

Leptospirosis presenting as ascending progressive leg weakness and complicating with acute pancreatitis

ABSTRACT

Leptospirosis is a spirochetal bacterial infection of great public health importance. It has a broad spectrum of clinical manifestations which goes from subclinical infection and self-limited anicteric febrile illness (80-90% of all cases) to icteric leptospirosis known as Weil's disease. This is a severe disease characterized by hemorrhage, acute renal failure and jaundice. It is uncommon for leptospirosis to present itself as a primary neurological disease. Additionally, acute pancreatitis is an unusual gastrointestinal manifestation. We report a case of leptospirosis presenting as ascending progressive leg weakness and complicating with acute pancreatitis in an adult patient treated at Hospital Universitário, Universidade Federal de Santa Catarina. The diagnosis was confirmed through ELISA-IgM antibody testing positive for leptospirosis. After antibiotic therapy and support treatment for a few weeks, total resolution of severe manifestations was achieved. Rare and unusual presentations of leptospirosis should be kept in mind in relevant epidemiological scenario.

Keywords: leptospirosis; pancreatitis; neurologic manifestations.

INTRODUCTION

Leptospirosis is a worldwide spirochetal bacterial infection of great public health importance in the tropics. The source of infection in humans is usually either direct or indirect contact with the urine of infected animals. These bacteria infect humans by entering through abraded skin, mucous membrane, conjunctivae.^{1,2} It is an endemic disease in several regions of Brazil, more often due to bad living conditions and seasonal floodings, seen in the rainy seasons.³ After an incubation period of 1-2 weeks, leptospirosis manifests as a biphasic illness with the leptospiremic phase followed by an immune phase.⁴

This disease is characterized by the development of vasculitis, endothelial damage, and inflammatory infiltration. Leptospirosis mostly affects tissues of the liver and kidney. Rarely, other organs such as brain, pancreas, lung, heart, gallbladder, brain, and ophthalmic tissues are involved, mainly due to vasculitis.^{1,2} Clinically, it shows a broad spectrum of clinical manifestations which goes from subclinical infection and self-

limited anicteric febrile illness (80-90% of all cases) to icteric leptospirosis known as Weil's disease, a severe and potentially fatal disease characterized by hemorrhage, acute renal failure and jaundice.²

It is uncommon for leptospirosis to present as a primary neurological disease. Both central and peripheral neurological manifestations of the disease may be seen, but usually in context of advanced infection, where the diagnosis has already been established.⁵ The commonest neurological manifestation is aseptic meningitis.⁶ Peripheral nerve involvement is rare, but abnormalities reported include transient lower limb weakness, areflexia, paraesthesiae, neuropathies and the Guillain-Barré syndrome (GBS). There are a few cases of GBS-like presentation during or following infection with *Leptospira interrogans* documented in the literature.^{5,7,8}

Acute pancreatitis is an uncommon gastrointestinal manifestation of leptospirosis. There are considerable number of cases documented in literature, but the involvement of the pancreas is not yet well understood in human leptospirosis.⁸⁻²¹ The diagnosis of

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acute pancreatitis may be complicated as acute renal failure can increase the serum amylase and lipase levels.^{10,19,22}

We report a case of leptospirosis presenting as ascending progressive leg weakness and complicating with acute pancreatitis in an adult patient seen at a tertiary care centre in Florianópolis. Medical records of this patient were retrospectively reviewed in preparation of the case.

CASE REPORT

A 48-year-old black male patient from southeast of Brazil was admitted in the emergency department of our hospital on the October 16th, 2010. At the time, he was working as a plumber in south of Brazil. He presented with complaints of progressive loss of strength and severe pain in both legs with four-day history. Previously to that, he reported being healthy and did not present any other known diseases. He also complained about a high grade fever and a bilateral headache, mainly occipital, of moderate intensity, in the past three days. One day after the appearance of the fever, he started with diarrhea, without fecal incontinence, abdominal pain, blood or pathological products. Urine alterations or urinary retention were not observed. On the day before being admitted to the hospital, he presented difficulty to stand up due to severe pain and loss of movement control on both legs. He referred 4-kg weight loss in the last week. He denied contact with jaundiced persons, blood transfusion and drug abuse, except for small amount of alcohol daily intake. He had contact with contaminated water 1-2 weeks before coming to the hospital.

