A re-emerging ancient disease: a case report

古老疾病的重現：個案報告

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There have been repeated outbreaks of leptospirosis reported all over the world. Being one of the largest cities in the world, Hong Kong is no exception. We report a local case involved in an outbreak of the disease with a typical route of acquisition but rare complications. A brief account on the epidemiology of both Hong Kong and Southern China is given. Discussions on the pathophysiology of the disease and its complications are also presented. (*Hong Kong j.emerg.med.* 2005;12:237-241)

鈎端螺旋體病在世界各地反覆地爆發，作為世界其中一個大城市，香港亦不能倖免。我們報告一宗在本地爆發的疾病個案，是由典型的途徑感染，但有罕見的併發症。我們並簡報香港及南中國的流行病學狀況，以及討論該疾病的病理生理學及其併發症。

Keywords: Acalculous cholecystitis, cardiomyopathy, leptospirosis, septic shock

關鍵詞：無結石膽囊炎、心肌病、鈎端螺旋體病、敗血性休克

Introduction

Leptospirosis has a long history. Icteric leptospirosis or Weil's syndrome was first reported more than 100 years ago. In 1915, the causative organism, spirochetes of the genus *Leptospira* was identified. It is a globally important zoonotic disease and has been reported all over the world. It has been reported in urban environments of industrialised and developing countries, as well as in rural regions worldwide.[1] In 1999, it was estimated that half a million cases of leptospirosis occurred in China.[2] It is a notifiable occupational disease in Hong Kong but the number of reported cases has remained low. There were only 11 reported cases in the past five years.[3] We report a recent local case of human leptospirosis with uncommon clinical features.

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Case summary

A 36-year-old male accountant with good past health attended our Accident and Emergency Department on 8th September 2004. He suffered from flu-like symptoms including low-grade fever, general malaise, bone pain and running nose for two days. He was seen previously by a private general practitioner and was managed as having flu. No antibiotic was given at that time. He noticed progressive dizziness, nausea and vomiting, epigastric pain, chills and rigor and attended our department on Day 3 after the onset of symptoms. There was no significant contact or travel history except that he participated in an outdoor activity (團隊挑戰 36) held in the New Territories on 29th August 2004 during which he sustained abrasions to his left lower leg and elbow. The event was a 70-km race including hiking, cycling and rafting sections starting from Ma

On Shan to Tai Lam Chung Reservoir, during which the participants were required to cross small rivers and streams. The examination showed a febrile patient (37.5°C) in shock: his blood pressure was only 65/40 mmHg with a pulse rate of 90/min. He was fully conscious with a Glasgow Coma Scale score of 15. Detailed physical examination revealed no definite focus of infection except mild and non-specific epigastric tenderness without any peritoneal sign and some healed superficial abrasions over his left lower leg. Chest X-ray did not show any pneumonic change. He was given fluid resuscitation and admitted to the medical ward.

After admission, initial blood results showed elevated white cell count (neutrophil predominant) and mildly elevated alanine transaminase. His renal function was largely unremarkable. Full sepsis workups including blood cultures, malaria screening, Monospot test, Widal test, anti-HIV and dengue IgM were performed but all of them were negative. In view of the epigastric tenderness, urgent CT abdomen was performed and showed diffuse gall-bladder wall thickening but no gallstone. Consulted surgeons opined that there was no definite sign of biliary obstruction nor infection and so surgical treatment was not indicated.

The clinical course of the patient was stormy. It was complicated by disseminated intravascular coagulopathy, with the lowest platelet count down to 40 x 10^9/L. He also suffered from profound heart failure. Echocardiography performed on the day of admission showed reduced ejection fraction of 35% with left ventricular apical stasis and suspected apical thrombus. He subsequently required to be managed in the intensive care unit where he received inotropic support, warfarinisation and broad-spectrum antibiotics. The patient recovered gradually and was able to be transferred back to the general medical ward on Day 7 and discharged on Day 12 after admission. A pre-discharge echocardiography showed normal ventricular function with no apical thrombus. It was not until two weeks after discharge when the IgM to *Leptospira interrogans* assayed by ELISA was found to be positive and so the final diagnosis of leptospirosis induced cardiogenic shock was made.

At around the same time, another young patient treated in Prince of Wales Hospital was also found to be suffering from leptospirosis. He attended the same event (團隊挑戰36) as our patient. Therefore it was suspected that there was an outbreak of the disease and the Centre for Health Protection of the Department of Health was notified.

Discussion

Leptospirosis is caused by the genus *Leptospira*. They are spirochetes with distinctive double-membrane architecture and can be classified by their phenotypes and genotypes. Experts in this field advocate the clinically significant phenotypic classification and there are more than 250 leptospiral serovars, of which more than 200 are pathogenic.[2] Some serovars can live freely in the environment without a dependent mammalian host.

