Radiographic Chest Findings and Clinical Correlations in Leptospirosis

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Objective: *To determine the clinical presentations, radiographic chest findings, and their correlation in patients with leptospirosis.*
Design: *A cross sectional study.*
Setting: *Between July 2001- December 2002 at 3 hospitals in North Eastern Thailand.*
Material and Method: *Two hundred and forty patients with laboratory confirmed leptospirosis.*
Results: *Two hundred and nine (87.1%) patients were males. The mean age was 37.53 years (range 13-76). The median duration of fever was 3 days (range 1-13). Overall, 154 patients (64.2%) had respiratory symptoms and 26 (10.8%) patients had hemoptysis. Jaundice was detected in 76 (31.7%) patients, hypotension in 50 (20.8%), renal dysfunction in 80 (30%), and multiorgan dysfunction in 62 (25.8%) on admission. One hundred and fifty-four (64.17%) patients had abnormal chest radiographs on admission (classified as cardiovascular, pulmonary, and mixed cardio-pulmonary involvement in 40 (25.97%), 41 (26.62%), and 73 (47.4%) patients, respectively). Jaundice was significantly associated with the likelihood of having abnormal chest radiography on admission. Air- space nodules detected on the chest radiograph were significantly more common in patients with renal dysfunction and patients who required mechanical ventilation.*
Conclusion: *Pulmonary and cardiovascular involvements are common in leptospirosis. Air-space nodules detected by chest radiography may indicate severe leptospirosis.*

Keywords: *Leptospirosis, Chest radiograph, Pulmonary*

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Leptospirosis is a zoonotic disease caused by infections with pathogenic spirochetes of the genus *Leptospira*. Human transmission results from contact with animal reservoirs or an environment contaminated by their urine. Leptospirosis occurs worldwide but is more common in the tropics where it has been considered a sporadic disease in rural and tropical countries, associated with specific occupational groups, such as farmers, miners, abattoir and sewer workers, and recreational activities[1]. However, leptospirosis continues to occur in developed countries. In the past decade, outbreaks were reported in many countries, including Thailand[2-4]. Lack of basic sanitation in urban slums, and frequent exposure to contaminated environment during heavy seasonal rainfall and flooding, is thought to contribute to annual epidemics.

Common symptoms of human leptospirosis are a sudden onset of high fever, headache, severe myalgia, and conjunctival suffusion. Clinical manife stations of leptospirosis are non-specific, varying from

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subclinical infection, a self-limited anicteric febrile illness with or without meningitis, to a severe and potentially lethal multisystem illness with jaundice, renal failure, and pulmonary hemorrhage known as Weil's syndrome. The mortality associated with severe leptospirosis may be as high as 22%[5].

Pulmonary manifestations of leptospirosis vary widely from dry cough and hemoptysis to fatal lung hemorrhage. Mild pulmonary involvement has been reported in 20-70% of leptospirosis cases[6]. Pulmonary hemorrhage is recognized increasingly as a major, often fatal, manifestation of leptospirosis[2, 3,5,7]. The authors report here results of the present study on pulmonary manifestations, the chest radiographic findings, and their clinical correlations in 240 patients with laboratory confirmed leptospirosis in Thailand.

Material and Method

The present cross-sectional study was part of a prospective study conducted in three hospitals in northeastern Thailand: Loei Hospital, Loei Province, Maharat Nakhon Ratchasima Hospital, Nakhon Ratchasima Province, and Banmai Chaiyapod Hospital, Bureerum Province. The present study was conducted between July 2001 and December 2002. The present study protocol was approved by the Ethical Review Subcommittee of the Ministry of Public Health of Thailand. Written informed consents were obtained from all patients before they entered the present study.

Study Protocol

After admission into the present study, a detailed history and results of physical examinations were recorded on standard forms. Baseline investigations included full blood cell and platelet count, blood culture for aerobic bacteria and leptospires, plasma glucose, serum urea, creatinine, liver function test, electrolytes concentration, urine analysis, and chest radiography.

