Chikungunya Pathogenesis: From the Clinics to the Bench

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Chikungunya alphavirus has caused large epidemics worldwide and leads to acute incapacitating polyarthralgia. The inflammatory reaction over several days will drive robust innate and humoral responses essential to control the infection. Critically, fatal cases and mother-to-child transmission have also been described. Chikungunya can give rise to chronic musculoskeletal diseases, which can last for months to years, particularly in elderly individuals, and occasionally leads to seronegative rheumatoid arthritis–like pathologies. Histopathological studies of patient biopsy specimens and animal models have revealed that chikungunya virus can hide in tissue sanctuaries, and ongoing research should help to decipher the inflammatory mechanisms of tissue injuries.

Keywords. alphavirus; polyarthralgia; arthritis; innate immunity; encephalitis; inflammation.

Chikungunya fever (CHIKF) is an arthropod-borne viral disease transmitted by Aedes aegypti and Aedes albopictus mosquitoes. CHIKF is characterized by fever, headache, rash, and debilitating polyarthralgia, with an incubation period of 3–7 days [1]. The disease is caused by chikungunya virus (CHIKV), an alphavirus that belongs to the Togaviridae family. In the Makonde language, chikungunya means “to walk bent over,” which is the classic posture adopted by patient with CHIKF who have excruciating joint and muscle pains during the acute phase of the disease. Acute and incapacitating polyarthralgia associated with myalgia are generally the most exacerbated clinical hallmarks that distinguish patients with CHIKF from those with other tropical infections, such as dengue and leptospirosis [2]. CHIKF is commonly associated with thrombocytopenia, lymphopenia, and elevated levels of transaminases [2]. The diagnosis can be established by the detection of the viral RNA and by serological detection of CHIKV-specific immunoglobulin M and immunoglobulin G. CHIKF has long been thought to be mainly an incapacitating disease, with 5%–15% of cases remaining asymptomatic. However, since the outbreaks in the Indian Ocean islands and coinciding with emergence of the mutation A226V in the A. albopictus East/Central/South African–adapted virus strains, severe forms (defined as forms requiring clinical support of at least 1 vital function) and deaths associated with comorbidities have been reported [3].

La Réunion was the scene of a major epidemic that affected one third of the population and yielded >250 000 cases. A new wave of CHIKV outbreaks has been reported in the Americas since November 2013, owing to the adaptation of the Asian A. aegypti strain in the French West Indies and Caribbean islands. The virus has since spread to several parts of Central and Latin America, resulting in >2 million suspected cases [4].

The 2005–2006 epidemic in La Réunion was the first time that mother-to-child transmissions and deaths due to CHIKV neuroinfection were documented [3, 5]. Guillain-Barré syndrome also occurred in adult patients and required respiratory support. CHIKF was found to cause profound acute arthritic symptoms, particularly in patients >45 years of age, leading to chronic incapacitating arthritis as described in many other alphaviral diseases. Rheumatic manifestations in adult patients (6 months to years after infection) typically consisted of a painful arthritis mainly affecting the extremities (ankles, wrists, and phalanges). Moreover, patients with rheumatoid arthritis–like illnesses after CHIKF infection were also reported. However and in contrast to what is known in canonical autoimmune rheumatoid arthritis, levels of rheumatoid factor and anticitrullinated protein antibodies were not necessarily elevated in the acute and chronic phases of the diseases [6]. This would indicate that arthritis emerging after CHIKF infection is driven by a distinct and chronic local inflammatory reaction in the joint.