On physical examination, he was in poor condition, dehydrated, oriented, anicteric, pulse rate 108 bpm and temperature of 39.1°C. Blood pressure was 140 x 80 mmHg with no dyspnea and with normal cardio-pulmonar and abdominal auscultation. His abdomen was flat, flaccid, and there was no hepatomegaly. The neurological examination disclosed paraparesis, Muscle Research Council (MRC) grade 2 strength in both legs, and painful skin upon touch. The patellar and ankle reflexes were absent. Strength was normal in upper limbs, biceps and flexor reflexes were normal. Sensibility was preserved. He did not present nuchal rigidity, exam of cranial nerves was normal and no other abnormalities were noticed. Autonomic dysfunctions, loss of sphincter control or swallowing disorders were not observed.

Laboratory findings on admission revealed Hb: 12.8 g/dL ; Htc: 37.6% ; WBC: 6770/mm³; platelet count: 41,000/mm³ (n: 150 x 10³ - 440 x 10³); creatinine: 1.3 Mg/dL (n: 0.8-1.3); Na: 132 mEq/L (n: 136-145); aspartate transaminase: 213 U/L (n: 15-37); alanine transaminase: 130 U/L (n: 25-64); alkaline phosphatase: 109 U/L (n: 50-136); gamma glutamyltransferase: 106 U/L (n: 15-85); total bilirubin, serum K, creatine kinase were normal; serology negative for viral hepatitis and HIV.

A lumbar puncture was performed on the fourth day of initial symptoms, and cerebrospinal fluid (CSF) was clear. CSF glucose and protein were normal, latex tests for cryptococcal antigen was negative, and no bacteria were found. B12 vitamin level and thyroid function were normal. Chest X-ray was normal.

On the admission day, the patient was put on intravenous hydration and received thiamine and medication for symptom relief. One day after being admitted to the hospital jaundice and severe abdominal pain ensued, and the patient remained presenting paraparesis and severe pain in both legs. A neurologic evaluation was requested and performed by a neurologist, who noted loss of strength not only restricted to legs, but also a paresis on upper limbs, MRC grade 4, biceps, triceps and supinator hyporeflexia. GBS was thought to be the main cause.

On the second day in hospital, the urinalysis showed moderate quantity of bacteria with 160 x 10³ leukocytes. Ceftriaxone was administered on the suspicion of urinary tract infection. At that moment, the amylase evaluation turned out 478 U/L (n: 25-115); lipase 898 U/L (n: 114-286) and creatinine: 4.9. Acute pancreatitis was diagnosed. No hemodialysis was necessary at that moment.

By the third day he continued with high grade fever and the jaundice was more evident. Total bilirubin increased to 11.05 mg/dL (direct bilirubin: 10.32). Creatine kinase increased to 413 U/L, as shown in Table 1. Uroculture was normal. Ceftriaxone was discontinued and treatment with penicillin G started as leptospirosis infection was the likely diagnosis. The patient's blood pressure dropped to 80 x 50 mmHg and capillary refill time was decreased. After rapid hydration he recovered his normal blood pressure with no vasopressors needed.

By the eighth day of initial symptoms, ELISA-IgM antibody testing for leptospirosis was performed.

An echocardiogram showed mild hypokinesia on left ventricle, ejection fraction of 49% and moderate diastolic dysfunction. However, the patient has never presented dyspnea during his clinical evolution. Abdominal ultrasonography showed free peritoneal fluid and abdomen CT-Scan showed free fluid in the pelvis and bilateral pleural effusion. Nothing was observed at the pancreas site.

The therapy with penicillin was continued. On the following days, the neurological symptoms presented progressive improvement. A mild improvement on laboratory findings was also noted. From hospital day 6 on the patient did not present fever, headache or diarrhea, although he remained icteric. His creatinine level gradually returned to normal levels.

The neurological findings remained unchanged until the 6th day, when a gradual daily improvement was observed. Spinal cord magnetic resonance imaging (MRI) and eletrophysiologic studies were not performed due to

Table 1. Laboratory findings of reported patient during hospitalization, Florianópolis - SC, 2010

Test	16/10	18/10	19/10	29/10	06/11	Reference value
Hemoglobin (g/dL)	12.8	12	10.8		10.4	13.5-18
Hematocrit (%)	37.6	35.2	31.8		31.9	40-52
Leukocytes (cells/mm ³)	6,770	7,860	8,480		5,150	3,800-11,000
Platelets (cells/mm ³)	41,000	22,000	39,000		562,000	150,000-400,000
Urea (mg/dL)	45	149	141	34	36	15-39
Creatinine (mg/dL)	1.3	4.9	3.5	1.2	1,1	0.8-1.3
Alanine aminotransferase (U/L)	213		142		83	25-64
Aspartate aminotransferase (U/L)	130		97		138	15-37
Alkaline phosphatase (U/L)	109	137	118		158	50-136
Glutamyltransferase (U/L)	106	362	287		131	15-85
Total bilirubin (mg/dL)	0.67		11.05		2.42	0-1
Direct bilirubin (mg/dL)			10.32		2.28	0-0.03
Amylase (U/L)		478	417	357	276	25-115
Lipase (U/L)		898	647	808	364	114-286
Creatine kinase (U/L)	119		413		95	35-232

the improvement of clinical findings with the introduction of leptospirosis treatment and due to financial constraints.

On hospital day 15 there was a total neurologic recovery and the patient was able to stand up and walk normally. His amylase and lipase were kept high (332 and 706 U/L, respectively) and total bilirubin was 2.49 (direct bilirubin: 2.23), as shown in Table 1. The patient was discharged on the 22nd day after admission, with a positive result for the immunoenzymatic ELISA-IgM antibody testing for leptospirosis (from Central Laboratory of Public Health of Santa Catarina). He was asymptomatic but remained with high levels of amylase and lipase. Appropriate advice for follow-up after 30 days was given. On November 30th 2010 the patient did not have any complaints or weaknesses.

DISCUSSION

Leptospirosis has protean manifestations and rare and unusual presentations should be kept in mind in relevant epidemiological scenario.²³

Neurological involvement in leptospirosis is rare. The neurological manifestations result from the effect of the organism on the central nervous system (CNS) and the host immune reaction to the organism. Following infection, leptospire reach the CNS rapidly. Changes in CSF content are a later manifestation, and it has therefore been suggested that some of the inflammatory neurological manifestations of leptospirosis result not from the

organism itself but from the antibody reaction to it.^{5,8} The prognosis after primary neuroleptospirosis is generally good but altered sensorium and seizures herald a worse prognosis.⁶

The striking feature of this case was initial presentation of leptospirosis with neurological symptoms. In the immune phase of the illness as aseptic meningitis is common, with up to 90% of cases having CSF pleocytosis. About half of these cases have symptoms of meningeal irritation.^{6,7} However, these features are usually incidental to an established and generalized illness. Opposite to the reported in this case, the majority of florid neurological features seen usually occur when the diagnosis has already been made and treatment is in progress.⁵

The present case had a notably symmetric ascending polyneuropathy and arreflexia as initial symptoms, in the absence of sensory loss and sphincter disorders. The probable cause was meningeal and radicular inflammation as a result of antibody production. The neurological picture was progressive and reminiscent of GBS, illness characterized by areflexic motor paralysis with mild sensory involvement and typical acellular rise in CSF total protein.⁷ No typical albuminocytologic dissociation was found, probably because of the time of evaluation (4th day after onset of symptoms). In patients with GBS, normal CSF protein is found in about one-third of patients when tested earlier than one week after symptom onset.²⁴ The diagnosis of GBS is confirmed when there

are compatible clinical features and neurological exam associated with typical CSF and electrophysiologic studies. MRI is usually helpful in excluding acute myelopathy as a differential diagnosis. Electrophysiologic tests and MRI were not performed in this patient because improvement of neurological alterations with the treatment for leptospirosis and due to financial constraints.

