Short Report: Endemic (Murine) Typhus in Returned Travelers from Asia, a Case Series: Clues to Early Diagnosis and Comparison with Dengue

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Two cases of endemic typhus are described in detail with a clinical summary of eight cases in returned travelers. Compared with a similar cohort of patients with dengue, typhus cases had higher CRP and less neutropenia. These findings may guide empirical therapy and improve use of definitive diagnostic tests.

A report of the GeoSentinel Network identified rickettsial infection in 280 (1.5%) of around 14,000 febrile travelers.¹ Only 10 individuals were considered to have endemic (murine) typhus caused by flea-borne infection with *Rickettsia typhi*. In a Swedish cohort of febrile returned travelers, 1% of 1,049 patients with routine testing and 4% of 383 patients with additional serological investigation were diagnosed with typhus group (*R. prowazekii* or *R. typhi*) rickettsiosis.² Thirty-two cases of endemic typhus were identified in a retrospective analysis of all samples sent to the World Health Organization (WHO) Collaborative Center for Rickettsial Diseases and Other Arthropod-Borne Bacterial Diseases, Marseille, France, over a 3-year period.³ Of these cases, 13 individuals had traveled to Africa, and 12 individuals had traveled to Southeast Asia. There have been sporadic case reports of endemic typhus in tourists returning from Southeast Asia, including seven cases acquired in Indonesia,^{4–7} one case acquired in Thailand, and one case acquired in Vietnam.^{8,9}

Conclusions from these reports are that endemic typhus remains a rare but probably underdiagnosed cause of febrile illness in returned travelers, severe presentations do occur,⁷ and Southeast Asia is the main source. Indonesia is the most popular holiday destination for Western Australians, accounting for 259,737 (42% of total) annual short-term overseas departures according to the Australian Bureau of Statistics (2011).

Since 2009, we have diagnosed endemic typhus in eight returned travelers. Here, we present two illustrative cases and a clinical summary of the series. Because it is a rare condition presenting as a non-specific febrile illness and most commonly diagnosed serologically, definitive diagnosis is often retrospective, requiring early treatment with doxycycline to provide adequate empiric cover. Because dengue fever was the most common working diagnosis in our series of patients, we compared initial laboratory parameters of endemic typhus patients with those parameters of a similar cohort of dengue patients to identify features that may help clinicians differentiate between these two infections.

CASE 1

A 53-year-old man became ill 1 week after return from a 2-week holiday to Bali, Indonesia. Initial fever, headache,

myalgia, and arthralgia lasted 5 days before the development of nausea, vomiting, dry cough, and somnolence. The next day, he became confused and developed a maculopapular rash with scattered petechiae, prompting presentation to the regional hospital, where he was found to be shocked with bilateral pulmonary infiltrates on X-ray. Admission blood results showed renal failure (plasma creatinine = 734 μ mol/L), mildly elevated liver enzymes, and significant thrombocytopenia (platelets = 28×10^9 /L). He was transferred to the intensive care unit at our hospital, where he remained for the next 10 days, requiring hemofiltration as well as ventilatory and inotropic support.

He had had close contact at a safari park in Bali with birds, an orangutan, an elephant, and a lion. He had also been swimming at the water slide park and in the ocean, and he had received multiple mosquito bites. Extensive microbiological workup identified rickettsiosis as the likely cause of his illness, with *R. typhi* indirect fluorescent antibody (IFA) titer increasing from 256 on arrival to 2,048 two weeks later without any rise in spotted fever group *Rickettsia* or *Orientia tsutsugamushi* titer. He received 10 days of meropenem plus doxycycline, making a slow but complete recovery, and was discharged home after 18 days.

CASE 2

A 59-year-old female presented 2 weeks after returning from Bali with a 1-week illness characterized by myalgia, headache, and fever. She developed a faint blanching rash over her abdomen and back and was thought likely to have dengue fever or chikungunya virus infection, but she developed worsening fever, rigors, dry cough, and increasing dyspnoea. She had biochemical evidence of hepatitis (alanine transaminase [ALT] = 321 U/L) and mild thrombocytopenia (platelets = 120×10^9 /L). Initial therapy with intravenous ceftriaxone plus azithromycin was switched to oral moxifloxacin 72 hours later to augment empirical treatment of possible legionellosis, because her respiratory symptoms had progressed with bilateral pulmonary infiltrates on chest X-ray. She made a slow recovery and was discharged on day 9. Admission *Leptospira longbeachae* IFA titer was 512 with no subsequent rise, whereas *R. typhi* antibody titer rose from 2,048 at 10 days after onset of illness to 8,192 in convalescence. Dengue, *Leptospira*, and respiratory virus acute and convalescent serological testing were all negative.

