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Acute Acalculous Cholecystitis Due To Leptospirosis: A Case Report

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Abstract
Background: *Acute acalculous cholecystitis has been described as a rare complication of leptospirosis.*
Case presentation: *Herein, we report a 64-year-old male diagnosed with acute acalculous cholecystitis and underwent an open cholecystectomy after 24 hours because peritonitis was suspected. Postoperatively, the patient's renal function continued to deteriorate and required renal replacement therapy. Serology for leptospira (ELISA IgM) came back strongly positive, while blood cultures grow leptospires. Therefore, a definite diagnosis of leptospirosis was made. On the forty-second postoperative day, the patient was discharged from the hospital with near-normal renal functions and good urine output.*
Conclusion *It seems that the best supportive care with the administration of antibiotics is the preferable treatment for leptospira induced acute acalculous cholecystitis, with less operative risk in these acutely unwell patients. A high level of awareness and appropriate laboratory studies should allow early diagnosis and prevent unnecessary surgical intervention.*
Keywords: *Acute acalculous cholecystitis; leptospira; cholecystectomy; conservative therapy; management.*

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I. Introduction

Leptospirosis is a widespread zoonosis that displays a seasonal incidence as it typically happens during the rainy season in the tropics and during the late summer or early fall in Western countries (1, 2). It is easily transmitted from infected animals through their urine, either directly or via urine-contaminated media like water, food, animal bedding, soil, mud, and aborted tissue. Leptospires may enter the human body through a cut or abraded skin, sodden skin, mucous membrane, and conjunctivae. Transmission is also possible through ingestion or inhalation of contaminated water or aerosols. The placenta is another means of transmission during pregnancy. The incubation period is few days to 4 weeks (typically 5-14 days) (3).

Anicteric syndrome is the most typical form of the disease (90%). It is self-limiting and non-fatal. Symptoms include fever, rigors, headache, myalgia, malaise, non-pruritic rash, anorexia, and diarrhea. Conjunctival suffusion should raise clinical suspicion towards leptospirosis. Icteric syndrome, also known as Weil's disease, is the severe form of the disease (10%). It results in multi-organ failure and has a high mortality. Manifestations encompass fever, renal failure, jaundice, hemorrhage, and respiratory distress (4, 5).

Leptospires might be isolated from blood or cerebrospinal fluid samples obtained during the first ten days of illness and in the urine following the first week of illness. The microscopic agglutination test (MAT) is the gold standard to diagnose leptospirosis, but it is time-consuming and difficult to perform. Although enzyme-linked immunosorbent assay (ELISA) is more accurate after the second week (immune phase) as IgM antibodies appear at low levels during the first week (acute phase), it is still highly reliable for early diagnosis of leptospirosis during the acute phase. Finally, Polymerase chain reaction (PCR) can detect leptospires during the first week (acute phase). However, it can't identify the specific pathogen strain (5).

Acute acalculous cholecystitis (AAC) is a type of cholecystitis brought about by dysfunction or hypokinesis of gallbladder emptying in the absence of calculi or sludge. It represents 10% of all cases of acute

cholecystitis and 5-10% of all cases of cholecystitis, with an equal predisposition between males and females. It is a potentially life-threatening disease as it displays a high risk of perforation and necrosis compared to calculous disease. Acute acalculous cholecystitis must be addressed urgently as rapid progression and deterioration might occur. The treatment of choice is cholecystectomy, preferable laparoscopic cholecystectomy. Open cholecystectomy is safe alternatively if laparoscopic cholecystectomy is contraindicated. Given that patients with AAC are very ill and unstable, percutaneous drainage of the gallbladder might be necessary with definite cholecystectomy later (6).

AAC has been described as a rare complication of leptospirosis in several case reports. The exact pathogenesis of AAC is unclear. The optimal management remains controversial. It seems that conservative treatment with the best supportive care and antibiotics is sufficient, with less operative risk in these acutely unwell patients (4, 7). Herein we describe the case of a 64-year-old patient who developed acute acalculous cholecystitis due to leptospirosis.

II. Case presentation

A 64-year-old male visited the emergency department with a three-day history of fever, right upper abdominal pain, and vomiting. He also reported a history of malaise, myalgia, anorexia, and headaches for three days. The patient had been well and denied any infectious diseases contacts or recent travel abroad. He had been recently exposed to rodents, having removed a mouse from a trap four days before the onset of the symptoms.

