Original Article

Typhoid and Scrub Typhus Coinfection in a Returned Traveler

Global Pediatric Health
Volume 4: 1–4
© The Author(s) 2017
Reprints and permissions:
sagepub.com/journalsPermissions.nav
DOI: 10.1177/2333794X17726941
journals.sagepub.com/home/gph
SAGE

Christopher Wen-Xing Seow, MBBS[1], Veena Logarajah, MB ChB, MRCPCH[1,2], and Natalie Woon Hui Tan, MBBS, MRCPCH[1,2,3,4]

Abstract

This is a case report of a 12-year-old returned traveler with typhoid and scrub typhus coinfection. The diagnosis of typhoid was made early with blood cultures and Widal Weil Felix serology. Persistent fever despite appropriate antibiotics for typhoid fever prompted a search for concomitant infection, which led to the diagnosis of scrub typhus confirmed by *Orientia tsutsugamushi* serology. The patient was given doxycycline with good clinical response. Scrub typhus infection should be an early consideration in the differential diagnoses of fever in a returned traveler from regions where it is endemic. Coinfections should be taken into consideration particularly when fever or symptoms persist despite adequate therapy for a previously identified microorganism.

Keywords

coinfections, typhoid, scrub typhus, *Orientia tsutsugamushi*, infectious diseases, general pediatrics

Received June 23, 2017. Accepted for publication July 14, 2017.

Case Report

A 12-year-old Indian boy was admitted to our institution with a prolonged fever of 1 month duration, with maximum temperatures above 40°C. This was associated with watery, nonbloody diarrhea, with intermittent vomiting and abdominal pain. There was a travel history to India for 1 month, and the patient had returned to Singapore 1 week prior to the admission. The patient had visited several rural areas in Kerala and Bangalore during his travel. There was no history of raw food intake or animal contact. His vaccinations were up-to-date according to the national immunization schedule, but he had not received the typhoid vaccine prior to travel. At this time, his 21-year-old older sister was also admitted to another hospital with fever and diarrhea. There was no prior treatment with antibiotics. No significant past illnesses were reported.

On admission, the child was alert and oriented and no pallor or jaundice was noted. Mucosal membranes appeared dry but perfusion was good with a capillary-refill time of less than 2 seconds. His temperature was 38.2°C, with a pulse rate of 150 bpm and a blood pressure of 90/48 mm Hg. On examination, his heart sounds were dual and breath sounds were vesicular, with no added sounds. His abdomen was soft, with mild tenderness over the right hypochondrium, and there was no guarding or rigidity. He had no hepatomegaly or splenomegaly. There was no rash or eschar noted. The rest of the systemic examination was unremarkable. Heart rate and blood pressure responded well to a fluid bolus given in the emergency department and subsequently remained stable. He was started empirically on intravenous ceftriaxone 100 mg/kg/day for presumptive enteric fever.

The aerobic and anaerobic blood cultures grew *Salmonella typhi*, which were sensitive to ampicillin, co-trimoxazole and ceftriaxone. Widal Weil Felix (WWF) serology showed titers of 1/160 for *S typhi* O-AB, 1/640 for *S typhi* H-AB, 1/80 for *Salmonella*

[1]KK Women's and Children's Hospital, Singapore, Singapore
[2]Yong Loo Lin School of Medicine, National University of Singapore, Singapore
[3]Duke-National University of Singapore Medical School, Singapore
[4]Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore

Corresponding Author:
Christopher Wen-Xing Seow, KK Women's and Children's Hospital, 100 Bukit Timah Road, Singapore 229899, Singapore.
Email: christopher.seow@mohh.com.sg

Table 1. Timeline of Hematological and Biochemical Investigations Done for the Patient.

	Day of Admission				
	Day 1	Day 4	Day 9	Day 12	Day 16
Hemoglobin (g/dL)	8.7	9.7	8.2	9.4	8.5
White blood cell count ($\times 10^9$/L)	3.47	5.71	8.46	5.81	6.84
Platelet count ($\times 10^9$/L)	90	163	487	422	408
C-reactive protein (mg/L)	92.3		13.2	11.8	12.2
Albumin (g/L)	21	23	25	27	30
Alanine transaminase (U/L)	82	210	119	177	71
Aspartate transaminase (U/L)	165	368	119	92	36

paratyphi A O-AB, 1/320 for *S paratyphi* A H-AB, and 1/80 for *S paratyphi* B O-AB. *Proteus* OXK AB and *Proteus* OX19 AB were not detected. The full blood count showed pancytopenia, with a hemoglobin level of 8.7 g/dL, white blood cell count of 3.47×10^9/L and a platelet count of 90×10^9/L. Liver function tests revealed elevated transaminases with an alanine transaminase level of 188 U/L and an aspartate transaminase level of 186 U/L. An ultrasound of the abdomen showed cecal and terminal ileal bowel wall thickening with enlargement of mesenteric lymph nodes.

