Pancreatitis and Acalculous Cholecystitis Secondary to Lancereaux-Mathieu-Weil Spirochetosis Disease in an HIV Patient

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Abstract

Leptospirosis is a zoonotic disease distributed worldwide, most commonly in the tropical and subtropical regions caused by the spirochete Leptospira spp. The incidence in the United States fluctuates from 1.63 to 2.85 per 100,000, with a mortality rate of 10% in the severe disease. This pathology develops after an incubation period of 5 - 14 days and ranges from a self-limiting disease to fulminant and catastrophic one, with the latter being named as Weil’s syndrome, which is characterized for the triad of jaundice, acute renal failure, and hemorrhage, affecting virtually every organ. We report a case of a 41-year-old Hispanic male with a medical history of HIV, hypertension and diabetes mellitus that arrived at the emergency room with unquantified fever, nausea, mild headache, multiple arthralgia and myalgia of 3 days of evolution. Patient was admitted to the internal medicine ward with a diagnosis of fever of unknown origin and systemic inflammatory response syndrome. During the admission, the patient deteriorated and was started on ceftriaxone with clinical improvement, although he developed severe abdominal pain. He was diagnosed with acalculous cholecystitis and acute pancreatitis, demonstrated by laboratories and imaging studies. We postulate that patients with a history of HIV that developed leptospirosis should be evaluated carefully with the expectation of development of multiple complications despite of adequate management. In countries lacking technologies for the early diagnosis of leptospirosis, the use of Faine’s criteria should be encouraged, which stratifies patients even only with clinical history and epidemiological factors. Medical literature lacks enough documentation about leptospirosis in HIV patients and we suggest further investigation in this population. Furthermore, survey investigation should be performed in urban and rural hospitals about the Faine’s criteria to assess general knowledge and implementation.

Keywords: Leptospirosis; Pancreatitis; Acalculous cholecystitis

Introduction

Leptospirosis is a disease distributed worldwide, most commonly in the tropical and subtropical regions caused by the spirochete Leptospira spp. [1]. Historically, the genus Leptospira was composed of two species: the pathogenic L. interrogans and the saprophytic L. biflexa, with the former being the culprit of this pathology, which poses an incidence in the United States that fluctuates from 1.63 to 2.85 per 100,000, with a mortality rate of 10% in the severe manifestation [2]. The most preponderant risk factors to contract leptospirosis include: occupational exposure (farmers, ranchers, and sewer workers), recreational activities (freshwater swimming) and household exposure (pets and domesticated livestock) [3]. As a zoonotic disease, it is transmitted by mammals, with the most common being cattle, pigs, horses, dogs and rodents, where they can continue to excrete the bacteria for a long period through the urine [4]. Infection occurs after contact with infected urine or body fluids from a reservoir animal, nonetheless, infection can be acquired from contaminated soil and water, where the pathogen enters through abrasions, cuts in the skin, the conjunctiva and mucous membranes [5]. Once the bacteria gain entry through the portals aforementioned, the incubation period begins and ranges from 7 to 12 days [6]. Leptospirosis presents a wide spectrum manifestation that ranges from a self-limiting disease to fulminant and catastrophic one, which is also known as Weil’s disease or Weil-Vasiliev disease, which is characterized for the triad of jaundice, acute renal failure, and hemorrhage [7]. The mild or self-limiting disease occurs in 90% of all reported cases of leptospirosis, thus the severe or Weil-Vasiliev disease accounts for 10% of patients with leptospirosis [8]. Pathologically, it is described as a biphasic illness: bacteremic phase and immune phase. Once the patient got infected, the bacteremic phase begins, where the spirochete gains access to the bloodstream and spreads to distant organs by crossing organs barriers. Factor H and C4b-binding protein, novel regulators of the alternative complement pathway, play a preeminent role in the pathogenesis of Weil-Vasiliev disease due to the binding and further inhibition of the factor, consequently inhibiting the complement as well [9]. This mechanism is re-
sponsible for the bacterial proliferation during the bacteremic phase, where the most common symptoms are fever and headache; furthermore, the most common clinical and laboratory findings are hemorrhagic diathesis, myalgias, bilateral enlarged kidneys sterile pyuria, hypokalemia and thrombocytopenia [10]. It is stipulated that non-pathogenic *Leptospira* sp. does not cause symptoms because of the inability to inhibit the factor H, thus is rapidly cleared by the immune system [11].

