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Case Report

Leptospirosis and melioidosis coinfection presenting as acute respiratory distress syndrome and osteomyelitis: Case report and systematic review

Manoj Kumar Panigrahi[1], Shakti Kumar Bal[1], Tara Prasad Tripathy[2], Akshaya Moorthy[1], Swadesh Kumar Mohanty[1], Ashoka Mahapatra[3], Sourin Bhuniya[1]

[1] Department of Pulmonary Medicine & Critical Care, All India Institute of Medical Sciences, Bhubaneswar, India
[2] Department of Radiodiagnosis & Imaging, All India Institute of Medical Sciences, Bhubaneswar, India
[3] Department of Microbiology, All India Institute of Medical Sciences, Bhubaneswar, India

Abstract

Introduction: Both leptospirosis and melioidosis are common in tropical and temperate climates and can be acquired by exposure to contaminated water and soil. However, concomitant leptospirosis and melioidosis infection is rarely described in the literature. We report here a case of leptospirosis-melioidosis coinfection and systematically review the literature.

Case presentation: A 42-year-old male presented with fever associated with chills and rigor, dull aching pain in the right thigh, myalgia, progressive breathlessness, and dry cough for 10 days. At presentation, he was tachypneic and had tachycardia, and oxygen saturation was 46% in room air. Chest radiography and computed tomography scan showed interstitial involvement. Magnetic resonance imaging for thigh pain revealed right femur osteomyelitis. Leptospira serology was positive, and blood culture grew *Burkholderia pseudomallei*, confirming the diagnosis of melioidosis. Thus, a diagnosis of presumptive leptospirosis based on modified Faine's criteria and systemic melioidosis was made. He received doxycycline and intravenous meropenem and improved.

Results: We performed a systematic review to understand the spectrum of leptospirosis-melioidosis coinfection. We identified only nine cases of coinfection described in the literature. Only one patient had septic arthritis, and our case is the only one presenting with osteomyelitis. Serology diagnosed leptospirosis, whereas melioidosis was confirmed by blood culture in most patients. The majority of coinfected patients developed some complications, and six patients died.

Conclusions: Leptospirosis-melioidosis coinfection is rarely reported in the literature. Physicians should maintain a high index suspicion of leptospirosis-melioidosis coinfection in patients presenting with acute febrile illness following exposure to soil or freshwater, particularly in tropical and endemic regions.

Key words: coinfection; leptospirosis; melioidosis; Weil's diseases; osteoarticular infection; respiratory failure.

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Introduction

Leptospirosis is a worldwide zoonotic disease caused by spirochetes of the genus *Leptospira*. The organism can be isolated from environmental water reservoirs and moist soil for several months. Usually, human infection occurs via contact of non-intact skin with contaminated water or soil and ingesting contaminated water [1,2]. The risk factors for leptospirosis are increased rainfall and flooding, inadequate floodwater drainage, poor housing or slum dwellings, contact with animals, farming and agricultural activities, bathing in the pond, and recreational water sports like surfing, caving, canoeing, etc [1-4]. Melioidosis is caused by a facultative intracellular gram-negative bacterium, *Burkholderia pseudomallei*. This organism is a widely distributed environmental saprophyte in soil and fresh surface water of endemic areas in northern Australia, northeast Thailand, and South Asia [5,6]. Recently, many melioidosis cases have been reported in India [6,7]. The infection is acquired mostly by cutaneous inoculation, ingestion in near drowning, and inhalation during tropical storms. A strong association exists between the reported number of melioidosis cases and rainfall. Diabetes mellitus, chronic lung disease, and excessive alcohol intake are well-known risk factors for melioidosis [5,6].

Both leptospirosis and melioidosis are prevalent in tropical and temperate climates and have shared environmental risk factors. Further, the presenting symptoms of both diseases may be similar, making a clinical diagnosis challenging. Most cases of leptospirosis are self-limiting; only 5% - 10% may develop severe disease with multi-organ involvement [2,8,9]. Melioidosis may present as an asymptomatic

disease to bacteremic sepsis, septic shock, and multisystem involvement [5].

