

A CASE STUDY OF A MAN WHO RETURNED FROM ABROAD WITH FEVER

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CASE HISTORY

At the General Practitioner's Clinic

Mr HKY was a 52-year-old Chinese male who presented initially to his general practitioner (GP) with a history of an intermittent fever for 6 days after his return to Singapore from Bintan, an island off Indonesia. This occurred when the Severe Acute Respiratory Syndrome (SARS) outbreak took place in Singapore during May 2003. The GP carried out a full blood count done which showed a haemoglobin (Hb) 11.8g/dl (13.5-18.0), platelets $259 \times 10^9/L$ (150-400), total leucocytes $8.11 \times 10^9/L$ (4.00-11.00), neutrophils $4.94 \times 10^9/L$ (2.00-7.50), lymphocytes $1.59 \times 10^9/L$ (1.50-4.00), monocytes $0.78 \times 10^9/L$ (0.20-0.80), eosinophils $0.75 \times 10^9/L$ (0.04-0.40), and basophils $0.05 \times 10^9/L$ (0.00-2.00). His previous Hb was documented as 15.0 g/dl. In view of the significant decline in Hb, his GP referred him to the nearby polyclinic for further management.

If you were the attending polyclinic doctor, how would you manage him at this point of time?

Mr HKY presented three days later, day 9 of his fever to a district polyclinic. He stated that his fever worsened in the evenings. He had no respiratory, abdominal, cardiac and neurological sign and symptoms. Clinical examination was unremarkable. There was no sign of rash, or organomegaly. Full blood count done in the polyclinic showed a Hb of 13.2g/dl (11.0-18.0), platelets $438 \times 10^3 /UL$ (150-450), total leucocyte count $10.2 \times 10^3 /UL$ (4.5-10.5), lymphocytes $2.3 \times 10^3 /UL$ (1.2-3.4), monocytes $1.0 \times 10^3 /UL$ (0.1-0.6), neutrophils 6.9×10^3 (1.4-6.5). Blood film for Malaria parasite was negative.

How would you now manage him?

The polyclinic doctor referred Mr. HKY to Tan Tock Seng Hospital (TTSH), the designated SARS hospital, for further investigation for his fever. The provisional diagnosis was malaria in view of his travel history and prolonged fever.

He was admitted to the infectious disease ward at TTSH. Investigations done were as follows, total white cell count $8.9 \times 10^9/L$ (4.5-10.5), polymorphs 63.5%, lymphocytes 18.6%, and eosinophils 9.1%, Hb 13.2g/dL (11.0-18.0), platelets $423 \times 10^3 /UL$ (1.2-3.4), Anti-nucleic antibody (ANA) 1:160 (<1:20), C-Reactive Protein (CRP) 117 (<10mg/dl),

negative blood and urine cultures. Malaria, Cytomegalovirus (CMV) and Epstein Barr virus (EBV) serologies were negative.

What would your diagnosis be?

Empirical treatment with Doxycycline commenced on the third day of hospitalization with subsequent rapid resolution of the fever. He was discharged well on the 5th day of admission. He was diagnosed as a case of typhus.

What is typhus?

Of the wide range of rickettsial diseases, typhus disease is the most commonly recognized entity in South East Asia¹. In Singapore murine typhus is more prevalent than scrub typhus². Rickettsial diseases are important but often under recognised causes of febrile illness locally.

Rickettsiae are obligate intracellular bacteria that are ecologically associated with an arthropod host. The genus *Rickettsia* includes three antigenic allied defined groups: spotted fever group, typhus group, and scrub typhus group, but the scrub typhus rickettsia, *Orientia* (formerly *Rickettsia*) *tsutsugamushi*, has no established evolutionary relationship with the other two³. However, these diseases have similar target tissues (blood vessels) and organs, with the result that the histopathology has many similarities. These microbiologically distinct pathogens cause diseases with many similar features. (Table 1)

What is the epidemiology of typhus?

Typhus is endemic in South East Asia. A comprehensive study of 1629 hospitalized patients with febrile illnesses in rural Malaysia revealed that scrub typhus was the cause of 19.3% of the febrile patients⁵. As Singapore is a modern urban city with a high standard of public health, typhus was considered a disease of the past⁶. In Singapore, six cases of Murine typhus occurring within a period of three months were reported⁶. Another study conducted at the National University Hospital in Singapore⁷ reported 21 cases of typhus between January 1999 and February 2000.

What is the differential diagnosis?

