

Presentation of leptospirosis in the emergency department: an analysis of different patterns of clinical features during an outbreak

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Summary Background. Typically, doctors consider a diagnosis of probable leptospirosis when there is a history of fever with kidney or liver involvement and an elevated serum creatine phosphokinase level. However, there are increasing numbers of cases with atypical presentation, which renders the diagnosis challenging.

Objectives. The aim of this study is to determine the presentation patterns of leptospirosis during an outbreak, in order to increase the understanding of this potentially complex disease.

Material and methods. This is a retrospective, observational study of an outbreak that occurred in an army camp in 2012. The data were collected by retrieving the patients' medical records, including signs and symptoms, laboratory findings, and outcomes.

Results. There were 47 cases of leptospirosis confirmed by a microscopic agglutination test (MAT). Of these, only 50% had a positive point-of-care serology test result at initial encounter in the emergency department. The majority (58%) presented with mild upper respiratory tract and gastrointestinal symptoms and 64% had no fever on presentation. Only five patients had leukocytosis (12%); 86% were within the normal range. Half of the patients (50%) had a normal platelet count and 60% had normal renal function. However, 74% had a creatine phosphokinase level over 200.

Conclusions. Leptospirosis is difficult to diagnose due to its ambiguous clinical presentation. Most of the laboratory findings can be unhelpful in excluding the diagnosis. The point-of-care serology test done in the primary setting should not be relied on in highly suspicious cases. In a cluster where leptospirosis is endemic, the MAT might be warranted; otherwise, empirical antibiotics may be considered, even for mild symptoms.

Key words: Malaysia, leptospirosis, point-of-care testing, agglutination test, emergency service, hospital.

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Background

Leptospirosis is a gram-negative aerobic spirochete of the genus *Leptospira*. It is transmitted to humans by direct contact with the urine or reproductive fluids of infected animals, mainly rodents, or by inoculation from contaminated soil or water. Since 1925, when the first case was recorded by Fletcher, the disease continuously causes a public health burden worldwide. It is a potentially fatal zoonotic disease that is endemic in many tropical regions, especially after a heavy rainfall or flooding [1]. Although traditionally the incidence is low in developed countries, outbreaks are reported especially after water recreational activities [2]. It is estimated that 1.03 million cases of leptospirosis (95% CI: 434,000–1,750,000) are reported every year worldwide, with an estimated 58,900 mortalities (95% CI: 23,800–95,900) [1]. It is increasingly causing a multinational public health and food security problem, with some considering it as a neglected tropical disease [1, 3]. The broad geographical distribution is mainly due to a large spectrum of mammalian hosts that harbor and excrete the spirochete agent from their renal tubules [4]. Human cross-migration is also thought to be responsible for the escalation of the disease [5].

Despite rapid modernization, leptospirosis remains an endemic disease in Malaysia with the emergence of more data for the past few years, since it was labelled a notifiable disease in 2010 [6–9]. The incidence of leptospirosis in Malaysia showed a progressively increasing trend from 2004 to 2014, with mortality rate ranging between 1–5% [7, 8, 10]. The recent data from Ministry of Health of Malaysia show an increase from 3,665 cases in 2012 to 5,284 in 2016 [5]. The humid and hot weather throughout the year is conducive to leptospires' survival for longer periods, hence increasing the risk of exposure.

The disease, classically manifests as a biphasic illness, starting off with a high fever which coincides with leptospiremia, followed by a brief period of being afebrile, then with a return of fever, this time with organ involvement, commonly the liver and kidneys. Deaths are usually associated with acute liver, kidney, or pulmonary injury [11].

One of the major challenges in managing leptospirosis in emergency departments (EDs) and primary healthcare facilities is the diagnosis itself. Cases and their related mortality have been underreported mainly due to the lack of an adequate diagnostic test [12–16]. Typically, medical personnel will diagnose a case as probable leptospirosis when there is history of fever with kidney or liver involvement and an elevated serum creatine



phosphokinase level. However, there are increasing numbers of cases with atypical and broad presentation, which renders the clinical diagnosis challenging [17, 18]. More data are needed to improve pattern recognition, to ensure rapid and accurate diagnosis, and to further reduce morbidity and mortality related to the disease.

In this incidence that we are describing, the leptospirosis outbreak occurred among the trainees of an army training facility, which is not a new trend and have been described before [18]. However, most of those studies were epidemiological studies which did not explore the clinical aspects of the patients from the outbreak.

The results of this study illustrate a different pattern of leptospirosis presentation during an outbreak in East Malaysia. It is hoped that the data collected and analyzed will be used on a larger scale to better understand the disease.

Objectives

The aim of this study is to analyze the clinical presentation of leptospirosis during an outbreak and to determine the relationship between laboratory parameters of the disease and the usual clinical practice when the disease is suspected by medical personnel in Sarawak, Malaysia. It is hoped that the findings from this study will be further explored in future research related to leptospirosis.

