A Lesson from a Fatal Case of Leptospirosis

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ABSTRACT

Leptospirosis is probably the most widespread and prevalent zoonotic disease in the world and it is difficult to diagnose. Therefore, the disease is frequently not recognized and consequently severely neglected. This infectious disease is re-emerging globally and numerous outbreaks have occurred worldwide during the past decade. It may occur wherever the risk of direct or indirect exposure to urine or kidneys of infected animals is present. Leptospirosis is likely to be underestimated because many patients have mild or subclinical infection and serological testing is imperfect and not always performed. Here it is presented a fatal case of Leptospirosis in Sicily, occurred at the Internal Medicine Division of the University Hospital of Palermo.

Key Words: *Leptospira interrogans, spirochaetes, human infection, rash, multi-organ failure*

INTRODUCTION

Leptospirosis is a major zoonotic disease occurring worldwide, but most commonly in rural areas of temperate regions especially in the late summer and early fall and in tropical regions during rainy seasons [1]. Although the incidence of the disease seems to have decreased in developed countries, it is apparently emerging rapidly as a significant widespread public health problem [2]. This report describes an unfavorable case of leptospirosis in Sicily; this is one of few reported cases over the last 20 years in this Mediterranean island, suggesting that this zoonosis is a relatively infrequent disease in this geographical area but highlights the importance of clinical suspicion in urban setting and in people who are not at risk of working exposure in order to quickly start the appropriate treatment.

CASE REPORT

A 71-year-old previously healthy woman was admitted to the Internal Medicine Division of the University Hospital of Palermo because of fever to 39,7°C, general malaise, rubella-like exanthema and lone atrial fibrillation. She referred that fever was continuous for ten days together with palpitations. She took amoxicillin/clavulanic acid for one day then the antibiotics administration was stopped because she complained the onset of a diffuse rash. She's a housewife and her past medical history was unremarkable except for duodenal ulcer, treated with prokinetic/anti-H2 drugs, and anxious-depressive syndrome, treated with antidepressant medications. She had no recent travel history and did not have a pet or direct contact with wild animals. When the patient was admitted to the Medical Division, she was in a sleepy, bradylalic and bradypsychic state; heart rate was 110/min irregular and blood pressure was 100/60 mmHg. She complained of a bad headache and calf pain. Chest objectivity revealed the presence of fine cracklings on the left pulmonary base. There was abdominal pain on right hypochondrium and epigastrium; anorexia and episodes of nausea and vomiting were also reported. She referred also dysuria. Blood tests and blood cultures were requested as well as microbiological tests for bacteria and viruses. Nasal swab for flu virus A was also performed. On the first day of ward admission, anemia and thrombocytopenia were found together with increased reactive protein C levels, altered liver and kidney functionality tests (Table 1). Urine testing showed hematuria, proteinuria and bacteriuria.

Table 1: Main laboratory findings during hospitalization

Lab analysis:	**Day I**	**Day II**	**Day III**	**Day IV**	**Day V**	**Day VI**
White blood cell count (cells/μL)	5.840	6.020	9.000	12.590	13.410	18.830
Segmented neutrophils (%)	92.6	94	92.3	93	91	92
Hemoglobin (g/dL)	12.4	11.9	10.9	12.6	12	12.6
Platelet count (cells/μL)	58.000	52.000	55.000	60.000	46.000	37.000
Serum total bilirubin (mg/dL)	0.60	0.72	0.91	2.33	2.8	4
AST/ALT (IU/L)	82 /54	70/44	92/51	134/64	143/66	147/61
Alcaline Phosphatase (IU/L)/GGT (IU/L)	129/77	120/56	176/90	312/183	300/182	239/123
LDH (IU/L)	959	793	937	1.283	1.339	1.129
Myoglobin (mg/dL)	200.6	250.6	400.5	403	400	509
Blood urea nitrogen (mg/dL)	76	104	150	189	209	240
Creatinine (mg/dL)	1.7	2.13	2.81	3.4	3.8	4.31
C-reactive protein (mg/dL)	25.12	27.2	28.13	30.31	27	28.37
INR	1.18	1.08	1.03	1.21	1.1	1.05
aPTT (sec)	31	30	34	41	40	45
Fibrinogen C (mg/dL)	353	300	313	275	260	224
D-Dimer (ng/mL) / ATIII (%)	1410/72	>1000/52	>1000/65	4597/53	4.323/53	3357/42

