

## CASE REPORT

## Fatal Pulmonary Haemorrhage in Co-infection with Dengue and Leptospirosis

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### ABSTRAK

*Leptospirosis merupakan penyakit berjangkit yang semakin banyak dilaporkan di serata dunia. Simptom-simptom penyakit ini adalah tidak spesifik dan hampir menyerupai simptom jangkitan lain seperti demam denggi, malaria, hepatitis dan demam kepialu, terutamanya di negara-negara tropika di mana penyakit-penyakit tersebut adalah endemik. Demam denggi pula adalah penyakit berjangkit yang dilihat sebagai krisis kesihatan awam disebabkan kadar jangkitan sedunia yang tinggi. Dalam laporan kes ini, kami melaporkan satu kes berkenaan seorang pesakit yang mengalami demam denggi yang juga disahkan positif dengan jangkitan leptospirosis melalui ujian serologi. Koinfeksi antara demam denggi dan leptospirosis boleh menimbulkan kerumitan pada peringkat diagnosis kerana simptom-simptom bagi kedua-dua jangkitan tersebut hampir serupa. Oleh itu, pakar klinikal harus mempunyai indeks wasangka yang tinggi, khususnya di kawasan di mana kedua-dua penyakit ini adalah endemik. Penggunaan ujian diagnosis yang berasaskan antigen adalah amat penting bagi membantu pakar klinikal dalam membuat diagnosis yang tepat secepat mungkin agar rawatan yang sewajarnya dapat diberikan.*

*Kata kunci: koinfeksi, penyakit berjangkit, demam denggi, leptospirosis*

### ABSTRACT

Leptospirosis is an emerging infectious disease with worldwide distribution. Its symptoms may mimic a number of other infections such as dengue, malaria, hepatitis and typhoid fever, particularly in tropical countries where these diseases are endemic. Similarly, dengue is an important infectious disease that poses as a public health emergency due to its rapid epidemic spread across the world. Here, we report a fatal case of dengue fever in a patient who was also serologically

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positive for leptospirosis. Co-infection of both dengue and leptospirosis can lead to an illness with overlapping symptoms and therefore present a clinical diagnostic dilemma to the treating physician. Hence, a high index of suspicion among clinicians is required, especially in high endemic areas. The optimal usage of antigen-based rapid diagnostic tests is essential to aid the clinicians to make timely and accurate diagnosis as well as to start appropriate treatment regimes.

Keywords: co-infection, communicable diseases, dengue, leptospirosis

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## INTRODUCTION

Dengue and leptospirosis, commonly found in humid tropical and subtropical areas, are infectious diseases of global importance. Mixed infections of these two pathogens which are associated with high mortality, are typically seen in areas of high endemicity, especially in Malaysia.

Dengue is the fastest spreading vector-borne disease in the world that is transmitted by mosquitoes *Aedes aegypti* and *Aedes albopictus*. The incidence of dengue infection continues to rise with growing geographic expansion to new countries for the past half-century, and a 30-fold increase has been reported for that period (World Health Organization 2009). In fact, the number of reported cases in Malaysia has notably increased over the previous decade; from 32 cases per 100,000 to 361 cases per 100,000 in 2014 (MOH 2015). This mosquito-borne viral illness places 2.5 million people in more than 100 countries at risk with an annual estimation of 50 million cases of dengue infections occur worldwide (World Health Organization 2009).

Leptospirosis is a bacterial infection caused by the spirochete leptospiraceae and is the most common zoonosis

worldwide. According to WHO, the yearly incidence of leptospirosis ranges from 0.1–1.0/100,000 in temperate climates to 10–100/100,000 in the humid tropics (World Health Organization 2003). In addition, the incidence may reach over 100 per 100,000 during out breaks particularly in five high-exposure risk groups (World Health Organization 2003).