Coinfection, defined as the simultaneous infection of a host by multiple pathogens, can influence the disease epidemiology and clinical severity and negatively impact host health compared to mono-infection [1]. Leptospirosis coinfection with other tropical diseases like dengue, malaria, and scrub typhus are well described. However, leptospirosis and melioidosis coinfection reports are sparse [1]. Such coinfection often leads to misdiagnosis, increases disease severity and mortality, and brings therapeutic challenges [1]. Therefore, early diagnosis of both diseases is crucial in initiating appropriate therapy and preventing mortality. We describe a case of leptospirosis-melioidosis coinfection in a middle-aged man presenting with acute respiratory distress syndrome (ARDS) and multiorgan dysfunction and systematically review the literature.

Case Report

A 42-year-old male presented to the emergency department in September 2022 with continuous high-grade fever associated with chills and rigor, dull aching pain in the right thigh, myalgia, progressive breathlessness, and dry cough for 10 days. He had no history of vomiting, loose motion, pain in the abdomen, numbness, paresthesia, or altered sensorium. He lives in a village in Odisha, India, and reported heavy rainfall in the residential area preceding his illness. He was engaged in agricultural work. He used to smoke and consume alcohol regularly. Two months ago, he was diagnosed with type 2 diabetes mellitus but was not on any treatment. At presentation, he had a respiratory rate of 46 breaths/minute, blood pressure of 148/70 mmHg, heart rate of 155 beats/minute, temperature of 39.2 °C, and oxygen saturation of 46% in room air.

General examination was unremarkable except for mild icterus. Chest auscultation revealed vesicular breath sounds with crackles in bilateral infra-axillary and infra-scapular areas. Examination of other systems was normal. An arterial blood gas (pH 7.34, $PaCO_2$ 26.4, PaO_2 76.7, HCO^{3-} 14.6, lactate 4.6) showed mixed metabolic acidosis and respiratory alkalosis, and the PaO_2:FiO_2 ratio was 173. Initial laboratory findings were notable for thrombocytopenia, hyperbilirubinemia, and mild azotemia (Table 1). His glycated hemoglobin level was 10.9% (reference range 4% – 6%). Chest radiograph showed bilateral diffuse infiltrates, predominantly in the upper and mid zones (Figure 1a), indicating ARDS. A high-resolution computed tomography (HRCT) scan of the chest showed bilateral ground glass opacities with central distribution and patchy consolidation in the right middle lobe (Figure 1b,c,d). The point-of-care ultrasound demonstrated normal biventricular systolic

Figure 1. (a) Chest radiograph showing interstitial pattern lung infiltrates predominantly in the upper and mid-zone. (b, c and d) High-resolution computed tomography scan of the chest showing patchy consolidation (white arrows) and bilateral diffuse ground-glass opacity (dotted arrows).

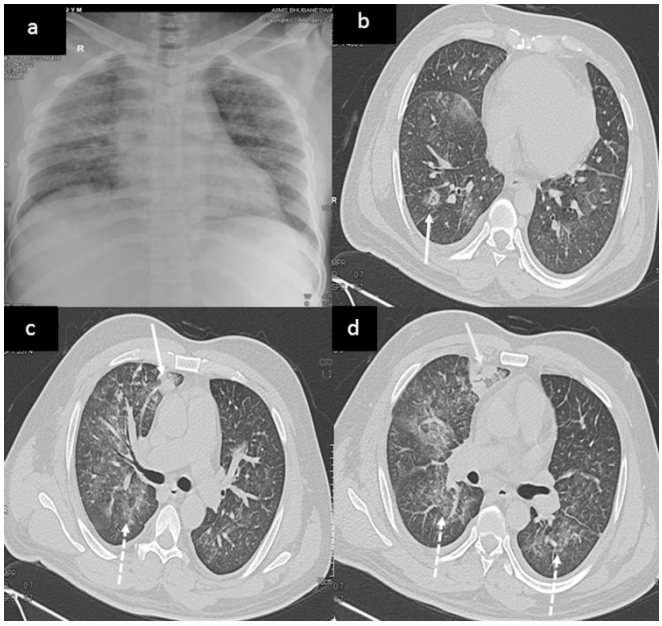


Table 1. Serial laboratory parameters in the patient with leptospirosis-melioidosis coinfection.

