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CASE REPORT

Severe pulmonary haemorrhage syndrome in leptospirosis in a returning traveller

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Abstract

Clinical presentation of leptospirosis ranges from asymptomatic infection to fulminant, life-threatening disease. Pulmonary involvement in terms of severe pulmonary haemorrhage syndrome (SPHS) has recently become a more frequently reported facet of leptospirosis and correlates with high mortality rates. It has not yet been described in returning German travellers. We present a case of a healthy young man developing massive pulmonary haemorrhage and severe ARDS requiring mechanical ventilation and high-dose catecholamines after travelling to Indonesia. Leptospirosis was verified by blood PCR as well as serology and treated with high-dose, intravenous penicillin. Outcome was favourable, the patient recovered completely. Leptospirosis and SPHS should be taken into account as an emerging infectious disease in patients with fever and lung involvement.

Keywords Leptospirosis · Severe pulmonary haemorrhage syndrome · Travel medicine · Emerging infectious disease

Background

Leptospirosis is one of the globally leading zoonotic diseases caused by spirochetes of the genus *Leptospira*. Infection occurs upon direct or indirect contact with excretions of infected rodents, usually involving occupational or recreational activities as well as poor living conditions. Asymptomatic and mild courses are frequent. Severe cases have traditionally been associated with renal failure and jaundice. However, recently there has been an increase in severe courses linked with severe pulmonary haemorrhage syndrome (SPHS), leading to mortality rates above 50% [1–3]. The general aspects of leptospirosis in international health were highlighted in a recent case series [4]. To our best knowledge, SPHS as a particularly severe form of leptospirosis has not yet been described in returning travellers to Germany. Here, we present a fulminant case of leptospirosis with SPHS in a young, previously healthy German traveller returning from Indonesia.

Case presentation

A 29-year-old male had travelled with his wife to Sumatra, Indonesia, for 3 weeks, involving trekking in the rainforest and swimming in fresh water pools. Apart from treatment with oral prednisolone (25 mg daily for 5 days) due to suspected lumbar disc prolapse until a few days before departure, he had never been severely ill. Less than 24 h after returning from Indonesia he presented to the emergency room of Düsseldorf university hospital to rule out malaria infection. He complained of fever, chills, headache, diarrhoea and myalgia lasting for less than 2 days. Similar symptoms had already occurred 8 days before and had ceased spontaneously. At first presentation, vital parameters were determined as following: heart frequency was 109 per minute (109/min), blood pressure 118/67 mmHg, respiratory rate 18/min, peripheral oxygen saturation 100% and body temperature 37.5 °C; no further abnormalities upon physical examination. Laboratory results revealed slight anaemia (12.9 g/dl) and thrombocytopenia (149,000/ul), a C-reactive protein (CrP) of 13.1 mg/dl, normal leucocytes as well as

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normal creatinine and bilirubin. Chest X-ray and electrocardiography showed no pathologies.

While there was no indication of malaria using rapid diagnostic test (BinaxNOW® Malaria) in the emergency room, the patient's general condition deteriorated markedly. Thus, he was admitted as inpatient with suspected diagnosis of dengue fever or alternatively febrile gastroenteritis and treated empirically with moderate volume resuscitation and ciprofloxacin.

After hospitalization, the patient's general condition further deteriorated and he was transferred to the infectious diseases ward. There, detailed laboratory analysis revealed elevated transaminases (AST 170 U/l; ALT 62 U/l), elevated high sensitive troponin T (110 ng/l) and creatine kinase (2939 U/l with normal CK-MB ratio) as well as an increasing CrP (20.2 mg/dl). Bilirubin, creatinine and sodium level remained normal. Notably, there was a severe drop in haemoglobin level (6.7 g/dl) and thrombocytes (62,000/ul) without signs of active bleeding or haemolysis. Concurrently, the patient's oxygen saturation level continued to fall, a repeated chest X-ray showed diffuse patchy infiltrations, more pronounced in both middle and lower lobes [Fig. 1]. Due to travel history in a highly endemic region, fever, myalgia and elevated creatine kinase as well as pulmonary involvement, leptospirosis was suspected and intravenous penicillin (4 × 5 mega daily) was started. Furthermore, levofloxacin (1 × 500 mg daily) due to possible legionellosis and piperacillin/tazobactam (3 × 4.5 g daily) in combination with clarithromycin (2 × 500 mg daily) due to severe lung disease were administered.

Less than 60 h after onset of symptoms and 36 h after first presentation to the emergency room, the patient was transferred to intensive care unit, intubated and mechanically ventilated. Upon intubation, a massive amount of fresh blood emerged via the endotracheal tube. Bronchoscopy confirmed diffuse haemorrhage. Mechanical ventilation proved highly complicated, lung protective ventilation according to acute respiratory distress syndrome (ARDS) protocol was implemented upon clinical diagnosis of severe ARDS. High-dose catecholamines were required to sustain sufficient circulation.

Peripheral blood, urine and bronchoalveolar lavage fluid were obtained and sent to the reference laboratory for tropical pathogens (Bernhard-Nocht-Institute of Tropical Medicine, Hamburg, Germany) where initial leptospirosis serology using a crude in-house *Leptospira interrogans* lysate ELISA was negative. Leptospiral DNA could be detected in blood by in-house leptospiral 23S rRNA gene-PCR. PCR from urine and bronchoalveolar lavage fluid remained negative. Subsequently, antibiotic therapy was deescalated to intravenous penicillin with above-mentioned dosage. After intensive discussion, it was decided not to administer prednisolone on account of conflicting evidence in literature. Due to rapid improvement of his respiratory condition, the patient could be extubated 5 days after initiation of mechanical ventilation. Altogether, six concentrated red cells and one thrombocyte concentrate were administered. During the entire course of the disease, the patient's bilirubin and creatinine level never rose above 2.09 mg/dl and 1.3 mg/dl, respectively; he did not develop hyponatremia.

The patient had fully recovered at a follow-up visit at our tropical medicine outpatient clinic 1 month after presenting to the emergency room. Repeated serology showed a positive IgM of 121 units (cut-off 10 units) and positive IgG of 53 units (cut-off 10 units). Serotyping using a microagglutination assay showed highest titers to *L. interrogans* serovar Pyrogenes (1:400). After sequencing of the PCR product, *L. interrogans* was confirmed by Basic Local Alignment Search Tool (BLAST) analysis.

The patient's wife had never experienced any symptoms. Both had performed all leisure activities simultaneously apart from diving, which only the patient had done. Contaminated diving equipment could be a possible source of infection. Alternatively, contact with contaminated fresh

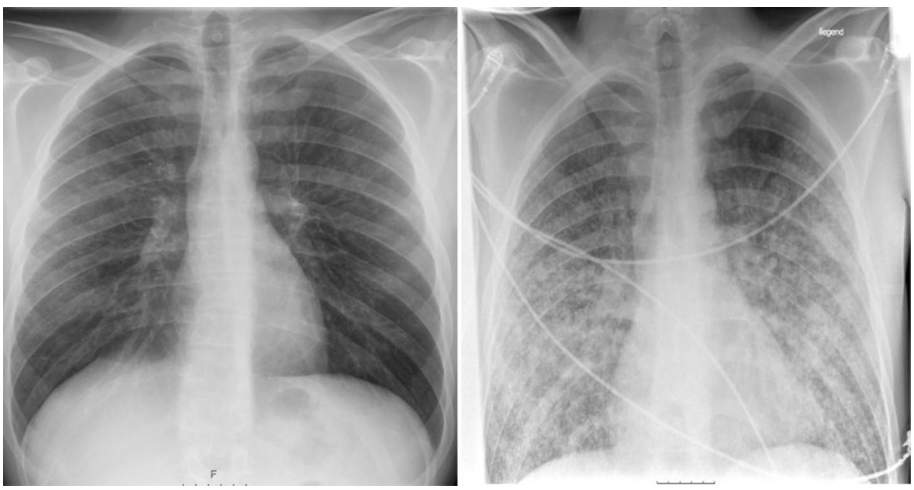

Fig. 1 Chest X-ray at first presentation and 42 h afterwards

water could well have occurred during trekking in the jungle without proper footwear or swimming in fresh water pools in Sumatra. Furthermore, the intake of prednisolone shortly before the journey may have increased the patient's susceptibility to infectious diseases.

Discussion

Leptospirosis, first described by Weil in 1886 [5], is a common zoonosis worldwide caused by different serovars of *Leptospira*. It can occur both in temperate and tropical regions, but the incidence is up to ten times higher in the tropics [6]. There are an estimated one million cases per year causing about 60.000 deaths [7]. Leptospirosis is contracted by direct or indirect contact with urine of infected wild and domestic animals, especially rodents. Under suitable circumstances, such as tropical climate, the organism can persist for several months in water or soil. Risk factors include poor living conditions as shown by outbreaks in slum populations [3], occupational (rice farmers, soldiers, sewage workers) and recreational (triathlon, canoeing, adventure travel) exposure [8]. After an incubation period of 10 (2–26) days, general symptoms such as fever, chills, myalgia and headache occur. Asymptomatic and self-limiting courses are common. Management includes early antibiotic therapy with penicillin, doxycycline or ceftriaxone plus symptomatic treatment.

Leptospirosis may occur in two phases, as possibly indicated by the symptoms our patient experienced several days before. If a second phase occurs, it is more severe and, according to the current concept of pathogenesis, largely an immune-mediated process. Severe courses have conventionally been associated with jaundice and renal failure, commonly referred to as Weil's syndrome. Pulmonary involvement in leptospirosis has first been described by Moeschlin in 1943 [9], but it was not until recently that several outbreaks and multiple individual cases involving SPHS have been described [1–3, 8].

Mild pulmonary symptoms, such as cough, chest pain or light haemoptysis, occur in 20–70% of patients with leptospirosis [10]. In SPHS, these can rapidly proceed to breathlessness, severe haemoptysis and ARDS, and result in death within 72 h [11], usually in the absence of renal or hepatic impairment. Overall mortality rates in patients with SPHS range above 50% [1–3, 12]. Furthermore, in leptospirosis, the strongest risk factor for lethal outcome has been shown to be that of pulmonary involvement [13, 14].

Detection of leptospiral antigen in lung tissue is uncommon, which supports the thesis of a toxin-mediated process causing pulmonary vasculitis in the course of leptospiral SPHS [11]. Since PCR for leptospiral DNA from pulmonary specimen is usually negative, diagnosis of SPHS highly depends on clinical suspicion including thorough (travel) anamnesis in combination with laboratory results (elevated creatine kinase) and imaging (bilateral patchy alveolar infiltrates and areas of consolidation). Serologic methods, such as the microscopic agglutination test (MAT), usually do not yield positive results until 5 days after onset of the disease. Detection of leptospiral DNA using PCR from blood, urine or cerebrospinal fluid can lead to rapid diagnosis, but the procedure is not broadly available yet.

Treatment includes early antibiosis with intravenous penicillin, ceftriaxone or doxycycline. There is no clear evidence that initiation of antibiotic treatment is effective later than 3 days after onset of symptoms which emphasizes the importance of clinical suspicion and rapid diagnosis. In severe cases, intensive care including mechanical ventilation and extracorporal membrane oxygenation benefits the patient [15, 16]. In addition, few studies have indicated that high-dose intravenous steroids could improve the outcome of pulmonary leptospirosis [17, 18].

Worldwide occurrence, high incidence and mortality rates underline the need for pertinent preventive measures such as effective waste water management, rodent control as well as protective clothing and foot wear. Furthermore, vaccines against leptospirosis have been introduced as early as 1933 [19], and shown their efficacy in different settings [20, 21]. Yet, development of a cross-protective universal vaccine still remains an ambitious goal in distant future. Further research is required to prevent morbidity and mortality caused by leptospirosis and to develop pertinent treatment strategies for severe courses such as the emerging leptospiral SPHS.

In conclusion, the incidence of leptospirosis is probably underestimated due to its unspecific symptoms and commonly mild, self-limiting course. But approximately 60,000 annual deaths require high alertness among physicians, especially when attending febrile patients with anamnestic risk factors such as occupational or recreational exposure to fresh water and/or rodents. Furthermore, pulmonary involvement needs to be taken into account as an emerging manifestation in leptospirosis, especially after exposure in the tropics, being associated with high mortality.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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