The patient continued to be persistently febrile despite 9 days of intravenous ceftriaxone. Repeat blood cultures were negative for bacterial growth. Oral co-trimoxazole 4 mg/kg BD was added to provide added cover for typhoid fever. Table 1 shows the timeline of his hematological and biochemical investigations. Microbiological investigations performed are summarized in Table 2.

On day 16 of ceftriaxone and oral co-trimoxazole, the patient remained persistently febrile. Diarrhea was also persistent although noted to be on an improving trend. At this point, a further infective workup was done, which included blood film for malaria parasite, *Rickettsia typhi* serology and *Orientia tsutsugamushi* serology. Two days later, *Orientia tsutsugamushi* serology results returned positive at IgG ≥64. The patient was started on oral doxycycline 100 mg twice daily. Ceftriaxone and co-trimoxazole were stopped. Fever resolved on day 2 of doxycycline, and the patient was discharged after being afebrile for more than 24 hours, to complete a 7-day course of doxycycline. Subsequent follow-up revealed a well child with complete resolution of fever and symptoms.

Discussion

Typhoid fever is a multisystemic infection caused by bloodstream invasion with the bacteria *Salmonella enterica* serotype *typhi*.[1] It has been well-described in literature and is a well-considered diagnosis of pyrexia in a returned traveler, being endemic in areas with low socioeconomic indices where sanitary conditions are suboptimal.[2] In a recent study of enteric fever (typhoid and paratyphoid fever) in Singapore by Ahmad Hatib et al, 94% of pediatric enteric fever cases were found to be imported, mainly from India and Indonesia.[3] This was comparable to a previous epidemiological study in Singapore by Ty et al reporting the incidence of indigenous enteric fever as 1.26 per 100 000 in 2009, with 90% of cases being imported.[4] As such, blood cultures as well as WWF serologies are common investigations being sent in the initial workup for patients presenting with fever and a positive travel history in our institution, particularly with the presence of concomitant constitutional and abdominal symptoms.[3]

Scrub typhus is a mite-borne infection caused by *Orientia tsutsugamushi*, a gram-negative coccobacillus.[5] The vector of *O tsutsugamushi* are larval trombiculid mites of the genus *Leptotrombidium* (chigger), with infection commonly presenting as an acute febrile illness 7 to 10 days after the bite of a chigger.[5] Clinical manifestations include rash, respiratory illness, gastrointestinal symptoms, and, often, an undifferentiated pyrexia.[6] In contrast to typhoid fever, the diagnosis of scrub typhus is often unconfirmed and overlooked. In our patient, pancytopenia and persistent fever despite appropriate antibiotics for typhoid fever prompted the search for concomitant infection with typhus. There is comparatively less surveillance data on scrub typhus, although recent evidence estimates an incidence of up to 1 million cases per year in Southeastern Asia.[7,8] The disease is known to be endemic in Korea, China, Japan, India, Thailand, Malaysia, and the tropical regions of Australia.[9] Imported cases to regions where it is not endemic have been well reported in case reports of returned travelers to the United States, Canada, and Europe from endemic regions.[10-13]

A coinfection of scrub typhus with other diseases, such as typhoid fever, may be further overlooked and

Table 2. Timeline of Microbiological Investigations Done for the Patient.

	Day of Admission		
	Day 1	Day 9	Day 16
Blood culture, aerobic	*Salmonella typhi* isolated	No bacterial growth	
Blood culture, anaerobic	*Salmonella typhi* isolated	No bacterial growth	
Dengue serology	Negative		
Widal Weil Felix serology	*Salmonella typhi* O-AB (1/60)		
	Salmonella typhi H-AB (≥1/640)		
	Salmonella paratyphi A O-AB (1/80)		
	Salmonella paratyphi A H-AB (1/320)		
	Salmonella paratyphi B O-AB (1/80)		
	Salmonella paratyphi B H-AB (not detected)		
	Proteus OXK AB (not detected)		
	Proteus OX19 AB (not detected)		
Stool culture	No bacterial growth		
Stool rotavirus antigen	Negative		
Mycoplasma pneumonia PCR (respiratory throat swab)		Not detected	
Respiratory virus antigen by immunofluorescence (nasopharyngeal aspirate)		Not detected for all	
Malaria parasite, blood film			Negative (×3)
Rickettsia serology			Negative
Orientia tsutsugamushi serology			IgG ≥ 64

Abbreviations: PCR, polymerase chain reaction; IgG, immunoglobulin G.

masked in view of overlapping clinical features. Coinfections of typhoid and typhus have been reported with 2 case reports from Bangladesh, in 2008 and 2013.[14,15] In the latter case, coinfection was only suspected in view of persistent febrile illness despite adequate treatment for typhoid, bearing similar traits to the case progression of our reported patient. Fever only subsided with the commencement of doxycycline. In the 2 case reports, coinfections of typhoid and typhus were based on WWF results, while in our patient, it was confirmed on positive blood culture and *O tsutsugamushi* serology. A recent case report from Nepal described coinfection of dengue and scrub typhus.[16] For this case, diagnosis of dengue was made early, with investigation for scrub typhus only considered in view of persistent symptoms. Enzyme-linked immunosorbent assay for scrub typhus returned positive, and by that time the patient had already been empirically commenced on doxycycline with a high clinical suspicion for scrub typhus infection in a known endemic area.