Material and methods

This is a retrospective, observational study involving a series of 47 consecutive patients from an army camp in Kuching Sarawak who were hospitalized in Sarawak Umum Hospital following an outbreak of leptospirosis in April 2012. All of them were screened with a microscopic agglutination test (MAT) and the diagnoses of leptospirosis were confirmed.

All of the patients were attended to by medical personnel at the ED. As they came from the same cohort with a high risk of leptospirosis and a history of fever, studies were conducted to confirm the diagnosis and to assess the severity and complications of the disease. Some of the patients were admitted to the intensive care unit (ICU) and general medical ward, while some were discharged home. All of them were diagnosed with leptospirosis, which was confirmed with an MAT.

The data extracted from these patients' records were the types of symptoms, symptom duration, and blood tests comprising a leptospirosis rapid test, a full blood count, a renal function test, electrolyte count, liver function test, and creatine phosphokinase. The antibiotic of choice and duration of admission were also analyzed.

Data analysis

Descriptive statistics with means and standard deviations were reported for continuous variables. The categorical variables are presented as frequencies and percentages. The comparison in symptom duration (in days) between results of the initial major laboratory tests – such as serology and creatinine,

platelet, and creatine phosphokinase levels – were analyzed using an independent *t*-test.

Ethical approval

This work received a positive opinion from the Ethics Committee (CRC MOH HSB 2017).

Results

The duration from onset of symptoms to admission, the signs and symptoms, choice of antibiotics during initial presentation at the ED, number of admissions to the ward and ICU, and the duration of admission are shown in Table 1. On average, the onset of symptoms to admission was 7.15 days (SD: 5.05). The majority of cases presented with a combination of upper respiratory tract and gastrointestinal symptoms (57.4%), with only 36% febrile patients. Only 53% were administered antibiotics, with Ceftriaxone being the antibiotic of choice more than half the time. Over half (57.5%) were admitted either to the general ward or the ICU, and the average duration of hospital stay was 4.3 days.

Table 1. Time from onset of symptoms to admission, signs and symptoms, choice of antibiotics during initial presentation at the Emergency Department, number of admissions to the ward and ICU, and duration of admission (n = 47)

	Freq. n (%)	Mean ± SD
Fever at presentation to Emergency Department	17 (36.2)	
Choice of antibiotics during initial presentation (n = 25):		
Ceftriaxone	14 (56.0)	
Amoxicillin/clavulanic acid	9 (36.0)	
Penicillin	2 (8.0)	
Onset of symptoms prior to admission (days)		7.15 ± 5.95
Sign & symptoms:		
Upper respiratory tract symptoms only	17 (36.2)	
Upper respiratory tract and gastrointestinal symptoms	27 (57.4)	
Gastrointestinal symptoms only	0 (0.0)	
Other symptoms	2 (4.3)	
Admission to ward	25 (53.2)	
Admission to ICU	2 (4.3)	
Duration of admission		4.32 ± 2.62

Table 2 shows the blood tests during admission. The bedside serology test was positive in only half of the samples, even though the MATs were all positive. The majority (85.7%) had normal white blood cell counts, with equally distributed platelet counts. The level of creatine phosphokinase (CPK) and serum creatinine were higher than normal (602.12 ± 723.13 and 111.13 ± 63.61 , respectively). Other laboratory findings were in the normal range.

Table 2. Blood tests during admission (n = 47)

	Freq. [n (%)]	Mean ± SD
Hemoglobin, g/dl (n = 43)		14.1 ± 1.73
White blood cells count ($\times 10^9/l$) (n = 42):		8.66 ± 3.83
< 4	1 (2.4)	
4–12	36 (85.7)	
≥ 12	5 (11.9)	
Platelet count ($\times 10^9/l$) (n = 42):		194.52 ± 117.80
< 150,000	20 (47.6)	
≥ 150,000	22 (52.4)	

Table 2. Blood tests during admission (n = 47)

	Freq. [n (%)]	Mean ± SD
Serum sodium, mmol/l (n = 40):		130.95 ± 3.29
Serum potassium, mmol/l (n = 37)		3.74 ± 0.38
Serum urea, mmol/l (n = 40):		4.49 ± 2.76
Serum creatinine, µmol/l (n = 40):		111.13 ± 63.61
< 110	24 (60.0)	
≥ 110	16 (40.0)	
Creatine phosphokinase (CPK), U/L (n = 39):		602.12 ± 723.13
< 200	10 (25.6)	
≥ 200	29 (74.4)	
Alkaline phosphatase (ALP), U/L (n = 40):		58.25 ± 27.50
Alanine aminotransferase (ALT), U/L (n = 40):		49.83 ± 64.56
Aspartate aminotransaminase (AST), U/L (n = 40):		55.43 ± 63.93
Bedside serology test (n = 30)		
Negative	15 (50.0)	
Positive	15 (50.0)	

