Unusual Clinical Manifestations of Leptospirosis

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ABSTRACT

Leptospirosis has protean clinical manifestations. The classical presentation of the disease is an acute biphasic febrile illness with or without jaundice. Unusual clinical manifestations may result from involvement of pulmonary, cardiovascular, neural, gastrointestinal, ocular and other systems. Immunological phenomena secondary to antigenic mimicry may also be an important component of many clinical features and may be responsible for reactive arthritis. Leptospirosis in early pregnancy may lead to fetal loss. There are a few reports of leptospirosis in HIV-infected individuals but no generalisation can be made due to paucity of data. It is important to bear in mind that leptosomal illness may be a significant component in cases of dual infections or in simultaneous infections with more than two pathogens.

KEY WORDS: Cardiac arrhythmia, Cholecystitis, Congenital infection, Guillain-Barre syndrome, Pancreatitis, Pancytopenia, Pregnancy, Leptospirosis

Leptospirosis is a zoonosis that is caused by the spirochete Leptospira interrogans. The species has several serological variants - the serovars. Antigenically related serovars are grouped together into serogroups. Serovar distribution varies with the geographical region. Recently, DNA relatedness studies have classified the genus Leptospira into 13 species. However, serovar based taxonomy continues to have epidemiological value.\(^1\)

Leptospirosis classically manifests as a biphasic illness. The first phase is characterised by high fever and coincides with leptospiremia. This is followed by a brief period when the patient is afebrile. Fever returns heralding the second phase of illness that may be accompanied by jaundice and renal failure. During this period, leptospires are not found in the blood but are excreted in the urine. Unfortunately, classical presentation is not synonymous with the most common presentation, a fact not always appreciated in clinical medicine. Leptospirosis has protean manifestations and rare and unusual presentations should be kept in mind in relevant epidemiological scenario.

This communication intends to summarise the unusual clinical features of leptospirosis. A thorough knowledge of clinical manifestations is especially valuable in communities that lack diagnostic facilities and hence the need for clinical judgement and suspicion is paramount.

Classical features of leptospirosis

Leptospirosis classically presents as a biphasic illness. The first phase of the disease is commonly referred to as the septicemic phase. It is characterised by fever, headache, myalgia, conjunctival congestion and a host of non-specific features that may include mild cough, lymphadenopathy, rash, anorexia, nausea, and vomiting. This phase is followed by a brief afebrile period of variable duration that, in turn, is followed by the immune phase of illness. The common organs involved during this phase are the liver and kidneys. Both organ derangements are reversible. The severe form of leptospirosis, also known as Weil’s disease, is characterised by a fulminant course with rapid onset of hepatic and renal failure and high mortality. In a retrospective report of 34 patients with leptospirosis, the common clinical features included fever (100%), headache (75%), myalgia (55%), arthralgia (45%) and vomiting (39%).\(^2\) In one of the largest reported series that included 353 cases, fever, headache, myalgia, chills, and anorexia were present in more than 80% of patients.\(^3\) Interestingly, an association between severity of illness and infection with serovar Leptospira interrogans was also observed. During the epidemic in Mumbai in the year 2000, the common clinical signs and symptoms included fever, headache, myalgia, conjunctival suffusion and cough with hemoptysis.\(^4\)

In an endemic area, suspecting leptospirosis on clinical grounds should not be very difficult. However, the disease is not commonly thought of and hence the diagnosis is often missed due to lack of awareness amongst the medical and medical support team. As an aid to clinical diagnosis, Fenech proposed a clinical scoring system.\(^5\) In my own experience, the scoring system had a moderately good sensitivity (81.8%) and specificity (72.9%). The positive predictive value was 40.9% and the negative predictive value was 94.5% when compared with serology.\(^6\) In one published work, the sensitivity, specificity, positive predictive value and negative predictive value were 71.2%, 76.5%, 51.2% and 85.4%, respectively.

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value of the scoring system was reported to be 81.8%, 72.9%, 40.9% and 94.5% respectively when compared with serology. Use of the scoring system would help exclude the diagnosis of leptospirosis. Modifications in the scoring system have been proposed recently and merit further evaluation. [7]

In an endemic area, leptospirosis is often confused with dengue fever due to the similarities of clinical features. LaRocque and colleagues summarised the data regarding clinical presentations of the two illnesses comparing 938 patients of dengue fever with 63 patients of leptospirosis. [9] Presence of rash, pruritus and a positive tourniquet test was significantly associated with dengue fever. Karande and colleagues in their report of a concurrent epidemic of leptospirosis and dengue fever in Mumbai, noted that clinical features such as conjunctival suffusion, hemorrhage, abdominal pain, hepatosplenomegaly and edema were significantly associated with leptospirosis, while arthralgia was significantly associated with dengue fever. [9]

