CLINICO-PATHOLOGIC CONFERENCE

(A weekly clinical and pathologic case conference participated jointly by members of the Departments of Internal Medicine and Pathology of the Chulalongkorn Hospital, Faculty of Medicine, Chulalongkorn University, and by the third and fourth year medical students)

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(FEVER – JAUNDICE – ABDOMINAL PAIN – EDEMA – ACUTE RENAL FAILURE)

Clinical History

A 75 year old Thai woman was admitted to Chulalongkorn Hospital on August 6, 1968 because of continuous fever without chills for 10 days. Accompanying fever were anorexia, nausea–vomiting and generalized abdominal pain which was unrelated to meal. Mild coughings were also present. The fever was remittent lasted 3–4 days, and on the second remission, she felt generalized weakness and severe dull calf muscle pain. Yellowish discoloration of the skin and dark yellowish urine were noted a few days before admission. During the past 5–6 months, the patient had experienced epigastric pain which was relieved by antacids. She was a native of Bangkok, and resided in areas where many strayed dogs and rats lived.

Physical examination showed a toxic appearing elderly woman with marked jaundice and mental confusion. The body temperature was 37.5 C. The blood pressure was 100/80 mm. Hg. Pulse rate and respiration were 100 and 22 per min. respectively. The conjunctivae were markedly injected. Fine crepitations and rhonchi were heard over both lung bases, especially the left. The abdomen was distended with slight tenderness on the right side. The liver and spleen were not palpable. Ascites was thought to be present by the examiner. Pitting edema of both legs was noted. There was mark tenderness of the calf muscles on both sides. Pelvic examination revealed procedentia.

The hemoglobin was 10.4 gm; the red-cell count was 3.7 millions. The white-cell count was 36200. with 78 per cent neutrophils and 22 per cent lymphocytes. Malarial parasites were not found. The urine specific gravity was 1.010 with a trace of albumin; the sediment contained 4–5 red cells and 3–4 white cells per high power field. The urea nitrogen was 93.5 mg. and creatinine, 3.2 mg. per 100 ml,

The carbon dioxide combining power was 14.2, sodium 128, potassium 3.6, and chloride 87 milliequiv. per liter. The serum osmolarity was 295 milliosmol. The liver function test showed a total bilirubin was 30.8 mg., direct bilirubin 15.4 mg. per 100 ml. The cephalin flocculation test was 4 plus; thymol turbidity, 11.4 and zinc turbidity 17.1 units. The alkaline phosphatase was 2.5 Bodansky units, the serum glutamic oxaloacetic acid transaminase was 150 units and serum glutamic pyruvic acid transaminase was 180 units. X-ray films of the chest on the admission day showed a slightly enlarged cardiac shadow and patchy pneumonic infiltration of both lung bases. The electrocardiogram showed auricular fibrillation. The hemoculture was negative but the urine culture grew Escherichia coli. Agglutinaton for leptospire was positive in 1:512 dilution for Group I organisms.

The patient was treated by antibiotics and other symptomatic measures without good result. She developed continuous fever between 38° – 39° C, tachycardia and oliguria. Five days after admission, the blood urea nitrogen was 91.6 mg. and the creatinine was 2.9 mg. per 100 ml. Sodium was 149 and potassium was 2.4 milliequiv. per liter. Serum osmolarity was 314 milliosmol. The total bilirubin was then 29.0 mg. per 100 ml. The agglutination test for leptospire went up to 1:1280 dilution. The alkaline phosphatase was 6.5 Bodansky units; glutamic oxaloacetic and glutamic pyruvic transaminases were 100 an 110 units respectively. Serum amylase was 259 units. On the 8th hospital day the patient became unconscious, had higher fever and was oliguric. X-ray films of the chest and abdomen showed pleural effusion on the left and much gas in the abdominal cavity suggestive of partial small bowel obstruction. Peritonitis from perforated peptic ulcer was suspected because of tenderness of the abdomen, fever and leucocytosis. Abdominal aspiration was done and purulent ascitic fluid was obtained. The patient immediately underwent surgical exploration. At operation, there was about 100 ml. of bile stained fluid in the abdominal cavity. No other definite abnormalities were found except for distention of the intestines. One day after the operation, the patient developed chills, hypotension and the oliguria became complete anuria. Hemodialysis was performed but no urine flow was obtained. The patient subsequently developed respiratory distress, and died 2 days after the operation.