**Case Report**

A 41-year-old Hispanic male farmer with a medical history of HIV, hypertension and diabetes mellitus and no toxic habits arrived at the emergency room complaining of unquantified fever, nausea, mild headache, multiple arthralgia and myalgia of 3 days before admission. Upon arrival to emergency room triage, vital signs were remarkable for blood pressure of 102/63 mm Hg, heart rate of 107, respiratory rate of 19, temperature of 38.6 °C, and pulse oximetry of 96% on room air. Physical exam was remarkable for an acutely ill patient with regular hygiene, clear to auscultation, no abdominal pain and no organomegaly. Initial laboratory studies were remarkable for white blood cells of $8.6 \times 10^3 / \mu L$, hemoglobin of 13.4 g/dL, hematocrit of 40%, platelets of $110 \times 10^3 / \mu L$, sodium of 133 mmol/L, potassium of 3.40 mmol/L, chloride of 95 mmol/L, carbon dioxide of 32 mmol/L, blood urea nitrogen of 25 mg/dL, creatinine of 0.9 mg/dL, BUN/CREA ratio of 27.8, albumin of 3.1 g/dL, bilirubin of 1.7 mg/dL, AST of 207 IU/L, ALT of 198 IU/L, alkaline phosphatase of 105 IU/L, PT of 30.90, PT of 16.30, INR of 1.29 and unremarkable urinalysis. Patient was admitted to internal medicine ward with diagnosis of fever of unknown origin, systemic inflammatory response syndrome (SIRS), dehydration and suspected arborvirus infection, being managed initially with aggressive hydration (normal saline solution at 225 mL/h) and antipyretics measures (cold compresses and acetaminophen 500 mg orally every 8 h if needed). Evaluation for Zika virus, Dengue virus and Chikungunya virus was requested, but it was not available for immediate assessment. The next day, patient stayed borderline tachycardic and febrile, despite of hydration and antipyretics measures.

Follow-up laboratories remained unchanged with exception of mild elevation of bilirubin (2.2 mg/dL); therefore, evaluation for acute hepatitis profile was requested. By the third day of admission, patient stated that myalgia had increased in intensity being unbearable along with epigastric and periumbilical pain 9/10 that radiated to the back, in addition, bilirubin level still showed an increasing trend (5.8 mg/dL) with still unchanged liver enzymes. Physical exam was remarkable for a new onset of mild gum bleeding, scleral and sublingual ictericia (Figs. 1 and 2). Abdomino-pelvic CT scan and new labs (lipase, amylase, CRP and CPK-total) were ordered as stat, which returned with lipase over three times the upper limit, CPK-total of 1,837 U/L, CRP of 23.2 mg/dL, blood urea nitrogen of 29 mg/dL, creatinine of 2.1 mg/dL, urinalysis of 35 - 40 RBC HPF and an imaging study being remarkable for peripancreatic fat stranding, congruent with pancreatitis (Fig. 3). Patient was placed NPO and infectious diseases services were consulted, which they recommended ceftriaxone 2 g IV daily and microscopic agglutination test for highly suspected leptospirosis. At seventh day of admission, patient was afebrile with no abdominal pain and diet was progressed. The next day patient complained of no nausea accompanied with mild non-radiating right upper quadrant pain 5/10 and physical exam was remarkable for a positive Murphy sign, thus abdominal sonogram was ordered, which showed gallbladder wall thickening with no calculous, congruent with acalculous cholecystitis (Fig. 4). An uneventful urgent cholecystectomy was performed. Finally, MAT test returned with a single titer of 1:1,600 for *Leptospira icterohaemorrhagiae* serovar, for which patient completed 10 days of ceftriaxone 2 g IV daily. Patient was discharged and followed at outpatient clinics in 1 month, where recent labs showed that renal function and bilirubin level returned to baseline, but liver enzymes remained with mild persistent elevation. Labs for Dengue, Chikungunya, Zika and viral hepatitis profile returned negative.