Although no single clinical feature is pathognomonic of leptospirosis, a cluster of findings should lead to clinical suspicion. Therapy should be initiated on the basis of clinical judgement, as laboratory confirmation can be delayed by days and weeks or is unavailable in several regions and early institution of appropriate therapy is known to reduce mortality. [10]

Severe leptospirosis may carry a high mortality if treatment is not instituted early. Poor prognostic markers in leptospirosis include hypotension (relative risk [RR] = 10.3), oliguria (RR = 8.8), hyperkalemia (RR = 5.9), and presence of pulmonary rales (RR = 5.2). [11] Other studies have reported dyspnea (odds ratio [OR] = 11.7), white blood cell count greater than 12,900/ mm³ (OR = 2.5), repolarization abnormalities on electrocardiograms (OR = 5.9), alveolar infiltrates (OR = 7.3), [12] hemoptysis, metabolic acidosis, and thrombocytopenia as markers of increased mortality. In hospitals that have adequate facilities, [13] patients with these risk factors should preferably be treated in an intensive care unit.

Unusual manifestations of leptospirosis

Pulmonary involvement

Although pulmonary involvement is not uncommon in leptospirosis, it is usually not suspected. In one study, 10 out of 176 hospital admissions with community-acquired pneumonia had positive leptospiral serology although only one patient had documented seroconversion. [14] Severe hemorrhagic pneumonitis may be a prominent manifestation of infection. [15] Three radiographic patterns have been described in patients with pulmonary involvement during leptospirosis infection - small nodular densities, diffuse ground glass densities and rarely, confluent areas of consolidation. [16] Pulmonary involvement may be the presenting feature of the illness or may complicate a frankly icteric disease. [17] Epidemic leptospirosis with pulmonary hemorrhage without jaundice or renal failure has been reported. [18] Severe pulmonary involvement in leptospirosis has been reported from Andaman and Nicobar islands. Serovar Grippotyphosa and more recently, [19] serovar V堡uzzi, [20] have caused such outbreaks. Independent predictors of mortality in pulmonary leptospirosis include hemodynamic disturbance, serum creatinine level more than 265.2 µmol/L and serum potassium level more than 4.0 µmol/L. [21] Karande and colleagues recently reported a case of pneumonia in a nine-year-old boy who presented with fever, cough, hemoptysis, and conjunctival suffusion. The patient was diagnosed to be suffering from leptospirosis following a rise in titer of antibodies reactive with serovar Australis. An autopsy study has reported the presence of diffuse bilateral pulmonary hemorrhage in fatal cases of leptospirosis. [22] A rare case of lung abscess due to leptospirosis has been reported in literature. [24]

Neurological manifestations

Although asymptomatic aseptic meningitis is a common feature of leptospirosis, severe symptomatic involvement is rare. Rare clinical presentations include myeloradiculopathy, myelopathy and cerebellar dysfunction. [25] Kavitha and Shastry reported a case of transverse myelitis following leptospirosis. Their patient presented with fever and jaundice and subsequently developed weakness of lower limbs and urinary retention. Sensory perceptions were decreased below T4 level and the illness was consistent with transverse myelitis. The patient had a positive anti-leptospira IgM serology. Costa et al reported a rare case of facial palsy following leptospirosis infection. The patient had a clinical illness consistent with leptospirosis. The authors did not perform microagglutination test (MAT) that is generally believed to be the confirmatory test. However, seroconversion was observed in the macroagglutination test. Although comparative clinical trials are lacking due to rarity of presentation, doxycycline has been used in such cases. [26] Mumford et al have reported a case of fatal leptospirosis with flaccid paraplegia in a patient with biochemical evidence of renal and hepatic involvement. Guillain Barre syndrome has been reported following an illness consistent with leptospirosis. [26] This patient had a history of fever, myalgia, and headache three weeks prior to the onset of paraplegia. The serum sample at the onset of the neurological illness had a titre of 6400 and a later sample had a titre of 800 with strongest reactivity to serovar Copenhageni. It is interesting to note that it was the falling titre and not the rising titre that was a clue to diagnosis as the patient presented comparatively late in illness. Because of the time lag between icteric illness and neurological manifestations, it may not be possible to obtain a culture confirmation or a rising antibody titre. An absence of such a confirmation therefore should not rule out an association. Whether leptospires are causally related to such neurological illness is a matter of conjecture. Treatment of neurological sequelae is supportive. It is unlikely that treatment of underlying cause will alter the natural course of the neurological illness.