IMMUNOPATHOGENESIS OF CHIKF IN ACUTE AND CHRONIC SETTINGS

A plethora of cutaneous manifestations, including erythematous maculopapular or morbilliform eruption, which subsides without any sequelae in 3–4 days, has been reported after CHIKF. This eruption could be a hallmark of an inflammatory response of the skin (the portal of entry of the virus after the mosquito’s bite) to mobilize resident cells such as keratinocytes, melanocytes, and dermal fibroblasts (Figure 1). CHIKV has been postulated to interact with other resident antigen-presenting skin cells, including Langerhans cells, which then spread the virus to other target organs, such as muscles, liver, kidney, heart, and brain. Experimental infection in several animal models has documented the capacity of CHIKV to infect fibroblasts of the...
joint connective tissue, cells of the leptomeningeal membrane, glial cells, liver macrophages, and sinusoidal capillary endothelial cells (Supplementary Table 1). It is now well established that hematopoietic and nonhematopoietic cells are engaged in the control of CHIKV infection [7, 8]. Viral load can be as high as $10^{10}$ virus particles per milliliter of blood during the first days of infection. This major viral load triggers a robust activation of the innate immune system, with the production of interferon type I and interferon-stimulated genes essential to thwart the infectious challenge. It has been established that primary monocytes and macrophages are the major hematopoietic subsets targeted by CHIKV, as reported in patients with CHIKF and in animal models [9, 10]. We were the first to report that CHIKV could also hide in human synovial tissue sanctuaries despite a robust adaptive immune response (Figure 1). Arthralgia experienced by patients with CHIKF closely resembles the symptoms induced by other alphaviruses and is characterized by severe joint pain due to inflammation and tissue destruction. Prostaglandins have been shown to be highly expressed by CHIKV-infected fibroblasts and may contribute to activation of nociceptors and sensitization, as described in osteoarthritis joints [11]. More recently, it was demonstrated that osteoblasts could be infected by CHIKV and drive osteoclastogenesis in vitro. Interestingly, cohort studies have revealed that high levels of RANKL/osteoprotegerin were detected in CHIKV-infected patients and could be implicated in the activation of macrophage-derived osteoclasts. Osteoclasts are known to cause bone erosion and may be involved in bone destruction in alphavirus-induced pathology [12]. The arthritis post-CHIKV is generally non erosive and particularly if the patients are treated with methotrexate [1].

**PATHOLOGY OF SEVERE AND FATAL CHIKF**

Studies have documented that mortality due to CHIKF can occur within the first days after hospital admission, despite aggressive intravenous fluids, antibiotic administration, and vasopressor support [13]. Most fatal cases showed neurological and respiratory deterioration with progression to multiple organ failure. According to clinical and laboratory findings reported in studies, renal failure with high creatinine values and elevated transaminase levels were frequent among fatal cases. Acute hepatitis also has been documented in severe CHIKF [14]. Moreover, acute myopericarditis diagnosed with ST-segment elevation on an electrocardiogram and an increase in...
troponin levels have been documented in patients with CHIKF. Severe encephalitis was confirmed by the detection of viral RNA or anti-CHIKV immunoglobulin M antibodies in the cerebrospinal fluid.

Histopathological studies of CHIKF in humans are difficult to perform because fatal cases are rare and occur mainly in remote parts of the world. It is interesting to note that, in cases of dengue virus infection, when complications set in, the virus is no longer detectable in blood, and therefore the overt host response might play a critical role in pathogenesis. Critically, the robust activation of immune cells can result in cascades of inflammatory cytokines, including tumor necrosis factor α, interleukins, and other biochemical mediators, that increase vascular endothelial permeability and trigger further tissue injuries. In contrast, studies have documented that mortality due to CHIKF has occurred within the first days of disease, when polymerase chain reaction analysis of serum detected CHIKV. The most frequent histopathological findings documented in lungs from fatal cases of CHIKF were generalized alveolar edema without inflammatory infiltrates. Similarly, pathological findings in kidney tissue specimens were glomerular edema and tubular interstitial nephritis, as well as tubular necrosis in some cases. Acute and incipient pericarditis with inflammatory mononuclear infiltrates have been documented. Coagulative nonconfluent hepatocellular necrosis was the most prominent finding in liver specimens, while congestion with reactive plasmocytosis has been documented in the spleen.

CONCLUSION

To date, several animal models can fully reproduce the acute arthralgia/arthritides and encephalitis syndrome as described in patients with CHIKF (Supplementary Table 1). The immune response is key to thwart off the infectious challenge from the systemic circulation [15]. Moreover, ongoing and further studies should help to delineate the mechanisms involved in virus persistence, particularly in tissue sanctuaries, such as the synovial tissue. In contrast, little is known about the mechanisms that contribute to the development of chronic disease due to CHIKV. Several elements should be dissected out and investigating for instance: (i) genetic predispositions; (ii) the role of pre-exist osteoarthritis and other co-morbidities; (iii) the mechanisms of virus-mediated tissue injury; (iv) the polarization of myeloid cells to an immunosuppressive state; (v) the role of macrophages and other innate immune cells in inflammation and tissue injuries; (vi) the activation if any of a unique type of autoimmune responses (humoral and cellular). More research involving cohort studies and improved animal models is highly warranted to identify and validate effective therapies.

Supplementary Data

Supplementary materials are available at http://jid.oxfordjournals.org. Consisting of data provided by the author to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the author, so questions or comments should be addressed to the author.

Notes

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