Dr. Suksa Bhamornsathit: This elderly woman had acute episode of fever, nausea vomiting followed by jaundice and later on renal impairment—all within short period of time. The total course was less than 20 days. I assume that she was in good health prior to this illness, because there was no history beyond that. Judging from the clinical picture alone, acute

infectious diseases are the most likely cause of the malady. The problem is what would that infection be ? Those which come to my mind are:

1. Fulminating viral hepatitis : The clinical picture fits well. This patient had fever, intestinal disturbances prior to developement of jaundice. Roughly, I may say that this patient had about one week period of pre-icterus. The liver may not be palpable in viral hepatitis, as in this case. Infact, the liver is usually not palpable in severe fulminating hepatitis. However, leucocytosis with neutrophilia are uncommon in infectious hepatitis; the reverse is usually found. Flocculation tests in our patient may be compatible with those found in viral hepatitis, but the serum enzymes are very much against it. We very seldom see SGOT and SGPT below 500 units in fulminant hepatitis. Not only the serum enzymes were not much elevated in our patient, but also they became lower as the disease progressed worsly. This is unusual for viral hepatitis. Another important picture is fever. The fever was high and continuous when jaundice had already developed, which again is not a common feature of infectious hepatitis.

2. Falciparum malaria must be included in the differential diagnosis in this case. We all know that hepatitis and acute renal failure are not uncommon in malarial fever. However, parasites were not found in the blood film of this case. Besides, if the history is correct, this woman was a native of Bangkok and she had not made any trip to the infested areas neither.

3. Scrub typhus may give a similar picture to this patient's. The hallmark of this disease is an eschar formation which was not present in our patient. Also, scrub typhus has never been reported to occur in the Bangkok area. In addition, we are likely to see leucopenia in the blood of the patient infected by the organism.

4. Leptospirosis. This is the most likely infectious disease that this patient might have. All clinical pictures fit. A survey of animal reservoir in Bangkok showed 70.9 per cent of rats and 45.2 per cent of dogs are carriers of the organism. The disease is more common during the rainy season; the percentage of infection goes up to 14.3 percent, in August. [3,6,7] This was the month which our patient was admitted. Sunddaragiati et al [6] reported leucocytosis to occur in 52 per cent of the patients affected by the disease. Calf muscle pain was found in 76 per cent; conjunctival injection in 47 per cent; gastro-intestitinal symptoms were found ranging from 40–60 per cent. Jaundice was common and accounted for 37 per cent of the studied cases by Sundharagiati. [6] Acute renal failure is also common. Albuminuria was found in 43 per cent of cases; red cells and white cells were reported 70 and 46

per cent respectively. Casts were not present in our patient's sediment; it was noted to be common, about 70 per cent of cases by Sundharagiati.[6] Sitprija reported elevation of BUN to occur in 33 per cent of total cases studied somewhere ago at this hospital.[7] The liver function tests in our patient were likewise, compatible with leptospirosis. In this disease, the liver damage is usually mild, compare to clinical manifestation. The flocculation tests are usually high during the second week of infection.

The very helpful lab finding in this case was the agglutination for leptospires which was 1:512 on the day of admission, and then went up to 1:1280, five days later. The hemoculture was, however negative and animal inoculation was not done. The agglutination was positive for group I organisms, and it probably showed a rising titer but I would like to leave this for the microbiologist to discuss it.

