Severe Pulmonary Leptospirosis Associated With High Fatality Rate: An Autopsy Series in Galle, Southern Sri Lanka

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SUMMARY
According to statistical unit of the Karapitiya Teaching Hospital, Galle, the main tertiary care institution of the Southern Province serving approximately three million population, in 2008, there were 459 patients with clinical diagnosis of leptospirosis, with 25 fatalities, 21 out of which were referred for autopsy examination.

Objectives: The present study to study and correlate pathological changes in deaths associated with pulmonary form of leptospirosis with clinico-diagnostic aspects of the infection.

Method: There had been 21 leptospirosis related autopsy examinations performed at forensic medicine unit of the Karapitiya Teaching Hospital from January to December 2008. The clinical, laboratory and autopsy findings of these cases were recorded in detail and analyzed.

Results: The characteristic autopsy feature of all these cases was a moderate to severe pulmonary haemorrhage in association with hepato-renal, myocardial and cerebral lesions. The histology of the lung tissues in most cases showed extensive alveolar haemorrhages, hyaline like deposits, neutrophilic infiltrations, swollen septa with congested blood vessels.

Conclusion: Severe pulmonary complications are mostly responsible for all fatalities due to leptospirosis in our series. Though there are no reliable clinical indicators that suggest probability of developing pulmonary haemorrhages, we emphasize that respiratory functions and haematological parameters need to be closely monitored in all hospitalized patients with leptospirosis for early detection and prevention of haemorrhagic complications.

KEY WORDS:
leptospirosis, pulmonary haemorrhage, Sri Lanka, Galle

INTRODUCTION
Leptospirosis, also known as Weil’s disease, an infectious disease, well known in all parts of the world since 1883, that affects humans and animals, which was first identified by Inada et al in Japan in 1916, is considered the most widespread zoonosis in the world. It has been recognized as an occupational disease, with 30-50% exposure among agricultural/field workers. Leptospirosis may present with a wide range of clinical manifestations, which may vary, from a mild flu-like illness to a serious and sometimes fatal disease. Case fatality rate is reported to range from less than 5% to 30% and principal causes of death include hepatorenal failure heart failure and widespread haemorrhage.

Situation in Sri Lanka and Galle Region
Sri Lanka is a Tropical Island off the south east coast of the Indian subcontinent of the Indian Ocean, of about 65,610 Km² in extent, with 2.1 million resident population, and consists of 25 administrative districts clustered into nine provinces. Galle is the Capital City of the Southern Province that accommodates 2.3 million in Galle, Matara and Hambantota districts.

Leptospirosis is a notifiable illness in Sri Lanka for past two decades and the epidemiological data revealed steady increase of incidence of notified cases in the island during recent past two decades, from 167 cases in 1991 to over 3000 incidents in 2008, with outbreaks in 2003 [2134 cases], 2007 [2198 cases] and 2008 [7099 cases]. A favorable tropical climate and monsoon rains enable the pathogenic spirochete Leptospira interrogans to survive in the environment.

According to national figures and our experience in Galle region for the past 10 years, the mortality rate in leptospirosis ranged from 1 – 3 %, which was mainly due to hepato-renal complications, and there were hardly any cases with severe pulmonary haemorrhages. The significant increase of death rate during 2007-2008 is attributed to escalation of severe pulmonary variant of the disease (Table I).

A notable increase of the haemorrhagic mode in deaths due to leptospirosis were present in 2008. The current endemic pattern of the disease with fatal pulmonary complications appears a newly emerging trend in many parts of the world since the first technical report from Korea in 1995. The main objective of this survey is to review clinical and pathophysiological aspects of severe pulmonary form of the disease.
MATERIALS AND METHODS

Case Definition: The disease is caused by pathogenic spiral bacteria of the genus Leptospira, and the recent studies revealed that, there are at least seven distinct pathogenic species, appear in about 250 serologic variants. The study was conducted on diagnosed cases of leptospirosis based on characteristic clinical findings [history, flu-like illness, myalgia, headache, anuria/oliguria, cardiac complications, meningeal symptoms, jaundice, haemorrhagic manifestations etc] and serology. The clinical diagnosis was further confirmed by characteristic pathological findings during autopsy examinations.

Study Area and Materials: Study has been conducted at Forensic Medicine Unit of the Karapitiya Teaching Hospital, Galle, [1600 Bed Hospital], a third largest in Sri Lanka and the main multidisciplinary tertiary care health establishment in the Southern Province of Sri catering approximately 1.05 million people from Galle District as well as referrals from two other districts with nearly 1.4 million.