The clinical manifestation of both infectious diseases at early stages of illness consists of an ample array of non-specific signs and symptoms such as high-grade fever, anorexia, generalised body ache, arthralgia, myalgia, nausea, and vomiting (Libraty et al. 2007; Flannery et al. 2001). Libraty et al. (2007) reported that the presence of petechial rash was significantly higher in dengue patients compared to those with leptospirosis. Another study conducted in Brazil by Flannery et al. (2001) showed that a greater proportion of patients develop jaundice in leptospirosis infection compared to those with dengue. However, both of the aforementioned symptoms present at the late stage of the diseases. Because their clinical manifestations at early stages are similar, it may complicate the diagnosis and management of such patients with acute fever. We report a

fatal case of a patient who presented with acute febrile illness (AFI) and was positive for dengue virus DENV-3 and *leptospiral spp.*

### CASE REPORT

A 43-yrs-old farmer presented to a district hospital in Sarawak, East Malaysia with a history of high grade fever, generalised bodyache as well as haemoptysis for three days. He was previously well. He denied abdominal pain, nausea or vomiting. Neither chest discomfort nor shortness of breath was reported. The initial blood investigation showed leukopenia and thrombocytopenia, which prompted his referral to the nearest tertiary centre for further management.

On examination, the patient was conscious and orientated with good hydration status. His blood pressure was 107/59 mmHg and the pulse rate was 85 beat/min which was regular and of good volume. He was not tachypnoeic with a respiratory rate of 20 breaths/min. Documented temperature in the Emergency Department was 39.9 °C. Examination of the abdomen showed enlarged liver 3 cm below the right costal margin with neither tenderness nor guarding. In addition, there was no jaundice or rash. Other systemic examinations were unremarkable.

Repeated blood investigations showed bicytopenia with deranged renal and liver function tests (Table 1). The initial chest radiograph was normal. The diagnosis of dengue fever with warning signs was initially made based on his presenting features and a positive dengue NS-1 antigen test.

The patient's serum was also tested for dengue specific IgM antibodies using enzyme-linked immunosorbent assay (ELISA) which came out to be positive. He was managed with appropriate supportive therapy and hydration with crystalloid fluids according to the established guidelines for dengue. However, four hours later, his condition drastically deteriorated. He developed fulminant pulmonary haemorrhage which required invasive ventilation. Intravenous (IV) Ceftriaxone was promptly started based on strong clinical suspicion of leptospirosis despite pending confirmatory serology. The leptospirosis IgM rapid test was then reported to be positive and was further confirmed with a positive microscopic agglutination test (MAT) as shown in Table 1. Reverse transcriptase polymerase chain reaction (RT-PCR) was also performed and dengue virus type 3 (DENV-3) infection was identified.

Throughout his admission in the intensive care unit, his condition did not improve despite aggressive medical regimes as well as escalation of antibiotics. Ventilation became increasingly difficult and required high ventilator settings due to persistent pulmonary haemorrhage with Type II respiratory failure and was further compounded by ventilator-acquired pneumonia. There was worsening of diffuse opacity over bilateral lung fields, as evidenced in the serial chest X-rays in Figure 1. In addition to that, severe thrombocytopenia persisted despite multiple blood product transfusions (Table 1). On day 23 of hospital admission, the patient, unfortunately, succumbed to death.

Table 1: Laboratory results on the first, seventh, fourteenth and twenty-first day of hospitalization, respectively.

| Laboratory Results                      | Day 1    | Day 4 | Day 17 | Day21 |
|---|----------|-------|--------|-------|
| Haemoglobin (g/dL)                      | 16.1     | 10.9  | 9.3    | 9.5   |
| White cell count (x 10 <sup>9</sup> /L) | 1.8      | 4.46  | 5.8    | 3.57  |
| Platelet (x 10 <sup>9</sup> /L)         | 6        | 50    | 42     | 30    |
| Haematocrit (%)                         | 44.7     | 34.2  | 30     | 31    |
| Urea (mmol/L)                           | 9.4      | 7.8   | 8.5    | 12    |
| Creatinine (umol/L)                     | 131      | 71    | 62     | 97    |
| Total bilirubin (mg/dL)                 | 7        | 38    | 19     |       |
| Alanine aminotransferase (U/L)          | 214      | 374   | 93     |       |
| Aspartate aminotransferase (U/L)        | 73       | 565   | 120    |       |
| Albumin                                 | 41       | 35    | 27     |       |
| Dengue NS-1 Antigen                     | Positive |       |        |       |
| Dengue IgM (ELISA)                      | Positive |       |        |       |
| Dengue RT-PCR                           | DENV-3   |       |        |       |