Dr. Suvanit Udomsak: The titer of 1:512 on the day of admission and then rose to 1:1280 was not actually called a rising titer, because the rise is only one fold. In rising titer, it is four folds. From this reading, it indicates only that the patient might have acute infection or recent infection with sustained antibody. Technical variation may also give this high figure. In the grouping of the organisms, we divide them into four groups using different pools of leptospira antigens. Pool one contains Leptospira ballum, L. canicola, and L. icterohemorrhagiae. Pool two contains L. bataviae, L. grippotyphosa and L. pyrogenes. Pool three contains L. autumnalis, L. pomona and L. sejroe. Pool four contains L. australis, L. hyos and L. mini, georgia. In our laboratory as well as in others in Bangkok, the strain of leptospires usually found in the city is L. icterohemorragiae, which accounts for approximatey 90 per cent of cases.

Dr. Suksa : Thank you. I think this patient had leptospirosis But, what has disturbed me is the fact that the patient had acute abdominal pain with tenderness. This, together with leucocytosis, jaundice and slight elevation of serum amylase make one wonder about the possibility of acute pancreatitis. May I see the X-ray, please.

Dr. Viraln khaoparisut: The first X-ray films of the chest showed a slightly enlarged heart. The second X-ray examination was done 8 days after admission. The left lung shows infiltration at the base. There is fluid in the left pleural cavity, which was not present at the first roentgenogram. The fluid, therefore, accumulates rather rapidly. Since the liver is not enlarged, and no fluid is noted in the right pleural cavity, it is suggestive that left pleural effusion is caused by primary disease of the lung itself, rather than secondary from

diseases outside the chest. Films of the abdomen on the 8th hospital day reveals much gas in the jejunum, middle part of ileum and in the ascending colon. Although it was read as possibility of gut obstruction in the protocol, in my opinion, this picture is more commonly seen in acute peritonitis or peritoneal irritation than intestinal obstruction. Pancreatitis can not be excluded even though there is no pancreatic or biliary calcification seen.

Dr. Suksa: This is what really bothering me. Obviously, when the patient developed abdominal pain and tenderness, with aspiration of pus from the peritoneal cavity, the possibility of perforated peptic ulcer is very strong, especially in thsi patient who had a long history of epigastric pain relieved by antacids. The problem is that, they did not find peritonitis, or even pus in the abdominal cavity at operation. Is it possible, then, that leptospirosis produces septicemia which becomes localize in the pancreas and acute pancreatitis is the source of abdominal pain ? I would like to have GI man's opinion on this.

Dr. Sachapan Isarasena: I saw this patient when she was admitted. My diagnosis at first, was leptospirosis and the patient was transfered from GI unit to infectious ward. However, one day, I was called by a resident to see the patient because of right abdominal pain with guarding, and later on he aspirated pus from the peritoneal cavity. I, then reviewed my previous diagnosis; the patient might after all, have something else such as gallbladder or gastric diseases. I consulted the surgeon who suggested a laparotomy. To my knowledge, I have never come across a case of leptospirosis complicated with acute peritonitis before. As for acute pancreatitis, the value of serum amylase of 259 was not really high. Uremic patient may very well have this high level of amylase. However, I am aware of the fact that abdominal pain is not uncommonly associated with leptospirosis. In fact many surgeons had open up the abdomens of patients with leptospirosis, mistaken for acute abdomens, such as appendicitis.

Dr. Suksa: Then, what really did the surgeon find at the operation?

Dr. Muenmai Sarapradit: There was no pus or peritonitis found at the operation. About 50–100 ml. of bile stained fluid was present. We explored thoroughly, but nothing abnormal was visualized, except for dilated small intestines.

Dr. Visith Sitprija: Three points stand-out in this patient, and I would like to discuss them separately. The abdominal pain, the renal complication and the cause of death.

