

ACUTE CHOLECYSTITIS AS AN UNUSUAL PRESENTATION OF SCRUB TYPHUS: A REPORT OF TWO CASES AND REVIEW OF THE LITERATURE

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Abstract. Scrub typhus rarely presents with acute cholecystitis. We present 2 cases of scrub typhus with cholecystitis. The first patient is a 62 year old female who presented to the hospital with fever and body aches for 1 week and right upper quadrant abdominal pain for 3 days. She gave a history of an insect bite 2 weeks previously. She was diagnosed as having acute cholecystitis and underwent cholecystectomy. She continued with fever post-operatively and physical examination revealed an eschar. She had an immunofluorescence assay (IFA) performed that revealed a high IgM titer for *Orientia tsutsugamushi*. She was diagnosed as having scrub typhus, treated with doxycycline and she recovered completely. The second patient also presented to the hospital with a 1 week history of fever and upper quadrant abdominal pain. She was diagnosed with having cholecystitis. Her symptoms did not improve with intravenous antibiotics and further investigation revealed elevated titers for *O. tsutsugamushi* and *Leptospira interrogans*. She was diagnosed as having a co-infection of scrub typhus and leptospirosis and treated with doxycycline. She recovered completely. Patients from scrub typhus endemic regions who present with acute cholecystitis but do not respond to traditional treatment should be tested for scrub typhus and leptospirosis and should have a careful admission physical examination looking for eschar formation, since scrub typhus may present with acute cholecystitis.

Keywords: scrub typhus, acute cholecystitis, case report, review

INTRODUCTION

Scrub typhus, caused by *Orientia tsutsugamushi*, is a common zoonotic disease and is endemic in East and Southeast Asia (Koh *et al*, 2010). The disease usually pres-

ents as fever, headache, rash and an eschar (Tsay and Chang, 1998). Diagnosis is often difficult because the symptoms overlap with other infectious diseases commonly found in endemic areas (Silverman and Bond, 1984). Acute cholecystitis rarely occurs in scrub typhus. We report two cases of scrub typhus that presented with acute cholecystitis. The objective of this study was to record the clinical presentation of scrub typhus with acute cholecystitis in order to inform other physicians about this uncommon occurrence.

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CASE REPORTS

Case 1

A previously healthy 62-year-old woman presented to Chonburi Hospital with a one week history of high-grade fever and myalgia. On day 4 of fever, she developed right upper quadrant abdominal pain. She had a history of an insect bite while working on a coconut farm two weeks prior to the onset of her symptoms. Her temperature was 39.4°C, blood pressure was 168/72 mmHg and pulse rate was 106 beats per minute. Abdominal examination revealed tenderness in the right upper abdomen and a positive Murphy's sign. Based on her history and physical exam, she was suspected to have acute cholecystitis and was admitted for further investigation and treatment.

On admission her complete blood count (CBC) showed a leukocyte count of 13,300 cells/mm³, with 60% polymorphonuclear (PMN) cells, a hematocrit of 37% and a platelet count of 222,000 /mm³. On liver function testing, the aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were elevated at 176 IU/l and ALT 213 IU/l, respectively; the alkaline phosphatase (AP) was 539 IU/l and the total bilirubin was 1.9 mg/dl. The serum creatinine was 0.6 mg/dl. A computed tomography (CT) scan of the abdomen showed mild gallbladder wall thickening and fluid in the upper abdomen. No gallstone was seen. A hypodense lesion was observed in the superior pole of the spleen; splenic infarction was suspected (Fig 1, c). The patient was diagnosed with having acute cholecystitis and treated with ceftriaxone 2 g intravenously once daily and metronidazole 500 mg every 8 hours. The patient remained febrile after 48 hours. An emergency exploratory laparotomy was performed for suspected