SUMMARY OF CASE SERIES

Including the two cases above, we diagnosed eight cases of endemic typhus between August of 2009 and June of 2012. Diagnosis was made on the basis of consistent clinical history, *R. typhi* immunoglobulin G (IgG) IFA (Scimedx, Denville, NJ) showing fourfold or greater rise between acute-phase and convalescent serology, or a single high titer with exclusion

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of other causes. Five of our patients had traveled to Bali, and one patient each had traveled to Thailand, India, and Vietnam. Observed clinical features were consistent with those features reported in a large South Texas cohort.¹⁰ Fever and headache were universal, and frank encephalitis was seen in two patients. One of these patients underwent lumbar puncture showing cerebrospinal fluid (CSF) leukocyte count of $7 \times 10^6/L$ (85% mononuclear cells) with normal glucose and protein. Myalgia or arthralgia was reported in six patients. Four patients suffered from dry cough, with two patients having significant respiratory distress. Chest X-ray was abnormal in four patients, with bilateral changes in three patients. Central maculopapular rash developed in five patients and was seen at presentation in three patients. Only one patient had petechiae. The initial working diagnosis was dengue fever in all but two patients, in whom legionellosis and typhoid fever were thought most likely. Acute *R. typhi* IFA titers were 128 in one patient, 256 in two patients, and 512 in two patients: all these patients subsequently had a fourfold rise. Three patients had only convalescent serology performed. One patient was case 2 above, and the other two patients had single high titers of 4,096 and 8,192. Hospital length of stay ranged from 1 to 18 days (median of 7 days). An in-house polymerase chain reaction (PCR) targeting the *R. typhi* 17 kDa antigen gene was performed on whole blood in two patients and was positive only in the case who was sampled before administration of antibiotics. Dengue non-structural protein 1 (NS1) antigen enzyme immunoassay (EIA; Bio-Rad Laboratories, Hercules, CA) and IgM enzyme-linked immunosorbent assay (ELISA; Standard Diagnostics, Kyonggi-Do, Korea) were negative in all typhus cases except case 1, where it was not done.

COMPARISON WITH DENGUE

Thirteen cases of dengue fever admitted to the hospital between 2007 and 2012 were identified by searching our departmental database that aims to capture all patients referred to our service for consultation; 7 cases were female, 7 cases had positive NS1 antigen EIA, and 10 cases had positive IgM ELISA, reflecting a range of stage of illness. Of nine cases undergoing in-house genotype-specific PCR targeting the non-structural (NS) region, eight cases were positive. Only three cases had *Rickettsia* IFA performed, and all had *R. typhi* titer less than 128. Mild thrombocytopenia was found in both groups (Table 1). Mild hepatitis was more common in the typhus group. C-reactive protein (CRP) was notably higher in the typhus cases, whereas neutrophil count was lower in dengue, with no overlap between the two groups.

TABLE 1

Laboratory investigations at admission for dengue ($N = 13$) and endemic typhus ($N = 8$)

	Dengue*	Typhus*	$P^\dagger$
Age (years)	29 (21, 41)	49 (43, 54)	0.02
CRP (mg/L)	6 (4, 19)	114 (78, 181)	< 0.01
White cells ($\times 10^9/L$)	2.68 (2.25, 2.86)	5.59 (5.03, 6.48)	< 0.01
Neutrophils ($\times 10^9/L$)	1.50 (1.06, 2.18)	4.45 (4.24, 4.89)	< 0.01
Lymphocytes ($\times 10^9/L$)	0.54 (0.38, 0.72)	0.88 (0.57, 1.26)	0.19
Platelets ($\times 10^9/L$)	111 (73, 141)	121 (104, 149)	0.89
ALT (U/L)	45 (38, 52)	91 (85, 132)	0.02

* Values presented as median (interquartile range).

$^\dagger P$ value of two-tailed Mann-Whitney test.

DISCUSSION

Although our conclusions are limited because of a lack of denominator data, hospitalized cases of endemic typhus seem more frequent than may have been expected from the European data,² likely reflecting the local choice of holiday destination.

Case 1 highlights the need to consider endemic typhus in the differential diagnosis of returned travelers with severe illness. This severity has not previously been described in a traveler; however, 7 of 80 (9%) patients in the South Texas cohort required intensive care admission, although details of comorbidities were not reported.¹⁰

Our data indicate that, in a patient presenting with a clinical syndrome consistent with dengue fever, neutropenia and low CRP strengthen the diagnostic likelihood pending confirmatory testing with NS1 antigen/IgM antibody. CRP has previously been found to be low in uncomplicated dengue fever in adults and children, with modest elevation in some cases of severe disease.^{11,12} We suggest that, if neutropenia is absent or CRP is significantly elevated, alternative diagnoses to dengue should be sought, and strong consideration should be given to the empiric use of doxycycline.

This clinical and laboratory picture should also prompt directed diagnostic testing. The majority of our cases had elevated *R. typhi* IFA titers at presentation, but these tests were often added retrospectively. Wider access to PCR with appropriate sampling before initiation of antibiotics holds promise for definitive early diagnosis.

There are clear limitations and biases in our data. Numbers are small in both groups, although this study is the largest series of endemic typhus cases in travelers from Asia with detailed clinical and laboratory data of which we are aware. Because only hospitalized patients were included, we have almost certainly captured the more severe end of the endemic typhus disease spectrum. Milder or subclinical infection may not produce the same degree of elevation in CRP, but because *R. typhi* usually causes a self-limiting disease, such cases will derive less benefit from prompt initiation of antibiotic therapy. Given referral patterns in our hospital, where the infectious diseases clinical service is routinely involved in the management of all febrile returned travelers, we believe that this study is a true representation of travelers as they present to our institution. We have not had the opportunity to investigate other infections in this patient group that may present in a similar manner, including other rickettsiosis and leptospirosis, and would also benefit from prompt administration of doxycycline.

We believe that, although the findings of this study are preliminary and limited by small numbers, they should stimulate larger-scale prospective studies aimed at improving triage and developing algorithms for diagnostic laboratory testing and empiric therapy of febrile returned travelers. Additional investigation is also required to more accurately define the incidence of typhus in travelers as well as clarify the contribution of *R. felis* infection, which may cause a very similar illness and be serologically indistinguishable from *R. typhi*.¹³

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