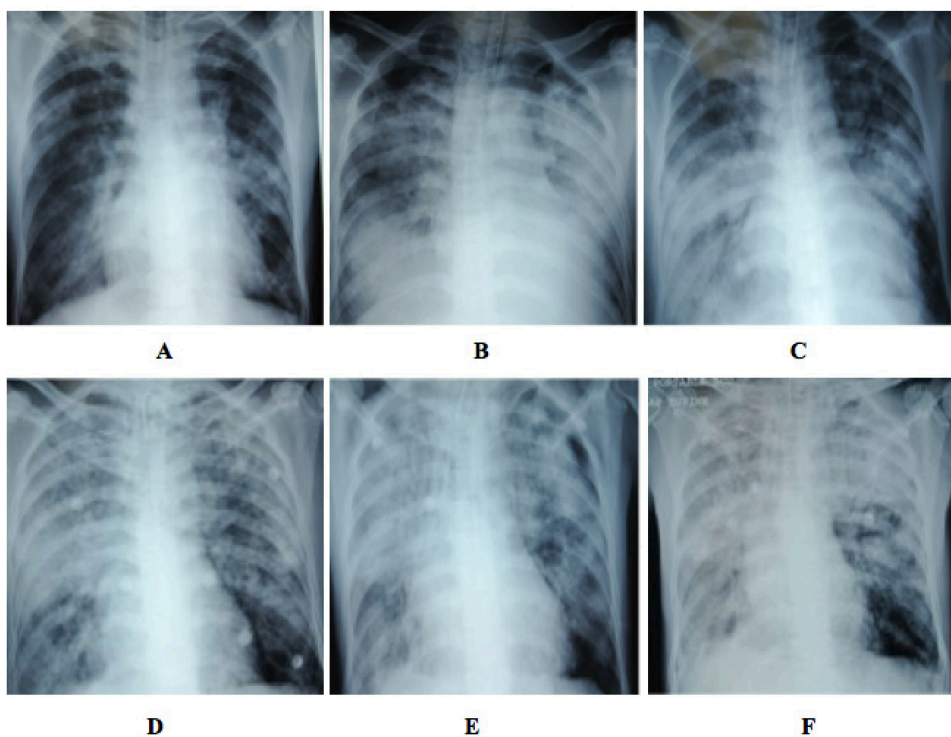


Figure 1: Serial chest radiographs throughout hospital admission. Chest radiograph taken at Day 2 (A) showed bilateral perihilar haziness. Serial chest radiographs were taken at Day 5 (B), Day 8 (C), Day 16 (D), Day 21 (E) and Day 22 (F) showed worsening opacities over both lung fields.

## DISCUSSION

Both dengue and leptospirosis are among the many medical conditions that cause AFI in humid tropical and subtropical areas. Because the clinical manifestations are similar, both dengue and leptospirosis are often indistinguishable at the early stages of illness. Hence, this can complicate the diagnosis of a patient presented with AFI especially in high endemic areas. In addition, co-infection cases are not uncommon. A study conducted in Jamaica showed that 2.5% of the 314 dengue IgM positive samples were also positive for leptospirosis infection (Brown et al. 2010). In another study conducted by Kumar et al. (2012), co-infection of dengue and leptospirosis was confirmed in 1.3% of 1,309 cases where both dengue and leptospirosis were investigated. Similar report is also found in a study done in India by with result of mixed infection of leptospirosis and dengue at 17.5% (Deodar & John 2011).

Our patient was initially presented with symptoms of viral-like illness with evidence of bleeding tendency. The positive dengue NS-1 antigen result together with leucopenia, thrombocytopenia and raised haematocrit level prompted us to treat him as dengue fever with warning signs as he came from a high endemic area for dengue. It is a common practice that if a patient with acute fever is confirmed to be dengue positive, dengue infection is assumed as the sole cause of the fever. Such assumption has caused leptospirosis, "The Great Mimicker", to be overlooked and under-diagnosed.