complicated cholecystitis. Intraoperative findings revealed a 7x3x2 cm distended gallbladder, without perforation. A large amount of clear yellowish free fluid was found in the upper abdomen. A wedge shaped infarction of the spleen was noticed in the upper pole. Cholecystectomy and total splenectomy were done. However, the fever and abdominal pain persisted for more than 48 hours after surgery. A complete physical examination was repeated and an eschar was found on her left thigh. Scrub typhus was clinically suspected and the patient was given oral doxycycline 100 mg twice daily. Seventy-two hours after initiating doxycycline, the fever gradually subsided. The abdominal pain then decreased 24 hours later. The doxycycline was continued for 7 days. An immunofluorescence assay (IFA) for *O. tsutsugamushi* was elevated (IgM titer >1:800), which confirmed the diagnosis of scrub typhus. A distended gallbladder, gallbladder wall thickening (5 mm) and hemorrhagic necrotic nodule of the spleen were found as gross pathological findings. Histopathology showed thickening of the mucosa of the gallbladder wall without PMN infiltration (Fig 1a). Focal sclerosis of the medium to small intrasplenic vessels was also found (Fig 1b).

Case 2

A 76-year-old woman presented to a district hospital with a one week history of high fever, generalized malaise and right upper quadrant abdominal pain. She had been working on a mango farm but denied a history of an insect bite. Her temperature was 39.0°C, blood pressure was 140/70 mmHg and pulse rate was 110 beats per minute. On physical examination, she had abdominal tenderness in the right upper quadrant and a positive Murphy's sign. A CT scan of the upper abdomen revealed a distended gallbladder with mild (7 mm)