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GGT: Glutamyl transpeptidase; LDH: Lactate dehydrogenase; INR: International Normalized Ratio; aPTT: Activated Partial Thromboplastin Time; ATIII: Antithrombin III

Treatment with levofloxacin intravenous (i.v.) was started (250 mg/day) adjusted for Glomerular Filtration rate (GFR: 31 mL/min/1.73 m^2), but it was stopped soon after because of the onset of erythema on the back and on the abdomen skin. Oral digoxin (0.125 mg) was administered for heart rate control and subcutaneous fondaparinux (1.5 mg) as anticoagulant. Normal saline was infused for initial signs of dehydration.
On day 2, X-ray and computed tomography (CT) of the chest showed lung congestion, interstitial broncho-vasal thickening and hyperplastic lymphonodes on mediastinal seat. Hemogasanalysis revealed hypoxemia with hypocapnia and it was initially suspected a pulmonary embolism (Table 2).

Table 2: Main hemogasanalysis data during hospitalization

BGA + ABE:	**Day I**	**Day II**	**Day III**
pH	7.438	7.45	7.41
pCO_2 mmHg	30.1	25.1	22.8
pO_2 mmHg	59.2	61.4	56.8
SO_2 (%)	90.6	93	88.9
cBase mmol/L	-3.4	- 6	-9.3
$cHCO_3^-$ mmol/L	22.2	20.7	17.6

BGA: Blood gas analysis; ABE: Acid-base equilibrium

pCO_2 : partial pressure of carbon dioxide; pO_2: partial pressure of oxygen; SO_2: Oxygen saturation

*c*Base: standard base excess; $cHCO_3^-$:concentration of bicarbonate

However, negative High Resolution CT suggested the possibility of other diagnostic hypothesis. Abdominal ultrasound revealed hepatomegaly, hepatic veins dilatation and splenomegaly; there were not enlarged kidneys and no dilatation in the biliary system. Cultures of blood collected during the fever peak (T > 38°C) were negative for bacterial and fungal growth on three samples. Tests for virus infections (CMV, EBV, HBV, and HCV) were negative as well. On the basis of clinical suspicion plus the information given by relatives of recent consumption of vegetables harvested close to a river shore after a heavy rainfall, a MAT (Microscopic Agglutination Test – MAT) test for leptospira was ordered. On hospital day 3, to evaluate the hypothesis of endocarditis, the patient underwent to echocardiogram that did not reveal any apparent vegetations, but revealed an atrial dilatation and mild mitral insufficiency. Persistent fever was treated with acetaminophen and hypoxiemia was managed with O2-therapy. On this same day 3, a cutaneous vasculitic reaction was suspected because of the spreading of erythema and the onset of petechias on ankles and trunk. Progressively, liver functionality worsened and kidney failure progressed to oligo-anuria. To hold blood pressure levels steroids and fluids were infused together to albumin and loop diuretics to promote diuresis. On day 4, leukocytoses together with further increase of inflammatory markers were evident; for this reason an empiric antibiotic therapy with clarithromycin and doxycycline was started. The choice was oriented toward a different antibiotic category, considering the anamnestic allergic-like rash manifested by the patient after amoxicillin-clavulanic acid intake first and later the erythema reaction to levofloxacin. Because of persistent fever and the evidence of chest lymphoadenopathy, a peripheral smear was ordered unto the hypothesis of hematologic disease and/or parasitic infection, but it didn't show any significant immature myeloid cells and/or schistocytes or intracytoplasmic inclusions. Blood film revealed no evidence of micro-angiopathic haemolytic anaemia. On day 4, sensory alterations were observed but a brain CT scan did not show signs of acute vascular events. Over the next day a disseminated intravascular coagulation with progressive thrombocytopenia and hemostasis alterations was treated with plasma infusions but the beginning of a multi-organ failure was already establishing. Despite circulatory support, she became anuric and continuous renal replacement therapy was indicated. During the femoral venous access positioning she died after unsuccessful resuscitation for cardiac arrest.