An epidemiological suspicion, a history of fever, headache, myalgias, low platelet count and acute renal dysfunction were compatible with leptospirosis. The diagnosis was confirmed later by ELISA-IgM antibody testing, which supported the presumption that neuropathy was triggered by an acute leptospiral infection. A total recovery after antibiotic therapy in this patient also confirmed that infection. Elisa-IgM antibody testing is an immunoenzymatic assay with good sensitivity and specificity, mainly after the 7th day of symptom onset.

GBS has been reported as sequelae to several infections including *Campylobacter jejuni* gastroenteritis, and infections due to Epstein-Barr virus and cytomegalovirus. Other cases occur on a background of Hodgkin's disease, systemic lupus erythematosus, and lymphoma. Although its pathogenesis is not clear, GBS may be induced by molecular mimicry, toxin, or immune deregulation. However, immunological studies delineating the mechanism for neuropathy triggered by *Leptospira* have not been carried out probably because of the rare association.⁷

Munford et al.⁵ also described a dramatic neurological presentation with a rapidly evolving flaccid paraplegia associated with biochemical evidence of renal and hepatic dysfunction, a fatal case in a 64-year old farm worker. Other authors reported cases of GBS following an infection with *Leptospira icterohaemorrhagiae* in a 65-year old woman and in a pediatric patient.^{7,8}

A definite relationship between an infection episode and neuropathy is difficult to establish as in most cases it is not possible to isolate the causative organism by the time neuropathy appears. The diagnosis is usually ascertained on the basis of relevant serological tests.⁵

Pancreatitis is a rare complication of leptospirosis.¹⁹ This patient presented epigastric pain and jaundice as the main manifestations of pancreatic involvement, and laboratory diagnosis could be achieved by the elevation of serum lipase levels of more than threefold the normal values and amylase levels more than four times of normal levels. There were no pancreatic morphologic changes detectable by ultrasound and abdominal CT examination revealed only intra-abdominal minimal fluid collection, with bilateral pleural effusion. The history of alcoholism may have mislead the etiology of pancreatitis in this case, but clinical features and leptospirosis serology confirmation weakened the suspicion of alcoholic pan-

creatitis. Other authors have described several cases of leptospirosis and pancreatitis diagnosed by elevated serum amylase and lipase, but without morphologic change detectable by pancreatic ultrasound.⁹⁻¹⁴ Daher et al.¹⁷ demonstrated that histopathological pancreatic changes are not well correlated with high level of serum amylase in human leptospirosis. So, the diagnosis of acute pancreatitis is somewhat controversial in this disease.¹⁹ Clinical symptoms of pancreatitis are not common findings and a true diagnosis of acute pancreatitis is complicated by the fact that acute renal failure, a leptospirosis usual manifestation, can increase serum amylase and lipase levels.¹⁰ It is suggested that, apart from the typical clinical features, serum amylase levels higher than twice the normal value could not be explained only by renal failure.²⁵ Therefore, in the presence of renal failure, Kishor et al.²¹ suggested laboratory diagnosis of acute pancreatitis should only be performed with amylase levels higher than 4.4 times the normal value. Sometimes, abdominal CT is essential for a correct diagnosis.

The patient reported here presented a favorable evolution, with total resolution of severe manifestations in a few weeks.

In conclusion, leptospirosis can be presented as a neurological primary disease. It should also be considered in the differential diagnosis of hyperamylasemia and jaundice in endemic areas. Clinicians need to be aware of the possibility of leptospirosis, even if the illness presents with unusual features, because early diagnosis and appropriate treatment is essential for life saving.