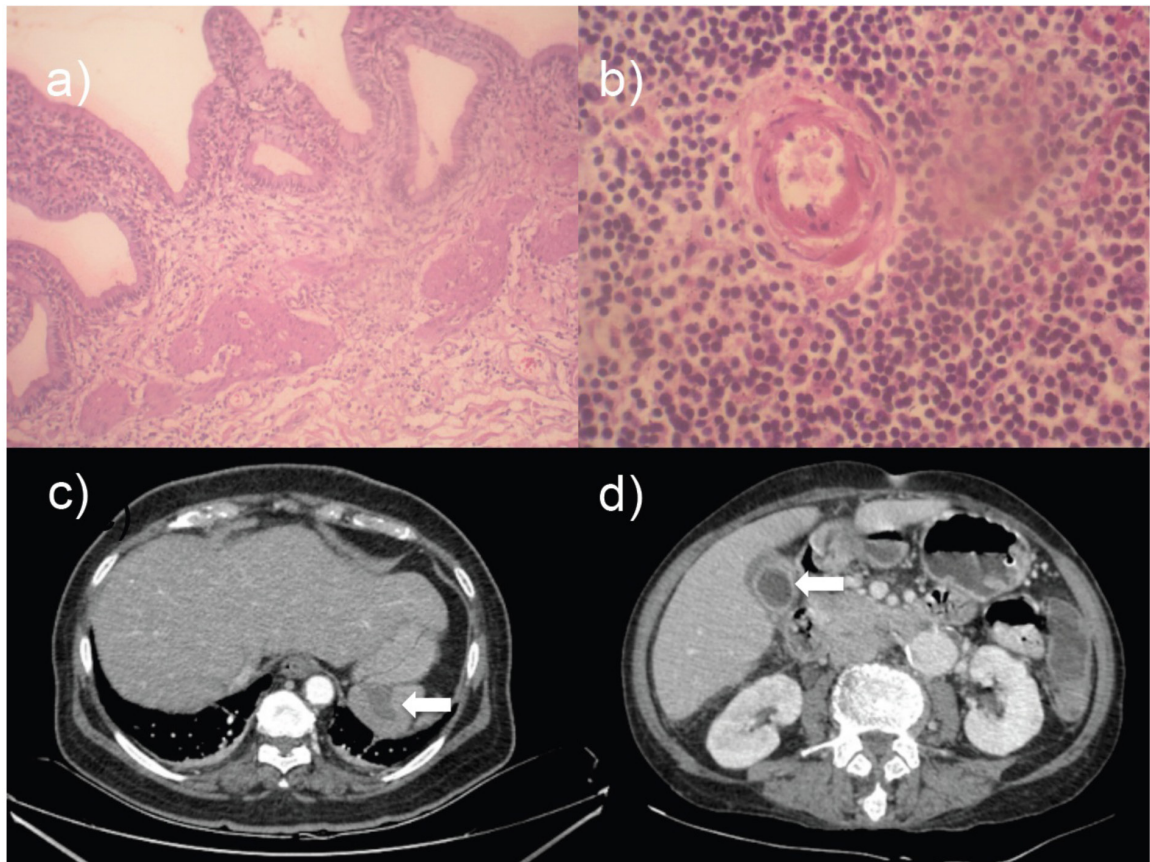


Fig 1–a) Histopathology of the gallbladder showing thickened mucosa of the gallbladder wall without PMN infiltration. b) Histopathology of splenic vessels showing focal sclerosis of small to medium sized intrasplenic vessels. c) CT scan of the abdomen showing a splenic infarction (arrow). d) CT scan of abdomen showing a distended gallbladder and thickening of the gallbladder wall (arrow). Fig 1 a, b, and c are from our first case and Fig 1 d is from our second case.

wall thickening, and pericholecystic fluid (Fig 1d). No gall stone was seen. She was diagnosed as having acute cholecystitis and admitted to the hospital and treated with ceftriaxone 2 g intravenously once daily and metronidazole 500 mg every 8 hours a day for 3 days. Her symptoms did not improved after 3 days of treatment.

After that, she was transferred to Chonburi Hospital. On presentation to our hospital, she had a blood pressure of 120/80 mmHg, a pulse rate of 110 beats per minute and a temperature of 39°C.

On physical examination, the patient had marked right upper quadrant abdomen tenderness. No eschar was observed. On CBC, the leukocyte count was 14,270 cells/mm³, with 68% PMN; her hematocrit was 28.8% and her platelet count was 106,000/mm³. On LFT, her AST was 119 IU/l, her ALT was 31 IU/l, her AP was 695 IU/l and her TB was 2.75 mg/dl. Her serum creatinine was 1.83 mg/dl. Leptospirosis and scrub typhus were considered in the differential diagnosis and she was continued on ceftriaxone 2 g once daily and

oral doxycycline 100 mg twice daily was added for 7 days. IFA serology testing for *O. tsutsugamushi* and *L. interrogans* were positive with IgM titers of 1:800 and 1:400, respectively. The patient was diagnosed with having concomitant scrub typhus and leptospirosis. After onset of doxycycline, the fever and abdominal tenderness subsided within 48 hours.

DISCUSSION

Scrub typhus is an acute febrile illness caused by *O. tsutsugamushi*. The symptoms are usually self-limited, but some cases can be severe or even fatal. The pathophysiology of scrub typhus is disseminated multi-organ vasculitis and perivasculitis of small vessels with destruction of endothelial cells and perivascular infiltration of leukocytes (Paris *et al*, 2012). The incubation period of scrub typhus is usually 10-12 days after a chigger bite (Koh *et al*, 2010). The patients usually have fever, headache and myalgia. They may also have nausea, vomiting and generalized abdominal pain. Acute cholecystitis may present as fever and right upper quadrant abdominal pain. Cholecystitis is infrequently found in scrub typhus.

We searched "scrub typhus and cholecystitis" in PUBMED and GOOGLE SCHOLAR and were only able to find 6 cases from 5 reports in English (Wang *et al*, 2003; Lee *et al*, 2009; Mahajan *et al*, 2011; Hayakawa *et al*, 2012; Lee *et al*, 2012). The clinical characteristics of our 2 cases and the 6 previously published case reports are summarized in Table 1. Seven of the 8 patients were females. The ages ranged from 41 to 76 years. The duration of symptoms ranged from 3 to 10 days and the time from outdoor exposure to onset of symptoms ranged from 10 to 21 days.

Eschars were found in 5 of the 8 patients. Two patients had concomitant leptospirosis. Two patients underwent surgery for cholecystectomy. However, the symptoms in both patients who underwent surgery did not improve until they were put on appropriate antimicrobial therapy for scrub typhus.

