Case Report: Typhoid Fever and Spotted Fever Group Rickettsiosis Presenting Concomitantly in an Indian Immigrant

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Abstract. We present a rare case of an Indian immigrant suffering from concomitant infection of *Salmonella typhi* and spotted fever group *Rickettsia*. We discuss the scarce reports of dual infections from the developing world and the related diagnostic challenges.

CASE PRESENTATION

A 26-year-old Indian female was admitted to our intensive care unit (ICU) because of fever, severe diarrhea, dehydration, and suspected disseminated intravascular coagulation. She was a previously healthy, certified nurse, who emigrated from India 7 days before her admission to work in Israel. Her past medical history included past infection with chikungunya virus. She originally lived in Kerala, but for 2 months before her emigration, she stayed in poor conditions in New Delhi. She recalled being bitten by “bed bugs” 2 weeks before arriving in Israel. One year earlier, she received a typhoid fever vaccine. She was human immunodeficiency virus negative.

Two days before her departure from India, she became ill with high fever, chills, severe diarrhea, recurrent vomiting, headache, abdominal pain, backache, and severe weakness. Cough was noted on the day before admission. She recalled similar symptoms a month earlier while in New Delhi, then she was treated with amoxicillin and metronidazole for 7 days with clinical improvement.

On her admission, she had a fever of 37.4°C, heart rate of 104 per minute, blood pressure of 97/64 mm of Hg, and oxygen saturation of 98% on room air. She looked ill, dehydrated, and stuporous. There was no dyspnea or confusion. Physical examination showed dry mucous membranes and a strawberry tongue. There were crepitations over both lung bases, heart sounds were normal, and there were no murmurs. Her abdomen was tender and distended with no organomegaly. There were no signs of rash, insect bites, eschar, or lymphadenopathy.

Laboratory results showed pancytopenia (white blood cell count of 2,600 cells/mL, hematocrit of 31.9%, and severe thrombocytopenia of 39,000 cells/mL), mild hyponatremia (131 mmol/L), hypokalemia (2.7 mmol/L), mildly elevated transaminases (aspartate transaminase 241 IU/L and alanine transaminase 89 IU/L), and lactic dehydrogenase of 1974 IU/L. Prothrombin time was only mildly increased (14.6 seconds), D-dimer levels were > 20 mcg/mL, and fibrinogen was 311 mg/dL. Schistocytes were not seen in the blood smear. The chest X-ray was normal.

Initial treatment with ceftriaxone, azithromycin, and metronidazole was commenced in the emergency room. She was admitted to the ICU with a clinical picture of septic shock and multi-organ failure and required inotropic support. The initial

differential diagnosis included imported viral diseases (including dengue virus, chikungunya virus, Epstein–Barr virus [EBV], cytomegalovirus [CMV], and other viruses), typhoid fever, malaria, *Clostridium difficile* colitis, hemophagocytic lymphohistiocytosis, and rickettsial diseases.

After 1 day in the ICU, four of six blood cultures were reported as positive, and Gram-negative bacilli were consequently identified as *Salmonella typhi*, sensitive to ampicillin, ceftriaxone, and trimethoprim/sulfamethoxazole but resistant to azithromycin and to ciprofloxacin. Stool culture was also positive for *S. typhi*. Stool antigen for *C. difficile* was negative, as well as serology for EBV, hepatitis A virus, hepatitis C virus, and *Coxiella burnetii*. Real-time polymerase chain reaction (PCR) tests for dengue (whole blood) and for enterovirus (stool) were negative. Malaria antigen (CareStart™ Malaria [Pan], RAPIDTEST, manufactured by APACOR, Wokingham, United Kingdom) was negative and CMV serology showed evidence of past infection. Initial *Rickettsia* serology for *Rickettsia typhi* and *Rickettsia conorii* was suspected to be positive and the serum was sent for confirmation to the Israeli reference laboratory for *Rickettsia* at the Israel Institute for Biological Research (IIBR). At the IIBR, serologic diagnosis was performed using the immunofluorescence assay method, as previously described,¹ and was found negative.

During the first 2 days, she improved clinically: the fever abated, she became more alert, and the abdominal pain and tenderness improved. The pancytopenia was also resolving and all antibiotic therapy apart from ampicillin was stopped. However, on her third day in the ICU, she developed acute respiratory distress syndrome and needed mechanical ventilation. Her temperature increased to 39.9°C. There were no signs of intestinal perforation on imaging. The antibiotic coverage was broadened again to include ertapenem, ampicillin, doxycycline, and metronidazole. A repeat malaria antigen test was negative. She also received nitric oxide, furosemide, and corticosteroids and gradually improved. After 5 days of mechanical ventilation, she was extubated and subsequently discharged from the ICU.

As stated, the first serology for *Rickettsia* spp. came back negative from the IIBR. Serum samples 11 days and 4 weeks later were borderline for *R. typhi* (typhus group [TG]) and for *R. conorii* (of the spotted fever group [SFG]) rickettsiosis. Because we still highly suspected a rickettsial disease, and the serology failed to show a conclusive 4-fold increase in the titers, all the samples were sent to the Centers of Disease Control (CDC) for PCR testing and for repeated serologic tests to include also *Orientia tsutsugamushi* and other *Rickettsia*. At

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the CDC, nested PCR was performed, as previously described² and was found to be positive for SFG *Rickettsia*. This test was repeated at the IIBR, using the same methods, and the positive nested PCR sample was further analyzed using the restriction fragment length polymorphism test,³ receiving the same results. Sequencing to the exact species was unsuccessful. Still, coupled sera, 4 weeks apart failed to show seroconversion for *R. typhi*, *Rickettsia prowazekii*, *R. conorii*, and for *O. tsutsugamushi* in both laboratories.

Repeat stool cultures were negative for *Salmonella* spp. and she was allowed to continue her work as a nurse in Israel.

DISCUSSION

Salmonella enterica serovar Typhi and *Rickettsia* are endemic in India. The diseases these microorganisms cause are similar in their clinical presentations and may be practically indistinguishable if one is devoid of access to advanced laboratory tests. Both diseases commonly present as undifferentiated febrile illness. In many developing countries, the approach to fever without localizing features is to treat *S. typhi* (usually with parenteral ceftriaxone), without rickettsial coverage, occasionally resulting in detrimental outcomes. