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REVIEW

Severe pulmonary manifestation of leptospirosis

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ABSTRACT

Based on increasing incidence and the occurrence of worldwide outbreaks, leptospirosis is recognised as an emerging zoonosis. Severe manifestations are associated with high morbidity and mortality rates and may therefore pose an important risk to public health, especially in certain high prevalence areas. A considerable number of infections progress to a severe form, which can present as the well-known triad of jaundice, impaired renal function and haemorrhage, known as Weil's disease. The severe pulmonary form of leptospirosis (SPFL) is a less known entity and is characterised by intra-alveolar haemorrhage and can lead to acute respiratory failure and death when adequate treatment fails. Prognostic factors correlating with severity and survival of leptospirosis include indicators of renal failure, pulmonary involvement and electrolyte imbalances. We report an imported case of SPFL in a returning traveller, and review the literature discussing epidemiology, clinical manifestations, prognostic factors and treatment of this resurgent disease.

KEYWORDS

Leptospirosis, lung, pulmonary manifestation, epidemiology, emerging infection

INTRODUCTION

Recent incidence estimates, combined with an increasing number of outbreaks in virtually every continent, have indicated leptospirosis as an emerging zoonosis with increasing numbers worldwide.[1-3] The disease has been identified as a potential threat for public health and can cause significant morbidity.[1] In recent years the severe pulmonary form of leptospirosis (SPFL), characterised by respiratory failure and haemorrhage with a mortality of >50%, is emerging and presents a cause for concern even in Western countries.[4]

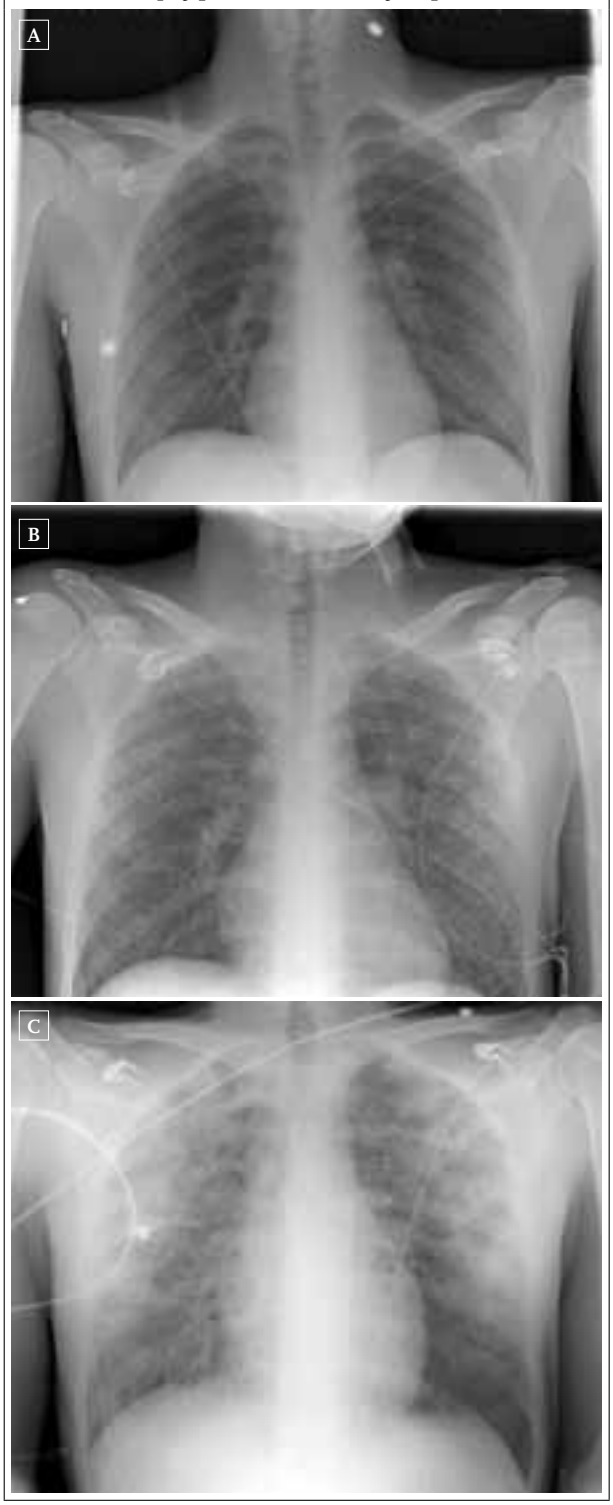
Leptospirosis is caused by spirochetes of the genus *Leptospira*. This dynamic group of bacteria consists of over 250 known serovars, surviving in warm and moist conditions. *Leptospira* can be carried and excreted by a wide range of mammalian species, which can serve as vectors. Infection can be acquired either through direct contact with animals, or through environmental contamination by animal urine. Consumption of contaminated food or water and exposure of mucosa or abraded skin to fresh surface water are the most important routes of infection.[5] Illness usually begins one to two weeks after infection and presents with fever accompanied by a broad spectrum of possible symptoms. In severe cases the disease can cause extensive tissue damage, vasculitis and, eventually, multi-organ failure. Worldwide incidence rates of leptospirosis seem to fluctuate annually, although a rising trend has been observed over the last years,[6] due to an increase in global flooding, which is driven by changes in climate, land use and socio-demographic factors.[5] Severe cases are estimated to occur >350,000 times each year throughout the world, with reported case fatality rates from about 5 to 30%.[1,2,7,8] However, reported numbers are likely to be a strong underestimation of the true incidence due to unawareness and neglect.[7] In the Netherlands, approximately 30 cases were reported per year over the last decade. However, the actual number of infections may be higher, as it is estimated that at least 30% of severe cases are missed.[2] In industrialised countries, recreational exposure and international travel have emerged as

increasingly important sources of infection over the past decades.[5,9-12] In our centre alone, we diagnosed 35 cases over the last 15 years. Only five cases (14%) were interpreted as locally acquired infections, and the remaining 30 infections were imported from another continent, of which 15 (43%) were from Thailand. Eighteen patients were hospitalised and four showed SPFL (haemoptysis, dyspnoea), which necessitated treatment on the intensive care unit (ICU). Of these four patients, serotype testing confirmed Icterohaemorrhagiae as the responsible serovar in three patients. The remaining patient is a case of SPFL from Thailand, imported to the Netherlands, and is discussed below. The aim of this manuscript is to elaborate on leptospirosis, and in particular the severe pulmonary form of leptospirosis, as a potential life-threatening disease.

CASE DESCRIPTION

A 22-year-old man presented to the emergency department ten days after a three-week trip to Thailand. His medical history did not reveal any medical abnormalities. He visited Bangkok and the North of Thailand and travelled through the jungle. One week after rafting in the jungle rivers he developed diarrhoea, myalgia and arthralgia. These symptoms resolved after a couple of days. Four days before presentation he experienced fevers up to 40° C, a nonproductive cough, watery stools, arthralgia and myalgia with pain in his neck and behind his eyes. On physical examination his vital signs were normal. A peripheral vascular redness of both sclerae was observed. Laboratory investigation revealed a mild thrombocytopenia of 110 x 10^9 E/l (normal 150 to 350), leukocytosis of 18.1 x 10^9 E/l (normal 4.0 to 10.5), with marked elevation of neutrophils (90%), total bilirubin 14 µmol/l (normal 0 to 17), alanine aminotransferase (ALAT) 60 IU/l (normal 0 to 40), aspartate aminotransferase (ASAT) 36 IU/l (normal 0 to 40), creatinine 120 µmol/l (normal 75 to 110), C-reactive protein 252 mg/l (normal <5), and albumin 20 g/l (normal 35 to 50). Urine examination showed a mild albuminuria, leukocyturia and erythrocyturia. An initial chest radiograph showed no signs of pneumonia (*figure 1A*). Leptospirosis was suspected, and the patient was admitted and treated with oral amoxicillin 750 mg three times daily. During the night of admission he developed high fever, hypotension, dyspnoea and haemoptysis. A second chest X-ray showed signs suggestive of intrapulmonary bleeding (*figure 1B*), and the patient was transferred to the ICU to be monitored for further respiratory impairment. Subsequently, he was supported with oxygen administration and treated with broad-spectrum antibiotics. A thick smear revealed no malaria parasites and the dengue rapid test was negative. The next day a leptospirosis rapid test was positive and antibiotics were changed to penicillin G 1 million units intravenously four times a day. The pulmonary abnormalities initially progressed (*figure 1C*), but after three days, the patient was discharged to the ward, where the X-ray of the lungs

Figure 1 A. *Chest X-ray of patient at presentation. B. Chest X-ray of patient four hours after presentation. C. Chest X-ray of patient 12 hours after presentation.*



showed substantial improvement. Two days later he left the hospital in good condition. The initial microscopic agglutination test (MAT) performed on serum taken on the day of admission was negative. However, six days later the test was positive for *Leptospira* serovar Mini, strain Sari (titre 1:2560). Blood cultures remained negative for leptospirosis.

PATHOGENESIS AND CLINICAL MANIFESTATIONS

Mortality of severe leptospirosis caused by cardiac and renal failure is roughly 5 to 15%, while SPFL and respiratory failure causes fatalities in >50%.[4,13-17] Pulmonary symptoms are found independently or concurrently with renal and hepatic manifestations. This suggests that SPFL is a different form of leptospirosis, rather than a form of Weil's disease with apparent pulmonary symptoms.[4,18,19] SPFL has now surpassed renal failure as cause of death among patients in Brazil and other parts of the world.[20] Although the serovars Icterohaemorrhagiae and Copenhageni are associated with more severe forms of leptospirosis, it is not possible to associate specific serovars with distinct manifestations of leptospirosis. Apart from the lungs, several other organ systems are generally involved in severe forms of leptospirosis.

Infection begins when leptospiral organisms invade the human body through skin abrasions and mucous membranes, in particular the oropharynx and nasopharynx. The pathogen multiplies and disseminates in blood, cerebral spinal fluid (CSF) and tissues. The mechanism through which *Leptospira* can cause illness has not yet been fully elucidated, although a systemic vasculitis, most commonly affecting the kidneys, liver and lungs, is thought to be responsible for the diverse sequelae described.[20-23]

After an incubation period of two to 30 days, the natural clinical course is typically biphasic. In the first spirochetemic phase, which lasts a week, the organisms cause a wide array of symptoms and can be cultured from blood. The production of antibodies heralds the second, or immune phase, in which the pathogen disappears from blood and CSF, but persists in tissues and is excreted in the urine. In the vast majority of patients a self-limiting subclinical flu-like illness occurs, which carries an excellent prognosis.[24,25] In patients who do develop symptoms, leptospirosis generally manifests as a mild anicteric form with low mortality. Symptoms may include fever, rigors, headache, myalgia, arthralgia, abdominal pain, nausea, vomiting, skin rash, and redness of the sclerae.[26,27] After roughly one week of illness, defervescence coincides with IgM emergence in peripheral blood and quick resolution of symptoms follows, while urinary excretion of spirochetes can persist for weeks or even months.[28] More severe forms of leptospiral infection comprise 5 to 10% of the cases, and can present as the triad of jaundice, impaired renal function and haemorrhage, known as Weil's disease. In contrast, SPFL is characterised by profuse intra-alveolar haemorrhage and seen in less than 5% of patients.[29] SPFL was not part of the original description by Weil, but is rather considered to be a complication occurring early in the course of the disease.[30] Commonly presenting symptoms in severe cases are listed in *table 1*.

Renal involvement manifests in 44 to 67% of patients.[31] Vasculitis may accompany interstitial haemorrhage, while decreased renal perfusion and hypotension facilitate further renal failure.[32] Renal function usually reflects the severity of infection and may require intravenous fluid therapy or even dialysis. Without supportive dialysis, mortality rates range up to 40%, although kidneys normally regain full function.

Lung involvement occurs in 20 to 70% of cases, and the clinical severity ranges from mild dyspnoea to SPFL.[33] Capillary injury in the lungs results in leakage and extravasation of blood cells. The inflammatory reaction, characterised by infiltration by monocytes and neutrophils, is surprisingly mild when compared with vascular damage. Pulmonary oedema, fibrin depositions and proliferative fibroblastic reactions are seen frequently and further hamper respiratory function.[33] These changes can lead to intra-alveolar haemorrhage and acute respiratory distress syndrome (ARDS), which is often fatal.[22,34,35] The initial symptoms of dyspnoea and haemoptysis, combined with auscultation anomalies, indicate severe lung involvement.[34-36] Imaging typically reveals bilateral patchy alveolar infiltrates, like large snow flakes, and areas of consolidation, as reported in the presented case.[37,38] Symptoms usually begin between the fourth and sixth day of disease, and may be fatal in less than 72 hours.[20,33,35] In addition to adequate antibiotic therapy, admission to the ICU and mechanical ventilation may be necessary to secure adequate blood oxygenation.

Although jaundice may be an apparent accompanying sign, liver involvement is usually transient, as it follows liver cell dysfunction rather than hepatocyte loss or apoptosis. Clinically, plasma bilirubin concentration levels are high, especially of conjugated bilirubin, with normal or slightly elevated transaminase plasma concentrations. In addition, thrombocytopenia is frequently observed during the acute stage, probably because of both diffuse intravascular coagulation and immune-mediated mechanisms.[22]

Table 1. *Characteristics, clinical manifestations and laboratory signs in severe forms of leptospirosis*

	Authors					
Variable	**Dupont[14]**	**Gouveia[4]**	**Herrmann-Storck[17]**	**Marotto[36]**	**Paganin[35]**	**Panaphut[15]**
Study population						
Patients	All cases	Hospitalised cases	Hospitalised cases	Hospitalised severe cases	Hospitalised cases	Hospitalised cases
Diagnosis (% of total)	MAT, IgM ELISA (100)	MAT (79), unconfirmed (21)	MAT (81), culture (19)	MAT (85), IgM ELISA (14), culture (1)	MAT (100)	MAT, IgM lepto stick (100)
Country	West Indies	Brazil	Guadelope	Brazil	Réunion	Thailand
Time period	1989-1993	2003-2005	2003-2004	1998-2004	1992-2003	1999
Sub group (% of total)	12 non survivors (18)	44 SPFL cases (9)	24 severe cases (14)	51 SPFL cases (25)	80 ICU admissions (54)	17 non survivors (14)
Mortality, %	18	40	74	31	20	14
Characteristics						
Mean age, y	57*	37.6	53*	39*	*31.3% >46**	38
Male sex, %	100	70*	75	90	-	94
Clinical signs						
Fever, %	42	-	43.5	80.9	-	100
Jaundice, %	100	85	75*	70.9	-	88.2*
Renal involvement						
Oligoanuria, %	75*	47*	43.5*	*1816 ml/24h*‡*	44.3*	76.5*
Urea nitrogen mean, mmol/l	37.7*	42.1	30.6	54.8*	*77.2% >15**	32.8*
Creatinine, µmol/l	550*	345	248*	433*	*83.3% >200**	690*
Cardiac involvement						
Hypotension, %	33	28	35*	82*	-	94.1*
Shock, %	-	-		17*	22.5*	-
Pulmonary involvement	67		47*		86.1	
Dyspnoea, %	58*	42*	31.2*	*31.4*§*	31.5*†	70.6*
Haemoptysis, %	-	15*	20.8*	39*	60	29.4
Neurological involvement	83					
GCS <15, %	-	-	30.8*	34*	-	-
Meningeal signs, %	-	-	16.7	-	-	-
Headache, %	-	-	71.4	-	-	88.2
Laboratory findings						
Mean no. leucocytes, x10^9	23.7*	15.3	*43.5% >12**	13.7*	*50.7% >13**	16.5*
Mean potassium, mmol/l	4.5*	-	3.8	3.9*	*12.5% >5.0*	4.7*
Mean no. thrombocytes, x10^9	71	*29% <100*	*34.8% <50**	63*	*36.9% <50**	56

– = not reported; * = p<0.05 when compared with survivors, non severe or non SPFL cases, values in italics are classified in deviating formats; † = mechanical ventilation needed; ‡ = mean diuresis (ml/24 h); § = mean respiratory rate (n/min); GCS = Glasgow Coma Scale; SPFL = severe pulmonary form of leptospirosis.

PROGNOSIS

Although renal deterioration may be rapid and severe, mortality rates have dropped significantly since the availability of renal replacement therapy. Studies on prognostic factors have been conducted on cohorts in Thailand, Guadeloupe and other countries, and are summarised in *table 2*.[4,14,15,17,25,35,39,40] Factors associated with an unfavourable outcome were pulmonary involvement, oligoanuria, hypotension, blood leucocyte counts above 12.9 x 10^9/l, impaired consciousness, and hyperkalaemia. Additionally, males, smokers and the elderly more often had adverse outcomes. In Sao Paolo, a cohort of 203 patients with SPFL was studied and prognostic factors were identified in a multivariate model. This model, including respiratory rate, serum creatinine, serum potassium, hypotension and Glasgow Coma Scale, was validated to predict the risk of SPFL.[36]

DIAGNOSIS AND DIFFERENTIATION FROM OTHER DISEASES

Given the nonspecific clinical manifestations and the low suspicion, the diagnosis of leptospirosis is often missed.[27,41] However, early recognition of leptospirosis

Table 2. *Odds ratios for different identified prognostic factors*

	Authors					
Variable	**Dupont[14]**	**Herrmann-Storck[17]**	**Marotto[36]**	**Paganin[35]**	**Panaphut[15]**	**Spichler[40]**
No. participants	68	168	203	134	121	370
Outcome	Death	Severity	SPFL	Death	Death	Death
Prognostic factor						
Older age	-	-	-	2.6 *	1.9	2.4 ***
Oligoanuria	9.0 *	5.6 **	-	2.8 **	8.8 **	7.1 ***
High creatinine	-	1.7 *	1.2 **	6.7 ***	6.0 **	4.2 ***
Pulmonary involvement	7.3 *¶	8.7 **#	1.1 ***†	85 ***‡	5.2 *#	9.1 ***
Hypotension / shock	3.0	3.3	69.2 ***	19.2 ***	10.3 *	-
Thrombocytopenia	-	1.0	-	2.8 **	1.0	2.6 ***
High potassium	-	-	2.6 *	1.5	5.9 **	-

