZIKV is also known to subvert DC immunogenicity by downregulating MHC class II expression and antagonizing type I IFN translation, while upregulating multiple other antiviral effector mechanisms.[9,11] The ability of ZIKV to modulate the immune response may be influenced by strain-related replication kinetics or host-related susceptibility factors.[11]

To our knowledge, this is the first report indicating ZIKV as a possible trigger for psoriasis. Experimental evidence suggests that the virus directly contributes to the release of keratinocyte-derived mediators of the inflammatory process and the T-cell driven immune reaction that drives the evolution of the psoriatic reaction. The association reported in this case provides important clinical insights for further studies.

Learning points

- ZIKV is an emerging arthropod-borne virus of the Flaviviridae family.
- Cutaneous clinical manifestations are nonspecific and often misdiagnosed with those of Chikungunya, Dengue and Mayaro viruses.
- Pruritic maculopapular rash, conjunctival hyperaemia and severe oedema of the distal joints are distinct signs of ZIKV infection.
- ZIKV may play a role as a triggering factor in the development of pustular psoriasis.
- Serological test and nucleic acid amplification test for ZIKV should be performed in all patients with acute-onset psoriasis following nonspecific arboviral-like exanthems.

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