His vital signs were as follows: T = 38.7 °C, beats 125 / minute, breaths 18 / minute, blood pressure 100/60 mmHg. Oxygen saturation was 94% with nasal oxygen delivery at 4 lt / min, while the PaO2 / FiO2 ratio was 230. Abdominal examination disclosed a positive Murphy sign. Laboratory studies revealed elevated inflammation markers (WBC 14000/μl, NEUT 85.2%, erythrocyte elevated white blood cell 75 mm/hr, and CRP 110 mg/L). Lymphopenia (750/μl), thrombocytopenia (95,000/μl), and coagulopathy (INR 1.6) were also observed. Biochemistry demonstrated hypokalemia (3 mEq/l), elevated urea (146 mg/dl), creatinine (3.8 mg/dl), alanine aminotransferase (128 U/l), aspartate aminotransferase (262 U/l), alkaline phosphatase (218 U/l), gamma-glutamyltransferase (150 U/l), total bilirubin (3.1 mg/dl), direct bilirubin (2.2 mg/dl), amylase (280 u/l), creatine kinase (950 U/l), and lactate dehydrogenase 800 U/l). Abdominal ultrasound showed a grossly edematous and thickened gallbladder wall (8 mm) and pericholecystic collection, which was consistent with acute acalculous cholecystitis.

The patient was admitted to the surgical department for observation. He was kept nil per orally, and antibiotics were commenced (ceftriaxone 2gr daily and metronidazole 500 mg t.i.d). Blood and urine cultures were also obtained. However, his condition deteriorated rapidly over the next 24 hours, leading to septic shock requiring ionotropic support. Not only did the pain not settle, but it became intense and rebound tenderness in the right iliac fossa on palpation was found. An urgent computed tomography of the abdomen was obtained and revealed irregularity of the gallbladder wall (Figure 1).

The patient underwent an exploratory laparotomy because peritonitis was suspected. A distended and edematous gallbladder was noted, but no signs of perforation were found. Therefore, a cholecystectomy was carried out. Postoperatively, the patient's renal function continued to deteriorate and required renal replacement therapy. Serology for leptospira (ELISA IgM) came back strongly positive, while blood cultures grow leptospires. A definite diagnosis of leptospirosis was made. On the sixth postoperative day, the patient was transferred to the nephrology department and the dialysis unit to continue renal replacement therapy. On the forty-second postoperative day, he was discharged from the hospital with near-normal renal functions and good urine output.

III. Discussion

Leptospirosis is an infectious disease that can affect both humans and animals. It is regarded as the most typical zoonosis in the world. Spirochete bacteria known as Leptospira are responsible for the development of the disease (1). Traditionally, leptospira is classified into two species: the pathogenic Leptospira interrogans with at least 218 serovars and the nonpathogenic saprophytic Leptospira biflexa with at least 60 serovars. In a recent study on the genomics of Leptospira, four species were categorized as pathogenic, ten as intermediates, and twelve as saprophytic (5).

The exact incidence of leptospirosis remains unclear as the clinical and serological diagnosis is difficult. The estimated incidence is 873,000 cases annually, with over 40,000 deaths according to World Health Organization. In the United States, 100-200 cases are identified annually, most of which occur in Hawaii. Leptospirosis displays a seasonal incidence as it typically happens during the rainy season in the tropics and during the late summer or early fall in Western countries (2, 8). Seasonal outbreaks have been associated with changes in water levels. Flood and drought raise the risk for exposure to leptospirosis. Participation in sports and recreation activities like triathlons, white water rafting, canoeing, caving, swimming, and racing have also been linked with leptospirosis outbreaks (5).

The disease is acquired by contact with infected animals or their infected urine or body tissues and is estimated that affects more than 160 species of animals. Some animals act as chronic carriers, in which leptospires spread hematogenously, colonize the proximal renal tubules, and are shed via urine into the environment. Many vectors have been identified, including rats, raccoons, dogs, cats, cattle, swine, hedgehogs, possums, mongooses, and bandicoots. The most important reservoirs are rodents, while rats are the most common source worldwide (3, 9). Leptospira is easily transmitted from infected animals through their urine, either directly or via urine-contaminated media like water, food, animal bedding, soil, mud, and aborted tissue. Worth noting that leptospires can survive in freshwater for 16 days and in soil for 24 days. They can enter the human host through abrasions in healthy skin, sodden skin, and mucous membranes. Transmission is also possible through ingestion or inhalation of contaminated water or aerosols. The placenta is another means of transmission during pregnancy. When entering the body, leptospires go into the lymphatics and then into the bloodstream. As a result, the infection can spread to all organs, particularly the liver and the kidney. The incubation period varies between 2 and 30 days (typically 5-14 days) (3).

