Review Article

Pulmonary manifestations of leptospirosis

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ABSTRACT

Leptospirosis has a spectrum of presentation which ranges from mild disease to a severe form comprising of jaundice and renal failure. Involvement of the lung can vary from subtle clinical features to deadly pulmonary hemorrhage and acute respiratory distress syndrome. Of late, it has been identified that leptospirosis can present atypically with predominant pulmonary manifestations. This can delay diagnosis making and hence optimum treatment. The purpose of this review is to bring together all the reported pulmonary manifestations of leptospirosis and the recent trends in the management.

KEY WORDS: ARDS, diffuse alveolar hemorrhage, leptospirosis, pulmonary hemorrhage, pulmonary manifestations

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INTRODUCTION

Sudden remission of fever and development of hepato-renal-pulmonary involvement due to capilliary vasculitis was first described as 'Leptospirosis' by Weil in 1886. Leptospirosis, an emerging zoonosis, is usually transmitted to humans by contact with soil or water contaminated with urine of rat. Usually it presents as flu like illness with mild hepatic and renal impairment. Acute/septicemic phase for one week followed by immune phase for another one week characterizes the biphasic pattern of the illness. The immune phase is marked by production of antibodies and excretion of leptospires in urine. The characteristic biphasic illness may not be found in all patients, with only a fulminant monophasic illness being a predominating clinical course in few. These patients present with an acute undifferentiated illness which rapidly progresses to refractory shock, jaundice, renal failure and massive pulmonary haemorrhage. [1] Diagnosis is made on the basis of epidemiological, clinical and laboratory features. Since, leptospirosis has protean manifestations; it is frequently misdiagnosed even in areas of high prevalence. [2] In patients presenting with less common forms of leptospirosis, the diagnosis is frequently either not considered or only discovered at autopsy.[3] A delay in diagnosis leads to progression of disease and development of its complications. Involvement of lung was first reported by Moeschlin in 1943.[4] Since then a number of studies have identified the association of leptospirosis with lung. Pulmonary involvement usually occurs in immune phase and the overt pulmonary manifestations occur in 20-70% of patients, most of which resolve without any sequelae.[5]

Association of leptospirosis with pulmonary involvement is not easily recognized even in areas endemic of this disease. This problem is compounded by the fact that the available diagnostic methods such as Microscopic agglutination testing (MAT) and culture are insufficiently sensitive, specific or timely to be of much practical use.

The purpose of present review is to put together the clinical spectrum of pulmonary manifestations in leptospirosis and its management.

METHOD

The popular search engine 'Pubmed' was used to find appropriate articles for this review. The search terms used were "Leptospirosis and Lung" and "Leptospirosis and chest X-ray" with limits for Human studies and articles only in English language. Related citations were then selected and included in the search.

PATHOLOGY

The immune status of the host, environmental conditions

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and the etiological agent itself are some of the suggested causal factors in the pathogenesis of leptospirosis.[6] For pulmonary involvement, cigarette smoking is an important causal factor.[7] A toxin mediated process induces vascular injury particularly a small vessel vasculitis. This vasculitis primarily affects capillaries. The possible toxins include outer membrane proteins, membrane glycolipoproteins, hemolysins and lipopolysaccharides. Tajiki *et al,* correlated tumor necrosis factor α (TNF-α) with renal failure, lung injury and hemorrhagic manifestations.[8] Besides vasculitis, pulmonary hemorrhage has also been attributed to thrombocytopenia and consumption coagulopathy.