As Dr. Sachapan has just mentioned, the surgeons had operated on many patients because of misdiagnosis in cases of leptospirosis. I am aware that this might be the case in our patient. Abdominal pain is present as high as 40 per cent of patients with leptospirosis. The cause of the pain is not quite clear in all cases. Anterior abdominal muscular pain was thought to be responsible for some. As for acute pancreatitis, it did occur in leptospirosis, and there are a few cases reported in the literature, epecially mentioned by Edwards and Domm[4]. Their publication on human leptospirosis is one of the best manuscripts I have read. Uremia in general may produce pancreatitis and abdominal pain, but I don't think this patient had pancreatitis. Serum amylase was not really high, and the abdominal pain was localized in the anterior abdomen which is not common in pancreatitis. The pain is usually in the back in that disease. Whether the leptospire itself is capable to produce abdominal pain or not, I don't know. I am quite sure, however, that no case has been reported concerning acute peritonitis complicating leptospinosis; retroperitoneal or subserosal hemorrhage may, although, occur.

Azotemia is found in 60–70 per cent in leptospirosis.[4,5] Half of these cases, it is pre-renal in mechanism, and dehydration is the main cause of it. Another half have true renal failure. In my series[5] I have noted that, if serum creatinine is above 2 mg. per 100 ml., the patients usuaally have true renal failure, but if it is below 2 mg., the cause of uremia is likely to be pre-renal. The elevation of creatinine in true renal failure is due to failure of tubular sodium reabsorption and concentration. In this case, it is likely that the patient really have true renal failure from acute tubular necrosis. In leptospirosis, the two most common renal lesions are interstitial nephritis and acute tubular necrosis. In my series of renal biopsy study in leptospirosis, interstitial nephritis is constantly found in all cases while tubular necrosis may or may not be present[5]. The cause of renal lesion in leptospirosis is not known. Bacterial toxin and hemodynamic derangement are the two most common factors believed to be resposible. Actually leptospires do not have either endo-or exotoxin, but what they have referred to as toxin, is infact, a certain metabolic products of the organisms. Interstitial nephritis may be found in the kidney having normal hemodynamic function, as well as in kidney with normal sodium reabsorption and concentration. Therefore, renal failure in this patient was not probably due to interstitial nephritis. It is more likely caused by hemodynamic disturbances, resulte from toxic effect of the organisms. However, interstitial

nephritis is likely present in the kidneys of this patient.

The cause of death in leptospirosis in general, depends on virulence of the organism and the age of the patient. There is a good chance that this patient was infected by a highly virulent strain as judged by the severity of jaundice and multiple organ involvment. Since uremia was treated by dialysis, it is unlikely that the patient died of renal shut-down. Overwhelming infection by highly virulent strain of leptospira, the multiple organ involvement and the old age of the patient together are responsible for the cause of death in this woman.

Dr. Sunisa Charoonruangrit : Complications of leptospirosis which I have studied in patients in this hospital, seven years ago, were identical with Dr. Bundham Sundharagiati's[6] series as well as series from Israel.[3] Acute renal failure is the most common complication and accounts for 1.5 per cent of the total cases of leptospirosis. Toxin of leptospire is not really a true toxin as Dr. Visith said it is believed to be a lipolytic substance which behaves as a toxin-like factor. The presece of bile in the peritoneal cavity in this patient might suggest lipolytic mechanism. Overall mortality rate, in my series, was 7.4 per cent.

Dr. Sira sirisambandh : Hemorrhagic interstitial pneumonia may follow leptospira septicemia, and in this caes, respiratory symptoms and signs were present. Therefore, there is still a possibility of leptospira pneumonia in this patient which might be responsible for the mechanism of death at the end.

Dr. Suksa : Yes, lung complication is occasionally reported in systemic leptcspirosis. For an unknown reason, this complication is more commonly found in Chieng Mai than in Bangkok.

Dr. Suksa's Diagnosis :

– Leptospirosis with acute renal failure, acute hepatitis, ? acute pancreatitis and ? acute peritonitis.

– Pneumonitis.

Cause of death : Bronchopneumonia.