**Discussion**

Leptospirosis is a zoonosis distributed worldwide, transmitted
by mammals, most commonly cattle, pigs, horses, dogs and rodents, and is related to activities such as freshwater swimming, sewer workers, farmers among others and is a heterogenous disease that can range from mild to severe clinical manifestation, where the latter is less common and is also known as Weil disease, Weil-Vasiliyev disease, swamp fever and nanukayami fever. Historically, the genus *Leptospira* is composed of two species: the pathogenic *Leptospira interrogans* and the saprophytic *Leptospira biflexa*, but nowadays scientists had described 21 species, where nine have been reported as pathogenic, including the most common: *Leptospira interrogans* [12]. The capability of the pathogenic species to infect humans remains in the ability of inhibiting the factor H, which is the corresponding mechanism of the immunogenic evasion during the bacteremic phase [13].

This pathology is presented as a biphasic disease, which contains the bacteremic phase and immunogenic phase. Despite of being a widespread zoonosis, endemic to most tropical and subtropical countries, it is underdiagnosed, misdiagnosed and usually confound with other viral and bacterial pathologies. Leptospirosis was in the list of national notifiable conditions in USA until 1994, but it was removed from the list due to be an underreported disease, among other reasons [14]. In tropical and subtropical areas, this pathology is misdiagnosis, due to the coexistence of several diseases with similar clinical manifestations, such as influenza, Dengue fever, Chikungunya fever and Zika. During the pandemic period of influenza H1N1, 2009 - 2010, several cases of leptospirosis were wrongly diagnosed as influenza, not receiving the appropriate treatment and ending with fatal results [15]. Dengue fever is the most common disease confounded with leptospirosis, and this finding is documented in a study performed in Puerto Rico, where 10 of 12 suspected Dengue deaths were found negative to Dengue titer and positive for leptospirosis [16].

Patients who developed Weil-Vasiliyev disease could develop several complications, where the most common is the renal involvement which is described as a non-oliguric interstitial nephritis [17]. A preponderant effect during renal involvement is the affection of the ascending limb of Henle, where the spirochete inhibits the sodium, potassium and chloride cotransporter, therefore the patient will be depleted from sodium and potassium [18]. A study demonstrated that 11% of patients developed oliguria and 49% required dialysis; however, regardless of the affection, most patients recovered renal function after 6 months [19]. Acute liver injury is another non-fatal, reversible complication which is characterized as elevation of hepatic transaminases usually less than 200 IU/L accompanied with hyperbilirubinemia that in some instances can reach levels of 60 - 80 mg/dL. The hyperbilirubinemia is at expenses of the conjugated bilirubin, stipulated to be secondary to bile canaliculi destruction and invasion with further destruction of hepatocytes intercellular junctions, which result in bile leaking from the canaliculi [20]. Lung involvement and CNS involvement are the two complications that pose higher mortality rate, where lung involvement has an incidence of 3.7% with a mortality rate of 71% [21]. Pancreatitis and acalculous cholecystitis are uncommon complications of leptospirosis and patient would benefit from lipase and amylase evaluation. However, hyperamylasemia has been observed in 65% of patients diagnosed with leptospirosis and careful evaluation must be taken to rule out other non-pancreatic causes of hyperamylasemia and hyperlipasemia [22]. For an accurate diagnosis of acute pancreatitis, a patient must meet at least two of the following criteria: acute abdominal pain, amylase or lipase elevation three time the upper limit and/or findings on imaging studies [23]. Despite of aforementioned complications, only white blood cells over 12.9 × 10³/µL, new onset of repolarizing electrocardiographic findings, urine output less than 0.5 mL/kg/h and alveolar infiltrates on imaging studies, are associated markers for poor prognosis.

There exist several tools for the diagnosis of leptospirosis: culture, molecular test and serology. *Leptospira* spp. can be culture, but this technique is not appropriate due to its low sensitivity and a long period up to the official report (several weeks) [24]. Molecular techniques available for the diagnosis include: PCR, loop-mediated isothermal amplification (LAMP) and next generation sequencing. Aforementioned techniques pose great sensitivity and specificity with the discouraged disadvantages of being expensive tests. Serology tests is widely
available, for which they are the most commonly used technique for the diagnosis of leptospirosis and are composed of microscopic agglutination test, macroscopic agglutination test and ELISA, where the microscopic agglutination has been the base for the design of other techniques [25, 26]. MAT is considered positive with a single titer of > 1:800 or a fourfold increase between the acute and convalescent phase; however, it is important to mention that cross-reaction with Treponema pallidum, Borrelia burgdorferi and Legionella pneumophila, has been reported.