Two distinct clinical syndromes have been identified: anicteric and icteric syndrome. Anicteric syndrome is self-limited, accounts for 90% of all documented cases of leptospirosis, and is rarely fatal. It is characterized by non-specific flu-like symptoms such as fever, rigors, headache, myalgia, malaise, non-pruritic rash, anorexia, and diarrhea. Conjunctival suffusion should raise clinical suspicion towards leptospirosis. The natural course of the icteric syndrome displays two distinct phases: the acute phase and the immune (delayed) phase. The acute phase lasts 5-7 days and is followed by a 1-3 day of improvement in which the fever falls and the patient becomes relatively asymptomatic. Then, the disease either regress or progress to a more severe form. Recurrence of fever indicates the onset of the immune phase. Aseptic meningitis is the most critical manifestation during the immune phase (3, 4, 9, 10).

Icteric syndrome, also known as Weil's disease, is a severe disease, accounts for 10% of all cases, and is potentially fatal. It is characterized by multiorgan involvement or even failure. Manifestations encompass fever, renal failure, jaundice, hemorrhage, and respiratory distress. The icteric syndrome might also involve the heart, central nervous system, and muscles. The two phases of illness (acute and immune) are often continuous and indistinguishable (3, 4, 9, 10).

There are some typical findings of leptospirosis in the hematological and biochemical panel. A normal or slightly elevated leukocyte count is noted in most patients. Worth noting that a marked leukocytosis on presentation is linked with increased mortality. Thrombocytopenia is found in 75% of patients at day five of illness, while overt lymphopenia is an early finding. Hemoglobin levels are usually normal; however, they might reduce due to hemorrhage. Hypokalemia is the most typical biochemical finding with or without the presence of acute kidney injury. Liver function tests, amylase, lipase, troponin, urea, and creatinine might be elevated depending on the disease's system involved and the severity (4). Edwards and Evarard reported that hyperamylasemia in patients with leptospirosis could be from pancreatic and non-pancreatic sources (11).

Conclusive testing involving laboratory diagnostics is vital for diagnosing leptospirosis due to the lack of specific symptoms. The microscopic agglutination test (MAT) is regarded as the gold standard to diagnose leptospirosis. It detects the ability of IgM and IgG antibodies in the patient's serum to agglutinate leptospires. These antibodies are detectable between the sixth and tenth day and peak up to a month later. Nonetheless, MAT can't determine Leptospira serovars. Diagnostic criteria include a greater than fourfold increase in titer between acute/immune samples and a MAT $\geq$1:400 in non-endemic countries or MAT $\geq$1:800 in endemic countries. Cultures are routinely used for the diagnosis of leptospirosis. Blood and cerebrospinal fluid samples can be cultured within the first ten days, while urine samples can be cultured after the second week. Enzyme-linked immunosorbent assay (ELISA) detects IgM or IgG antibodies. It is more accurate after the second week (immune phase) as IgM antibodies appear at low levels during the first week (acute phase). However, it is still highly reliable for early diagnosis of leptospirosis during the acute phase. Finally, Polymerase chain reaction (PCR) detects the leptospires using primers that target either bacteria-specific genes or pathogenic Leptospira-specific genes. Positive results are likely during the first week (acute phase). However, it can't identify the specific pathogen strain (5).

Acute acalculous cholecystitis (AAC) is a type of cholecystitis brought about by dysfunction or hypokinesis of gallbladder emptying in the absence of calculi or sludge. It is a potentially life-threatening disease as it displays a high risk of perforation and necrosis compared to calculous disease. AAC accounts for 10% of all cases of acute cholecystitis and 5-10% of all cases of cholecystitis, with an equal predisposition between males and females. Known risk factors encompass long periods of fasting, parenteral nutrition, and drastic weight loss. Patients in the intensive care unit or those recovering from major surgeries or other serious ailments such as stroke, sepsis, heart attack, severe burns are at increased risk to develop acute acalculous cholecystitis (6). Bacteria associated with AAC encompass Salmonella typhi, Vibrio cholerae, Escherichia coli, Serratia marcesens, Klebsiella species, Staphylococcus species, and Leptospira species. Viral agents that have been linked with AAC include hepatitis A virus, hepatitis B virus, cytomegalovirus, Epstein-Barr virus, and dengue virus. Parasites like Isoprora belli, Microsporidia, Malaria, and Fungus like Candida species have also

been correlated with AAC (6, 12). The diagnosis of AAC is made by ultrasound. Radiological features encompass thickened gallbladder wall with edema, pericholecystic fluid, a striated gallbladder, and a positive sonographic Murphy's sign (4, 6).