There had been 21 leptospirosis related autopsy examinations performed at the forensic medicine unit of the Karapitiya teaching hospital from January to December 2008.

Methodology: All cases were subjected to thorough autopsy examination, that includes, external observation, detailed organ dissection with estimation of weights, muscular skeletal examination, cerebro-spinal examinations supported by histopathological investigation of brain, lungs, heart, liver, kidney using H&E staining etc. Autopsy findings of all cases were recorded in master sheet and important changes were included in the results table. The recorded details of clinical, laboratory and autopsy findings of the cases were qualitatively analyzed.

RESULTS

There were 25 deaths due to leptospirosis during the study period, twenty one out of which were subjected to autopsy examinations. Other 4 cases were released on the clinical certificates of the cause of death without autopsy. All patients presented with flu-like illness accompanied by one or more other clinical symptoms such as headache, myalgia, vomiting, icterus, shortness of breath, epigastric pain and oliguria. The clinical picture was characterized by relatively low platelet counts, high white blood cell counts and positive agglutination lysis test in 10 cases. The histology of the lung tissues in most cases showed extensive alveolar haemorrhages, hyaline like deposits, neutrophilic infiltrations, and swollen septa with congested blood vessels [Fig 1 – 3].

The age of victims were from 17 to 59 years with predominance of males [91%]. Five patients had neurorogical symptoms due to cerebral haemorrhages. Two patients complained of hemoptosis. A 35 year old woman with clinical diagnosis of leptospirosis who had pancytopenia and negative serology was excluded due to uncertainty of the diagnosis.

Haematological complications: The striking pathophysiological feature of the entire series was a moderate to severe pulmonary haemorrhages [lunp fields were flooded with unclotted fresh blood] in association with hepato-renal, myocardial and cerebral, lesions. Two victims had intracerebral haemorrhages, and four autopsies revealed subendocardial/myocardial haemorrhages. The white blood cell counts were elevated in all cases [8000 – 20,000] with significant neutrophilic reaction. Platelet counts were assessed in 18 patients and ranged below 100,000 /mm³, with lowest being 20,000 in 48 years old male victim. Prothrombin time was tested in eight cases and found to be prolonged [ > 12Sec] in five patients.

The essential details of all twenty one cases are summarized in the table II.

DISCUSSION

National records revealed that, in 2007, there were 1197 cases of leptospirosis, with 700 laboratory confirmed cases in Sri Lanka¹. The country experienced the largest outbreak of the diseases during late 2007 – 2008 with almost 400% increase of the number of cases². The database of Karapitiya Teaching Hospital, Galle, revealed that in 2008, there were 459 patients admitted with the clinical diagnosis of leptospirosis, and 25 patients had succumbed to their illness. The death rate during the year 2008 is ~ 6%, contrast to 4.9% during 2007, when 105 patients were diagnosed with leptospirosis. The epidemiological reasons behind the present escalation of the disease are yet to be revealed.

The diagnosis of leptospirosis has been confirmed by clinical features, laboratory findings, serological examination¹ [over 65%] and autopsy data including histology. Though a single diagnostic titre of [MAT – IgG] of 1: 800 dilution is confirmatory of diagnosis, single agglutination test at 1:600 dilution in association with characteristic clinical and pathological findings are generally applicable inclinical setup. However, the serological test conducted here was not subtype specific and therefore, we were unable to pin-point microbiological type of leptospires’ responsible for the fatalities.