On gross examination, diffuse petechiae are found involving the lung parenchyma, pleural surfaces and tracheobronchial tree. Microscopic examination reveals areas of intra-alveolar and interstitial hemorrhage. Other findings include pulmonary edema, fibrin deposition, hyaline membrane formation and proliferative fibroblastic reactions. There is an intense leakage of fluid and proteins into the intravascular space along with extrusion of erythrocytes which result into a picture of widespread hemorrhagic infiltrates. Bronchiolitis obliterans with organizing fibroplastic polyps (BOOP) in bronchioles, alveolar ducts and alveoli has been reported.[9] Although leptospiral antigen can be found from other sites of tissue injury, finding leptospira is uncommon in lung tissue.[10] Microscopic examination also does not reveal much of inflammatory infiltrate. Immunohistochemical stains reveal presence of inducible nitric oxide synthase (INOS) activity in multiple organs.[11] Electron microscopy finds damage to capillaries as primary lesion. Endothelial cells swell and detach from the basement membrane leaving areas of exposed interstitium, even in areas free of hemorrhage. Multiple organ failure results due to hypoxia, hyperglycemia, increased nitrite/nitrate and methyl guanidine which are responsible for severe hypotension and bradycardia along with autonomic dysfunction.[11] Amongst the various infecting serovars, icterohaemorrhagiae progresses rapidly to multi organ failure.[12]

CLINICAL FEATURES

Leptospirosis is typically considered by physicians in the differential diagnosis of acute undifferentiated febrile illness only when patients present classically with triad of fever, jaundice and renal failure. Pulmonary symptoms occur in 20-70% of the patients, which are usually mild and without any sequelae.[13] Patients may present with just respiratory complaints and findings.

Pulmonary Symptoms and Signs

Patients with leptospirosis may present with predominant pulmonary symptoms, ranging from cough, chest pain, breathlessness and mild to severe hemoptysis to acute respiratory distress syndrome (ARDS). The pulmonary symptoms usually appear between fourth and sixth day of illness. The evolution of the disease may be very rapid and may result in death in less than 72 hours.[10]

The commonest pulmonary symptom is dry cough especially during the leptospiraemic phase.[14] Severe pulmonary forms of leptospirosis (SPFL) manifests itself as pulmonary hemorrhage which is usually massive and leads to respiratory insufficiency and death by asphyxiation.[15,16] Pulmonary hemorrhage may precede all other manifestations of leptospirosis such as jaundice and acute renal failure.[17] Hemoptysis, a manifestation of pulmonary hemorrhage, has been reported to be present in 17-50% of patients.[18-20] SPFL has a rapid and severe course with high mortality rates (30-60%).[21] Rarely patients may develop ARDS, which requires mechanical ventilation and has a high mortality rate of upto 51%.[22] ARDS is often associated with pulmonary hemorrhage because of endothelial damage.[21,23] Myocarditis, renal failure and/or over hydration in the setting of oliguria may lead to pulmonary edema.[24]

On general physical examination, patients with severe pulmonary forms of leptospirosis may have tachypnea and cyanosis. Though jaundice is present in the classical triad, Poh *et al* found that it may be inconspicuously absent in 30% of the patients.[25] Besides, the severity of respiratory involvement does not correlate with presence of icterus.[26] The respiratory system examination may be completely normal or may reveal the presence of rales at the bases. Most common cause of death is respiratory failure due to diffuse pulmonary hemorrhage.[27]

Laboratory Investigations

Either an isolation of the organism from the patient or seroconversion or a rise in antibody titer in the microscopic agglutination test (MAT) forms the basis of a definitive diagnosis of leptospirosis. With strong clinical evidence of infection a single antibody titer of 1:200 – 1:800 in MAT supports a diagnosis. Detectable levels of antibodies are not achieved until the second week of illness. This antibody response can be affected by early treatment. Polymerase chain reaction (PCR) techniques are usually available only in research laboratories. Isolation of the organisms can be done from blood and/or cerebrospinal fluid in first 10 days and from urine for several weeks after the first week of illness. Ellinghausen McCullough Johnson Harris (EMJH), Fletcher and Korthof media are used to isolate the leptospires. Dark field examination of blood or urine frquently results in misdiagnosis and should not be used.[28] Faines criteria has been proposed to assist in diagnosis making. These criteria are based on epidemiological, clinical and laboratory parameters.[29]