AAC must be addressed urgently as rapid progression and deterioration might occur. The treatment of choice is cholecystectomy, preferable laparoscopic cholecystectomy. Open cholecystectomy is safe alternatively if laparoscopic cholecystectomy is contraindicated. Given that patients with AAC are very ill and unstable, percutaneous drainage of the gallbladder might be necessary with definite cholecystectomy later (6).

AAC has been described as a rare complication of leptospirosis in a few case reports (4, 7, 9, 10, 12, 13). The estimated incidence of AAC in leptospirosis is 2.6%. The incidence has been deduced from a mass exposure of 876 athletes who participated in a triathlon in Illinois in the United States of America, in which the swimming event took place in a freshwater lake. After the event, 120 triathletes sought medical care, while 22 triathletes were hospitalized. Seventy-five triathletes experienced acute febrile illness accompanied by at least two of the following: chills, headache, myalgia, eye pain, red eyes, and diarrhea. Leptospirosis was confirmed in 75 cases, from which two patients (2.6%) developed AAC (7).

The mechanism of AAC in leptospirosis remains unclear. A proposed pathogenesis is an immunological response to the leptospira infiltrating the gallbladder. In a previous study, the histopathologic examination of two gallbladders disclosed thickened walls with smooth serosal surface and bile-stained mucosa. Marked edema and sparse foci of mononuclear inflammation were identified in the submucosa and around some blood vessels (7).

In a literature review of 14 reported cases of leptospirosis presenting with AAC since 1993, AAC typically affects males (male to female ratio 7:1) of working age (mean age 46.4 years, range 19-83 years). Worth noting that two patients (14.3%) were older than 75 years. Coexisting pancreatitis was reported in 25% of cases. Serovars belonging to leptospira interrogans were identified as the cause of AAC in six patients, while leptospira species in the rest eight patients could not be identified. A high rate of surgical management was also observed as 36% of patients underwent emergency cholecystectomy. One death and one admission to the Intensive Care Unit were reported (4).

The management of Leptospira induced AAC by surgical or medical therapy remains controversial. On the one hand, patients with AAC are very ill and unstable, while the risk of progression and deterioration is high (6). On the other hand, in the literature review of Davies and Aoyagi, 64% of the patients with Leptospira induced AAC were treated conservatively with antibiotics and supportive care, and they recovered fully (4). Moreover, the histopathological examination of two gallbladders by Guarner et al. disclosed submucosal mononuclear infiltration with edema and positive immune-histochemistry for Leptospira. In this study, a clinical presentation of severe cholecystitis was associated with mild findings on histology (7). It seems that the best supportive care with the administration of antibiotics is the preferable treatment for leptospira induced AAC, with less operative risk in these acutely unwell patients. Early administration of antibiotics would be sufficient to treat AAC due to leptospirosis rather than cholecystectomy.

IV. Conclusion

Leptospirosis is a leading infectious disease worldwide and can affect both humans and animals. It displays a seasonal incidence as it typically happens during the rainy season in the tropics and during the late summer or early fall in Western countries. The disease is acquired by contact with infected animals or their infected urine or body tissues. Some animals act as chronic carriers, in which leptospires spread hematogenously, colonize the proximal renal tubules, and are shed via urine into the environment. Leptospires enter the human body through abrasions in healthy skin, sodden skin, and mucous membranes. Transmission is also possible through ingestion or inhalation of contaminated water or aerosols. The placenta is another means of transmission during pregnancy. When entering the body, leptospires go into the lymphatics and then into the bloodstream. The incubation period is few days to 4 weeks (typically 5-14 days).

Two distinct clinical syndromes have been identified: anicteric and icteric syndrome. Anicteric syndrome is self-limited, accounts for 90% of all documented cases of leptospirosis, and is rarely fatal. Icteric syndrome, also known as Weil's disease, is a severe disease, accounts for 10% of all cases, and is potentially fatal. The microscopic agglutination test (MAT) is regarded as the gold standard to diagnose leptospirosis, but it is time-consuming and difficult to perform. The organism might be isolated from blood and cerebrospinal fluid samples obtained during the first ten days of the onset of symptoms and in the urine following the first week of illness. Enzyme-linked immunosorbent assay (ELISA) and polymerase chain reaction (PCR) can diagnose leptospirosis during the first week of the disease.

