CASE REPORT

Q fever: underdiagnosed in Hong Kong?

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We report the first imported case of chronic Q fever with multi-organ involvement seen in Hong Kong. Although the disease is found worldwide, its chronic form is very rare in our locality. Familiarity with the clinical presentation, useful diagnostic tools, and appropriate treatment is necessary for the prevention of the serious morbidity and mortality associated with chronic Q fever. To the best of our knowledge, this article represents the first comprehensive review to compare the local experience with Q fever with international data, and establishes a management approach for this unusual infectious disease while suggesting possible explanations for its exceptionally low incidence in this locality.

Introduction

Q fever is an important zoonotic disease caused by the Gram-negative coccobacillus *Coxiella burnetii*. While it is distributed worldwide and is most common in parts of Australia, North America and Europe, it has seldom been reported in Hong Kong.[1,2] Only eight serologically confirmed cases of Q fever have been reported since June 2004, when the Centre for Health Protection (CHP) was established (oral communication, A Wong, 2008).

Case report

On 11 June 2008, a 52-year-old Chinese resident of Macau, with a history of good past health, presented to a regional Macau hospital with a 2-week history of fever. He worked as an electrical technician and had cleaned up bird excreta while repairing outdoor electrical wires 4 to 6 months earlier. He was married with two children, did not smoke or drink, and did not consume uncooked meat or animal products such as ovine placentas. On physical examination, he was noticed to have a swinging fever, gross hepatomegaly, and bilateral iridocyclitis. Serial blood tests showed a progressive normochromic normocytic anaemia (haemoglobin 91 g/L), leukocytosis with predominant neutrophilia (white cell count 22.0 x 10^9/dL, neutrophil 64%), abnormal liver function with a mixed cholangiohepatitic pattern (aspartate transaminase 205 U/L, alanine transaminase 204 U/L, alkaline phosphatase 683 U/L, gamma-glutamyl transpeptidase 323 U/L, total bilirubin 87 μmol/L, direct bilirubin 48 μmol/L), and an isolated prolonged activated partial thromboplastin time (53.6 seconds) with a positive lupus anticoagulant.

The fever persisted despite antibiotic treatment consisting of an intravenous amoxicillin/clavulanate combination 1.2 g every 8 hours for 5 days, followed by intravenous ceftazidime 2 g every 8 hours for another week. Extensive investigations were performed to seek the underlying cause of his fever. Autoimmune markers, including antinuclear antibody, antineutrophil cytoplasmic antibody and rheumatoid factor levels, were unremarkable. Tumour marker levels, namely carcinoembryonic antigen, alpha-fetoprotein and prostate-specific antigen, were all normal. Bacterial and fungal cultures of his blood, urine, stools, and cerebrospinal fluid grew nothing. Tests for other infective aetiologies including the human immunodeficiency virus; Epstein-Barr virus; cytomegalovirus; hepatitis A, B, C and E viruses; the Widal test; Weil-Felix test; Brucelloside test; Mantoux test; and the Venereal Disease Research Laboratory test were all unremarkable. A transthoracic echocardiogram showed normal valves with no vegetation. A bone marrow aspirate and trephine biopsy revealed a hypercellular marrow and reactive changes. A positron emission tomographic/computed tomographic scan showed diffuse liver uptake with hepatomegaly, suggestive of hepatitis.

His condition did not improve despite extensive investigations and the prolonged course of antibiotics, so the patient was transferred to Hong Kong for further management on 28 July 2008. Significant findings during this period included multiple fibrin-ring 'doughnut' granulomas seen on a specimen from a transjugular liver biopsy (Fig) and ruptured chordae tendineae with possible vegetation on the anterior leaflet of his mitral valve seen on a transthoracic echocardiogram. Serum antibodies to *C burnetii* were detected by immunofluorescent assay (IFA) with phase 1 titres being 800 and 1600 in paired serum samples taken 14 days apart, and phase 2 titres being over 3200 on both occasions. The final diagnosis was chronic Q fever with multi-organ involvement including granulomatous

Key words
Animals; *Coxiella burnetii*; Q fever; Tick-borne diseases; Zoonoses

Hong Kong Med J 2010;16:56-8

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hepatitis, mitral valve endocarditis and iridocyclitis.

He was treated with oral doxycycline 100 mg twice per day and hydroxychloroquine 200 mg thrice per day. A clinical response was apparent over the ensuing week with his fever, iridocyclitis, liver malfunction and coagulopathy all subsiding. He was followed up regularly at the out-patient clinic, with periodic cardiac and ophthalmological assessments. His therapy will last for at least 18 months depending on his serological response.