Abnormalities in arterial blood gases and spirometry have also been studied in a few studies. Nery *et al* studied the abnormalities in arterial blood gases in patients of leptospirosis with liver and kidney involvement. Most of the cases showed alveolar hyperventilation with hypocapnia as evidence. Hypoxemia was observed in 75% of the patients, probably due to pulmonary veno-arterial shunts in impaired pulmonary areas, as indicated by the high values of the Qs/Qt% and $P(A\text{-}a)O_2$. The diffusing capacity

for carbon monoxide remained normal. Average values of PaO_2 were higher in patients with acute non oliguric renal failure. Patients with a combination of oliguric renal failure, pulmonary abnormalities and chest radiograph involvement had lower PaO_2 values. In this study authors highlighted the high incidence of disturbances in arterial blood gases even in patients not having any other clinical evidence of pulmonary involvement.[30]

Fontes *et al* evaluated 21 patients with spirometry at initial evaluation and after around 28 days. Most of the patients (38.1%) had normal spirometric observations. Individuals with normal spirometry showed no radiographic changes. Restrictive pattern was observed in 33.3% and obstructive pattern in 19% of the patients. Those with abnormal spirometry findings were associated with worse APACHE II scores and chest X-ray. Spirometric improvement coincided with clinical recovery. This improvement was recorded within a brief period of 28 days. The authors concluded that the resolution of pulmonary affliction is faster as compared to bacterial pneumonias.[31]

Bronchoscopy with bronchoalveolar lavage may help in identifying hemorrhage which may otherwise remain occult. Bronchoalveolar lavage reveals hemorrhage in 100% of patients having respiratory symptoms. On the contrary, only 70% of patients not having any chest symptoms have evidence of hemorrhage on bronchoscopy.[32] Higher serum activity of platelet activating factor acetylhydrolase (PAF-AH) is found to be associated with pulmonary hemorrhage in severe cases. This marker also seems to be a candidate for disease monitoring.[33]

Chest Radiography

Estimates of frequency of pulmonary radiographic alterations in leptospirosis have varied from 11% to 67%.[16,18,34,35] Radiographic findings appear as early as 24 hours after appearance of pulmonary symptoms, although occurring more commonly 3-9 days later.

As chest X-ray can show the abnormalities in first 24 – 72 hours, it can help in early diagnosis making along with appropriate history of fever, as compared to the serological tests for leptospirosis which generally do not become positive until 6^{th} to 12^{th} day of illness. There are various patterns of abnormalities evident on chest X-rays. These are a combination of pulmonary and cardiac abnormalities. Cardiomegaly and congestive heart failure highlight a cardiac cause of radiographic abnormalities.[36]

CHEST X-RAY IN LEPTOSPIROSIS

- Rapidly evolving predominantly peripheral diffuse nodular or confluent pulmonary lesions are typical of leptospirosis.
- Pleural effusions less common.
- Subsegmental atelectasis is a nonspecific finding.
- Pulmonary abnormalities usually resolve in 15 days without any permanent damage.
- Radiological severity correlates with severity of pulmonary symptoms.
- Hypoxemia and PaO_2/FiO_2 ratios do not correlate with severity of chest symptoms.
- Patients with jaundice, renal failure and respiratory failure requiring mechanical ventilation have more likelihood of having abnormal chest radiographs.

