Weil's Disease: An Unusually Fulminant Presentation Characterized by Pulmonary Hemorrhage and Shock

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A case of fulminant leptospirosis is presented, manifesting as rapid progression from acute undifferentiated febrile illness to refractory shock, jaundice, renal failure and massive pulmonary hemorrhage. The patient received aggressive intensive care unit support including prolonged intubation and ventilation. This case emphasizes that acute leptospirosis may well not be characterized by the classic scenario of a biphasic illness, but rather by a fulminant, monophasic illness.
Key Words: Weil's Disease, hemorrhage, shock.

Leptospirosis has recently come to international attention as a globally important emerging infectious disease. The clinical spectrum of infection by *Leptospira* may be subclinical or can range from mild influenza-like illness to fulminantly fatal disease characterized by jaundice, renal failure, hemorrhage and refractory shock known as Weil's Disease [1].

Classic descriptions of leptospirosis have focused on its being a biphasic illness. In the initial acute or septicemic phase is characterized by bacteremia typically lasting about 1 week. Weil's disease represents only the most severe form of the illness [1-3]. This syndrome can develop after the acute phase of the second phase of a biphasic illness, or simply present as a single progressive illness [3].

Here we present a case of Weil's disease characterized by having only a very brief period of time between the onset of symptoms and the development of fulminant, severe disease leading to intensive care management but ultimately recovery and discharge.

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Case Report

A 24 year old man was admitted with 1 day of fever, severe unremitting headache, myalgia, and vomiting. His neighborhood in Sao Paulo city was poor with many rodents frequently seen. The patient had walked and swam through flood waters one week prior to the onset of illness. He denied history of respiratory, jaundice or renal abnormalities.

On admission, he was alert, with fever, and vomiting. Temperature was 39ºC Pulse rate =105, blood pressure= 100/60mm/hg, respiratory rate=18/min.

He had two open wounds about 3 cm each on the right lower leg. Otherwise, there were no other abnormal findings on physical examination.

On admission, the first clinical impression was that the patient had meningitis. CT of the head was normal. Lumbar puncture (LP) showed the following in cerebrospinal fluid: 2 cells/mm^3; total protein, 78 mg/dL (normal < 40 mg/dL) glucose, 74 mg/dL (simultaneous serum glucose was 110 mg/dL), no bacteria were observed on Gram stain.

The patient was treated symptomatically with metoclopramide and acetaminophen. Fever was unremitting, and the patient returned to the infirmary for further evaluation. Blood and urine culture were collected. Ceftriaxone was started.

During the second day fever (38ºC)and severe myalgia persisted.

On day 3, the patient developed dyspnea, jaundice and oliguria and was admitted to the Intensive Care Unit (ICU). Just prior to transfer, he developed massive hemoptysis and was intubated.

Laboratory data are shown in Table 1. The first chest radiograph was normal. The second chest radiograph on day 3 showed alveolar infiltrates in the right lower lung consistent with pulmonary hemorrhage (Figure 1).

In the ICU pulmonary hemorrhage persisted, requiring continued airway and ventilatory support (FiO_2 (100%), PEEP, 23 mm Hg, and O_2 saturation = 88%. The patient developed refractory shock requering pressor support, oliguric renal failure, and severe jaundice. On day 4 hemodialysis was initiated but the patient's overall clinical picture did not improve rapidly.

Hemodialysis was done daily, and he was intubated from 12/16 until 01/10. Over 26 days of ICU support, serum BUN and creatinine normalized with normal urine output and breathing room air with a tracheostomy. He was discharged from ICU at 01/17/05, in good condition.

Diagnosis of leptospirosis was suggested by a positive ELISA IgM test and confirmed by high microscopic agglutination titer against *Leptospira copenhageni* of 1/1600.

Discussion

Leptospirosis is a zoonotic disease associated with the environment: transmission depends on interaction between humans and mammalian reservoir hosts [4,5]. The source of infection in humans is usually either direct or indirect contact with the urine of an infected animal. The mammalian source of transmission differs by locale, typically being rats, sometime dogs, in the urban environment, but more varied, including domestic livestock (cattle, pigs) in rural environments. Men seem to be more likely to demonstrate clinical manifestations than are woman, in settings where transmission is sporadic. The highest prevalence is typically observed in the age group from 19 to 39 years [6]. However, we found in Iquitos, Peru, that men and women are equally likely to be seropositive [7].

The incidence of human infection is higher in the tropics than in temperate regions but transmission occurs in both industrialized and developing countries [1,2,8].

In Brazil, leptospirosis is common yet potentially preventable through improvements in sanitary conditions. However, there continued to be excessively high rates of morbidity and mortality due to leptospirosis, occurring throughout Brazil with an especially high incidence in Sao Paulo, Salvador, and Rio de Janeiro [9,10]. Previous studies have indicated that in São Paulo State, the incidence of leptospirosis was 2.2, 1.78 and 1,98 per 100,000 inhabitants respectively in 1999, 2000 and 2001 [11].