The epidemiology of this disease reflects the ecologic relationship between humans and chronically infected mammalian reservoir hosts. It is maintained in nature by chronic infection of the renal tubules of the maintenance hosts, most of which are small mammals. Leptospires are excreted in their urine, thus contaminating the surrounding water and soil. In Hong Kong, rats, mice, dogs and bats are considered to be their major natural hosts. Typically, humans are infected through occupational or recreational exposure to contaminated water, soil or vegetation. Contact through mucous membranes including the conjunctiva, abrasions or cut wounds in the skin and inhalation of aerosols or contaminated water are possible routes of infection.

Our patient took part in a triathlon race on 29th August 2004, during which he sustained a left leg injury with superficial abrasions and therefore contracted the disease. This is one of the typical routes of leptospirosis infection. There are many reports of similar outbreaks of large number of cases associated with outdoor activities or events. In 1998, triathlons were held in Wisconsin and Illinois in the USA with participants of 692 and 961 respectively. Amongst the athletes that had participated in one or both of the

triathlons, 78 case-patients of leptospirosis infection were identified.[4] In 2000, an international event "EcoChallenge" took place in Malaysian Borneo during which 4-person teams competed in events such as jungle trekking, open-water swimming and spelunking. After this event, nearly half of the 300 participants were reported to have acute febrile illness and were later identified to have contracted leptospirosis.[5]

The occurrence of flooding or heavy rains just before or during outdoor events can highly increase the spread of the disease. This is believed to leach out leptospires that are deposited earlier on soil by urinating rodents.[6] This predisposing factor is exemplified by a local sporadic case reported in 2001.[7] A patient in the New Territories contracted leptospirosis through an abrasion in his shin area sustained when he cleaned up his flooded house caused by torrential rains. It is also to be noted that heavy rainfall was recorded on 28-29th August 2004 in the New Territories prior to and during our patient's triathlon race.[3] This certainly enhanced the risk of the disease to our patient significantly.

Concerning epidemiology, leptospirosis is considered to be the most widespread zoonotic disease in the world and Asia is no exception. In 2003, its prevalence in Anhui province (安徽省) of Mainland China was estimated to be from 0.44 to 1.89 per 10,000.[8] A recent study in Huaiyuen county (懷遠縣), one of the counties in Anhui province (安徽省), demonstrated the overall prevalence to be ranging from 4.37% to 6.71%. In rural areas, especially the rice-growing regions, the prevalence was more than 10%.[8] The prevalence is also higher in counties affected by regular floods during summer months. Moreover, studies had shown that the prevalence of leptospirosis in Anhui province (安徽省) and Hunan province (湖南省) were related to the high rat densities in these two provinces.[9,10] However, the exact number of cases in the whole of China is still unknown.

The number of local cases in Hong Kong over the years has been very low. It seems to be incompatible with the scene in Mainland China. From 2000 to 2004, there were 11 laboratory confirmed cases including the cluster of cases reported (four patients involved) related to this outbreak.[3] Possible reasons for the underreporting may include the lack of awareness of the local healthcare personnel about this disease. In fact, the vague initial presenting symptoms of leptospirosis may easily be mistaken as common upper respiratory viral infections as what had happened to our patient. Certainly, the increasingly indiscriminating use of antibiotics by the medical profession in our locality may prevent the disease to develop to its typical state with characteristic clinical features.

Concerning the pathophysiology of leptospirosis, toxins production and immune mechanism are thought to be the major mechanisms of tissue damage.[11] The leptospiral lipopolysaccharides, which also serve as the basis of serovar identification, function as endotoxins. Immune complex mediated inflammation response, autoantibodies formation including anti-platelet antibodies and apoptosis via induction of tumour necrosis factor have been described as possible damaging immune mechanisms.[12]

The incubation period of leptospirosis ranges from four days to four weeks, typically around five days to 14 days. The clinical manifestations are highly variable and can be divided into icteric and anicteric forms, with the latter form more common (icteric form up to 20%) and usually less severe. The clinical presentations of both icteric and anicteric leptospirosis are classically biphasic.[11] Following the incubation period, a leptospiraemic phase of about one week sets in. It is characterised by a sudden onset of febrile illness, myalgia, chills, flu-like symptoms, abdominal pain and gastrointestinal complaints. An immune phase in which most of the complications develop will follow the leptospiraemic phase. This is characterised by antibodies formation and excretion of the organism in the urine. The anicteric form of leptospirosis will now present with recurrence of fever and systemic upset. Aseptic meningitis may occur in this phase. For the icteric form, abrupt high fever with rapid liver failure, renal failure, pneumonitis, cardiac arrhythmia and circulatory collapse may occur. Isolated pulmonary involvement may occur occasionally (relatively common in China), resulting in pulmonary haemorrhage. Ocular involvements include conjunctival suffusion

during the acute phase and uveitis may become chronic. The classical Weil's syndrome comprising high fever, intense jaundice, haemorrhagic diathesis, hepatic and renal dysfunction, mental status changes and cardiovascular collapse is rare. However the overall mortality rate is estimated to be only around 5%. The differential diagnoses of leptospirosis include dengue fever, HIV seroconversion illness, brucellosis, typhoid fever and malaria.