Parameters	Reference Range	Day 1	Day 2	Day 4	Day 7	Day 11
Hemoglobin (gm/dL)	13-17	13.9	13.9	12.6	12.3	11.1
White blood cell count (per µL)	4000-11000	7320	7340	8450	6520	9230
Differential count (%)						
Neutrophil	40-80	78.8	77.8	84	70	78
Lymphocyte	20-40	17.8	18.7	13	23	15
Eosinophil	1-6	0	0	0.1	1.1	2.6
Platelet (per µL)	150000-450000	87000	93000	126000	247000	315000
Blood Urea (mg/dL)	17-43	86.6	95.6	76.6	54	-
Serum Creatinine (mg/dL)	0.7-1.3	2.3	1.6	1.4	0.91	-
Total Bilirubin (mg/dL)	0.3-1.2	5.0	3.9	1.6	1.5	1.2
Direct bilirubin (mg/dL)	0.1-0.2	2.5	1.9	0.5	0.6	0.3
Aspartate aminotransferase (U/L)	5-50	55.8	53	30	25	24
Alanine aminotransferase (U/L)	5-50	49.8	43.9	42.3	40	28

function and confluent B lines in all lung zones. Inferior vena cava collapsibility was more than 50%. With the suspicion of complicated tropical fever and moderate ARDS, empirical piperacillin-tazobactam and doxycycline were started, and non-invasive ventilation was initiated. He also received intravenous dexamethasone 6 mg once daily for 48 hours until the coronavirus disease 2019 testing was negative. A tropical fever workup revealed IgM ELISA (Panbio, *LEPTOSPIRA* IgM ELISA) positive for leptospirosis with a titer of 13 IU/mL (cut off > 11 Panbio units). Therefore, presumptive leptospirosis (total score of clinical, epidemiological, and laboratory findings = 31) was diagnosed based on modified Faine's criteria (amendment 2012) [10].

Abdominal sonography showed hepato-splenomegaly and a hypoechoic lesion measuring 2 × 2.4 cm in segment VI of the liver. However, the microbiology of liver aspirate was non-contributory. Right thigh ultrasonography revealed mild subcutaneous inflammation at the lateral aspect. He improved clinically, was off non-invasive ventilation in 48 hours, and maintained a saturation of 98% with oxygen at 3 L/min. However, the fever recurred on the 4th day, associated with tachypnea and tachycardia. The antibiotic was escalated to meropenem on day 5th of admission, pending culture reports. The next day bacteriology laboratory confirmed the growth of *Burkholderia pseudomallei* in the blood, which was sensitive to carbapenems, ceftazidime, and cotrimoxazole (Figure 2a,b). In due course, the fever subsided, and chest radiographic clearance was noticed in 48 hours. Doxycycline was stopped after seven days.

Figure 2. (a) shows smooth, creamy-white and wrinkled colonies of Burkholderia pseudomallei on blood agar. (b) pink mucoid colonies of Burkholderia pseudomallei on MacConkey agar that turned colorless at 48 hours.