Dr. Somsak Dechkaisaya : At autopsy, edema of both lower extremities and deep jaundice were still evident. There was no free fluid in either pleural eavities or peritoneal cavity. The heart weighed 380 grams, and the wall of the left ventricle measured 20 mm. The papillary muscles were prominent, therefore this patient had left ventricular hypertrophy. There was no valvular, endocardial or pericardial lesion, thus the enlargement of the heart was probably due to hypertensive heart disease. The coronary arteries showed moderate arteriosclerosis,

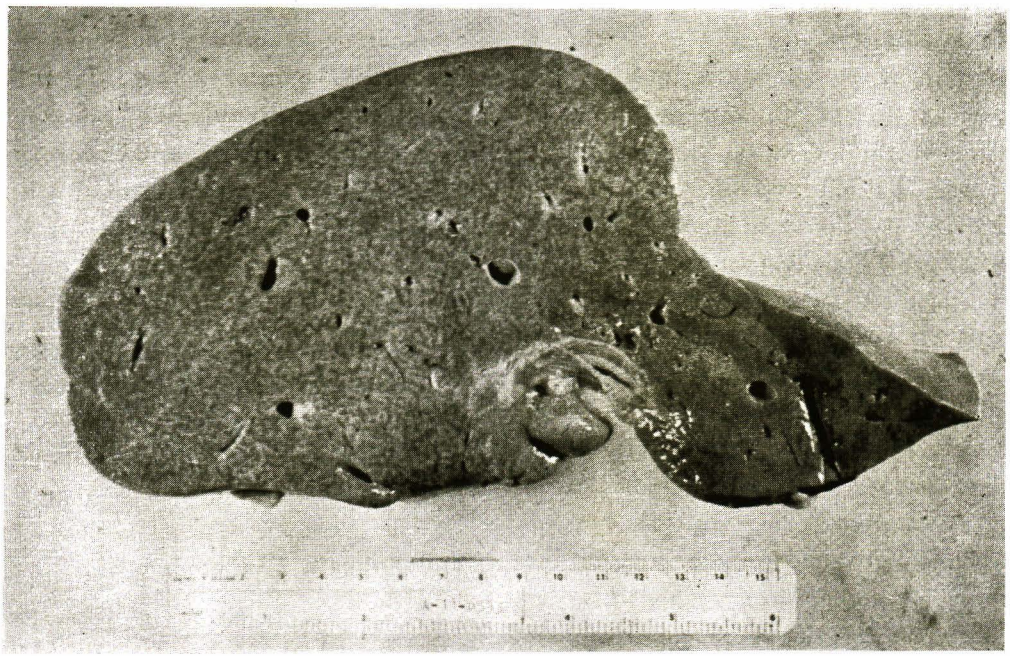

Fig. 1 : The cut surface of the liver showing nut-meg appearance.