Discussion

Q fever occurs worldwide with the notable exception of New Zealand.[3,4] In Hong Kong, the disease has seldom been reported. Only eight serologically confirmed cases have been confirmed since the establishment of the CHP in June 2004 (Table[1,2]). Of these, only one other case, reported in 2007, presented in the chronic form as culture-negative endocarditis complicated by septic embolism causing an acute ischaemic stroke.[2] While Q fever is a well-known cause of culture-negative endocarditis, the case we report here is unique in that multi-organ involvement including systemic (fever), cardiovascular (endocarditis), hepatic (granulomatous hepatitis), ophthalmological (iridocyclitis), and autoimmune (lupus anticoagulant) phenomena has never been reported in our locality before.

Besides illustrating the protean nature of chronic Q fever, the case reported here is also distinctive in that it is the first imported case of Q fever from Macau, reflecting the importance of Hong Kong as a tertiary referral centre in the region. Analysis of the eight cases reported since 2004 yields some other interesting points. All the patients were males aged 41 to 76 with a median age of 60 years. They all presented with fever and abnormal liver function. While the man in the case reported here had a history of exposure to bird excreta during work, most patients (75%) did not have any definite history of exposure to animals. These characteristics are similar to those seen in other countries where there is also a male preponderance (2.5-5 times), a similar age-group (53±20 years), a high incidence of fever (60-80%), and abnormal liver function (40-80%) consisting of raised transaminases and hepatomegaly, with or without 'doughnut' granulomas seen on liver

香港的Q型熱是否診斷不足？

本文報告香港首宗涉及多種器官的慢性Q型熱的輸入病例。雖然Q型熱廣泛分佈於世界各地，但其慢性病例於香港則較為罕見。要防止Q型熱所引致的罹病與死亡，醫生必須要熟悉此病的臨床徵狀、有效的診斷工具，以及適當的治療。據我們所知，本文是首個對Q型熱作全面的綜述，包括把本地經驗與外國數據作比較、對此罕有的傳染病提出處理的方案，以及對本地極低的發病率作出闡釋。

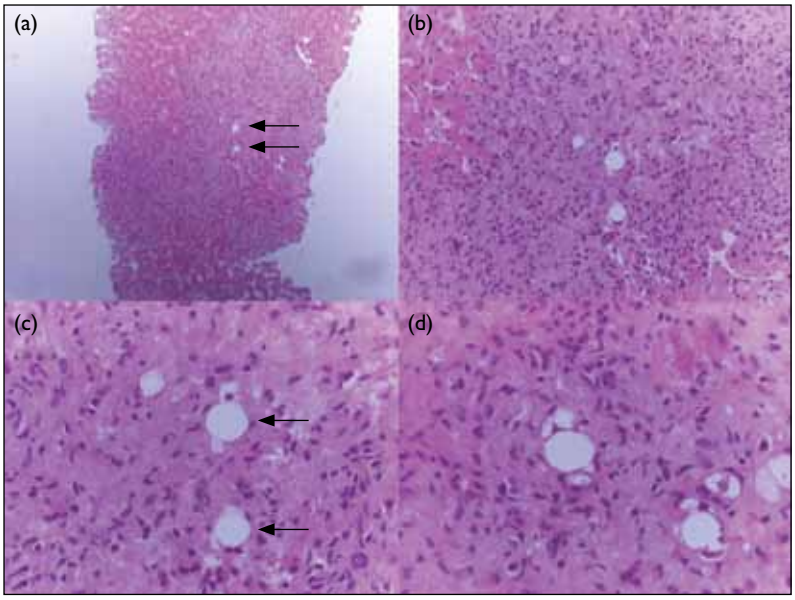

FIG. Liver biopsy of the present case showing multiple fibrin ring 'doughnut' granulomata (arrows) in Haematoxylin and Eosin stains under light microscopy
(a) ×10; (b) ×40; (c) and (d) ×100

TABLE. Cases of Q fever reported in Hong Kong from June 2004 to December 2004[1,2*]

	Case No.							Present Case
	1	2	3	4	5	6	7	
Sex	Male	Male	Male	Male	Male	Male	Male	Male
Age (years)	49	76	65	60	41	60	41	52
Date of symptom onset (month/year)	08/2004	12/2004	06/2005	09/2005	05/2006	07/2006	01/2007	06/2008
Occupational exposure	No	No	No	Yes	No	No	No	Yes
Fever	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Liver dysfunction	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Pulmonary involvement	Yes	No	No	No	No	Yes	No	No
Cardiac involvement	No	No	No	No	No	No	Yes	Yes
Disease form	Acute	Acute	Acute	Acute	Acute	Acute	Chronic	Chronic

* Cases 1-6, all representing acute Q fever, have been adopted from the data provided by the Centre for Health Protection for comparison with the chronic form found in case 7 and the present case

biopsy specimens, and lack of an epidemiological link in a significant number of patients.[3,5-9]

