



## Case report

# Fatal leptospirosis and chikungunya co-infection: Do not forget leptospirosis during chikungunya outbreaks



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## ABSTRACT

In endemic areas, leptospirosis can be missed by erroneous clinical or laboratory diagnosis of arboviroses or co-infections with arboviruses and an increase in mortality due to leptospirosis has already been reported during arboviruses outbreaks. During the French Polynesian chikungunya virus outbreak in 2014–2015, two leptospirosis and chikungunya co-infections were reported, one of which was fatal. Diagnosis of leptospirosis was delayed in the context of chikungunya outbreak. In the context of arbovirus outbreak, the risk of misdiagnosis of leptospirosis is maximum and clinicians should initiate early antibiotic therapy if leptospirosis is suspected. A delayed diagnosis of leptospirosis can be responsible for fatal outcome. Leptospirosis should be considered even if dengue or chikungunya virus infections are confirmed by reference molecular testing

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## Introduction

The Pacific region is a high endemic area for leptospirosis [1] and arboviruses [2]. In French Polynesia, leptospirosis, caused by *Leptospira* spp., occurs annually with a peak in the rainy season, while arboviroses, caused by dengue (DENVs), chikungunya (CHIKV) or Zika viruses, occur mainly during outbreaks. Because of a non-specific clinical presentation, leptospirosis can be misdiagnosed as arboviroses, especially dengue [3,4]. In addition, leptospirosis can be missed by erroneous clinical or laboratory diagnosis of arboviroses or co-infections with arboviruses [5–7]. To illustrate this risk we report two co-infections with *Leptospira* spp. and chikungunya virus that occurred during the CHIKV outbreak in French Polynesia in 2014–2015 (about 60,000 infections) [8], in a context of co-circulation with DENV serotypes 1 and 3. Both co-infections occurred in December 2014, during the rainy season.

## Cases

Patient 1, a 70-year-old man with a history of type 2 diabetes, severe chronic renal failure, arterial hypertension and gout, was hospitalized for severe sepsis. He had been unwell for three weeks (asthenia and diffuse arthralgia) and had experienced diffuse arthromyalgia for the past week. Members of his family had been diagnosed with chikungunya infection. On admission, he presented with severe sepsis including respiratory, hepatic and severe renal failures. Results of laboratory tests showed anemia (hemoglobin: 11.6 g/dL), leukocytosis ( $14.9 \times 10^9/L$ ) with predominance of neutrophils, lymphopenia ( $700 \times 10^6/L$ ) with associated stimulated lymphocytes, thrombocytopenia ( $35 \times 10^9/L$ ), raised liver enzymes and bilirubin (aspartate aminotransferase: 97 U/L, alanine aminotransferase: 50 U/L), total bilirubin: 46  $\mu\text{mol/L}$ , severe renal failure (creatinine: 398  $\mu\text{mol/L}$ ), hyperkalemia (4.8 mmol/L), increased C-reactive protein (351 mg/L) and procalcitonin (34 ng/mL). Chest radiography showed a right basal consolidation and perihilar infiltrates. Given the clinical picture and the absence of any obvious focus of infection, leptospirosis was suspected. The patient was treated with amoxicillin, intravenous saline and oxygen therapy and was admitted to the intensive care unit. The patient's condition rapidly worsened and he died of multiple organ failure a few hours after admission.

Patient 2, a 77-year-old man with treated pharynx cancer, presented with a one-week history of fever and myalgia. On

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admission, he was found to have septic shock, jaundice, and hepatomegaly. Results of laboratory tests showed anemia (hemoglobin: 9.7 g/dL), leukocytosis ( $37.1 \times 10^9/L$ ) with predominance of neutrophils, thrombocytopenia ( $5 \times 10^9/L$ ), raised liver enzymes and bilirubin (aspartate aminotransferase: 257 U/L, alanine aminotransferase: 78 U/L), total bilirubin: 370  $\mu\text{mol/L}$ , pancreatitis (lipase: 1133 U/L), severe renal failure (creatinine: 776  $\mu\text{mol/L}$ ), hyperkalemia (5.5 mmol/L) and increased C-reactive protein (180 mg/L). Abdominal echography was normal. Chest radiography showed a left basal condensation. The patient was treated with piperacilline + tazobactam and second generation quinolone (ciprofloxacin), and required red blood cell and aphaeresis platelets transfusion and continuous hemofiltration. Abdominal CT scan showed acute pancreatitis. After confirmation of leptospirosis, antibiotic regimen was changed to amoxicillin. His condition improved and he was discharged from the intensive care unit 10 days later.

For both patients, diagnosis was performed by *Leptospira* spp. and CHIKV detection from blood by real time PCR using commercial kits for CHIKV (RealStar<sup>®</sup> CHIKV, Altona Diagnostics) and primers and probes previously reported for *Leptospira* spp. [9]. Both patients tested negative for DENV by reverse transcription PCR [10].

Publication of identified clinical cases was approved by the ethics committee of French Polynesia (N° 61 CEPF), written consent was obtained from the patients for publication.

## Discussion

We report the first cases of leptospirosis and chikungunya co-infections, both confirmed by molecular diagnosis.

The possibility of leptospirosis and chikungunya co-infections was raised during the CHIKV outbreak in La Reunion Island, Indian Ocean, in 2006. During this outbreak there was an excess of leptospirosis mortality (from 6% for the past years to 38% during the outbreak) resulting mainly from delays in diagnosis or leptospirosis infections being initially mistaken for chikungunya, while the annual number of reported cases was stable over the period [11]. The increased fatality rate was specific to leptospirosis and was not observed for other infectious diseases. The diagnosis of leptospirosis could also have been delayed because of a delay in consulting a doctor in the context of a chikungunya outbreak, as was the case in our two patients. No leptospirosis and chikungunya co-infection was reported during the outbreak in La Reunion.