Ocular manifestations

Ocular manifestations of leptospirosis can lead to significant morbidity. During the acute phase of illness, conjunctival congestion is a common clinical finding. [11] Uveitis is a rare sequel of the disease. It usually presents as a panuveitis with or with-
out hypopyon. Visual damage can occur in as many as 35% of patients. Topical quinolones have been used to treat such infections. A majority (95.5%) of 73 cases of leptospiral uveitis reported by Rathinam et al. had panuveitis, retinal periphlebitis (51.4%) and hypopyon (12.6%). A few patients had anterior uveitis without hypopyon (2.7%) and isolated vitreous inflammatory reaction (1.8%).

Gastrointestinal manifestations
Pai and Adhikari reported a rare case of pancreatitis following leptospirosis. Hyperamylasemia was persistent but returned to normal in three months following the institution of leptospirosis-specific therapy. There are other reports too of pancreatitis complicating leptospirosis. Monno and Mizushima reported a rare case of acute acalculous cholecystitis in a patient with infection due to serovar Autumnalis. In an outbreak of leptospirosis reported from the United States, two out of 22 hospitalised patients had symptoms suggestive of acute cholecystitis. Cross examination of the gall bladders removed at surgery revealed thickened walls with smooth serosal surface and bile-stained mucosa. Calculi were not found. The submucosal tissue had mononuclear cell infiltration and also showed edematous changes. Leptospires were detected by immunohistochemistry techniques. Staining for the granular and filamentous antigens was found positive in the vessel walls and also in the submucosa. Paz and colleagues reported a case of enteritis in an Israeli patient who had a history of travel to Thailand, a region where leptospirosis is an emerging disease. The patient presented with fever, diarrhea, and vomiting and leptosporal serology was performed because creatinine levels were high. The patient had a rising antibody titers detected by MAT. He was treated with penicillin and azithromycin along with intravenous fluids. Peritonitis is another rare manifestation of leptospirosis.

Cardiac involvement
An analysis of data of 50 patients with serologically proven leptospirosis demonstrated that 70% of the patients had electrocardiographic abnormalities, with atrial fibrillation being the commonest major arrhythmia noted. Thirty-six percent of the patients had conduction system abnormalities and 30% had T wave changes. Another series has reported AV block in 44% of patients with leptospirosis. A glycoprotein fraction of leptospiral cell wall has been incriminated in the pathogenesis of these rhythm disturbances. This protein is thought to inhibit the Na-K ATPase and may be responsible for the arrhythmia. Univariate analysis has shown that cardiac arrhythmia is more common in patients dying of leptospirosis than in the survivors. Other reported cardiac abnormalities include myocarditis and pericarditis. In seven cases of fatal leptospirosis, petechial haemorrhages were found in the heart and the pericardium in all the autopsy specimens and interstitial myocarditis was found in five specimens. In another study, acute coronary arteritis was found in 7% of patients who died of leptospirosis and evidence of aortitis was present in more than half. One case of leptospira endocarditis, possibly caused by serovar Icterohaemorrhagiae has been reported in literature.

Musculoskeletal symptoms
Various musculoskeletal abnormalities have been reported in patients with leptospiral infection. In a case reported by Coursin and colleagues, a 63-year-old man presented with multiorgan dysfunction and rhabdomyolysis. Although myalgia and mild elevation of muscle enzymes are common in leptospirosis, severe involvement of muscle tissue is rare. A fatal case of rhabdomyolysis was reported by O’Leary et al. In this report, acute infection with leptospira belonging to serogroup Grippotyphosa was diagnosed on the basis of serology. Skeletal muscle involvement independently correlates with the severity of disease.

Hematological manifestations
Somers et al reported a rare case of erythroid hypoplasia in a case of leptospirosis. The patient presented with fever, jaundice, shortness of breath, and meningism. His haematologic parameters showed normocytic normochromic anaemia, reticulocytopenia, and thrombocytopenia. Severe erythroid hypoplasia was observed on bone marrow examination. It is possible that this complication results from a direct action of toxic leptospiral products on the progenitor cells of the marrow. Stefos and colleagues reported two cases of pancytopenia following infection with leptospira. Interestingly, neither patient had a history of jaundice. According to Bishara and co-workers, pancytopenia could occur in as many as 28% of patients with leptospirosis. Most of the infections in their series of cases were caused by leptospira belonging to serogroup Icterohaemorrhagiae and it is possible that infection with this serogroup is associated with hematologic abnormalities. Isolated thrombotic thrombocytopenia purpura has been reported following infection with leptospires.