While the clinical features are similar to those reported in other parts of the world, the incidence is exceptionally low in Hong Kong. There are a number of possible explanations for this phenomenon. The first is geographic: Hong Kong is a metropolitan city with few farm animals, and research has shown that livestock handlers, such as veterinarians, farmers and slaughterhouse workers, have the highest seroprevalence of antibodies to *C burnetti*.[3] However, this is unlikely to be the sole reason for the low prevalence of Q fever in Hong Kong as many other species such as cats, dogs, rodents, birds, fish, reptiles, amphibians, and ticks have been implicated as reservoirs as well.[10]

Q fever is also often underdiagnosed because of its clinical presentation. Most patients with acute Q fever present with a self-limiting acute febrile illness and are misdiagnosed as having influenza. Only 3 to 5% of affected individuals progress to the chronic form. On the other hand, when Q fever presents as a case of pyrexia of unknown origin, the diagnosis can also be missed if an antibiotic like doxycycline is used as empirical coverage for atypical bacterial infections. In reality, it is unlikely that local clinicians would routinely check Q fever serology in the acute phase, unlike those in countries where it is endemic, such as Australia. Furthermore, the likelihood that the patient would return for a second blood test is questionable, especially in those who have improved either spontaneously or after a short course of antibiotics. Thus, the clinician must adopt a high index of clinical suspicion in order to diagnose Q fever and administer the treatment for an adequate period to prevent complications and recurrence.

Besides the geographical and clinical aspects, there are diagnostic laboratory issues that may account for the apparently low incidence of Q fever in Hong Kong. Firstly, testing is not readily available in most public and private hospitals. Most tests are performed at the Public Health Laboratory Centre (PHLC). The present confirmatory laboratory test, which uses IFA to detect phase 1 and 2 antibodies, has only been used by the PHLC since 2004 (oral communication, A Wong, 2008). Immunofluorescent assay is usually performed after detecting a positive titre or a 4-fold rise using a complement fixation test (CFT) on paired sera taken at least 14 days apart. Before IFA became available, CFT was the only means of testing suspected cases. This approach has generally been considered inferior to IFA.[11] Hence, there are no clear data on the incidence of Q fever before 2004. Furthermore, as in other countries, the patient's failure to return for a second blood test may also contribute to underestimation of the true incidence, especially when the first titre level yields an intermediate result.[3]

Finally, the reporting system is also responsible for the underestimated incidence of Q fever in our locality. Q fever has only recently become a statutory notifiable disease in Hong Kong, since the new Prevention and Control of Disease Ordinance (Cap. 599) became effective on 14 July 2008. Before this time, the reporting system was effectively voluntary. Thus the epidemiological data available at present are hardly representative of the true scenario.

In conclusion, the case reported here illustrates the classical presentation of chronic Q fever with multi-organ involvement, an exceptionally rare clinical entity in Hong Kong. This is also the first comprehensive review of Q fever in our locality, highlighting the clinical similarities between the local and international experiences, and providing insight into the possible reasons for the seemingly low incidence in Hong Kong. We believe that the incidence of Q fever, both in its acute and chronic forms, has been underestimated in the past for a number of reasons including geographical uniqueness, clinical bias, diagnostic difficulty, and suboptimal surveillance. While the clinician must maintain a high index of suspicion and be vigilant in following up suspected patients, the recently adopted laboratory diagnostic tools and improved reporting system will certainly enhance our ability to establish the true incidence. As our knowledge of the disease improves, a prompt diagnosis can be made which will in turn prevent serious morbidity and mortality in our patients.

References

1. Shu BY. A review of Q fever infection in Hong Kong. Communicable Diseases Watch 2008;5:70-1.
2. Ng YY. A gentleman presented with fever and stroke. Bulletin of the Hong Kong Society for Infectious Diseases 2008;12:7-12.
3. Maurin M, Raoult D. Q fever. Clin Microbiol Rev 1999;12:518-53.
4. Hilbink F, Penrose M, Kovacova E, Kazar J. Q Fever is absent from New Zealand. Int J Epidemiol 1993;22:945-9.
5. Lai CH, Huang CK, Chin C, et al. Acute Q fever: an emerging and endemic disease in southern Taiwan. Scand J Infect Dis 2008;40:105-10.
6. Raoult D, Tissot-Dupont H, Foucault C, et al. Q fever 1985-1998. Clinical and epidemiologic features of 1,383 infections. Medicine (Baltimore) 2000;79:109-23.
7. Marrie TJ, Raoult D. Q fever—a review and issues for the next century. Int J Antimicrob Agents 1997;8:145-61.
8. Garner MG, Longbottom HM, Cannon RM, Plant AJ. A review of Q fever in Australia 1991-1994. Aust N Z J Public Health 1997;21:722-30.
9. Tissot-Dupont H, Torres S, Nezri M, Raoult D. Hyperendemic focus of Q fever related to sheep and wind. Am J Epidemiol 1999;150:67-74.
10. Parker NR, Barralet JH, Bell AM. Q fever. Lancet 2006;367:679-88.
11. Cutler SJ, Bouzid M, Cutler RR. Q fever. J Infect 2007;54:313-8.