The radiographic abnormalities have been a subject of various studies. Matos *et al* analyzed chest radiographs of 139 patients admitted with a diagnosis of leptospirosis. Out of these alveolar infiltrates were seen in 74.3% of the patients. These lesions were bilateral in 54.3% and involved the inferior lobes in 45.5% of the patients. 8.6% of the involved chest X rays had pleural effusions. These reported alveolar infiltrates were associated with intra alveolar hemorrhages.[35] Lee *et al* observed non segmental opacification and basal linear opacities on chest radiographs of patients with leptospirosis. They also recorded a first radiographic demonstration of a large pleural effusion in leptospirosis.[34] Subsegmental atelectasis has also been reported as a nonspecific abnormal radiographic finding.[18] In a series of 58 patients, findings ranged from small nodular densities (57%), large confluent areas of consolidation (16%) to diffuse ill defined ground glass densities (27%). On serial radiographs, the nodular pattern showed a tendency to be followed by confluent consolidation and/or ground glass density. These abnormalities were bilateral nonlobar with a tendency for peripheral distribution. In most of the surviving patients (50/58) in this series, pulmonary abnormalities resolved in 15 days, without permanent damage.[16] It can be safely concluded that a rapidly evolving predominantly peripheral diffuse nodular or confluent pulmonary lesions are typical of leptospirosis. Whereas one study reported that most common finding on chest radiograph was bilateral diffuse airspace disease followed by bilateral patchy infiltration,[18] another study identified reticular infiltration as most common abnormality.[36]

Radiological severity correlates with severity of pulmonary symptoms. Patients with radiographic abnormalities required longer hospitalization as compared to those without it.[18] Similar correlation was reported by Chawalparit *et al*. They found out that presence of airspace nodules in the chest radiograph was associated with severe leptospirosis. But they also highlighted that, in contrast to airspace nodules reticular infiltration represented a milder form of pulmonary involvement.[36] Hypoxemia does not correlate with radiological presentation. Similarly, arterial blood gas pressures (PaO_2/FiO_2 ratio) also do not correlate with severity of chest radiographs and prediction of outcome.[37]

Certain clinical parameters have been related to occurrence of findings on chest radiography. Patients with jaundice, abnormal renal function and those requiring mechanical ventilation had higher likelihood of having abnormal chest X-rays on admission. Even though hypotension was not significantly associated with the likelihood of

abnormal chest radiography on admission, there were a higher proportion of patients with hypotension having abnormal chest radiography.[18,36] It should be remembered that vice versa is not always true. In a retrospective study comprising of medical records and pulmonary radiographs of 118 leptospirosis patients, Tanomkiat *et al* noted that 22% of patients 'not' having renal involvement or jaundice had abnormal chest radiographs.[18]

Differential diagnosis of these radiological findings include viral pneumonia, bronchopneumonia, miliary tuberculosis, pulmonary hemorrhages due to any other cause, aspiration, bronchoalveolar carcinoma and ARDS.[18,38] Certain radiographic characteristics help in differentiating radiographic abnormalities due to leptospirosis, ARDS and pulmonary edema. ARDS chest radiographs usually take much longer time to show complete clearing as compared to those of leptospirosis. Pulmonary edema usually does not have peripheral distribution and it has other supportive evidence such as Kerley B lines and pleural effusions.[39-41]

High Resolution Computed Tomography

Marchiori *et al* studied findings in high resolution computed tomography (HRCT) in patients of leptospirosis. They found out that the findings predominantly consisted of extensive ground glass opacities involving all lobes. The abnormalities predominantly afflict the peripheral and dorsal lung regions and the lower lung zones. In particular, HRCT picks up more extensive abnormalities such as ground glass abnormalities in the upper lobes which are not appreciated on chest radiographs. Comparison of the HRCT with the histological findings showed that these ground glass opacities, airspace consolidation and airspace nodules were caused by airspace hemorrhage.[42]

PROGNOSIS

Mortality rates of 5-15% in severe leptospirosis have been documented. Various parameters have been identified to be associated with prognosis. In a study conducted by Marotto *et al* three variables were independently associated with mortality - hemodynamic disturbances, serum creatinine level > 265.2 μmol/L and serum potassium level > 4 mmol/L.[43] Another retrospective case control study identified predictors of mortality as - age > 40 years, development of oliguria, platelet count < 70,000/ μL, creatinine > 3 mg/dl, and pulmonary involvement. The strongest risk factor was that of pulmonary involvement, which has also been reported by Budiono *et al*.[44,45] Number of quadrants involved on chest X-ray and thrombocytopenia are also related with mortality.[19,20] One of the determinants of poor outcome is a delay in hospitalization. This is of concern in tropical settings where a primary diagnosis of dengue may delay appropriate treatment.[46]