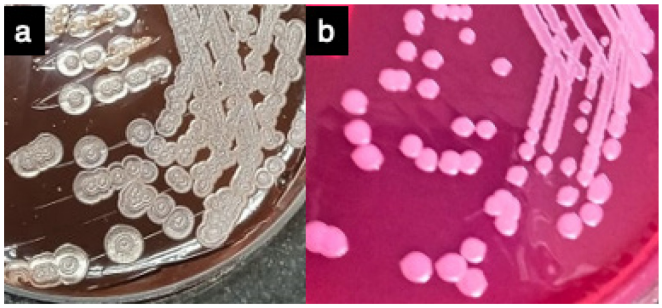
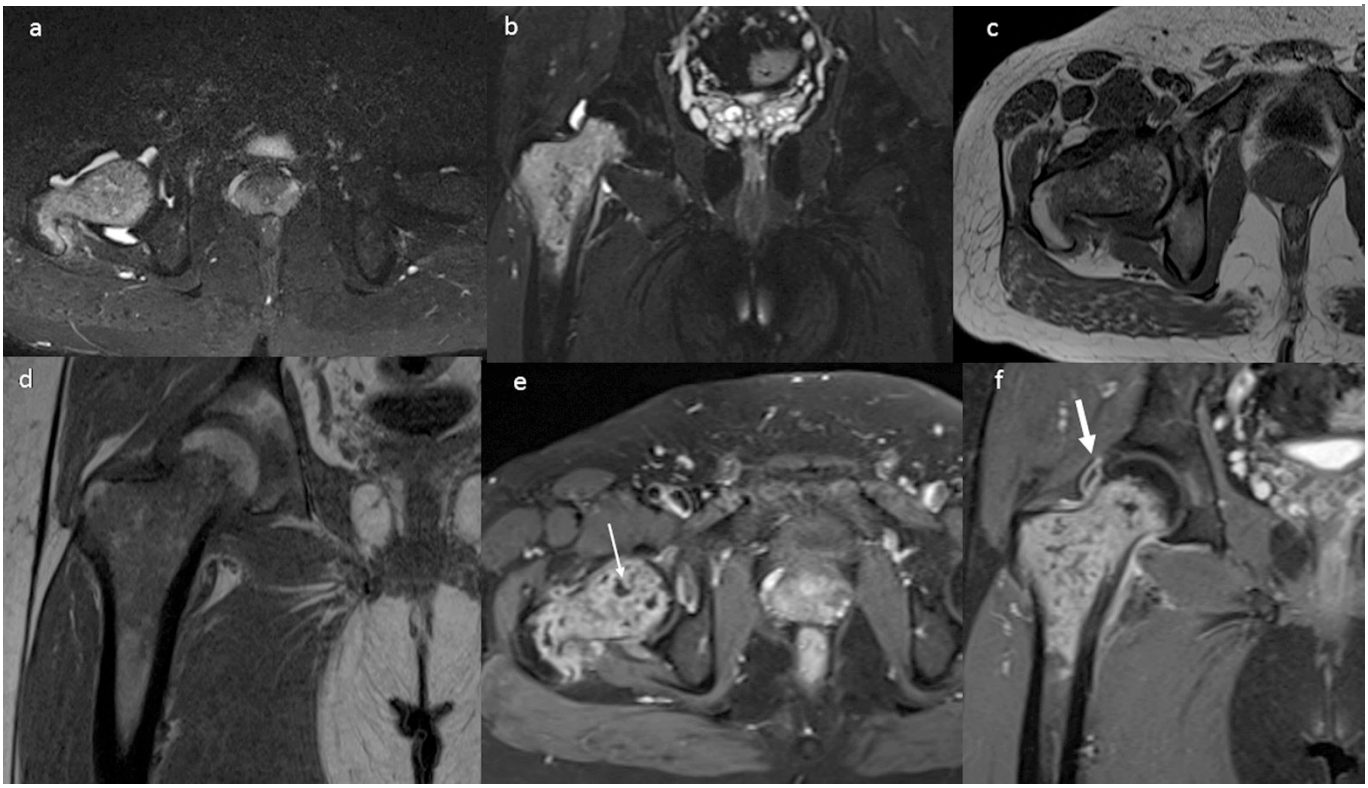