The classical triad of typhus disease was described as fever, headache and rash. Other common symptoms are myalgia, cough and gastrointestinal complaints. Fever was the most consistent feature, followed by headache. Only 1.8% had rash on presentation. Important laboratory clues of typhus disease were a normal total white count with thrombocytopenia and the presence of mild transaminitis⁷.

The clinical features of typhus and laboratory findings of typhus thus mimic dengue fever, which is another endemic but

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Table 1⁴ of the tabulation of Rickettsial diseases known

Etiology, Epidemiology and Ecology of Rickettsial Diseases

Disease	Agent	Geographic Distribution	Natural History	Transmission to human
Murine typhus	R typhi	Worldwide, predominantly tropical & subtropical especially coastal California & Texas in the United States	Rattus to rat flea to Rattus; opossum to cat flea to opossum	Flea faeces scratched into skin rubbed into conjunctiva or inhaled
Scrub typhus	O tsutsugamushi	Japan, southern and eastern Asia, northern Australia, islands of the western and southwestern Pacific	Transovarial transmission in Leptothrombidium chiggers	Chigger bite
Rocky Mountain spotted fever	R rickettsii	North, Central, and South America	Transovarial maintenance in Dermacentor, Rhipicephalus and Amblyomma ticks; less extensive horizontal transmission from tick to mammal to tick	Tick bite
Boutonneuse fever	R conorii	Mediterranean basin, Africa, Asia	Transovarial maintenance in Rhipicephalus, Hyalomma, and Amblyomma ticks; role of horizontal transmission is not clear	Tick bite
North Asian tick typhus	R sibirica	Russia, China, Mongolia, Pakistan, Kazakhstan, Kirgizia, Tadzhikistan	Transovarial maintenance in Dermacentor, Haemaphysalis, and Hyalomma ticks; horizontal transmission from tick to mammal to tick	Tick bite
Oriental spotted fever	R japonica	Japan	Presumably a transovarial tick host; the role of horizontal transmission is not clear	Tick bite
Queensland tick typhus	R australis	Eastern Australia	Transovarial transmission in Ixodes ticks; the role of horizontal transmission is not clear	Tick bite
Rickettsialpox	R akari	United States, Ukraine, Croatia, possibly worldwide	Transovarial transmission in Liporhynchus sanguine mites; horizontal transmission from mite to Mus musculus to mite	Mite bite
Murine typhus-like illness	R felis	California, Texas	Transovarial transmission in cat flea; role of horizontal transmission is not clear	Presumably flea faeces
Epidemic typhus	R prowazekii	South America, Africa, Asia, Central America, Mexico	Human to Pediculus corporis humanus louse to human	Louse faeces scratched into skin
Sylvatic typhus	R prowazekii	United States	Flying squirrel to louse and flea ectoparasites to flying squirrels	Ectoparasites of flying squirrels to humans
Recrudescence typhus	R prowazekii	Worldwide	Reactivation of latent human infection years after acute illness	None

more prevalent infection in Singapore. Therefore physicians should be wary of typhus in cases of suspected dengue virus infection when the fever becomes persistent.

Typhus fever is not exclusive to foreign workers as Murine and scrub typhus has been found in Singaporeans with occupational or recreational epidemiological risks².

This is significant in the context for the above patient as onset of symptoms took place within days of returning from his foreign travel. Thus typhus must be considered in tourists and travellers returning from endemic regions and presenting with a febrile illness⁷.

What is the diagnostic test for typhus?

Currently two types of test are used to diagnose typhus. The Weil-Widal Felix (WWF) is known to lack specificity and sensitivity in diagnosing typhus disease. It yields false positive results with Leptospirosis, malaria, Proteus infections and other febrile illnesses^{8, 9}. The indirect immunoperoxidase test (IIP) is the gold standard in diagnosing typhus disease. The IIP is sensitive and specific for typhus fever but it is limited by complexity of the test and cost much more than the WWF test.

How do you manage typhus?

As typhus is easily treatable with a course of tetracycline, Dr Chen et al¹ recommended that an empirical course of Doxycycline, which would serve as a quick and effective diagnostic tool in clinically suspected typhus fever. After 72 hours of drug initiation, close to 90% of infected patients had resolution of their fevers⁷. A therapeutic course of Doxycycline currently is significantly less expensive than rickettsial serology using IIP. In addition, such an approach cuts short the clinical course of the disease, which while usually benign, has been known to result in serious complications for example hepatic, renal failure, aseptic meningitis and encephalitis, and pneumonitis with respiratory failure¹.

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