The group of victims presented with close clinical picture related to other infectious diseases such as Dengue fever, Hanataan virus, mycoplasma etc. was excluded on the clinical, serological and pathological findings.
<table>
<thead>
<tr>
<th>Case No</th>
<th>Age &amp; Sex</th>
<th>Main Clinical Features</th>
<th>WBC/DC</th>
<th>Platelet count</th>
<th>Prothrombin time/control seconds</th>
<th>Significant Autopsy Findings including histology</th>
<th>Leptospira agglutination Lysis Test Titre</th>
</tr>
</thead>
<tbody>
<tr>
<td>1)</td>
<td>29 Male</td>
<td>Fever, Headache, N 87%</td>
<td>13,000</td>
<td>56,000</td>
<td>16/12</td>
<td>Necrosis swollen Severe Hemorrhages Myocardial oedema</td>
<td>600</td>
</tr>
<tr>
<td>2)</td>
<td>48 Female</td>
<td>Fever, Shortness of Breath, diarreha N 81%</td>
<td>14,000</td>
<td>84,000</td>
<td>12/12</td>
<td>Fatty enlargement swollen Severe Hemorrhages Sunendocardial Haemorrhages</td>
<td>800</td>
</tr>
<tr>
<td>3)</td>
<td>52 Male</td>
<td>Fever, Shortness of Breath, myalgia</td>
<td>12,000</td>
<td>40,000</td>
<td>Not done</td>
<td>Enlarged Fatty swollen Severe Hemorrhages Acute Myocarditis</td>
<td>600</td>
</tr>
<tr>
<td>4)</td>
<td>44 Male</td>
<td>Fever, myalgia N 78%</td>
<td>9000</td>
<td>60,000</td>
<td>Not done</td>
<td>Fatty enlargement swollen Severe hemorrhages Bain stem haemorrhages</td>
<td>600</td>
</tr>
<tr>
<td>5)</td>
<td>39 Male</td>
<td>Fever, headache N 90%</td>
<td>20,000</td>
<td>60,000</td>
<td>Not done</td>
<td>Fatty, focal necrosis swollen Severe haemorrhages Acute myocarditis</td>
<td>600</td>
</tr>
<tr>
<td>6)</td>
<td>53 Female</td>
<td>Fever, myalgia N 89%</td>
<td>16,000</td>
<td>60,000</td>
<td>Not done</td>
<td>Fatty enlargement Acute Tubular necrosis Normal</td>
<td>600</td>
</tr>
<tr>
<td>7)</td>
<td>37 Male</td>
<td>Fever, vomiting, icterus N 97%</td>
<td>20,800</td>
<td>58,000</td>
<td>Not done</td>
<td>Fatty focal necrosis Swollen Severe haemorrhages Normal</td>
<td>600</td>
</tr>
<tr>
<td>8)</td>
<td>24 Male</td>
<td>High Fever myalgia admission N 80%</td>
<td>17,000</td>
<td>45,000</td>
<td>Not done</td>
<td>Fatty diffuse necrosis Acute Tubular necrosis Moderate haemorrhages Subarachnoid and brain stem haemorrhages</td>
<td>600</td>
</tr>
<tr>
<td>9)</td>
<td>17 Male</td>
<td>High fever, vomiting, cough, shortness of breath N 90%</td>
<td>16,000</td>
<td>30,000</td>
<td>Not done</td>
<td>Fatty SGPT 150 Swollen Severe haemorrhages Interstitial oedema in myocardium</td>
<td>600</td>
</tr>
<tr>
<td>10)</td>
<td>38 Male</td>
<td>Fever, headache N 76%</td>
<td>12,000</td>
<td>Not done</td>
<td>Not done</td>
<td>Fatty focal necrosis Pale swollen Moderate haemorrhages Oedema, Subepicardial haemorrhages Not done</td>
<td>600</td>
</tr>
<tr>
<td>11)</td>
<td>48 Male</td>
<td>Fever, icterus, myalgia N 87%</td>
<td>14,000</td>
<td>40,000</td>
<td>19/12</td>
<td>Fatty enlargement Pale swollen Severe haemorrhages Interstitial oedema of myocardium</td>
<td>600</td>
</tr>
<tr>
<td>12)</td>
<td>56 Male</td>
<td>Fever 2 days N 87%</td>
<td>13,000</td>
<td>Not done</td>
<td>Not done</td>
<td>Fatty, focal necrosis Swollen Severe haemorrhages Myocarditis Not done</td>
<td>600</td>
</tr>
<tr>
<td>13)</td>
<td>48 Male</td>
<td>Fever, vomiting, Diarrhoea N 85%</td>
<td>13,800</td>
<td>20,000</td>
<td>Not done</td>
<td>Acute fatty changes Swollen Severe haemorrhages Pericardial and subendocardial haemorrhages Not done</td>
<td>600</td>
</tr>
<tr>
<td>14)</td>
<td>51 Male</td>
<td>Body aches, intermittent fever, semiconscious on admission N 82%</td>
<td>15,000</td>
<td>90,000</td>
<td>Not done</td>
<td>Acute fatty changes Pale, swollen Haemorrhages Cerebral oedema, flabby dilated myocardium</td>
<td>600</td>
</tr>
<tr>
<td>15)</td>
<td>53 Male</td>
<td>Fever with Chills N 90%</td>
<td>19,000</td>
<td>130,000</td>
<td>Not done</td>
<td>Fatty liver, Hepatomegaly Swollen Severe haemorrhages Cerebral oedema, Haemorrhagic mocardium Not done</td>
<td>600</td>
</tr>
<tr>
<td>16)</td>
<td>49 Male</td>
<td>Fever, myalgia, cough, shortness of breath N 82%</td>
<td>17,000</td>
<td>60,000</td>
<td>16/12</td>
<td>Fatty liver, pale cortex with congested medulla Swollen, moderate haemorrhages Unremarkable Not done</td>
<td>600</td>
</tr>
<tr>
<td>17)</td>
<td>49 Male</td>
<td>Fever with Chills N 78%</td>
<td>14,000</td>
<td>100,000</td>
<td>14/12</td>
<td>Swollen, necrotic foci Pale, swollen Severe haemorrhages and oedema Swollen myocardium</td>
<td>600</td>
</tr>
<tr>
<td>18)</td>
<td>47 Male</td>
<td>Fever, body aches, fever with Chills, oliguria N 75%</td>
<td>14,200</td>
<td>97,000</td>
<td>Not done</td>
<td>Acute fatty changes Swollen Moderate haemorrhages Flabby pale myocardium Not done</td>
<td>600</td>
</tr>
<tr>
<td>19)</td>
<td>38 Male</td>
<td>Fever Chills, oliguria, shortness of breath N 80%</td>
<td>15,000</td>
<td>90,000</td>
<td>12/12</td>
<td>Fatty and swollen Pale, swollen Severe haemorrhages Cerebral oedema Not done</td>
<td>600</td>
</tr>
<tr>
<td>20)</td>
<td>59 Male</td>
<td>Fever Chills, myalgia N 70%</td>
<td>16,000</td>
<td>85,000</td>
<td>Not done</td>
<td>Acute fatty liver with necrotic foci Pale and swollen Moderate haemorrhages Unremarkable Not done</td>
<td>600</td>
</tr>
<tr>
<td>21)</td>
<td>51 Male</td>
<td>Fever, Chills, icterus, haemoptisis N 80%</td>
<td>14,500</td>
<td>80,000</td>
<td>11/12</td>
<td>Swollen Moderate haemorrhages Unremarkable</td>
<td>600</td>
</tr>
</tbody>
</table>
While having primary reservoir in wild mammals, urinary spreading of organisms from infected animals is the most significant source of these bacterial pathogens. The organism enters the body via damaged skin or mucous membranes of the conjunctiva or alimentary tract.