Segura *et al* and Truccolo *et al* have found an association between level of leptospiremia and development of pulmonary manifestations. At least 10^4 leptospires/ml of blood or milligram of tissue is associated with severe pulmonary hemorrhage syndrome and consequently poor prognosis. Thus Polymerase chain reaction (PCR) seems to be promising investigational modality in leptospirosis for diagnosis and prognosis.[47,48]

TREATMENT

Most of the patients of leptospirosis show spontaneous recovery and they do not require any specific therapy. Patients with severe leptospirosis may require correction of hypovolemia, hypotension and electrolyte abnormalities. Dialysis and transfusion of blood and blood products may be required to mange renal failure and severe bleeding respectively.[49] Early platelet transfusion is recommended in patients with less than fifty thousand platelets per cubic milliliter or in those with significant reduction in platelet counts in a short period of time.

The use of antibiotics has been controversial. A Cochrane systematic review failed to find sufficient evidence to provide clear guidelines for use of antibiotics.[50] Antibiotics should be used early in the disease i.e. up to fourth day of illness. Penicillin (penicillin G 1,00,000 U/Kg/24 h – divided doses every 4 hours), tetracycline (25–40 mg/kg/day – every 6 hours) and doxycycline (100 mg twice a day) over seven days are the preferred antibiotics.

Meaudre *et al* suggested some form immunomodulation like plasmaphresis, immunoglobulin or glucocorticoids may be helpful in multi organ dysfunction in severe leptospirosis.[51] Several reports from India have supported use of glucocorticoids in leptospiral pulmonary hemorrhage.[19,52-54] Shenoy *et al* evaluated the efficacy of bolus methylprednisone followed by oral prednisolone for 7 days. (Dose: 1 gram methylprednisone given intravenously for first 3 days followed by oral prednisolone 1 mg/kg for 7 days.) The use of corticosteroids reduced the need for ventilator support; however the mortality benefit was not passed on to patients already on mechanical ventilation. They concluded that corticosteroids were of use only if given within first 24 hours of onset of pulmonary symptoms.[19]

Trivedi *et al* evaluated the efficacy of cyclophosphamide and plasma exchange in patients with leptospiral pulmonary hemorrhage. Two cycles of plasma exchange, 24 hrs apart were done, 25 ml/kg body weight of plasma removed in each cycle. Cyclophosphamide (20 ml/kg body weight) was given after the first cycle. Author's findings showed that plasma exchange with immunosuppression improved survival in patients of pulmonary alveolar haemorrhage due to leptospirosis, suggesting that immune mechanisms play a key role in the pathogenesis of the disease.[20] Plasma exchange removes coagulation factors and platelets along with offending antibodies and immune complexes. This is hazardous in patients of alveolar hemorrhage consequent to dilutional coagulopathy and thrombocytopenia. For this reason authors recommend only removal of 25 ml/kg plasma and selection of patients

with mild disease. They feared that patients with severe disease may not tolerate transient hypoxemia associated with plasma exchange. Also, since plasmapharesis takes some time to show results, patients with severe disease may succumb to the disease before any obvious benefits of this risky procedure.[20]

Management of respiratory failure should be done with timely initiation of mechanical ventilation with PEEP and high concentration of inspired oxygen. This may be life saving considering the speed of appearance and extent of hemorrhage which may lead to asphyxia and death.[17,55-58] Hypoxemia in leptospirosis with pulmonary hemorrhage may be difficult to treat inspite of maximal mechanical ventilation. Arokianathan *et al* have reported successful treatment with extra corporeal membrane oxygenation (ECMO). ECMO is a method of cardiopulmonary support which relieves lungs of its gas exchange function. It minimizes the damage done by mechanical ventilation requiring high FiO_2, high tidal volumes and high airway pressures thus reducing the morbidity and mortality. However, use of ECMO in adults is still under evaluation. Best results of ECMO is seen in patients referred early as higher the duration of conventional mechanical ventilation higher the mortality rates. The patient described by Arokianathan *et al* also required Molecular adsorbent Recycling system (MARS) because of high bilirubin levels.[59-61]