Leptospirosis and dengue co-infections have been described in Mexico [12], Barbados [6], India [13], Pakistan [14], Jamaica [15] and Peru [16]; including fatal cases in Puerto Rico [5], Sri Lanka [17] and India [13]. Increased mortality due to leptospirosis during dengue outbreaks was observed in Barbados in 1995 [6], Brazil in 2006 [7] and Puerto Rico in 2010–2012 [5]. In Barbados, leptospirosis mortality during a dengue outbreak was twice the average suggesting that some leptospirosis cases were misdiagnosed and treated inappropriately. In Brazil, it was hypothesized that, during the outbreak, the large number of dengue cases and the publicity about dengue led to missed diagnosis of leptospirosis; within the first days of the illness, 61% of leptospirosis patients received a diagnosis of dengue [7]. During a dengue epidemic in South India, the highest mortality (29.6%) was observed in dengue/leptospirosis co-infected versus leptospirosis (14.6%) and dengue (3.7%) infected patients [18]. Although difficult to assess, the impact of co-infection on case fatality rate of leptospirosis and chikungunya could be influenced by a potential synergistic effect of both pathogens, and/or a delayed diagnosis of one of the pathogens.

These data confirm that diagnostic confusion with dengue or chikungunya had a detrimental effect on leptospirosis outcome

especially because antibiotic therapy in leptospirosis is widely believed to provide the greatest benefit when initiated in the early phase of the disease [19]. For the two French Polynesian co-infected patients, the diagnosis was delayed and performed at admission in hospital because of severe sepsis. The first patient was unwell for three weeks and had experienced diffuse arthromyalgia for the past week before admission in the setting of similar cases in his family diagnosed as CHIKV infections and the second patient presented with a one-week history of fever and myalgia. CHIKV infection was initially suspected. In the setting of chikungunya outbreak the patients do not medical care, had no standard blood tests nor received antibiotics within the first week post symptoms onset. We cannot excluded that both patients were first infected by CHIKV and then presented a “chikungunya like syndrome” and by *Leptospira* sp in a second time. A the time of admission, laboratory testing of both patients yielded increase bilirubin, leukocytosis with predominance of neutrophils, increased C-reactive protein, increase creatinine and thrombocytopenia. These laboratory results are common in leptospirosis but uncommon in chikungunya [20]. However, both patients had severe thrombocytopenia. Rapid decrease of platelet count is a warning sign of severe dengue [3], it is uncommon in chikungunya but can be found in leptospirosis [4] and a slight increased C-reactive protein can be found in chikungunya [21]. We reported in Table 1 these laboratory abnormalities in leptospirosis, chikungunya and dengue. In order to avoid such mistake we recommend to patients to seek medical care during arboviruses outbreaks in case of fever and arthralgia, especially during the raining season because of the risk of leptospirosis being misdiagnosed as dengue or chikungunya. If patients seek medical care, we recommend to perform standard laboratory tests at initial presentation of patients presenting with fever and arthralgia, even in the context of arboviruses outbreak, including standard blood count (to detect leukocytosis and thrombocytopenia), renal and hepatic markers and C-reactive protein. We also recommend reevaluation of the patients a few days after initial consultation.

Several studies have shown that leptospirosis is often confused with dengue and remains underdiagnosed, as previously reported in other Pacific Islands (Federated States of Micronesia) [9]. Following a dengue fever outbreak in 2012, five diagnosis of leptospirosis were made retrospectively from 172 dengue suspected patients [9].

The risk of misdiagnosis of leptospirosis is high if the diagnosis of arboviruses relies only on serological assays due false positive results for dengue. In addition, serological testing for leptospirosis detects antibodies from the second week of illness, resulting in false negative results at the acute phase of the disease, the risk is higher when using rapid diagnostic tests that lack sensitivity and specificity for dengue and leptospirosis [22].

In developing countries, including most of the Pacific islands, diagnosis at ambulatory health services are often based on clinical findings only. In this setting and in regards to overlapping clinical features of leptospirosis with dengue or chikungunya, misdiagnosis are frequent.

**Table 1**

Laboratory abnormalities for patients 1 and 2 and comparison with mono infections by *Leptospira*, chikungunya virus and dengue virus.

| Laboratory abnormalities     | Leptospirosis | Chikungunya            | Dengue |
|------------------------------|---------------|------------------------|--------|
| Leukocytosis                 | ++            | -                      | -      |
| Thrombocytopenia             | ++            | -                      | ++     |
| Increased bilirubin          | +             | -                      | -      |
| Increased creatinine         | ++            | -                      | +      |
| Increased C-reactive protein | ++            | - (or slight increase) | -      |

During arboviruses outbreaks, the attack rate of infections is usually high, especially when it occurs in a population with low levels or no pre-existing immunity as during La Reunion and French Polynesian CHIKV outbreaks. An increased rate of leptospirosis is observed during heavy rainfall and flooding [7]. In the setting of arbovirus outbreaks, especially when climatic conditions favors leptospirosis emergence (as rainy season in French Polynesia), even if DENV or CHIKV infections are confirmed by reference molecular testing, leptospirosis should be considered if other symptoms or laboratory abnormalities raise a suspicion of leptospirosis.

Early diagnosis of leptospirosis is essential in order to implement appropriate treatment and reduce severity of illness and mortality. During arboviruses outbreaks, diagnostic strategy should systematically include leptospirosis as a differential diagnosis of dengue-like illness and consider the possibility of co-infection with arboviruses in endemic areas and in travelers returning from these regions.

### Conflict of interest

The authors state that they have no conflict of interest.

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