CASE REPORT

A Case of Severe Leptospirosis with Pancytopaenia

P C Bee, MD, S K Chow, MRCP, L H Tan, MMed

Department of Medicine, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur

Summary

Pancytopaenia is a rare clinical presentation of severe leptospirosis. We would like to report a case of severe leptospirosis that progressed to pancytopaenia despite initial penicillin therapy. The patient needed a second course of antibiotic with doxycycline to improve his persistent symptoms and cytopaenia. Persistent pancytopaenia in severe leptospirosis and its management were reviewed.

Key Words: Severe leptospirosis, Pancytopaenia

Introduction

Leptospirosis is a zoonosis characterized by a broad spectrum of clinical manifestations which include subclinical infection, self-limited anicteric febrile illness, and a severe and potentially fatal illness known as Weil`s syndrome that presents with jaundice, renal failure and haemorrhage[1]. The laboratory findings include renal and hepatic dysfunction, raised creatine phosphokinase level, thrombocytopaenia, normochromic normocytic anaemia, and leucocytosis (especially in Weil`s syndrome)[1]. The definitive diagnosis of leptospirosis is based either on isolation of the organism from clinical specimens or a fourfold or greater rise in antibody titre in the convalescence phase sera. The management of leptospirosis includes supportive measures and the use of penicillin or tetracycline to eradicate the organism[1]. The efficacy of antibiotics remains controversial although some studies showed that administration of intravenous penicillin or doxycycline at an early stage of the illness was beneficial.

Case Report

A 51 year-old previously healthy Malay man was admitted to the medical ward of the University of Malaya Medical Centre (UMMC) on the 7.2.02 with fever, generalised myalgia, lethargy and right hypochondrial pain for one-week. He was anuric for 4 days. On examination he was found to be febrile (38°c), dehydrated, jaundiced, tachycardic (pulse rate of 100/min) and a blood pressure of 110/70mmHg. He had generalised muscle tenderness. Abdominal examination revealed right hypochondrial tenderness but no organomegaly. Cardiovascular and respiratory systems were normal.

Blood investigations showed that he had acute renal failure, mild liver dysfunction with elevated conjugated bilirubin level, mild anaemia, thrombocytopaenia, and mild leucocytosis. His creatine phosphokinase was elevated and his initial leptospiral serological titre was significantly elevated (1:640) (Table I). Blood and urine cultures, blood film for malaria parasites, dengue serology, Widal-weil Felix, legionella, chlamydia as well as mycoplasma serology tests were all negative.

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Corresponding Author: P C bee, Department of Medicine, Faculty of medicine, University of Malaya, 50603 Kuala Lumpur

Ultrasonography of the abdomen showed normal kidneys, spleen and liver. A diagnosis of severe leptospirosis was made.

He was treated with aggressive fluid therapy and intravenous penicillin 2 mega units 6hourly. His symptoms and hepatic function improved 10 days later and his renal failure recovered without a need for dialysis (Table I). However his haemoglobin level and platelet counts remained low. He was discharged following clinical and biochemical improvement and was advised to return to repeat his full blood counts two weeks later. However, he only returned one month later with severe headache, nausea and vomiting. He complained that his fever had never settled since discharge. On examination, he was febrile (38°c), pale but not jaundiced. There was no neck stiffness and his abdomen, cardiovascular and respiratory systems were normal.

His full blood counts showed pancytopaenia with a normochromic normocytic anaemia. (Table I). His leptospiral titre was markedly elevated (1:10,240). Bone marrow aspiration and trephine examination showed a reactive marrow with slight hypocellularity but adequate erythropoiesis. His renal and liver functions were mildly impaired, similar to the level of impairment noted on discharge previously. Again, an extensive septic workup was done but was negative.

In view of the persistent clinical symptoms and pancytopaenia, he was given doxycycline 100mg bid for two weeks. His fever and headache settled 2 days after the initiation of therapy. His white cells and platelet counts started to rise one week after the treatment. On return for review 12 days later, his white cell and platelet counts were normal but he was still mildly anaemic (Table I). His renal and liver functions had returned to normal completely.