The same day (sixth hospitalization day) the report of the microscopic agglutination test (MAT for Leptospira) came back positive allowing to make a diagnosis of Leptospirosis. Titers of antibodies against L. Interrogans and L. Borgpetersenii in the serum sample of fifth hospital day were respectively 1:100 and 1:400 (Table 3).

Table 3. Results of Microscopic Agglutination Test (MAT) with Paired Sera

	Antigens			Agglutination titer
	Species	Serovar	Lineage	
Leptospira	***Interrogans***	***Pomona***	***Mezzano***	
	Interrogans	***Bataviae***	***Pavia***	
	Kirschneri	***GrippoTyphosa***	***Moskva***	**1:100**
	Interrogans	***Icterohaemorragiae***	***Bianchi***	
	Interrogans	***Australis***	***Ballico***	
	Borgpetersenii	***Castellonis***	***Castellon***	
	Interrogans	***Copenhageni***	***Wijnberg***	
	Interrogans	***Hardjo***	***Hardjoprajitno***	**1:400**
	Interrogans	***Autumnalis***	***Akiyami***	
	Interrogans	***Canicola***	***Alarik***	
	Borgpetersenii	***Poi***	***Poi***	

DISCUSSION

Leptospirosis is caused by the Leptospira species of Spirochaetes and is presumed to be the world's most common zoonosis [1]. Infection usually follows contact with the urine of infected animals through broken or water-soaked skin or the conjunctivae. The largest reservoir of infection is rat, although leptospires have been isolated from cattle populations, and contact with livestock is an established risk factor [1].

In developed countries, leptospirosis has been considered a sporadic disease associated with occupational risk (farming and animal husbandry, butchery and veterinarians). More recently it has been increasingly associated with recreation and water sports and travels and has become the cause of outbreaks during athletic events, in disaster situations and in adventure tourism. Heavy rainfall may influence the risk for acquiring leptospirosis in different ways. It may affect the normal demographic cycle of rodent reservoirs by altering the reproductive periods and peak population densities. In addition, flooding may increase transmission to humans by either driving reservoirs into human dwellings or by facilitating the dissemination of pathogenic *Leptospira* excreted from rodent urine. The disease follows a biphasic course [2-3]. An initial 'infective' or 'septicemic' phase (4 to 7 days) characterized by non-specific symptoms (fever, headache, myalgia, abdominal pain and uveitis) is followed by a period of 1 to 3 days during which the fever resolves. An 'immune' phase follows, during which leptospires are excreted in the urine and circulating anti-*Leptospira* immunoglobulin M (IgM) antibodies are detectable in blood stream [1]. Symptoms of the first phase can resume in association to neurologic involvement. 5 to 10 percent of patients progress to the severe form of the disease which is also known as Weil's disease [3]. This comprises jaundice due to hepatocellular dysfunction and multi-organ involvement including Acute Kidney Injury (AKI), pulmonary haemorrhage and adult respiratory distress syndrome. In this study case, the patient presented with the clinical characteristics of Weil's syndrome (multi-organ failure: impaired renal and hepatic function, hemorrhage, vascular collapse, mental status changes) 7 to 10 days after the onset of symptoms possibly related to *Leptospira* infection.

Leptospiral renal involvement is usually characterized by tubulointerstitial nephritis with interstitial edema and a cellular infiltrate [7-9] leading to hypoxia and hypoperfusion, manifested by a decreased GFR, elevated BUN to creatinine ratio, inability to concentrate urine and hypokalemia. This typically manifests as non-oliguric AKI with hypokalemia. These typical features of renal damage were not observed in our patient with AKI characterized by anuria without electrolyte disturbances.

