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# Successful Live Kidney Transplantation After Chikungunya Disease in the Donor

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## INTRODUCTION

With more than 30% of the world's population living in risk areas, the global dissemination of arbovirus infections is a matter of increasing concern.[1,2] Besides numerous barriers to effective vector control, there is the added challenge of dealing with pathologic entities that are not yet fully understood.

Decisions involving donors and the recipients of organs and tissues regarding arbovirus infections are complicated by uncertainty about the risk of disease transmission. Because of this, a 4-week quarantine for blood donation has been recommended after travel to endemic areas.[2] However, the risk of blood-borne transmission may differ for different arboviruses. For example, even in individuals who are free of symptoms, it may be greater for infections with higher viremic loads, such as chikungunya virus (CHIKV) infections, as compared with some of the arthropod-borne viral diseases.[3,4]

Despite the high counts of circulating virions, in its usual clinical presentation, CHIKV infection is rarely fatal. Nevertheless, extremes of age, underlying diseases, and states of immunosuppression are believed to carry a heightened risk of severe multisystem disease and mortality.[1] Furthermore, during the 2005–2006 epidemic on Réunion Island, infectious CHIKV was isolated from the corneal grafts of potential donors who died during early stages of the disease, detected by nucleic acid testing (NAT) or positive IgM serology.[5] These concerns have led to the recommendation to screen potential deceased donors in or returning from areas endemic for CHIKV infection with the purpose of exclusion from organ donation.[6,7]

In live kidney donation, transplantation can be theoretically postponed and carried out at a later date after protective immunity has developed, if it were not for the observation in humans and in experimental models that CHIKV may persist in deep tissue sanctuaries for many months after the original infection.[8,9] For example, in an experimental model in primates, CHIKV persistence was observed in the joints, muscles, lymphoid organs, and liver, with macrophages being identified as the main cellular reservoir.[8] This persistence phenomenon is a concern in connection with the transplantation of macrophage-harboring solid organs, such as the kidney. In this report, we present how we dealt with this uncertainty, discuss our results, and propose a decision flowchart to aid in making the decision in similar cases.

## CASE REPORT

A 42-year-old HIV-positive woman, who had been undergoing hemodialysis for 5 years, was being prepared for kidney transplantation. The candidate for the donation was her previously healthy 41-year-old sister.

For 2 years, the recipient was being considered as a candidate for transplantation; she initially presented with a CD4+ T-cell count below the limit allowed for transplant approval. In a joint follow-up with an assistant physician, in December 2015, the patient had a CD4 count above 200 cells/mm$^3$. Because of her history, this result was confirmed (326 cells/mm$^3$), and the

procedure was electively scheduled. During this period, she maintained an undetectable viral load.

On admission to the hospital for surgery, the donor was noted to have a fever, rash, generalized malaise, and joint pain that had started 4 days earlier. Because the state of Rio de Janeiro was in the midst of an epidemic of arbovirus infections that included dengue, Zika, and chikungunya fevers, surgery was deferred, and a diagnosis was sought.

RNA was extracted from 140-µl samples of the donor's serum, plasma, and urine using the QIA amp Viral RNA Mini Kit (Qiagen, Hilden, Germany), according to the manufacturer's recommendations. Samples were tested for Zika virus and CHIKV by real-time polymerase chain reaction using specific primer and probe sets; 5-FAM was used as the reporter for the probe (Zika virus 1086, Zika virus 1162c, and Zika virus 1107-FAM; CHIKV 6856, CHIKV 6981, and CHIKV 6919-FAM).[10,11] RNA was amplified by real-time polymerase chain reaction in an ABI Prism 7500 real-time cycler (Applied Biosystems, Foster City, CA). The reaction was performed with 10 µl of RNA using the TaqMan One-Step Real-Time PCR Master Mix reagents (Applied Biosystems) according to the manufacturer's protocol. For Zika real-time polymerase chain reaction, a cutoff value corresponding to 38.5 was defined as indicating a positive result.

Based on the positive result of qualitative NAT of the blood, CHIKV infection was diagnosed, and renal transplantation was suspended pending further testing. Results of tests for dengue and Zika virus infection were negative. The donor was followed up with periodic collection of blood and urine for NAT and serology for CHIKV. Two weeks after the initial symptoms appeared, the patient was free of symptoms and reaffirmed her desire to donate. Results of subsequent qualitative of the donor's blood and urine were negative at 52 and 101 days after the onset of symptoms. Chikungunya IgM and IgG enzyme-linked immunosorbent assay (Euroimmun, Luebeck, Germany) results are shown in Table 1.