In Brazil, morbidity and mortality due to leptospirosis occurs due to severe complications characterized as Weil´s disease. Case fatality rates in severe leptospirosis have been reported to be as high as 15% in Salvador [9]. Mortality remains significant, likely due to intrinsic pathogenicity of leptospiral infection in some people as well as related to delays in diagnosis due to lack of infrastructure and adequate clinical suspicion.

Environmental conditions strongly affect the transmission of leptospirosis by modifying the population biology, behavior, or community ecology of spirochetes and their hosts; particular mammalian reservoirs, notably rats, harbor the more virulent leptospires such as *L. interrogans* serovar Copenhageni. Most patients live in areas where the transmission is high because of poor conditions of hygiene combined with high precipitation.

The variable clinical manifestations of leptospiral infection suggest that diverse mechanisms may contribute to acute and chronic infectious processes of pathogenesis in people and reservoir hosts. Host infection produces a diverse array of clinical manifestations ranging from subclinical infection to

Table 1. Laboratory data

	12/16	12/17	12/18	01/17
Hb	14	10	6.6	11
Hct	43%	31%	18%	39%
WBC	21,900/mm^3	15,500	20,600	11,000
SCr	0.5 mg/dL	1.1	3.3	1.9
Surea	18	53	89	120
TB	1.3 mg/dL	2.4	6.6	1.2
DB	1.2	1.4	5.9	0.9
Platelets	124,000	62,000	41,000	280,000
CPK	93	219	277	50
ALT	55	60	45	30

Figure 1. PA chest radiograph on initial presentation showed normal lungs.

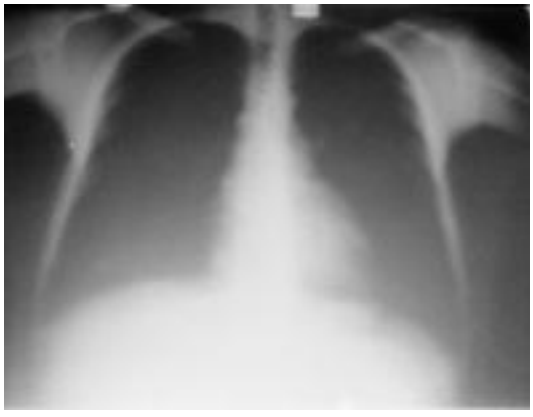
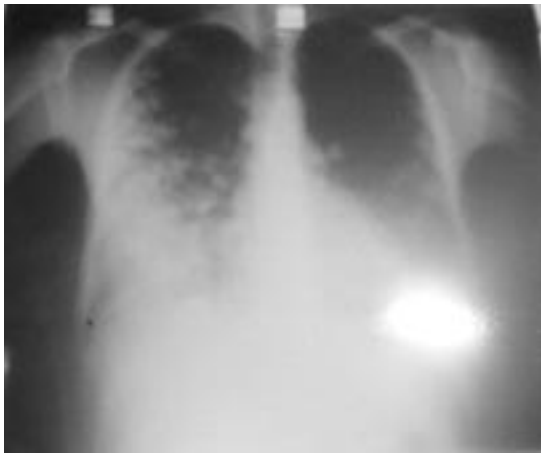


Figure 2. PA chest radiograph showed on day 3, appearance of bilateral alveolar infiltrates with a right lower lung predominance, consistent with pulmonary hemorrhage.



undifferentiated febrile illness to jaundice, renal failure, and potentially lethal pulmonary haemorrhage [1]. The more common form of leptospirosis, anicteric leptospirosis, is self-limited; this form of infection occurs in 90% of recognized cases [1-3]. Fever is present in most or all cases. Asymptomatic infection is common in endemic areas where acquired immunity may develop after repeated infection [12]. Fever, chills, headache, severe myalgia, conjunctival suffusion, anorexia, nausea, vomiting, and prostration usually characterized acute leptospirosis. The resolution of symptoms may coincide with the immune phase when antibody begin to be produced, accompanied by excretion of spirochetes in the urine. Headache is often severe and aseptic meningitis may be seen in up to one-quarter of all case. These clinical features appeared early, however jaundice, pulmonary haemorrhage, and renal failure are not early signs.

Icteric leptospirosis or Weil´s disease represents about 5% to 10% of the patients actually infected by leptospira.

In Weil's disease, case fatality rates range from 5% to 15 %. These patients typically require hospitalizations when the disease is brought to medical attention [1-3].

In this case the patient presented with a very short duration of time between the onset of symptoms and the development of severe diseases characterized by the abrupt onset of massive pulmonary hemorrhage.

Because fever was the only clinical feature initially found on physical examination, he was discharged from the hospital, only to return for more clinical evaluation because of continued acute symptoms. It is well recognized that leptospirosis diagnosis is very difficult to consider diagnostically when presenting as acute undifferentiated fever. Two days after, he developed severe pulmonary hemorrhage, but treatment was started early. Even with a long stay in the ICU, he fully recovered.