Immunological manifestations
Rare immune-mediated manifestations of leptospirosis include antiphospholipid syndrome and reactive arthritis. Such manifestations are likely to be a result of an immunologic cross reactivity. Antibodies generated in response to leptospiral infection may cross react with host antigens and could lead to an inflammatory response. Finsterer et al. have reported an interesting case of carpal tunnel syndrome in a pet-shop worker who was later found to have a positive leptospiral IgG and IgM serology. Symptoms improved on doxycycline therapy, although the antibody levels remained elevated over the next three years. Explaining the disappearance of symptoms is difficult especially because the patient continued to have high antibody titres and hence immunological cross reactivity could still have taken place. The authors hypothesized that persistence of antibodies could be the result of re-exposure at workplace or a long-term immunological response. However, this does not necessarily explain the resolution of symptoms. A plausible explanation is that immune-mediated illness is caused by antigen-antibody complexes rather than by cross-reactive antibodies. Doxycycline therapy, by eradicating the leptospires and thereby removing the source of antigens, could prevent the
formation of the immune complexes leading to a decrease in the inflammatory response.

Endocrine abnormalities

Panidis et al. described a rare case of male hypogonadism, presumably related to hormone deficiency at the hypothalamus-pituitary level, following leptospirosis. Abnormalities in hormonal secretion have been found in experimental infection in animals, but there is paucity of data regarding the incidence and effects of such abnormalities following infection in humans.

Leptospirosis in pregnancy and congenital leptospirosis

In a review of 15 patients with documented leptospirosis late in pregnancy, Shaked et al. found that eight women had abortions, two delivered healthy babies, four delivered babies who had signs of active leptospirosis and in one case, the clinical outcome was not stated. Carles et al. reported 11 cases of leptospirosis in pregnant women in French Guiana and foetal death occurred in more than 50% of the cases. Chedraui and San Miguel reported a case of leptospirosis in a 28-week pregnant patient. The patient presented with fever, myalgia and jaundice and serology was positive for serovar lysterohaemorrhagiae. The patient was treated with penicillin and delivered a healthy baby at 37 weeks. Leptospirosis, early in pregnancy often leads to abortion. Congenital infections are rare and long-term serious effects have not been documented. Hence, leptospirosis acquired in pregnancy is not an indication for its termination. In one report, transmission of infection to infant was thought to have taken place through the breastmilk.

Leptospirosis in HIV seropositive individuals

Jones and Kim reported a case of leptospirosis in a patient with acquired immunodeficiency syndrome. The patient initially presented with non-specific illness but later developed jaundice, renal failure and acute respiratory distress syndrome. The recovery was probably slower than is usual for leptospirosis and there was residual renal impairment. Others have reported a similar clinical course of illness as in non-immunocompromised patients.

Leptospirosis with concomitant illnesses

Because of epidemiological similarities, it is not unusual to experience concurrent epidemics of leptospirosis with other infections such as dengue fever. Dual infection in the same patient is however rarely reported. Kaur and John reported dual infection with leptospirosis and dengue fever virus. Markotic and colleagues reported dual infection with leptospirosis and dobra virus in a Croatian soldier while Kudesia et al. reported hanta virus and leptospira coinfection. Simultaneous infection with leptospirosis and Hepatitis E virus has been reported from China. Liver biopsy from this patient showed evidence of fibrosis that is considered unusual in Hepatitis E and it is possible that infection with leptospirosis might have influenced the pathological process. Kaushik and colleagues described a case of leptospirosis with concomitant Hepatitis B. Herpes simplex virus pneumonitis was diagnosed at autopsy in a patient who had died of leptospirosis and viral superinfection could possibly have resulted from a transient immunosuppression associated with the disease or its treatment. Wongsrichanalai et al. reported two cases of dual infection with malaria parasites and leptospirosis. One patient was infected with Plasmodium falciparum and the other with P. vivax. Co-infection with three different pathogens has also been reported in what probably is an extremely rare event. Lu and Tseng described a Taiwanese patient with fever and pneumonia in whom blood cultures grew Burkholderia pseudomallei and serological tests were consistent with scrub typhus and leptospirosis. Melioidosis is an emerging disease in Taiwan and B. pseudomallei shares similar ecological niche with leptospirosis and Orientia tsutsugamushi, the causative organism of scrub typhus. It is important to look for leptospirosis in an appropriate setting particularly if the patient does not show clinical signs of improvement despite pathogen-directed therapy for an established alternative infectious etiology.

Conclusions

It is imperative that a high index of suspicion for the disease be maintained particularly in endemic areas. There is a need for increasing the awareness of the disease so that timely therapy can be instituted to patients. An effective network of clinicians, medical microbiologists, public health doctors and program managers needs to be in place during epidemics. It is equally important to collect and report data to a centralised surveillance cell so that future planning and monitoring can be done easily. Clinicians need to be aware of the possibility of leptospirosis, even if the illness presents with unusual features. A problem-solving approach to the clinical suspicion and diagnosis of leptospirosis has recently been elucidated and could be a useful guide for doctors.

References