Diagnostic criteria

The diagnostic tests for leptospirosis included a culture in EMJH media; serological tests for leptospirosis included the microagglutination test (MAT), the indirect immunofluorescent antibody test (IFAT), and the microcapsule agglutination test (MCAT). The isolation of leptospires from blood or a fourfold or greater rise in the agglutinin antibody titer (using MAT) to at least 1:200, or in the specific IgG and IgM antibody titers (using IFAT) to at least 1:200, or a single titer or stable antibody titer of 1: 400 or more was considered a definite serological diagnosis of leptospirosis[8,9]. When the MAT and IFAT tests were negative, patients were also classified as having confirmed leptospirosis if the MCAT was positive and they had no evidence of other infections[10]. All leptospires isolated from the present study were confirmed and serotyped at the WHO/FAO/OIE Collaborating Centre for Reference & Research on Leptospirosis, Brisbane, Australia. The patients suspected of having co-infections such as scrub typhus were excluded from the present study.

Patients with confirmed leptospirosis were classified prospectively by organ system involvement manifested by hypotension (systolic blood pressure of < 90 mmHg or a sustained decrease in systolic BP $\geq$ 40 mmHg); jaundice (a rise in total bilirubin to ≥ 50 µmol/L, normal range 5-17 µmol/L); renal dysfunction (either oliguria, i.e., urine output < 0.5 ml/kg/hr for at least one hour or azotemia (serum creatinine of ≥ 265 µmol/L) and pulmonary involvement (history of hemoptysis or patients who required treatment with mechanical ventilation). Any patient who was presented with more than two organ dysfunctions was classified as having multiorgan dysfunction.

The chest radiograph was retrospectively reviewed by two radiologists unaware of the clinical presentation. The interpretations of chest radiographs were performed individually and the final conclusion reached by consensus.

The radiographic interpretations were assessed for the presence of reticular infiltration, air-space nodules, consolidation, cardiomegaly, congestive heart failure, cavity formation, atelectasis, hilar adenopathy, and pleural effusion. The air-space nodules were defined as nodular opacities with ill-defined or puffy margins and/or areas of confluent lesion. The reticular infiltration was defined as linear opacities with sharp border and no predominant distribution. Because most CXR were supine view, for assessment of cardiomegaly, a cardiothoracic ratio greater than 0.6 was defined as cardiomegaly. If the film showed cardiomegaly with linear opacities that had a puffy margin and centrally distribution, the CXR was interpreted as congestive heart failure. (Fig. 1) In order to correlate the clinical and radiographic findings, these radiographic findings were classified into pulmonary involvement (reticular infiltration, air-space nodules, consolidation, pleural effusion, and atelectasis), cardiovascular involvement (cardiomegaly without pulmonary congestion or congestive heart failure), and mixed pulmonary and cardiovascular involvement. A