In our two reported cases, the patients presented with high-grade fever, myalgia, right upper abdominal quadrant pain and a history of outdoor activity on farms. In the first case, the preoperative diagnosis of acute cholecystitis was made by an experienced surgeon and based on the clinical findings and imaging studies. The Murphy's sign, although not highly specific for acute cholecystitis, supported the diagnosis of acute cholecystitis. Imaging of the abdomen showed increased gallbladder wall thickness and free fluid in the upper abdomen, supporting the clinical diagnosis of acute cholecystitis. One study of 19 scrub typhus patients who had an abdominal CT scan reported these patients had the presence of splenomegaly, gallbladder wall thickening, splenic infarction and pleural effusions (Jeong *et al*, 2007). Splenic infarctions in that review were found less frequently than gallbladder thickening (16% vs 47%, respectively). In the first patient reported here, we found both splenic infarction and gall bladder wall thickening. The pathophysiology of acute cholecystitis and splenic infarction in scrub typhus are unknown (Silverman *et al*, 1984). In our first case, the histopathology of the gallbladder showed a thickened gallbladder wall mucosa without PMN infiltration and the spleen showed focal sclerosis of the medium and small sized intrasplenic vessels. This suggests the acute cholecystitis and splenic infarction in scrub typhus may have been due vasculitis.

Table 1
Clinical characteristics, laboratory findings and treatment of our 2 cases and 6 patients reported in the literature with scrub typhus presenting with acute cholecystitis.

Clinical characteristics	Authors																
	Charoenphak <i>et al.</i> , 2016			Lee <i>et al.</i> , 2009			Lee <i>et al.</i> , 2012			Mahajan <i>et al.</i> , 2011		Mahajan <i>et al.</i> , 2011		Wang <i>et al.</i> , 2003		Hayakawa <i>et al.</i> , 2012	
Sex	F	F	F	F	F	F	F	F	F	F	F	F	M	M	F	F	
Age (years)	62	76	76	76	69	69	76	76	50	75	75	41	41	41	72	72	
Duration of symptoms (days)	7	10	10	7	3	3	10	7	7	10	10	7	7	7	7	7	
Time from exposure to symptoms (days)	14	14	14	21	10	10	14	21	10	10	10	36.7	36.7	36.7	14	14	
Temperature ^a (°C)	39.4	39	39	38.5	38.5	38.5	39.4	38.5	38.5	38.5	38.5	38.5	38.5	38.5	40	40	
Mean arterial blood pressure ^a (mmHg)	104	86	86	96	96	96	104	86	96	96	96	96	96	96	92	92	
Heart rate ^a (/min)	106	110	110	72	78	78	106	110	72	78	78	100	100	100	113	113	
Eschar	Left thigh			Popliteal fossa											Right axilla	Anterior chest	Right knee
Co-infection		Leptospirosis													leptospirosis		
Hematocrit ^a (%)	37	28.8	28.8	34.8	42	42	37	28.8	34.8	34.2	34.2	35.7	35.7	35.7	37	37	
White blood cell count ^a (cells/mm ³)	13,330	14,270	14,270	11,300	4,510	4,510	13,330	14,270	26,850	14,520	14,520	15,000	15,000	15,000	9,500	9,500	
Neutrophils ^a (%)	60	68	68				60	68		70	70	88	88	88			
Platelet ^a (/mm ³)	222,000	105,000	105,000	260,000	57,000	57,000	222,000	105,000	28,000	69,000	69,000	39,000	39,000	39,000	130,000	130,000	
Alkaline phosphatase ^a (IU/l)	539	695	695	239	982	982	539	695	279	876	876	601	601	601	225	225	
Aspartate transaminase ^a (IU/l)	176	119	119	72	374	374	176	119	239	230	230	79	79	79	39	39	
Alanine transaminase ^a (IU/l)	213	31	31	43	254	254	213	31	67	129	129	116	116	116	20	20	
Total bilirubin ^a (mg/dl)	1.9	2.75	2.75	0.4	1.2	1.2	1.9	2.75				12.50	12.50	12.50			
Creatinine ^a (mg/dl)	0.60	1.83	1.83	1.30			0.60	1.83	1.10	2.20	2.20	2.80	2.80	2.80			
Amylase ^a (IU/l)	41	57	57				41	57	115	115	115	175	175	175			
Lipase ^a (IU/l)		17	17					17				920	920	920			
Surgical treatment	OC + SP			PC													
Medical treatment	DX + C3	DX + C3	DX + C3	DX	DX + PI	DX + PI	DX + C3	DX + C3	AZ + C3 + MT	AZ + CP + MT	AZ + CP + MT	DX + C3	DX + C3	DX + C3	DX + C3	DX + C3	
Duration of antibiotic treatment (days)	7	7	7	7	13	13	7	7	7	5	5	10	10	10	10	10	
Time until fever improved (hours)	72	48	48	24	216	216	72	48	48	24	24	144	144	144	240	240	
Time until abd. pain improved (hours)	96	48	48	72	216	216	96	48	96	96	96	240	240	240	240	240	
Hospital stay (days)	11	7	7	3	17	17	11	7	7	8	8	17	17	17	17	17	