Inhaled nitric oxide, desmopressin, hemofiltration, activated factor VII and activated protein C are few of the novel approaches which have been tried in resistant cases of leptospirosis. Borer *et al* suggest that nitric oxide inhalation and hemofiltration should be considered in patients with pulmonary hemorrhage and renal failure caused by leptospirosis in which conventional therapy fails. Continuous hemofilteration has been earlier used for removal of cytokines in patients of systemic inflammatory response syndrome or multiple organ dysfunction syndrome.[62] Hemofilteration can result in cerebral edema especially in patients with severe oliguria.[63] Antiplatelet effect of nitric oxide and the use of anticoagulants during hemofilteration can be hazardous in the setting of pulmonary hemorrhage.[64,65]

A resistant case leptospirosis with diffuse alveolar hemorrhage is described which was subsequently treated with recombinant activated factor VII.[66] Recombinant activated factor VII can be administered locally[67] or systemically as used by Tatopoulos *et al*.[66] Several thrombotic complications, including myocardial ischemia and deep venous thrombosis, have been reported with use of recombinant activated factor VII.[68]

Srinivas *et al* describe a case of malaria and leptospira coinfection with sepsis and multi organ dysfunction treated with activated protein C. Activated protein C was given at the dose of 24 μg/kg/hr for 96 hours, apart from routine standard of care for malaria and leptospirosis.[69] Use of activated protein C in leptospirosis has also been highlighted by Kapadia *et al*.[70]

To conclude, leptospirosis is an emerging zoonosis which can cause significant morbidity and mortality in today's era of rapid globalization. It can present with predominant pulmonary involvement, instead of classical triad of Weil. This form of presentation should be identified promptly to facilitate optimum management.

TREATMENT

- Most of the patients show spontaneous recovery, not requiring any specific therapy.
- Supportive therapy requires correction of hypotension, hypovolemia and electrolyte abnormalities. Dialysis and transfusion of blood and blood products may also be required.
- Role of antibiotics controversial. If used, should be used within four days of illness.
- Use of Methylprednisone has been found to be beneficial only if used within 24 hours of onset of pulmonary symptoms.
- A low dose plasmapharesis (removal of 25 ml/kg) has been recommended in patients with mild disease. However the benefits of the procedure show up later and are not instantaneous.
- Respiratory failure managed with timely initiation of mechanical ventilation with PEEP and high concentration of inspired oxygen.
- ECMO for resistant hypoxemia in spite of maximal ventilation. Use in adults not well validated.
- Inhaled nitric oxide, desmopressin, activated factor VII, activated protein C and hemofilteration may be used when conventional therapy fails.

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Announcement

Fellowship of Indian Chest Society

Fellowship of Indian Chest Society is open for members of Indian Chest Society. This fellowship is to recognize members of the Indian Chest Society who have excelled in the field of Respiratory Medicine. The fellowship will be given after the approval of the application by a High Power Credential Committee. The process of selection of fellowship is highly objective, transparent and accountable. The Credential Committee assesses and scores all the applications as per predefined criteria and recommends 10 top scorers for fellowship each year. To be eligible the applicant should have completed at least five years as a primary (life) member and there should be no indictment in professional/academic misconduct ever. The selected fellow will be allowed to use "FICS" as a subtitle. The fellowship fee is Rs.10,000/- to be paid only on selection or invitation. For further details please refer to Indian Chest Society website www.indianchestsociety.in or contact at following address:

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