Cardiac abnormalities, including alterations in cardiac rhythm (atrial fibrillation, supraventricular tachycardia, bundle branch and second degree heart block), are common during the early phase of leptospiral infection. Endocarditis need to be excluded as well [6-7].

Pulmonary involvement with hypoxia seen in this patient mimics pulmonary embolism that needed to be excluded by imaging. Pulmonary lesions, when present, are presumed to be due to vascular injury and are predictor of poor outcome [6-7]. The involvement of blood vessels either localized or systemic is related to sepsis and due to a process of endothelial activation/damage rather than as a classical systemic vasculitis.

The serological diagnosis of leptospirosis remains challenging and in this case the diagnosis was made and the suspicion was confirmed on the basis of the serological data. MAT is considered the gold standard for diagnosis but, it is not helpful in the first few days after exposure [1-4]. We performed MAT against 11 serovars which have been mainly associated to the disease (Table 3): high antibody titer was detected against L. interrogans.

The diagnosis of leptospirosis in this patient was delayed: patient's non-specific signs were not completely clear in her clinical presentation especially for a wrong interpretation of a rash as a drug-reaction, ruling out the possibility of a vasculitic-like reaction. The delay of subsequent antibiotic treatment for ten days before her admission in the ward may have changed the prognosis in this patient due to the progression of the infection and the systemic involvement. Although a small percentage of patients with Leptospirosis present with severe liver and kidney failure together to electrocardiographic alterations, in many patients it remains undiagnosed and the disease is only recognized and treated after the serologic test becomes positive.

Penicillins or doxycycline traditionally have been the antimicrobials of choice for treatment of leptospirosis. Ceftriaxone and cefotaxime are as efficacious as penicillin. Azithromycin also may be effective. First generation cephalosporins appear less effective, and leptospires are resistant to chloramphenicol. The use of fluoroquinolones has been controversial. Penicillins may shorten the duration of disease if given during the infective phase and have been shown to reduce urinary shedding of leptospires [4-5]. Treatment of severe disease after this stage is supportive, and may require intensive care support. There is a considerable risk of death especially in cases with pulmonary involvement, where reported survival rates are as low as 16% [6-9]. In this patient all the established treatments were inefficacious probably because the latest stage of the infection characterized by a multi-organ involvement that was already established. This case demonstrates the importance of a correct differential diagnosis that does not overlook medical history clues or signs that seem to be of minor importance. However, it also emphasizes the essential role of state-of-the-art laboratory tests and diagnostic imaging. Prognosis is as good as quickly and adequate is the treatment. The present case description suggests the need for an adequate diagnostic approach based on simple and inexpensive tests (including serum and urine laboratory tests along with arterial blood gas analysis) that focus on the early identification of the cause and its correct treatment. Leptospirosis is likely to be underestimates as many patients have mild or subclinical infection and serological testing is imperfect and not always performed. For this reason is largely under diagnosed because a low index of the suspicion among physicians. Sometimes an isolated sign is not considered as related to a systemic disease context and for this reason a pathology is undiagnosed (i.e. in our patient, an incorrect clinical framework of a rash, considered as drug-effect related and not in order to a sign of a systemic disease). A high index of suspicion is needed not only in endemic areas: leptospirosis must be considered when a patient presents with acute onset of fever, headache and myalgia. Laboratory confirmation is crucial, especially when these diseases are occurring simultaneously during the rainy season. Monitoring of rainfall may thus be used to alert health services and communities of outbreak threats and in turn promote rapid responses aimed at early case identification and prevention of mortality due to severe leptospirosis.

In conclusion this report, to best of knowledge, is one of few reported cases of Leptospirosis in Sicily over the last 20 years [10], suggesting that leptospirosis is a relatively infrequent disease in this geographical

area. However the risk should not be underestimated also in urban setting and in people who are not at risk of working exposure.

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