Pathophysiology of pulmonary leptospirosis

The pulmonary haemorrhagic form of leptospirosis is known over the years, yet the scientific reports of endemic cases are relevantly scanty, except for the few series available from Korean\(^8\) and Indian subcontinents and also from the South American region\(^9\). A recent surveillance report from Brazil showed significant escalation of severe pulmonary form of the disease during 2000 to 2005 with 74% fatality rate compared to 12% in other forms of the disease\(^10\). The basic clinical picture of severe pulmonary form of leptospirosis in our series is in keeping with the previously reported incidents.

Pulmonary haemorrhages are considered to be one of the most serious, and often fatal complication\(^11\), caused by Leptospira icterohaemorrhagiae and several other subtypes, which was first identified in Sri Lanka in 1959. The histological findings are not indicative of secondary haemorrhages following DIC or isolated pulmonary injuries due to ventilation. Hence, deteriorating platelet functions and prothrombine time could be used as one of the clinical indications to evaluate probability of development of haemorrhagic complications.

Other case studies in Sri Lanka and Indian region

A number of studies pertaining to clinical and epidemiological aspects of leptospirosis outbreaks in Sri Lanka\(^12\) being carried out since 1960, but a very few conferred to detailed pathological aspects and pathomorphism of the disease. A similar clinico-pathological study conducted on seven leptospiro related deaths at North Colombo Teaching Hospital in Sri Lanka in 1976 revealed that the pathological profile of pulmonary involvement in leptospirosis appears to fall into an adult respiratory distress syndrome and, when present, carries a serious prognosis and would then be a prime factor in mortality. Another study conducted in Galle region revealed that, clinical impression is insensitive, and immunoglobulin M results are more insensitive and costly for identifying acute leptospirosis, and stressed the need of rapid, pathogen-based tests for early diagnosis\(^13\).

The recent Indian studies showed that the incidence of pulmonary involvement in leptospirosis has been reported to be increasing in the last years, affecting up to 70% of the patients. Alveolar hemorrhage clinically presented as dyspnoea and hemoptysis is the main pulmonary manifestation. The emergence of massive hemoptysis and acute respiratory distress syndrome has characterized the recent changes reported in the clinical patterns of leptospirosis\(^14\). The histopathological features of pulmonary involvement include hyaline membranes and micro thrombi.