Our case is interesting in that the patient had two rare complications. Firstly there was clinical (epigastric tenderness) and radiographic (CT scan revealed diffuse thickening of the gallbladder wall, Figure 1) evidence of acalculous cholecystitis. In 1998, two patients who took part in a triathlon in the United States underwent cholecystectomy because of a clinical diagnosis of acute abdomen. No histopathologic evidence of the classical cholecystitis was seen but immunohistochemical staining of the gall bladder was positive for leptospirosis.[13] Lucky enough, our patient did not have a cholecystectomy performed. The second rare complication that had occurred in our patient was the septic cardiomyopathy. He initially presented with profound cardiogenic shock. There was echocardiographic evidence of depressed left ventricular contraction and ventricular thrombus formation. The control of his leptospiral infection by antibiotic treatment and good supportive care gave rise to an astonishingly complete resolution of his cardiac dysfunction, documented by a normal pre-discharge echocardiography. In fact, it is commonly observed that in patients with prolonged sepsis for more than 24 hours, left ventricular ejection fraction is decreased with increases in end-diastolic and end-systolic volumes. The underlying mechanism is still unclear but may be related to the combinations of (1) inflammatory mediators such as tumour necrosis factor alpha (TNF-α), platelet activating factor, interleukin-1, interlukin-2; (2) myocardial oedema; (3) uncoupling of β-adrenergic receptor transduction; and (4) alterations of intracellular calcium regulations.[14,15] Our patient received warfarin for three months after discharge because of the apical thrombus.

In general, treatment of leptospirosis relies mainly on supportive care: aggressive fluid replacements, correction of electrolyte imbalance, treatment of systemic organ failures including the renal, hepatic and respiratory systems. The concerned pathogens can usually be treated by appropriate antibiotics. Choices of antibiotics include penicillin and tetracycline. Penicillin G 100,000 U/kg/day in 3 to 4 divided doses or tetracycline 25-40 mg/kg/day given every 6 hours are the most effective regimes.[16] Some experts suggested that the once-daily administration and extended spectrum of ceftriaxone may provide additional benefits over penicillin.[17] Doxycycline 200 mg per week is advocated by some authorities as chemical prophylaxis against leptospirosis for those involved in high risk activities.[2,16]

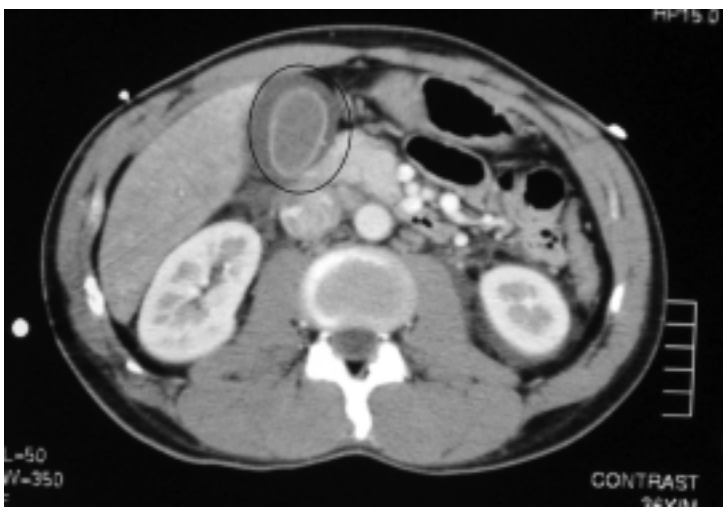

Figure 1. CT showing acalculous cholecystitis of the patient – note the oedematous, dilated, thickened-walled gall-bladder (black circle).

Conclusion

Leptospirosis, being one of the most widespread global diseases, has a remarkably low incidence in Hong Kong. Although it is supposed to be an occupational disease, many contract this disease without occupational exposure. Outbreaks are preventable if information can be given to participants of large-scale activities beforehand and chemoprophylaxis is considered. Frontline healthcare workers such as emergency physicians have to understand its route of transmission, the non-specific

presenting features and to maintain a high index of suspicion in order to arrive at the correct diagnosis early. A history of outdoor activities particularly those involving water is invaluable. With the increasing popularity of outdoor sports and activities, particularly those involving water, we should be prepared to encounter more cases of leptospirosis in Hong Kong.

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