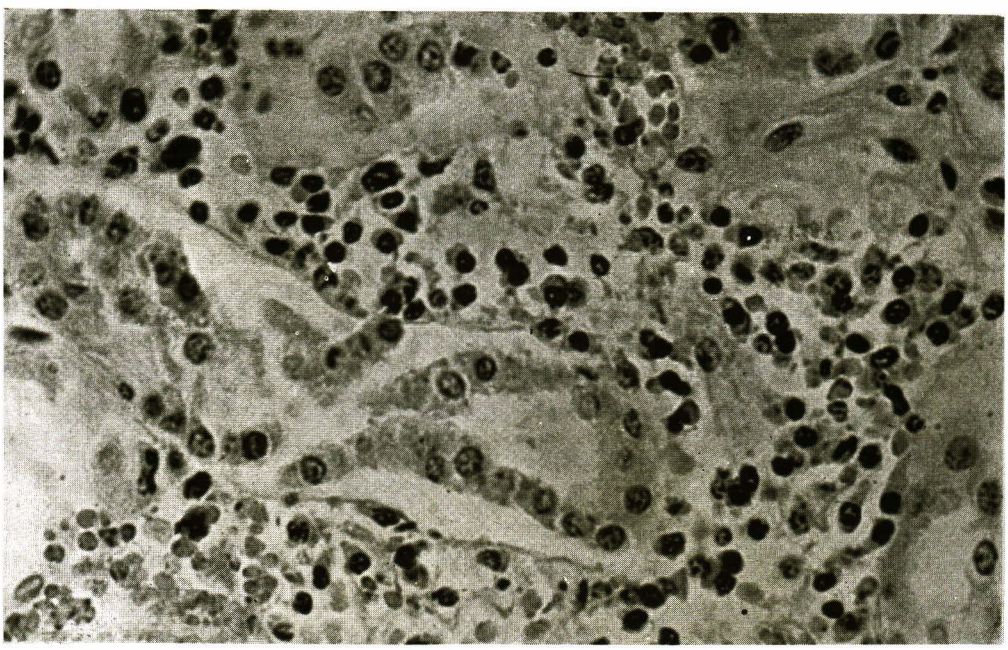

Fig. 2 : A section of the kidney showing leucocytic infiltration and tubular changes in leptospirosis. H & E x 400

and the myocardium, histologically, contained patchy fibrosis. The liver was markedly congested and appears "nut meg". This is a picture one usually sees in passive congestion from chronic heart disease. Microscopically, there was diffuse cholestasis with bile necrosis especially in the central zones. The liver cells, at times, appeared larger with hyperchromatic nuclei and prominent nucleoli. Mitotic figures were present. The Kupffer' cells were proliferative. The portal tracts contained some yellowish pigment. These features are not specific but are commonly found in association with leptospirosis. The skeletal muscle showed loss of striations, hyalinization, and frequently, sarcolemmal proliferation. and vacuolation. Some neutrophils were present. This muscular lesion is, likewise, not specific but very commonly found in leptospirosis.

The kidneys were enlarged and yellowish. The interstitium contained numerous mononuclear and a few polymorphonuclear cells. There was also evidence of tubular necrosis shown by the presene of casts in the tubules with cellular reactions. Bile casts were numerous. The cause of renal damage is most likely due to he modynamic derangement and tissue hypoxia rather than from the effects of the organisms per se.

There was a three-feet long hemorrhagic infarction of the terminal ileum. No arterial occlusionis demonstrated. The sections showed an extensive involvment of the entire coat of the intestine. It showed massive necrcsis, vascular engorgement and hemrrhage, and in the inner portion of the wall of the intestine, numerous bacterial colonies were found. The venules contained fresh thrombi without perivascular infiltrates. Therefore, throm bosis is probably the result of hypotension and vascular stasis. Subsequent ischemia produces infarction and hemorrhage. The mechanism of this type of small bowel lesion has been ascribed to acute heart failure or effect of digitalis.(1) In this case, hemosiderin was also present in the lesion indicating that the pathology has occurred for sometimes prior to death. The peritoneum contained fibrinopurulent exudate microscopically.

No fluid was found in the left pleural cavity as was seen in x-ray films of the chest. The lungs showed pneumonic process, the exudate of which was composed mainly of neutrophils with a small amount of red cells and fibrin. The cause of pneumonia is probably a secondary bacterial infection as judged by the appearance of reactions. However, becterial culture was not done.

FINAL ANATOMICAL DIAGNOSIS:

I. Hypertrohy and dilatation of the heart; Arteriosclerosis of the coronary arteries, moderate; diffuse;

Fig. 3 : A photograph of small intestine showing a long segment of hemorrhagic infarction.

Fig. 4 : Hemorrhagic infarction of small intestine in leptospirosis.

patchy myocardial fibaosis; Passive congestion of the liver; Pitting edema of lower extremities;

II. Interstitial nephritis; Cholestasis with bile necrosis of the liver; Acute focal myositis (gastrocnemius); Hemorragic necrosis of the ileum; acute diffuse fibrinopurulent peritonitis; Icterus, moderate; Bronchopneumonia; congestion and edema of lungs;

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