The early consideration of scrub typhus coinfection is of clinical significance as it is detectable and treatable. The indirect fluorescent antibody test for serologic diagnosis of *O tsutsugamushi* is becoming more readily available in most state health laboratories. Once detected, chloramphenicol and doxycycline have both shown to be effective in treatment.[17] A systematic review of mortality from untreated scrub typhus by Taylor et al suggested that, while mortality is lower than commonly reported estimates, morbidity is significant, particularly due to prolonged duration of fever.[8] Other complications of untreated disease include myocarditis, respiratory distress syndrome, and central nervous system disease.[8] While these complications are rare, they result in significantly higher mortality,[8] further reinforcing the importance of prompt diagnosis and treatment.

Conclusion

Scrub typhus infection should be a consideration in the differential diagnoses of fever in a returned traveler from regions where it is endemic. Coinfections are possible, with infections such as typhoid, and should be considered early, particularly when fever or symptoms persist despite adequate therapy for a previously identified microorganism.

Author Contributions

CWXS: Contributed to design; contributed to analysis and interpretation; drafted manuscript; gave final approval;

agrees to be accountable for all aspects of work ensuring integrity and accuracy.
VL: Contributed to analysis and interpretation; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.
NWHT: Contributed to conception and design; contributed to analysis and interpretation; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

References

1. Parry CM, Hien TT, Dougan G, White NJ, Farrar JJ. Typhoid fever. *N Engl J Med*. 2002;347:1770-1782.
2. Crump JA, Luby SP, Mintz ED. The global burden of typhoid fever. *Bull World Health Organ*. 2004;82: 346-353.
3. Ahmad Hatib NA, Chong CY, Thoon KC, Tee NW, Krishnamoorthy SS, Tan NW. Enteric fever in a tertiary paediatric hospital: a retrospective six-year review. *Ann Acad Med Singapore*. 2016;45:297-302.
4. Ty AU, Ang GY, Ang LW, James L, Goh KT. Changing epidemiology of enteric fevers in Singapore. *Ann Acad Med Singapore*. 2010;39:889-896.
5. Watt G, Parola P. Scrub typhus and tropical rickettsioses. *Curr Opin Infect Dis*. 2003;16:429-436.
6. Sonthayanon P, Chierakul W, Wuthiekanun V, et al. Rapid diagnosis of scrub typhus in rural Thailand using polymerase chain reaction. *Am J Trop Med Hyg*. 2006;75: 1099-1102.
7. Paris DH, Shelite TR, Day NP, Walker DH. Unresolved problems related to scrub typhus: a seriously neglected life-threatening disease. *Am J Trop Med Hyg*. 2013;89: 301-307.
8. Taylor AJ, Paris DH, Newton PN. A systematic review of mortality from untreated scrub typhus (*Orientia tsutsugamushi*). *PLoS Negl Trop Dis*. 2015;9(8):e0003971.
9. Currie B, O'Connor L, Dwyer B. A new focus of scrub typhus in tropical Australia. *Am J Trop Med Hyg*. 1993;49:425-429.
10. Watt G, Strickman D. Life-threatening scrub typhus in a traveler returning from Thailand. *Clin Infect Dis*. 1994;18:624-626.
11. Dupon M, Rogues AM, Malou M, d'Ivernois C, Lacut JY. Scrub typhus: an imported rickettsial disease. *Infection*. 1992;20:153-154.
12. Marschang A, Nothdurft HD, Kumlien S, von Sonnenburg F. Imported rickettsioses in German travelers. *Infection*. 1995;23:94-97.
13. McDonald JC, MacLean JD, McDade JE. Imported rickettsial disease: clinical and epidemiologic features. *Am J Med*. 1988;85:799-805.
14. Mazumder RN, Pietroni MA, Mosabbir N, Salam MA. Typhus fever: an overlooked diagnosis. *J Health Popul Nutr*. 2009;27:419-421.
15. Basak R, Islam N. Typhus fever: an uncommon childhood infection—report of a case from northern region of Bangladesh. *Chattagram Maa-O-Shishu Hosp Med Coll J*. 2013;12(2):49-51.
16. Sapkota S, Bhandari S, Sapkota S, Hamal R. Dengue and scrub typhus coinfection in a patient presenting with febrile illness. *Case Rep Infect Dis*. 2017;2017: 6214083.
17. Panpanich R, Garner P. Antibiotics for treating scrub typhus. *Cochrane Database Syst Rev*. 2000;(2):CD002150.