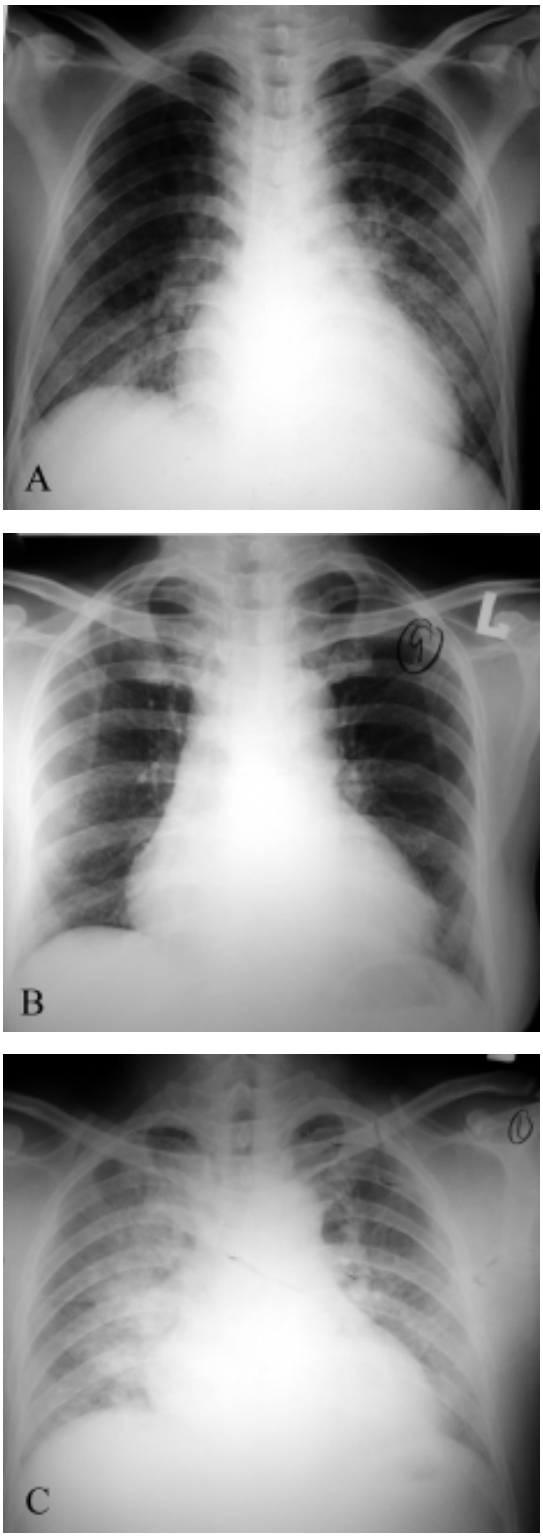

Fig. 1 Chest radiography show (A) air-space nodules, (B) cardiomegaly, and (C) congestive heart failure

review of the follow-up chest radiograph, performed within 7 days and more than 7 days after admission, was also analyzed.

Statistical analysis

Descriptive analyses, such as number and percentage distributions, range means and median, were calculated at the appropriate place. Univariate and multivariate analyses to determine the association between organ dysfunction and chest radiographic findings in leptospirosis were conducted using the Chi-square and multiple logistic regression model (SPSS 11.5; Chicago, IL), respectively. The association was considered significant when $p < 0.05$.

Results

Of 257 patients with laboratory confirmed leptospirosis, 240 with completed clinical information and chest radiographies were included in this analysis. There were 209 (87.1%) males and 31 (12.9%) females with a mean age of 37.53 years (range 13-76). The median duration of fever was 3 days (range 1-13). Overall, 154 patients (64.2%) had respiratory symptoms such as cough (130 patients, 54.2%), dyspnea (75 patients, 31.3%), and hemoptysis (26 patients, 10.8%). Seventy-six (31.7%) patients had jaundice, 50 (20.8%) patients had hypotension, 80 (30%) patients had renal dysfunction, and 62 (25.8%) patients had a multiorgan dysfunction on admission. Twenty-seven patients required mechanical ventilation; nine patients had hemoptysis ($p = 0.001$). Pulmonary hemorrhage was evidenced in eight patients and three of them died, all of them with multiorgan dysfunction, including pulmonary involvement.

Radiographic Chest Findings

Chest radiograph on admission were normal in 86 (35.8%) patients. Among 154 patients with abnormal chest radiographs, reticular infiltration was the most common abnormal finding (86, 55.8%). Cardiomegaly without evidence of pulmonary congestion was found in 75 (48.7%), congestive heart failure in 38 (24.7%), air-space nodules in 37 (24.0%), consolidation in two (1.3%), pleural effusion in 12 (7.8%), and atelectasis and hilar adenopathy in one each (0.6%). Half of these patients had mixed pulmonary infiltrates with or without cardiomegaly or congestive heart failure. Data are summarized in Table 1. Overall, these abnormal findings were classified as cardiovascular, pulmonary, and mixed cardio-pulmonary involvement in 40 (25.97%), 41 (26.62%), and 73 (47.4%) patients, respectively.