Despite of all modern techniques for the accurate diagnosis of leptospirosis, there are developing countries that lack availability for those tests, or at least not available expeditiously. Faine’s criteria are a clinically diagnostic tool introduced by the World Health Organization, which has been modified to increase the sensitivity and specificity with the aim to help clinician to stratify and diagnose patients in the setting of poor resources. Faine’s criteria are composed of three parts: clinical history, epidemiological history and laboratory parameter (Table 1). Modified Faine’s criteria have been evaluated statistically for its utility and were found to have a sensitivity of 95.45% and specificity of 65% [27]. Once the diagnosis of leptospirosis is made, the treatment is divided into two groups: inpatient and outpatient. Doxycycline and azithromycin can be considered for the treatment in the outpatient setting. For the inpatient management, the most recommended drugs are: penicillin, doxycycline, ceftriaxone and cefotaxime, usually for 7 days. Special attention should be paid to the reaction named Jarisch-Herxheimer, which consists of fever, rigors and hypotension, and has been stipulated that endotoxin-like material, TNF-α and cytokines play a key role in this reaction. Steroids, acetaminophen and anti-TNF-α have shown no benefit, but drugs such as anti-TNF-α has shown a considerable decrease in the incidence of this reaction.

Medical literature lacks enough documentation about leptospirosis in HIV patients and we suggest further investigation in this population. Furthermore, survey investigation should be performed in urban and rural hospitals about the Faine’s criteria to assess general knowledge and implementation.

**Table 1.** Modified Faine’s Criteria

<table>
<thead>
<tr>
<th>Part A: clinical data</th>
<th>Score</th>
<th>Part B: epidemiologic factors</th>
<th>Score</th>
<th>Part C: bacteria and lab findings</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>2</td>
<td>Rainfall</td>
<td>5</td>
<td>PCR</td>
<td>25</td>
</tr>
<tr>
<td>Fever</td>
<td>2</td>
<td>Contact with contaminated environment</td>
<td>4</td>
<td>ELISA IgM</td>
<td>15</td>
</tr>
<tr>
<td>Fever &gt; 39 °C</td>
<td>2</td>
<td>Animal contact</td>
<td>1</td>
<td>SAT</td>
<td>15</td>
</tr>
<tr>
<td>Conjunctival suffusion</td>
<td>4</td>
<td></td>
<td></td>
<td>Others rapid test</td>
<td>15</td>
</tr>
<tr>
<td>Meningism</td>
<td>4</td>
<td></td>
<td></td>
<td>MAT high titer</td>
<td>15</td>
</tr>
<tr>
<td>Myalgia</td>
<td>4</td>
<td></td>
<td></td>
<td>MAT fourfold increase</td>
<td>25</td>
</tr>
<tr>
<td>Suffusion + meningism + myalgia</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jaundice</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albuminuria/nitrogen retention</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>2</td>
<td></td>
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Presumptive diagnosis: part A/part A + part B: 26 points or part A + B + C: 25 points. Score between 20 and 25 suggests leptospirosis.

**Conclusion**

We postulate that patients with history of HIV that developed leptospirosis should be evaluated carefully with the expectation of development of multiple complications despite of adequate management. Early recognition is the cornerstone in the management of this zoonosis, although there are several techniques for the accurate diagnosis of leptospirosis, and there are countries that lack technologic resources for the diagnosis of this disease. Therefore, more effort should be paid to orientation and dissemination of the Faine’s criteria, where a patient can be stratified as high risk, deserving initial management for leptospirosis even only in clinical history and epidemiological, if the patient scored more than 25 points (Table 1, part A and part B). Once the treatment is initiated, patients can develop the reaction Jarisch-Herxheimer, where certain drugs such as steroid and acetaminophen have shown no benefit, but drugs such as anti-TNF-α has shown a considerable decrease in the incidence of this reaction.

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**Conflict of Interest**

We have no conflict of interest to declare.
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