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Fig. 1: Necrotic lesions in the myocardium infiltrated with polymorphs.

Fig. 2: Diffuse polymorph infiltration of liver sinusoids.

Fig. 3: Massive pulmonary haemorrhages with hyaline like deposits in alveoli.
in the capillaries in addition to massive alveolar haemorrhages. Pulmonary haemorrhage has been recognized increasingly as a major, often lethal, manifestation of leptospirosis, the pathogenesis of which remains unclear. The immunofluorescence studies performed on infected lung tissues confirmed the presence of IgM, IgG, IgA, and C3 along the alveolar basement membrane. This suggests that an autoimmune process may be the etiology of fatal pulmonary hemorrhage in leptospirosis. Many researchers have emphasized the importance of radiological investigations and blood gas analysis for prompt clinical diagnosis, and suggested that corticosteroids, associated with antibiotics, early respiratory support, and platelet transfusions are useful as an efforts to prevent further development of severe pulmonary haemorrhages.

Non pulmonary fatal complications of leptospirosis

There had been a very few fatal cases (~1-2% - generally late admissions) in our study area due to non pulmonary complications of leptospirosis during past decades. Until recent escalation of mortality rates associated with unusual clinical symptom complex, majority cases were clinically confirmed and bodies were released on clinical certificates of death without requesting for autopsy examination. Hence, authors possess limited own data pertaining to pathological aspects of non pulmonary forms of leptospirosis and the comparison has been made by utilizing existing literature sources and findings of other regional studies.

Cardiac involvement is common in leptospirosis, may range over 90% but generally masked by overt pulmonary haemorrhage or hepato-renal involvement and hence may be underestimated. About 67% of the cases in present study showed cardiac lesions consist of myocarditis, epicardial haemorrhages, myocardial oedema and dilatation. Findings are in keeping with the results of other studies. Furthermore, most autopsies revealed combination of pulmonary haemorrhages with direct involvement of myocardial tissues and reckoning number of central nerves system involvements [24%], including two cases of intracerebral haemorrhages, which is an extremely rare presentation of the disease.

The liver damage consist of fatty enlargement with centrilobular necrosis associated with renal dysfunction is one of the pathognomonic features of leptospirosis which was seen in the present series. The liver necrosis and renal tubular damages are attributed to the direct effect of the bacillus. After the organism gains access to the kidney, it migrates to the interstitial tissues, renal tubules, and tubular lumen, causing interstitial nephritis and tubular necrosis. Liver involvement is seen as centrilobular necrosis with the proliferation of Kupffer cells.

Haemotopathological aspects

The significant increase of white blood cell count with predominant neutrophilia is characteristic of severe bacterial infection, with the exception of one case, which showed pancytopenia probably due to bone marrow depression. However, the acute bone marrow suppression in leptospirosis is rather unlikely according to published data. Previous studies revealed that leptospirosis did not affect the functional ability of the bone marrow and no oppressive myelotoxic action as produced by Leptospira was observed. A moderate activation of erythropoiesis, irritation of the lymphomononocytic sprout as well as oppression of the basophile and neutrophile series were the characteristic features of myelograms at the acute illness stage.

In all cases, platelets were decreased to significantly lower levels but still not sufficient to cause wide spread haemorrhages. The prolonged prothrombin time is likely to be due to dysfunction of the liver. However, the combination of lower platelet counts and prolonged prothrombin time makes the patient more vulnerable to haemorrhagic complications. Certainly, a number of pathogenic mechanisms appeared to be responsible for platelet dysfunction and haemorrhagic complications. Vasculitis should be considered as the most important factor for the pathogenesis of the bleeding disturbances in Leptospirosis. In addition to that, thrombocytopenia, uremia and coagulation disorders, individually or as a group, should be included among the contributing factors that lead to and worsen bleeding episodes, which represent the leading cause of death in this disease.

CONCLUSIONS

The reasons for unpredicted outbreaks of the severe form of leptospirosis is yet unknown and need further research and surveillance. A hemorrhagic form of leptospirosis is confirmed to be a potentially fatal variant of leptospira infection with over 70% mortality rate and therefore, precise clinical and laboratory parameters must be streamlined for early detection and prevention of the acute pulmonary complications. Severe pulmonary complications are mostly responsible for all fatalities due to leptospirosis in our series.

Though there are no reliable clinical indicators that suggest probability of developing pulmonary haemorrhages, we emphasize that radiological findings, respiratory functions and haematological parameters need to be closely monitored in all hospitalized patients with leptospirosis for early detection and prevention of haemorrhagic complications.

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