SPFL = severe pulmonary form of leptospirosis, defined as massive pulmonary bleeding (haemoptysis >300 ml or aspiration of fresh blood after endotracheal intubation which did not clear with suctioning) and respiratory failure requiring mechanical ventilation, and mortality; * = p=<0.05; ** = p=<0.01; *** = p=<0.001; - = not reported; † = odds ratio for respiratory rate; # = odds ratio for abnormalities on chest auscultation; ‡ = odds ratio for mechanical ventilation needed; ¶ = odds ratio for alveolar infiltrates.

may be crucial, especially since acute respiratory distress in SPFL may progress swiftly. In tropical regions with a high prevalence of multiple serovars that cause mild disease, leptospirosis is often not distinguished from other causes of undifferentiated fevers, of which dengue is the most common.[19,41] Peripheral redness of the sclera may differentiate between dengue and leptospirosis. This redness is often referred to as 'conjunctival suffusion', but is actually an episcleritis that is not irritating or itching. The headache in leptospirosis is mainly occipital and may mimic meningismus whereas the headache in dengue is more frontal and retrobulbar. Myalgia is common in leptospirosis, classically in the lower legs, but also severe abdominal pain may occur. Nausea and vomiting are quite common in leptospirosis and rather rare in dengue.

During the spirochetemic phase the organism can be cultured from blood, CSF, and urine samples. A positive culture provides definite proof of infection, but it is too slow to contribute to an early diagnosis. Alternatively, PCR on blood, urine or CSF samples can rapidly confirm the diagnosis in the spirochetemic phase.

Serology is applicable after five to ten days post onset of symptoms, when antibodies against *Leptospira* reach detectable levels. The MAT is the gold standard due to its high specificity. A live panel of *Leptospira* representing all pathogenic serovars in the area is required to adequately perform this test. False-negative results can occur when the infecting serovar is not represented in the panel, as infection may be acquired in regions where other serovars are endemic.[42]

The IgM ELISA is a genus-specific test that is widely applicable, standardised and can detect infection slightly earlier than MAT.[1] However, low specificity and cross reactions warrant confirmation by MAT. Similar to dengue antibody tests, leptospira ELISA or MAT are often negative in the very early stage of disease. In contrast, dengue antigen tests are helpful in the very early stages of disease and could help to differentiate between dengue and leptospirosis.

TREATMENT

At present, there is no consensus on the most effective and safe antibiotic treatment for leptospirosis, as convincing evidence is still lacking.

In most mild cases, leptospirosis is self-limiting. Amoxicillin, ampicillin, doxycycline or erythromycin can reduce symptoms and prevent further progression. However, in a more severe manifestation, treatment with cephalosporins or high doses of penicillin intravenously is recommended and early administration is associated with more favourable outcomes.[1,43,44] Mortality can also be reduced by adequate monitoring, supportive therapy and correction of electrolyte balances by intravenous fluid administration or renal replacement therapy. There is only modest evidence that plasma exchange or immunosuppression may improve survival of patients with SPFL.[45-48] In Brazil, a randomised placebo-controlled trial is currently evaluating the efficacy of pulse methylprednisolone in SPFL patients.[45-48]

Prevention may be the most effective approach to control the zoonosis. Doxycycline as chemoprohylaxis may prevent further infection and reduce morbidity and mortality.[49,50] To date, vaccination is inadequate,[51] not widely available

and provides only limited protection for specific serovars.[1] Serovars are to a large extent associated with their chronic carriers and serovar information may therefore be important for effective control and prevention.

CONCLUSIONS

Leptospirosis is a zoonosis with a wide range of clinical manifestations that can cause severe morbidity and mortality if left untreated. The disease is endemic in tropical regions, but may be increasing in temperate regions because of global warming. While leptospirosis is predominantly an occupational disease at a global scale, it has been marked as an emerging recreational disease in travellers to tropical and subtropical countries, as illustrated by the presented case. In recent years, the severe pulmonary form of leptospirosis (SPFL) seems to emerge as a distinct manifestation with high mortality rates. The course of the disease should be carefully monitored as respiratory distress may progress rapidly and requires adequate work-up and intervention. Treatment consists of antibiotics and should certainly be considered when a severe (pulmonary) course is suspected.

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