It is likely that the severity of this patient's clinical manifestations of leptospirosis was do to an overly robust immune innate response in the absence of preceding acquired immunity. Recent data indicate that the lipid A of leptospiral LPS interacts with human Toll-like-receptor-2. Following from this observation, if there is a particularly high leptospiral burden during infection in some individuals for reasons as yet unknown, oxcessive cytokine responses due to innate immune system stimulation may lead to a severe form of leptospirosis [13,14].

The differential diagnosis of the form of leptospirosis presented here includes hantavirus infection. Hantavirus infection is associated with two main clinical diseases in humans: Hemorrhagic fever with renal syndrome (HFRS) and hantavirus pulmonary syndrome (HPS) [15].

Both diseases are associated with changes in vascular permeability and both may have pulmonary or renal symptoms.

In HFRS, the clinical course can be divided into five distinct phases and viremia is though to occur subsequent to infection of alveolar macrophage, leading to infection of kidney and lung endothelial cells.Jaundice is not very common [15].

In HPS, prevalent in some specific areas in São Paulo, Brazil, the disease is characterized by a brief prodromal illness, included: fever, myalgia, followed by rapidly progressive, noncardiogenic pulmonary edema, with a high case fatality [16,17]

In summary, the case of fulminant leptospirosis presented here should serve to alert clinicians to the clinical importance of this severe, often fatal disease. Leptospirosis often presents in a non-classic, non-textbook manner, typically as acute undifferentiated fever occasionally complicated by severe disease. Currently, the only way to prevent leptospirosis is through proper sanitation; vaccines have not yet proven efficacious but are under active development, particularly in Brazil. To decrease morbidity and mortality physicians need to maintain a high level of clinical suspicion and initiate effective antimicrobial therapy (penicillin, ceftriaxone, doxycycline) immediately. While only a minority of patients with leptospirosis will have Weil's disease, genetic predisposition to severe disease may be related to an overly active innate immune system.

References

1. Bharti A.R., Nally J.E., Vinetz J.M. Leptospirosis: a zoonotic disease of global importance. Lancet Infectious Disease **2003**;3:757-71.
2. Levett P.N.Leptospirosis. Clin Microbiol Rev **2001**;14:296-326.
3. Vinetz J.M. Leptospirosis. Curr Opinion Infect Dis **2001**:14:527-38.
4. Vinetz J.M., Glass J.E., Flexner C.E.,et al. Sporadic urban Leptospirosis. Ann Intern Med **1996**;125:794-8.
5. Meites E., Jay M.T., Deresinski S., Smith S. Reemerging Leptospirosis, California. Emerging Infectious Diseases **2004**;10:406-11.
6. Lomar A., Diament D., Torres J. Leptospirosis in Latin America, 2000. Infect Dis Clin North Am **2000**;14(1):23-39.
7. Jonhson M.A., Smith H., Vinetz J.M. Environmental exposure and Leptospirosis, Peru. Emerg Infect Dis **2004**;(6):1016-22.
8. Jansen A., Schoneberg I., Schneider T., Stark K. Leptopsirosis in Germany, 1962-2003. Emerg Infect Dis **2005**;11(7):1048-54.
9. Ko A.I., Reis G.M., Riley L.W. Urban epidemic of severe Leptospirosis in Brazil. The Lancet **1999**;354:820-25.
10. Romero E.C.,Bernardo C.C.M., Yasuda P. Human Leptospirosis: a twenty-nine year serological study in São Paulo, Brazil. Revista do Inst Med Trop São Paulo **2003**;45(5):245-8.
11. www.cve.saude.sp.gov.br/htm/zoo/LEPTO. Acessed 5 August 2005.
12. Ashford D.A., Kaiser R.M., Spiegel R.A., et al. Asymptomatic infection and risk factors for leptospirosis in Nicaragua. Am J Trop Med Hyg **2000**;63:240-59.
13. Nanette L.S.Q., Ribeiro A.A., Raetz C.R.H. A Methylated phosphate group and four amide-linked acyl chains in Leptospira interrogans Lipid A.The Journal of Biological Chemistry **2004**;279(24):25420-9.
14. Segura E.R., Ganoza C.A., Vinetz J.M., Peru-United States Leptospirosis Consortium. Clinical spectrum of pulmonary involvement in leptospirosis in a region of endemicity, with quantification of leptospiral burden. Clin Infect Dis **2005**;40(3):343-51.
15. Maes P., Clement J., Ranst M.V. Hantaviruses: Immunology, treatment,and Prevention. Viral Immunology **2004**;17(4):481-97.
16. Figueiredo L.T.M., Morelli M.L., Sousa R.L.M. Emerging Infectious Diseases **2003**;9(7):892-3.
17. Duchin J.S., Koster F.T., Breiman Robert F. Hantavirus Pulmonary Syndrome: A Clinical Description Of 17 Patients With A Newly Recognized Disease. N Engl J Med **1994**;330(14):949-55.