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REFERENCES

1. Farr RW. Leptospirosis. Clin Infect Dis 1995; 21:1-6.
2. Levett PN. Leptospirosis. Clin Microbiol Rev 2001; 14:296-326.
3. Reis RB, Ribeiro GS, Felzemburgh RD et al. Impact of environment and social gradient on *Leptospira* infection in urban slums. PLoS Negl Trop Dis 2008; 2:228.
4. Ramakrishna P, Sai Naresh VV, Chakrapani B et al. Indian J Nephrol 2008; 18:130-1.
5. Mumford C, Dudley N, Terry H. Leptospirosis presenting as a flaccid paraplegia. Postgrad Med J 1990; 66:218-20.
6. Panicker JN, Mammachan R, Jayakumar RV. Primary neuroleptospirosis. Postgrad Med J 2001; 77:589-90.
7. Bal AM, Bharadwaj RS, Gita N et al. Guillain-Barré syndrome in a pediatric patient following infection due to *Leptospira*. Jpn J Infect Dis 2003; 56:29-31.
8. Morgan AG, Cawich F. Ascending polyneuropathy in leptospirosis-a case study. Ann Trop Med Parasitol 1980; 74:567-8.

9. Casella G, Scatena LF. Mild pancreatitis in leptospirosis infection. *Am J Gastroenterol* 2000; 95:1843-4.
10. Edwards CN, Nicholson GD, Hassel TA et al. Leptospirosis in Barbados. *W. Indian Med J* 1990; 39:27-34.
11. Edwards CN, Evarard COR. Hyperamylasemia and pancreatitis in leptospirosis. *Am J Gastroenterol* 1991; 86:1665-8.
12. Mana D, Karantzias J, Bagilet D et al. Leptospiroses e hiperamylasemia. *Med Intens* 2000; 19:16-8.
13. Monno S, Mizushima Y. Leptospirosis with acute acalculous cholecystitis and pancreatitis. *J Clin Gastroenterol* 1993; 16:52-4.
14. O'Brien MM, Vincent JM, Person DA et al. Leptospirosis and pancreatitis: a report of ten cases. *Pediatr Infect Dis J* 1998; 17:436-8.
15. Stolze E, Schaads JDG, Bool PH. Weil's Disease associated with pancreatic necrosis. Report on a case. *Trop Geogr Med* 1959; 11:93-5.
16. Vincent JM, O'Brien MM, Person DA et al. Leptospirosis and pancreatitis. *Pediatr Infect Dis J* 1999; 18:400.
17. Daher EF, Brunetta DM, Silva Junior GB et al. Pancreatic involvement in fatal human leptospirosis: clinical and histopathological features. *Rev Inst Med Trop S Paulo* 2003; 45:307-13.
18. Leblebicioglu H, Sencan I, Sunbul M et al. Weil's disease: Report of 12 cases. *Scand J Infect Dis* 1996; 28:637-9.
19. Kaya E, Dervisoglu A, Eroglu C et al. Acute pancreatitis caused by leptospirosis: Report of two cases. *World J Gastroenterol* 2005; 11:4447-9.
20. Pai ND, Adhikari P. Painless pancreatitis: a rare manifestation of leptospirosis. *J Assoc Physic Ind* 2002; 50:1318-9.
21. Kishor KK, Rao PV, Bhat KR et al. Pancreatitis in Weil's disease. *Trop Doct* 2002; 32:230-1.
22. Rosa RH, Dias A, Pascoa B et al. Leptospirose e pancreatite aguda. *J Port Gastroenterol* 2004; 11:210-2.
23. Bal AM. Unusual clinical manifestations of leptospirosis. *J Postgrad Med* 2005; 51:179-83.
24. Ropper AH, Wijdicks EFM, Truax BT. Chapter 6. *In: Guillain-Barré syndrome*, FA Davis, Philadelphia 1991. p.57
25. Levvit MD, Cooperband SR. The renal clearance of amylase in renal insufficiency, acute pancreatitis, and macroamylasemia. *Ann intern Med* 1969; 71:919-25.