In spite of the recipient's history of HIV infection, both the transplant and the virology teams believed that the chance of CHIKV transmission by the transplanted kidney was very low. The situation was discussed with the recipient and relatives who chose to sign the informed consent form and accept the known and unknown risks of proceeding with transplantation. Special approval from the hospital ethics committee was obtained.

Renal transplantation took place on October 6, 2016, 4 months after the originally scheduled date. The recipient was discharged 1 week later with a serum creatinine level of 0.8 mg/dl.

Serology obtained 3 weeks after the procedure was negative for both anti-CHIKV IgG and IgM antibodies. Results of NAT were also negative.

The patient developed mild lymphopenia in the first month. Because of the satisfactory clinical outcome and the absence of other abnormalities, we associated this finding with the temporary interruption of the HIV antiretroviral therapy for 1 week, followed by the change in the regimen, which was recommended by the infectious disease assistant team to avoid drug interaction with immunosuppressants in the initial phase of transplantation. After adjustment of the new HIV antiretroviral drugs, the lymphocyte levels returned to normal range in the second month.

Six months later, the patient remains stable with a serum creatinine level of 0.8 mg/dl, and she is being followed up at the transplant outpatient clinic.

**Table 1.** Results of serologic and qualitative nucleic acid testing assays in the donor

| Days from onset of symptoms | CHIKV IgM ELISA (S/CO) | CHIKV IgG ELISA (S/CO) | Nucleic acid testing for CHIKV urine | Nucleic acid testing for CHIKV serum |
|---|---|---|---|---|
| 4 | Positive (5,05) | Negative (0,72) | Undetected | Positive |
| 52 | Positive (4,35) | Positive (3,49) | Undetected | Undetected |
| 101 | Borderline (0,94) | Positive (3,95) | Undetected | Undetected |

CHIKV, chikungunya virus; ELISA, enzyme-linked immunosorbent assay; S/CO, sample optical density/assay cutoff.

## DISCUSSION

Infections caused by CHIKV have emerged on the American continent over the last 5 years and have rapidly assumed epidemic proportions. More than 90% of CHIKV infections already identified in the Americas have occurred in Brazil, with a significant surge in recent years. In 2016, the number of probable cases reached 272,000, an increase of more than 700% over the previous year.[12]

The incubation period for CHIKV varies from 1 to 12 days, with an average of 2 to 4 days.[13] Viremia has an average duration of 5 to 7 days.[2] The virus can be spread through a mosquito bite or the transfusion of blood products, by vertical transmission, or during the peripartum period.[1,2]

In spite of the recent rapid global spread of arbovirus infections, reports of transfusion or transplant-related transmissions have been rare so far.[14,15] Very few confirmed or possible cases of transplant-transmitted infections caused by West Nile and dengue viruses have been reported.[15] So far, no cases of CHIKV transmission by tissue or organ grafting have been documented, although infective viral particles have been identified in tissue grafts from deceased

donors with recent infections.[5] The relatively short viremic phase, careful clinical screening and NAT, and occasional bans of potential donors from risk areas may have been instrumental in achieving this favorable result. On the other hand, the long-term persistence of CHIKV RNA in tissue "sanctuaries" is cause for additional concern regarding the appropriate timing for organ donation after an acute infection, although in an experimental model, the kidneys were apparently spared from harboring persistent viral RNA.[8]

In dealing with the situation, we identified issues related to bioethics, patient autonomy, and risk management. The novelty of the clinical entity and the scarcity of medical literature on the subject did not provide us with a sufficient background to be confident that transplantation could be carried out with safety, even after the apparent resolution of the donor infection and her willingness to go ahead with surgery. We therefore approached the risk from 2 perspectives: the probability and the severity of the event, if it occurred. In addition, the autonomy of the patient was a determining factor in our decision.

In the case of the donor, all symptoms disappeared completely within 2 weeks. Considering what is already known about the clinical behavior of the infection, the short viremic phase, the absence of chronic symptoms indicative of potential viral persistence, and her prompt seroconversion, we believed that the probability of CHIKV transmission was very low. Nevertheless, as an extra measure of safety, we extended the follow-up for 3 more months, with repeated viral testing, before proceeding with transplantation.