Figure 3. Magnetic resonance imaging of the thigh and pelvis showing (a) short Tau inversion recovery (STIR) axial and (b) STIR coronal section of right hip joint shows hyperintense signal intensities in right femoral head, neck and proximal femoral shaft with right hip joint effusion. (c) T1 weighted image (T1WI) axial and (d) T1WI coronal section showing the hypointense signal intensity of lesion. The above findings are suggestive of marrow edema or intramedullary abscess. (e) Axial post-contrast T1WI and (f) coronal post-contrast T1WI showing heterogeneous enhancement of marrow and cortex with ring-enhancing lesions (thin arrow) and subperiosteal abscess (thick arrow) within marrow suggestive of abscesses. These features indicate acute osteomyelitis involving the epi-metaphyseal region of the right femur.

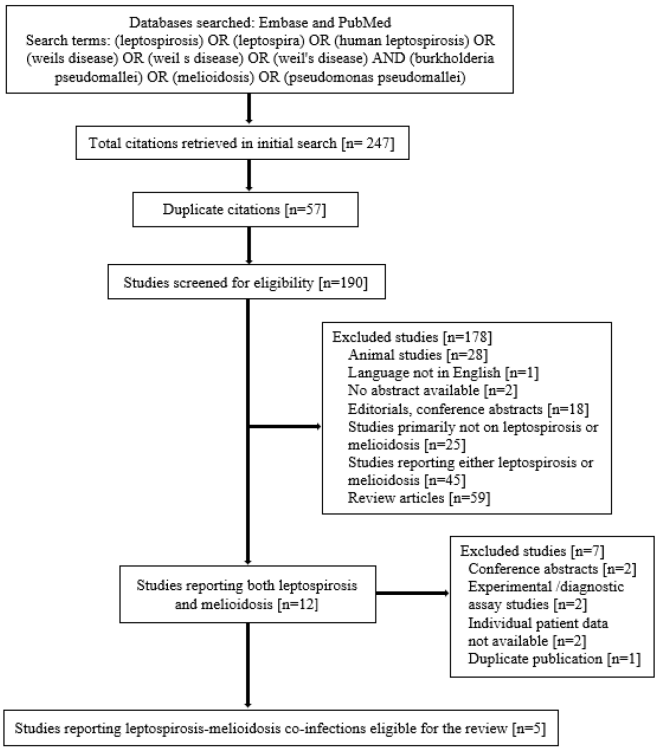


Glycemic control was ensured with insulin therapy. Given persisting right thigh pain, magnetic resonance imaging was performed that revealed heterogenous post-contrast enhancement in the epi-metaphyseal region of the right femur suggestive of osteomyelitis (Figure 3a-f), a manifestation attributable to melioidosis. Thus, a final diagnosis of leptospirosis and disseminated melioidosis co-infection was made. A repeat blood culture after two weeks of meropenem was sterile. He received six weeks of intravenous meropenem with the addition of oral cotrimoxazole later in the intensive phase and was discharged home in stable condition. He completed six months of maintenance cotrimoxazole and was found healthy and free from thigh pain in the last follow-up.

Systematic review

We searched the PubMed and Embase databases till November 2022, using the following search terms: (leptospirosis) OR (leptospira) OR (human leptospirosis) OR (weils disease) OR (weil s disease) OR (weil's disease) AND (burkholderia pseudomallei) OR (melioidosis) OR (pseudomonas pseudomallei). The citations retrieved were imported to the reference manager software (EndNote 20), and duplicate citations were removed. Further, conference abstracts, editorials, review articles, animal studies, and non-English publications were excluded. Initially, the abstracts were screened, and the authors accessed the full texts. Articles not relevant for the review or those reporting only leptospirosis or melioidosis were excluded. Any disagreement between the authors was resolved by consensus. Relevant data from the eligible articles were recorded in a standard data extraction form for final analysis.