The second and third chest radiographs were taken by 135 and 107 patients, respectively. One-third (36/108) of the pulmonary lesions were resolved completely on the second chest radiograph, and 26 out of 44 (59.1%) with persistent pulmonary lesion on the second chest radiograph were resolved completely on the third chest radiograph. Cardiac size returned to normal in a subsequent chest radiograph in 31 of 40 (77.5%) patients in whom cardiomegaly was detected in the first chest radiograph. Findings compatible with congestive heart failure was also resolved in 15 out of 18 patients at the follow-up chest radiograph. One patient developed new reticular infiltrate 2 days after admission and was completely resolved 1 week later. Overall, 22 out of 79 (27.8%) pulmonary lesions persisted on the third chest radiograph.

Table 1. Abnormal chest radiographic findings in leptospirosis (n = 154)

Findings	N (%)
Single pattern (n = 76)	
- Reticular infiltration	29 (18.8)
- Cardiomegaly	29 (18.8)
- Congestive heart failure	11 (7.1)
- Air-space nodules	4 (2.6)
- Pleural effusion	3 (1.9)
Multiple abnormal patterns (n = 78)	
- Cardiomegaly or CHF	
• with reticular infiltration	37 (24.0)
• with air-space nodules	19 (12.3)
• with mixed reticular infiltration and air-space nodules	15 (9.7)
• with other abnormal patterns	2 (1.3)
- Reticular infiltration with other abnormal patterns	5 (3.2)

Table 2. The associations between clinical parameters and the patterns of chest radiographs in leptospirosis

		Pattern of abnormal chest radiograph				
	Normal N (%)	Pulmonary N (%)	Cardiovascular N (%)	Mixed N (%)	p-value	OR (95% CI)
Respiratory symptoms						
Yes (n = 154)	48 (31.2)	24 (15.6)	23 (14.9)	59 (38.3)	0.005	
No (n = 86)	38 (44.2)	17 (19.8)	17 (19.8)	14 (16.3)		
Hemoptysis						
Yes (n = 26)	5 (19.2)	7 (26.9)	3 (11.5)	11 (42.3)	0.127	
No (n = 214)	81 (37.9)	34 (15.9)	37 (17.3)	62 (29.0)		
Hypotension						
Yes (n = 50)	13 (26.0)	6 (12.0)	9 (18.0)	22 (44.0)	0.087	
No (n = 190)	73 (38.4)	35 (18.4)	31 (16.4)	51 (26.8)		
Jaundice						
Yes (n = 76)	15 (19.7)	14 (18.4)	10 (13.2)	37 (48.7)	<0.001	2.41 (p = .02)
No (n = 164)	71 (43.3)	27 (16.5)	30 (18.3)	36 (22.0)		(1.14-5.11)
Renal dysfunction						
Yes (n = 80)	15 (18.8)	12 (15.0)	13 (16.3)	40 (50.0)	<0.001	3.78 (p = .009)
No (n = 160)	71 (44.4)	29 (18.1)	27 (16.9)	33 (20.6)		(1.39-10.30)
Mechanical ventilation						
Yes (n = 27)	2 (7.4)	4 (14.8)	1 (3.7)	20 (74.1)	<0.001	23.25 (p < .001)
No (n = 213)	83 (39.7)	35 (16.7)	38 (18.2)	53 (25.4)		(7.69-71.43)

Correlation between Clinical Parameters and Radiographic FChest indings

Univariate analysis showed that the presence of any respiratory symptom, jaundice and renal dysfunction on admission, and the requirement of a mechanical ventilator were significantly associated with the likelihood of having an abnormal chest radiograph on admission (Table 2).