Acute acalculous cholecystitis is an uncommon presentation of leptospirosis. The pathogenesis could be an immunogenic reaction against the infiltrating leptospira in the gallbladder wall. Only a few cases reports presenting leptospirosis as acute acalculous cholecystitis have been found in the literature. Whether the best treatment is supportive care and antibiotics or cholecystectomy remains controversial. Nevertheless, most

authors recommend that conservative treatment is sufficient and efficient. A high level of awareness and appropriate laboratory studies should allow early diagnosis and prevent unnecessary surgical intervention.

Abbreviations:
AAC: Acute Acalculous Cholecystitis
MAT: Microscopic Agglutination Test
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Author contribution:

1. Tepelenis N: Study conception and design, drafting of manuscript.
2. Stefanou SK: Study conception and design, drafting of manuscript.
3. StefanouCK: Literature search and acquisition of data.
4. Paxinos AK: Literature search and acquisition of data.
5. Tsiantis T: Analysis and interpretation of data.
6. Papingioti G: Analysis and interpretation of data.
7. Mpakas K: Critical revision.
8. Tepelenis K: Final approval of the version to be submitted.

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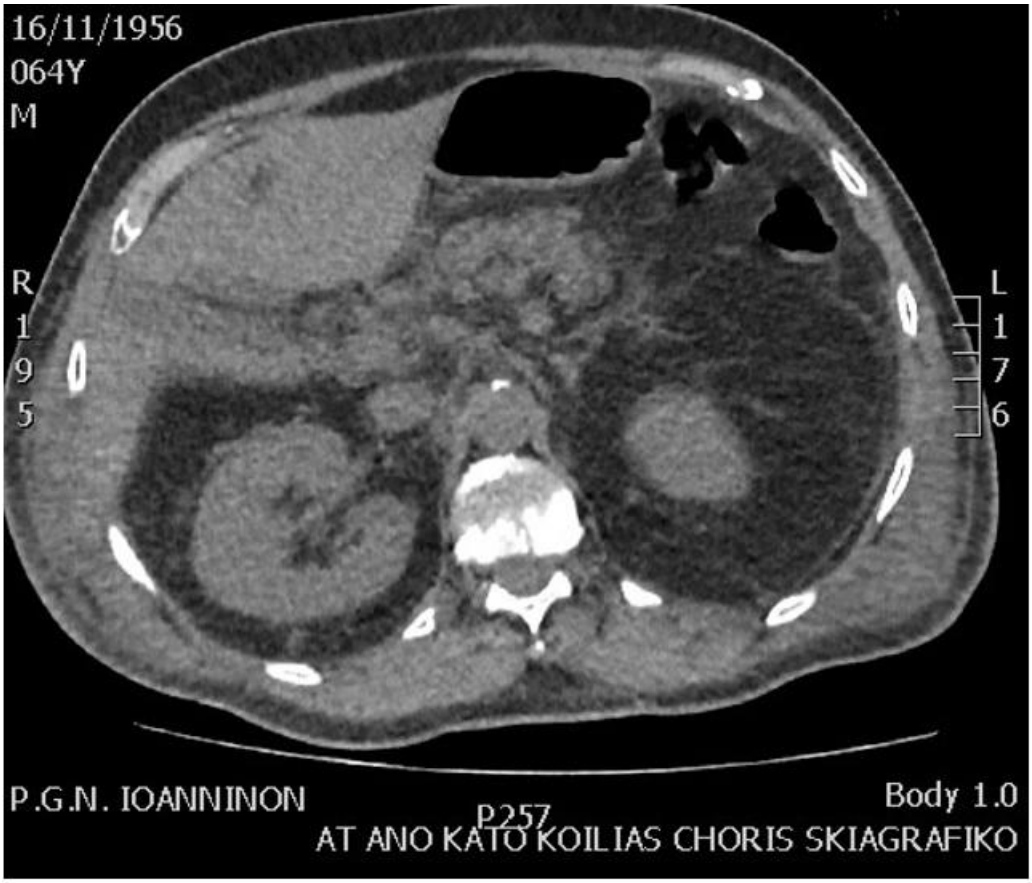

Figure 1: Abdominal computed tomography without radiocontrast shows irregularity of the gallbladder wall.

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