Figure 4. PRISMA flowchart depicting the systematic selection of citations.



Our initial search retrieved 247 articles, of which 57 were duplicate citations. Another 178 articles were excluded due to pre-set criteria. The remaining 12 studies reported concomitant leptospirosis-melioidosis infection, seven of which were ineligible for review (Figure 4). Finally, five studies reporting nine cases (excluding the index case) of leptospirosis-melioidosis coinfection were selected for the review [11-15]. The demographic details, clinical characteristics, diagnostic modalities, and outcomes of patients are summarized in Table 2. The median age of patients, including our case, was 34.5 (Range 19-60) years, and eight were male.

Diabetes mellitus was the most common comorbidity found in seven cases. The preceding risk factor was reported in six patients. Fever, myalgia, arthralgia, and headache were the usual presenting symptoms. Thrombocytopenia was seen in five patients, whereas transaminase elevation was found in six patients. One patient had concomitant leptospirosis, melioidosis, and scrub typhus [12]. Leptospirosis was diagnosed by serology alone in five patients (hemolytic test 2, microagglutination test 2, IgM 1), by PCR alone in 4 patients, and by combined PCR and IgM in one patient. Melioidosis was diagnosed by only serology in 3 patients; blood culture was positive in seven patients. Two were additionally PCR positive, and one case with septic arthritis had the pus culture positive for melioidosis. Eight patients were diagnosed with antemortem. The initial antibiotics coverage was inadequate for melioidosis in all patients. Excluding the two subclinical cases of melioidosis reported by Thin *et al.* [11], all other patients developed some complications. Septic shock or respiratory distress/ARDS was seen in six patients each. Osteomyelitis was noted in our case only. All six patients with septic shock died.

Discussion

Leptospirosis coinfection with diseases like malaria, dengue, and scrub typhus, is a well-recognized entity [1]. Surprisingly, leptospirosis-melioidosis coinfections are rarely described despite being common in tropical climates and having similar environmental risk factors. Here we presented a case of severe

leptospirosis and melioidosis coinfection who recovered uneventfully and systematically reviewed the literature. To our surprise, we could find only nine cases of leptospirosis-melioidosis coinfection reported over five decades. This is possibly due to a lack of awareness among clinicians and a low index of suspicion of coinfection. As the clinical presentation of both diseases overlaps, often the initial diagnostic tests and therapeutic interventions are directed towards one disease leading to delayed diagnosis of coinfection and increased mortality [12-15].

Our patient presented with acute febrile illness associated with ARDS, deranged liver and renal function, and thrombocytopenia consistent with a clinical diagnosis of leptospirosis. Further, the combined score of clinical data (Part A), epidemiological data (Part B), and laboratory findings (Part C) was 31 (cut off = 25) as per modified Faine's criteria [10], confirming presumptive leptospirosis. Studies have shown that modified Faine's criteria performed better than Faine's criteria in diagnosing leptospirosis [3,10,16]. Culture confirmation is the most definitive for diagnosing leptospirosis; however, it takes weeks to months and does not help diagnose acute cases. Though considered the gold standard for leptospirosis diagnosis, the microscopic agglutination test is complicated and not widely available. Serological test ELISA IgM is a simple, sensitive, and specific test, and a single positive sample is adequate for diagnosing leptospirosis. It becomes positive earlier

Table 2. Clinical characteristics of patients reported with leptospirosis-melioidosis coinfection.