Table 3. The comparison between duration of symptoms (days) and results of the initial major laboratory tests

Laboratory tests	Results	n	Duration of symptoms (days) [Mean (SD)]	Mean Diff. (95% CI)	p-value
Serology Rapid Test	Positive	15	9.27 (1.87)	-3.33 (-7.64–0.97)	0.124
	Negative	15	5.93 (0.95)		
Creatinine, µmol/l	< 110	24	7.42 (6.35)	0.48 (-3.77–4.73)	0.821
	≥ 110	16	6.94 (6.75)		
Platelet (x10 ⁹ /l)	< 150	20	6.05 (5.10)	-1.91 (-5.76–1.95)	0.323
	≥ 150	23	7.96 (7.07)		
Creatine phosphokinase, U/L	< 200	10	5.20 (2.57)	2.39 (-2.37–7.14)	0.316
	≥ 200	29	7.93 (7.21)		

The comparison in duration of symptoms (days) between results of the initial major laboratory tests (serology and creatinine, platelet, and creatine phosphokinase counts) are shown in Table 3. There were no significant differences between the duration of symptoms (days) and the results of the initial major laboratory tests.

Discussion

This study showed the challenge of diagnosing and confirming leptospirosis in the ED and the primary care center. Out of 47 cases of leptospirosis confirmed by MAT, only 50% of them had a positive result on the point-of-care serology or rapid test carried out on arrival to the ED. This can be attributed to the fact that most rapid tests for leptospirosis detect IgM, which is only detectable two weeks after the onset of symptoms [19]. The sensitivity and specificity of the point-of-care test also varies widely depending on the manufacturer [20].

Various studies have revealed how undefined the clinical presentation of leptospirosis is, ranging from a mild flu-like illness to life-threatening pulmonary hemorrhages [16]. Fever has been described as common presentation, with cough being the least common symptom on presentation [21, 22]. This is in contrast with the current study, in which 64% presented without fever and the majority presented with mild upper respiratory and gastrointestinal symptoms – despite having a positive MAT. This makes it more challenging for the healthcare provider when fever is not an initial complaint, especially in a non-cluster situation. Healthcare personnel treating patients with an upper respiratory tract illness need to be more vigilant, as a diagnosis of leptospirosis might be overlooked.

Laboratory tests were also done to diagnose and assess the severity of the illness. Commonly, healthcare personnel would first think of a leptospirosis infection when there is leukocytosis with thrombocytopenia [23]. In this study, we found that more

than half of the patients had a normal platelet count, and that only five patients had a white cell count of more than 12,000/mm³. This is in contrast with another study which stated that a white blood cell count of more than 11,000/mm³ is more likely to indicate leptospirosis than dengue [24]. Another study in Hawaii revealed mild leukocytosis with a shift to the left as commonly observed in leptospirosis [25]. As for platelet count, in this study there was a higher percentage of thrombocytopenia (47%) than in another study which reported around 20–30% [26]. Renal function was normal in 60% of the patients. The almost consistently elevated blood parameter, creatine phosphokinase – which was high in 74% of patients – has previously been described as a reliable marker in leptospirosis [27].

ED doctors and other frontline healthcare personnel should not rely on baseline blood tests alone, as abnormal blood parameters can only imply a possible leptospirosis infection. Another interesting finding is that there was no significant difference in the blood test results in comparison with the duration of the illness. This is in contrast with dengue fever, where blood parameters such as white blood cell count and platelet count change at different phases of the illness.

Additionally, in an outbreak, as in this case, all of the patients will undergo serological testing. However, in isolated cases, when a highly sensitive point-of-care test is not always available, the clinician needs to have a high index of suspicion in order not to miss the diagnosis of leptospirosis.

The majority of patients will present with a mild form of the disease, whereby only symptomatic treatment for the flu-like illness is warranted. If antibiotic treatment is needed, doxycycline can be administered, which was not used at all in this case series. For moderate to severe forms of illness, a penicillin-based antibiotic is favorable, and cephalosporins such as ceftriaxone and cefotaxime were found to be effective, with the former being the antibiotic of choice in this group of patients.

Limitations of the study

There are a few limitations with this study. Being a retrospective study, the analysis was done on preexisting data, which is subject to biases. This study was also unable to identify the risk factors involved, since no comparison was made with non-infected subjects. More studies are needed in order to address these limitations.

Conclusions

There is no specific clinical presentation or pattern or laboratory test (apart from MAT) that will facilitate the diagnosis of leptospirosis. Clinicians need to be vigilant and have a high acumen in order to diagnose the disease when the pretest probability is high and even the clinical presentation and biochemical markers show otherwise. In an endemic situation, high index of suspicion is needed to rule out the diagnosis.

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Tables: 3

Figures: 0

References: 27

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