^aOn admission; OC, open cholecystectomy; PC, percutaneous cholecystostomy; SP, splenectomy; C3, intravenous ceftriaxone; DX, oral doxycycline; PI, piperacillin; MT, intravenous metronidazole; AZ, intravenous azithromycin; CP, intravenous ciprofloxacin; MN, intravenous minocycline.

Our first patient underwent exploratory laparotomy with cholecystectomy and total splenectomy but the symptoms continued for 48 hours after surgery. The symptoms improved significantly only after treatment with oral doxycycline. Our second patient was successfully treated with antibiotics without surgery because the earlier laboratory investigation for scrub typhus was positive.

A previous study also reported the case of a patient diagnosed with acute cholecystitis who was treated with intravenous ceftriaxone and cholecystostomy but persisted in having symptoms until she was treated with oral doxycycline (Lee *et al*, 2012), similar to our first reported case. We conclude cholecystectomy may not be necessary in acute cholecystitis patients who have scrub typhus.

About 90% of cases of acute cholecystitis are associated with cholelithiasis (Indar and Beckingham, 2002). The pathogenesis of an acute cholecystitis with cholelithiasis is an obstruction of the cystic duct accompanied by cholesterol supersaturation (Roslyn *et al*, 1980) and superimposed infection with bacteria in the Enterobacteriaceae family, enterococci or anaerobic bacteria (Järvinen *et al*, 1978). Without cholecystectomy, the patient may develop gangrenous cholecystitis, emphysematous cholecystitis, perforation of the gallbladder or severe sepsis. We suggest patients diagnosed with acute acalculous cholecystitis from scrub typhus endemic areas should be tested for scrub typhus. A history of outdoor exposure and a careful physical examination for signs of scrub typhus, such as an eschar, may help physicians choose whom to screen for scrub typhus.

In our second case, the diagnosis of concomitant scrub typhus and leptospirosis was made by IFA serology. Other stud-

ies have reported co-infection with these two pathogens (Watt *et al*, 2003; Lee and Liu, 2007). The clinical manifestations of these two diseases are similar, and include fever, headache, myalgia and abdominal pain (Mahajan *et al*, 2011) found in both our reported cases. Laboratory investigations can help establish the diagnosis of scrub typhus and leptospirosis. The combination of jaundice and acute renal dysfunction favors leptospirosis while elevated alkaline phosphatase levels favor scrub typhus (Lee and Liu, 2007). Early diagnosis of the co-infection can prompt physicians to choose appropriate antimicrobial therapy.

Doxycycline is the drug of choice for scrub typhus and other rickettsial diseases (Purvis and Edwards, 2000). Intravenous penicillin G has been the drug of choice for severe leptospirosis (Watt *et al*, 1988). Third-generation cephalosporins, such as cefotaxime and ceftriaxone, has been widely used to treat leptospirosis (Murray and Hospenthal, 2004). Doxycycline is also used to treat mild forms of leptospirosis (Murray and Hospenthal, 2004).

In conclusion, acute cholecystitis can be associated with scrub typhus in endemic areas. The results of this study have raise the awareness of scrub typhus in patients clinically presenting with acute cholecystitis. Physicians should obtain an adequate history, including outdoor exposure and evaluated for the clinical manifestations of scrub typhus, including the presence of an eschar. A correct diagnosis may avoid unnecessary surgery. Once scrub typhus is diagnosed, co-infection with leptospirosis should be considered. Oral doxycycline is the best treatment for scrub typhus presenting with acute cholecystitis. A combination of doxycycline and intravenous penicillin G or ceftriaxone are recommended to treat patients co-infected with of scrub typhus and leptospirosis.

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