Author/ Year/ Reference	Country	No. of cases	Cases	Age, Sex	Comorbid Illness	Preceding risk factor	Clinical presentations	Laboratory abnormalities	Diagnostic methods		Timing of diagnosis	Antibiotics received	Compli-cations	Outcome
									Leptos-pirosis	Melioi-dosis				
Thin RNT *et al.* 1970 [11]	Malaysia	2	1	28 M	Nil	Nil	Headache, backache, joint pains, sore throat, skin rash, conjunctival suffusion, palpable spleen	Leucocytosis	HL titre	HA titre > 1:40	AM	P	Nil	Recovered
			2	23 M	Nil	Nil	Headache, myalgia, arthralgia, dry cough, conjunctival suffusion, hepatomegaly	Normal	HL titre	HA titre > 1:40	AM	EM	Nil	Recovered
Lu PL *et al.* 2005 [12]	Taiwan	1	1	19 M	Nil	Battlefield training course	Fever, sore throat, cough, myalgia, abdominal pain	Leucocytosis, Thrombocytopenia, Transaminitis, AKI, Raised CPK	MAT	BC, PCR	AM	P, MC, CT, AZM, DC,	Septic shock, ARDS, DIC, MOF	Died
Hin HS *et al.* 2012 [13]	Malaysia	4	1	50 M	DM	Rescue operation in river and waterfall	Fever, myalgia, arthralgia, headache, diarrhoea, nausea, vomiting, Hepatomegaly	Leucocytosis, Transaminitis	PCR	BC, PC	AM	CA, EM, CT, DC, CZ, P, MP	Right knee septic arthritis, Septic shock	Died
			2	29 M	DM, Obesity, HTN	Rescue operation in river and waterfall	Fever, myalgia, diarrhoea, vomiting	Hyponatremia, Thrombocytopenia	PCR	BC	PM	C, AZM	ARDS Shock	Died
			3	55 M	HTN	Rescue operation in river and waterfall	Cough, nausea, vomiting, diarrhoea, myalgia, dyspnoea	Hyponatremia, Thrombocytopenia, AKI	PCR	BC	PM	CA, CT, AZM	Septic shock, ARDS, ARF, AF	Died
			4	60 M	DM	Rescue operation in river and waterfall	Fever, nausea, arthralgia, diarrhoea, myalgia, hepatomegaly	Leucocytosis, Transaminitis	PCR	BC	AM	CT, DC, CZ, P	Unstable angina	Recovered
Mohm Ali MR *et al.* 2017 [14]	Malaysia	1	1	40 F	DM	Recent visit to waterfall. Contact with rats and mice at home	Fever, headache, arthralgia, myalgia, poor appetite, epigastric pain, HSM, right hypochondriac tenderness	Thrombocytopenia, Hyperbilirubinemia, Transaminitis	PCR, IgM	PCR, BC	AM	CT, CZ, MP	Septic shock, Respiratory distress	Died
Lim KY *et al.* 2022 [15]	Malaysia	1	1	29 F	DM, HTN	Nil	Fever, pain abdomen, jaundice, tea coloured urine, hepatomegaly, right hypochondriac tenderness	Leucocytosis, Transaminitis	MAT	IgM > 1:80	AM	CP, MN, MP	Respiratory distress, Septic Shock, MOF	Died
Index case	India	1	1	42 M	DM	Nil	Fever, cough, dyspnoea, myalgia, right thigh pain	Thrombocytopenia, Hyperbilirubinemia, Transaminitis, AKI	IgM	BC	AM	PT, DC, MP, CM	ARDS, Osteomyelitis	Recovered

M: male; HL: hemolytic test HA: hemagglutination; AM: antemortem; P: penicillin; EM: erythromycin; AKI: acute kidney injury; CPK: creatinine phosphokinase; MAT: microscopic agglutination test; BC: blood culture; PCR: polymerase chain reaction; MC: minocycline; CT: ceftriaxone; AZM: azithromycin; DC: doxycycline; ARDS: acute respiratory distress syndrome; DIC: disseminated intravascular coagulation; MOF: multiorgan failure; DM: diabetes mellitus; PC: pus culture; CA: co-amoxiclav; CZ: ceftazidime; MP: meropenem; HTN: hypertension; PM: post-mortem; C: cefepime; ARF: acute renal failure; AF: atrial fibrillation; F: female; HSM: hepatosplenomegaly; IgM: immunoglobulin M; CP: cefoperazone; MN: metronidazole; PT: piperacillin:tazobactam; CM: cotrimoxazole.

than microscopic agglutination test and can even be done in small rural hospitals [10].