In terms of the criticality of the event of possible CHIKV transmission by the graft, there is also little published information. Most cases of CHIKV infection are either asymptomatic or benign and self-limited.[1,2] However, an increased risk of severe disease has been described in patients with underlying medical conditions, including immunosuppressed individuals.[1]

We are aware of 3 cases of CHIKV infection in long-term transplant recipients. One was a liver transplant recipient with suspected encephalitis.[16] Another was an HIV-positive recipient who developed an acute viral-like illness while travelling in an endemic area who presented with persistent joint symptoms more than 1 month later.[6] The third patient presented with a 3-week history of arthralgias after travel to an endemic area in Brazil but did not report any acute symptoms.[17] The 3 patients had negative test results for viral RNA and were diagnosed based on serology. All became free of symptoms during follow-up. Although these cases point to the benign nature of CHIKV infection after solid organ transplantation, we could not rule out the possibility that an infection transmitted by the graft in association with immunosuppression would behave more aggressively than when the recipient is infected at a later date after transplantation, as appears to be the case with West Nile virus infections.[18]

We could not identify pressing concerns regarding the probability and severity of the event of virus transmission via the graft, but we also believed it was important to address the additional topic of patient autonomy. In a recent study, 175 candidates for kidney transplantation were confronted with a simulation regarding the acceptance of an organ that carried an increased risk of viral infection. Only 24% rejected the kidney under all conditions presented. Most patients would accept the kidney in certain situations.[19] These data indicate that such decisions ought to be shared and that patients must be consulted about the acceptance of organs at risk. In our case, the patient was very determined and coherent regarding her decision to undergo transplantation, even shortly after the donor's infection when the risks were believed to be too high and unacceptable by the medical team.

Because up to 15% of infections with CHIKV run an asymptomatic course,[20] we were able to confirm the absence of transmission by serology and NAT in the recipient. Therefore, although our findings are based

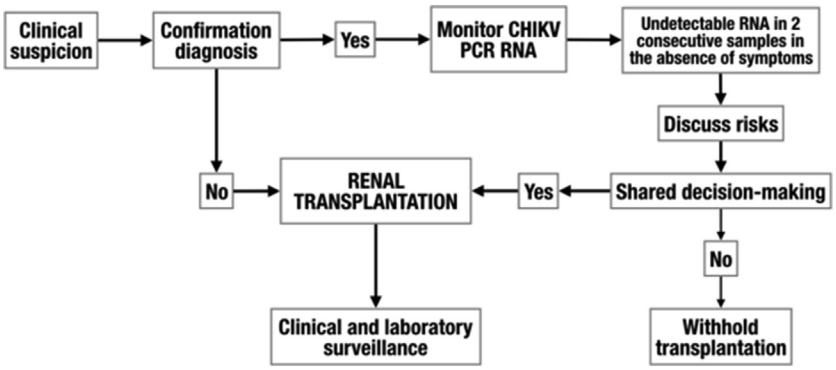


**Figure 1.** Flowchart to assist with the decision-making process. CHIKV, chikungunya virus; PCR, polymerase chain reaction

on a single report, we have demonstrated the feasibility of kidney donation within a relatively short period after a mild case of CHIKV infection. Because of doubts related to the persistence of viable virus in the tissues of patients with long-term joint symptoms, we suggest that until greater knowledge is gathered, one should wait until the symptoms have completely disappeared before accepting a donor candidate with a recent CHIKV infection.

In addition, we recommend clinical and laboratory surveillance for the recipient. Based on the incubation period of CHIKV, NAT or serologic testing performed 2 to 3 weeks after the procedure has good accuracy in detection of transmission by transplantation. After the initial period, especially in the context of an endemic area, the recommendation is controversial, and serial NAT or serologic evaluation does not have support. In these cases, a late infection does not necessarily represent a graft transmission, and simple monitoring of clinical symptoms could be sufficient.

Finally, on the basis of what we present, a flowchart is proposed to assist with the decision-making process in similar cases (Figure 1). In the absence of robust evidence, we believe that this information may be useful for transplant teams dealing with this increasingly recognized infection.

## DISCLOSURE

All the authors declared no competing interests.

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