Table I: Laboratory results at the first admission, second admission and 2 weeks after oral doxycycline therapy

	First admission (08/02/02)	Second admission (09/03/02)	2 weeks after Doxycycline (21/08/02)
Haemaglobin (g/dl)	10.6	10.9	11.2
Total white cells count (10^9/l)	12.2	3.7	4.6
Platelet (10^9/l)	22	68	155
Sodium (mmol/l)	129	134	139
Potassium (mmol/l)	3.1	3.8	3.4
Creatinine (umol/l)	847	145	103
Urea (mmol/l)	56.9	5.2	4.6
Total protine (g/l)	49	68	76
Total bilirubin (umol/l)	76	11	13
Alkaline phosphatase (iu/l)	116	120	152
Alanine transaminase (iu/l)	132	71	73
Aspartate transaminase (iu/l)	113	69	44
Leptospiral titer	1:640	1:10240	

Discussion

Although there was no obvious predisposing factor noted from the history, we believe this patient had severe leptospirosis during the first admission in view of the compatible symptoms, renal failure, liver dysfunction, raised creatine phosphokinase level and a greater than 4 fold rise in leptospiral antibody titre in the convalescent sera after excluding other common infective causes. We would like to highlight two interesting points observed in this case. First, the persistent symptoms and pancytopenia despite being given penicillin therapy during the initial presentation. Secondly, the role of doxycycline in improving the clinical symptoms and laboratory parameters although it was given at a much later stage of the illness.

The persistent fever and pancytopaenia observed in this patient following penicillin therapy raised the issue of incomplete eradication of leptospira by the penicillin therapy or a possible immune mediated phenomenon not altered by the penicillin therapy. We failed to isolate any leptospira from the blood culture specimens because there was no specific medium for it in our centre. Therefore we were not able to ascertain the possibility of persistent leptospiremia. However, to the best of our knowledge there has not been any report of persistent leptopspiremia following penicillin therapy. The persistent fever and pancytopaenia observed were more likely to be an immune mediated phenomenon based on the well described natural progression of the disease. Interestingly if this is true, penicillin was not able to alter the progression of the immune mediated phenomena in our patient although it was of some benefit on the improvement of the liver and renal dysfunction.

Pancytopaenia is classically a rare laboratory finding in leptospirosis. A recent epidemiological study done by Bishara et al revealed that 28% of their patients with leptospirosis had pancytopaenia[2]. They did not specifiy the percentage of patients with severe leptospirosis in their study. Furthermore, the pancytopenia in their patients was noted on initial presentation as compared to our patient who had only anemia and thrombocytopenia as part of his initial presentation but progressed further to prolonged pancytopaenia from the leptospiral infection despite treatment. We believe the above findings are rather unusual.

Supportive management and the use of penicillin or tetracycline are the recommended therapy in leptospirosis[1]. However the role of penicillin and tetracycline remains controversial especially in severe leptospirosis. It is generally believed that penicillin is effective only if given early in the course (before the end of first week) of disease. Although there were reported cases on the benefit of penicillin even when it was instituted late, a study done in Brazil found that penicillin therapy for leptospirosis patients with acute renal failure had no demonstrable efficacy[3]. In our case, the hepatic and renal function improved after 10 days of penicillin therapy although it was given late. He later developed pancytopaenia with persistent clinical symptoms. At this stage, oral doxycycline was empirically given. One may argue that the improvement of the symptoms and blood count following doxycycline could be a coincidence and as part of the natural progression of the disease. But we believe oral doxycycline might play a role either due to its antimicrobial effect if there was persistent leptospiremia, or to its immunomodulatory effect in the immune phase of leptospirosis. The latter effect is well documented in some studies, based on the role of tetracycline in rheumatoid arthritis and reactive arthritis[4]. They exert their immunomodulatory effect by inhibiting expression of nitric oxide and their antioxidant effect on neutrophils. From the rapid and good response to doxycycline observed in our patient, we believe doxycycline might have a role to play in a patient with leptospirosis who presents late i.e. in the immune phase. However, further studies need to be done to evaluate this effect.

References

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