Considering the consistent clinical presentation, laboratory findings, and prompt response to doxycycline therapy, the positive leptospiral IgM, in our case, indicates an acute rather than a past infection. He also had diabetes mellitus and complained of thigh pain with tenderness, prompting us to initiate broad-spectrum antibiotics suspecting soft-tissue infection. Clinical defervescence was noticed in 48 hours, and the laboratory parameters improved within a week. However, the recurrence of fever led to the initiation of meropenem on the 5th day of admission, a day before the culture confirmation of melioidosis. We believe this early initiation of meropenem prevented further complications of melioidosis and saved his life. Leptospirosis-melioidosis coinfection can complicate the clinical course and increase mortality compared to individual infections [12-15]. The reported mortality in severe leptospirosis varies from 5% to 40% [2]; in melioidosis, 14% to 65% [5], whereas we found 60% (6 of 10 patients) mortality in this review among the coinfected patients.

Melioidosis most commonly presents with pneumonia followed by genitourinary or skin/soft tissue infections. Skeletal manifestations such as septic arthritis and osteomyelitis are uncommon in melioidosis. The Darwin prospective study, including 540 patients over 20 years, reported septic arthritis and/or osteomyelitis in only 20 (4%) patients [5]. In a retrospective study in India, only six (3.7%) of 163 melioidosis patients had osteomyelitis [17]. Among the reported cases of leptospirosis-melioidosis coinfection, only one patient had septic arthritis [13], and our case was the only one presenting with osteomyelitis. Musculoskeletal involvement can present in isolation or with pulmonary involvement. Usually, a single bone or joint is affected [17,18]. It is crucial to diagnose osteoarticular complications of melioidosis, considering its therapeutic implications. Generally, a prolonged intensive therapy of 4-8 weeks is recommended in the osteomyelitis [19], and a combination of either meropenem or ceftazidime with cotrimoxazole is the preferred therapy [17-19]. Local debridement may be needed on a case-to-case basis [5,17,18].

Pulmonary involvement in leptospirosis varies from 20–70% [2,9]. Besides dyspnea and hemoptysis, severe disease may present as ARDS and respiratory failure. According to a study conducted in an urban tropical setting, leptospirosis was the most common cause of ARDS, accounting for 18.7% of cases [20]. Radiographically, leptospirosis presents as small nodular densities, confluent areas of consolidation, and diffuse, ill-defined, ground-glass density. Bilateral diffuse ground glass opacity is usually seen in HRCT scans which pathologically corresponds to pulmonary congestion and alveolar haemorrhages [9]. The exact mechanism of lung injury in leptospirosis is unknown. Still, it is believed to be either due to toxin-mediated capillary vasculitis and/or a function of the host immune response [9]. Death in leptospirosis is usually attributed to severe pulmonary haemorrhages, myocarditis, or complications of acute kidney injury [9]. Our case presented with diffuse ground-glass opacity that resolved completely within a week, indicating an exclusive manifestation of leptospirosis.

Conclusions

In summary, clinicians should maintain a high index suspicion of leptospirosis-melioidosis coinfection, particularly in tropical and endemic regions. For patients presenting with acute febrile illness and multisystem involvement following exposure to soil or freshwater and in those with diabetes, such coinfection should be suspected. Coinfection leads to increased mortality. Timely diagnosis and appropriate treatment can prevent complications and mortality.

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Corresponding author

Dr. Manoj Kumar Panigrahi MD, DNB
Additional Professor, Department of Pulmonary Medicine & Critical Care,
All India Institute of Medical Sciences, Bhubaneswar
751019, India
E-mail: panigrahimanoj75@gmail.com
ORCID ID: https://orcid.org/0000-0002-2743-1068

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