Multivariate analysis, using logistic regression analyses, revealed that jaundice (OR 2.41, 95% CI 1.14-5.11, p = 0.02) was significantly associated with the likelihood of having an abnormal chest radiograph on admission. Results of the multivariate analysis also showed that the presence of air-space nodules on the chest radiograph was significantly more common in patients who presented with renal dysfunction (OR 3.78, 95% CI 1.39-10.30, p = 0.009), and in patients who required mechanical ventilation during admission (OR 23.25, 95% CI 7.69-71.43, p < 0.001). The reticular infiltration was significantly more common in patients with jaundice (OR 2.21, 95% CI 1.17-4.15, p = 0.01)) in the present study.

Discussion

A large outbreak of leptospirosis has occurred in Thailand since 1996. Leptospirosis is now recognized as one of the important emerging infectious diseases in this country. The epidemic mainly occurred in males during the mid-rainy season and the beginning of winter. The most likely explanation was an increased exposure to flood waters that were contaminated with urine from animals infected with the *Leptospira* species during rice farming and fishing. Severe pulmonary involvement, especially pulmonary hemorrhage, associated with a large outbreak of leptospirosis has been reported in many countries[2,3,11]. Severe pulmonary involvement has also been recognized as one of the most important causes of death in Thailand. The authors conducted the present study to determine the incidences, characteristics, and severity of pulmonary involvement in leptospirosis in Thailand.

Pulmonary symptoms and abnormal chest radiographies have been reported in 11-67% of patients with leptospirosis[1,7,12]. The incidence of hemoptysis varied from 3 to 50%. Most reports revealed an association between the presence of pulmonary symptoms, especially hemoptysis, and the likelihood of having an abnormal chest radiograph[6,13,14]. The association between jaundice and an abnormal chest radiography was controversial, but the correlation between renal dysfunction and chest radiographic abnormalities was not addressed[6,7,14].

Respiratory symptoms including hemoptysis were presented in two-thirds of the patients in the present study. Although the proportion of patients with abnormal chest radiographs was similar to those previously reported, they were mainly a mixture of pulmonary and cardiovascular abnormalities and not only pulmonary involvement as previously reported. Results of the present study also showed that only jaundice was confirmed to be associated with the likelihood of having abnormal chest radiography on admission after the multivariate analysis. Though the hypotension was not significantly associated with the likelihood of abnormal chest radiography on admission, there was a higher proportion of patients with hypotension having abnormal chest radiography (p = 0.087).

Reticular infiltration, the most common pulmonary infiltration found in the present study, occurred more commonly in patients with jaundice rather than in those without. Patchy alveolar patterns or air-space nodules were the most common abnormalities previously reported[6,7]. This finding corresponded to intra-alveolar and interstitial hemorrhage in animal studies and in autopsies of fatal cases[7,15]. Alveolar infiltrates on chest radiographs, dyspnea, hemoptysis, oliguria, hypotension, and hyperkalemia were identified as poor prognostic indicators in severe leptospirosis from various reports[16-20]. The authors were not able to identify risk factors for death in the present study. However, all three patients who died had multiorgan dysfunctions including pulmonary hemorrhage; the results of the study showed that the presence of air-space nodules in the chest radiograph was associated with severe leptospirosis, including renal dysfunction and pro-gressive respiratory failure that required mechanical ventilation support. Reticular infiltration represented a milder form of pulmonary involvement of leptospirosis in the present study.