Due to the overlapping symptoms and signs, it remains difficult to diagnose without serologic test and this problem is proven in a recent cross-sectional study conducted among 10 healthcare facilities done in Northeastern Malaysia. Only 31% of confirmed leptospirosis cases were diagnosed as leptospirosis at the time of hospital discharge while another 38% were wrongly diagnosed as dengue fever or dengue hemorrhagic fever (Rafizah et al. 2012). A study in Thailand by Libraty et al. (2007) also reported that 19% of the children with confirmed leptospirosis were not diagnosed correctly on discharge from hospital. Because the specific treatment differs for both infectious diseases, the availability of antigen-based rapid diagnostic tests is essential to aid the clinicians to make timely and accurate diagnosis as well as to start appropriate treatment regimes, which is even more important in co-infection cases.

The mechanisms causing the increased vascular permeability in severe dengue are not well defined yet. Many theories have been postulated about the pathogenesis of severe dengue infection. Among all, the most studied one is about the development of imbalance immune response. Expression of cytokine, chemokines, and adhesion molecules as well activation of T-lymphocytes and complement system are responsible for the endothelial dysfunction (World Health Organization 2009). In addition, dengue virus infection can affect megakaryocytopoieses, leading to platelet dysfunction and thrombocytopenia (World Health Organization 2009). Similarly,

the development of endothelial dysfunction in severe leptospirosis is due to activation of immune mediators (Maciel et al. 2006; Yang & Hsu 2005). Hence, in our case, we believe that the synergistic actions of both organisms lead to generalized endothelial damage, thrombocytopenia as well as platelet dysfunction, resulting in fulminant pulmonary haemorrhage. Mixed infection of dengue and leptospirosis is associated with a higher mortality rate as reported by Kumar et al. (2012) The mortality rate was reported at 29.6% (5/17) in co-infected cases, followed by leptospirosis 14.6% (42/287) and dengue 3.7% (9/239). Sharma et al. (2012) also reported that highest mortality of 12.69% (5/63) in co-infected cases followed by leptospirosis 1.91% (27/63) and dengue 0.425% (6/63).

Co-infection with dengue and leptospirosis requires a variation of treatment modalities. Transfusion of blood products such as fresh packed red cells or fresh whole blood is mandatory in severe dengue with haemorrhagic complication (World Health Organization 2009). To date, the use of antibiotics in leptospirosis remains controversial. However, a Cochrane systemic review showed that antibiotic treatment might shorten the duration of illness (Brett-Major & Coldren 2012). Few studies have advocated the use of glucocorticoids in haemorrhagic pulmonary leptospirosis (Trivedi et al. 2001; Ittyachen et al. 2005; Shenoy et al. 2006). The role of glucocorticoids is imminently significant, particularly within the first 12 hrs of respiratory involvement (Shenoy et al. 2006). It reduces the need for mechanical

ventilation and the mortality rate in severe leptospirosis (Shenoy et al. 2006; Kularatne et al. 2011). In addition, other immunomodulation approaches such as plasmapheresis and immunoglobulin may also be helpful (Meaudre et al. 2008). Some novel approaches such as desmopressin, inhaled nitric oxide, activated Protein C and activated Factor VII were also proven beneficial in severe leptospirosis when conventional therapy ceases to work (Gulati & Gulati 2008). However, the potential of such treatments in co-infection with dengue and leptospirosis still remain unclear.

## CONCLUSION

Infection of dengue and leptospirosis may co-exist, especially in high endemic areas. Hence, a high index of suspicion is necessary to diagnose a co-infection as most clinicians are used to linking every symptom and sign to a single pathology. In addition, the optimal usage of rapid diagnostic laboratory investigation plays a crucial role in determining the management of undifferentiated AFI, particularly in mixed infection cases. Co-infection with dengue and leptospirosis, as depicted in the case report, warrants a variation of treatment regimes that has to be initiated the earliest possible in order to reduce its severity and, ultimately leading to the favourable outcome of this condition.

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