Results of the present study also showed that cardiovascular abnormalities were more common than previously reported. Cardiovascular involvement in leptospirosis varied widely from subclinical pericarditis or myocarditis and hypotension to cardiomegaly and fatal heart failure[7,15,21,22]. Subclinical cardiovascular involvement was evidenced by a high incidence of electrocardiography abnormalities reported in leptospirosis[21,23,24]. Hypotension occurred in one-fifth of the patients, and cardiovascular abnormalities including cardiomegaly or congestive heart failure occurred in almost 75% of the radiographic abnormalities found

in the present study. Electrocardiography was not routinely tested in the present study. Although hypotension could result from either hypovolemia or cardiovascular dysfunction, only six patients with hypotension on admission did not require dopamine infusion. More detailed studies on the clinical manifestations and pathogenesis of cardiovascular involvement are needed.

In conclusion, pulmonary and cardiovascular involvements are common in leptospirosis. A chest radiography should be included in the initial investigation of these patients. Air-space nodules detected by the chest radiography may indicate severe leptospirosis.

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ความสัมพันธ์ระหว่างความผิดปกติของภาพรังสีทรวงอกกับความรุนแรงของโรคในผู้ป่วยติดเชื้อเลปโตสไปโรสิส

อรสา ชวาลภาฤทธิ์, อภิญญา เจริญศักดิ์, กรรณิกา นิวัตยะกุล, ชวนพิศ สุทธินนท์, กิตติ โล่สุวรรณรักษ์, เสาวลักษณ์ ศิลปสาคร, ยุพิน ศุพุทธมงคล

เป็นการศึกษาเพื่อหาความสัมพันธ์ระหว่างความผิดปกติของภาพรังสีทรวงอกและอาการทางคลินิกในผู้ป่วยติดเชื้อเลปโตสไปโรสิส ระหว่างเดือนกรกฎาคม พ.ศ. 2544 ถึงเดือนธันวาคม พ.ศ. 2545 ในโรงพยาบาลจังหวัดสามแห่งในภาคตะวันออกเฉียงเหนือของไทย ผู้ป่วย 240 รายที่ได้รับการยืนยันทางห้องปฏิบัติการว่าติดเชื้อเลปโตสไปโรสิส และมีข้อมูลครบถ้วนเป็นชาย 209 ราย (87.1%) และหญิง 31 ราย (12.9%) อายุเฉลี่ย 37.53 ปี มีไข้เฉลี่ย 3 วันก่อนมาพบแพทย์ เมื่อแรกรับไว้ในโรงพยาบาล 154 ราย (64.2%) มีอาการทางระบบทางเดินหายใจ และ 26 ราย (10.8%) มีไอเป็นเลือด ผู้ป่วยมีอาการตาเหลือง 76 ราย(31.7%) ไตล้มเหลว 80 ราย(30%), ความดันโลหิตต่ำ 50 ราย (20.8%) อวัยวะหลายระบบทำงานล้มเหลว 62 ราย (25.8%) ภาพรังสีทรวงอกแรกรับมีความผิดปกติ 154 ราย (64.17%) โดยแบ่งเป็น ความผิดปกติของหัวใจ, ความผิดปกติของเนื้อปอด, และความผิดปกติของทั้งหัวใจและเนื้อปอด ในผู้ป่วย 40 ราย (25.97%), 41 ราย (26.62%), และ 73 ราย (47.4%) ตามลำดับ การศึกษานี้พบว่าอาการตาเหลืองมีความสัมพันธ์กับความผิดปกติของภาพรังสีทรวงอกอย่างมีนัยสำคัญทางสถิติ ลักษณะทึบรังสีในช่องอากาศของเนื้อปอดเป็นจุดบนภาพรังสีทรวงอกพบมากกว่าในผู้ป่วยที่มีอาการไตล้มเหลวและผู้ป่วยที่จำเป็นต้องใช้เครื่องช่วยหายใจอย่างมีนัยสำคัญทางสถิติ

***สรุป**: ความผิดปกติของระบบหายใจ และหัวใจพบได้บ่อยในผู้ป่วยติดเชื้อเลปโตสไปโรสิส ลักษณะเนื้อปอดเป็นจุดที่พบในภาพรังสีทรวงอกอาจบอกถึงความรุนแรงของโรคได้*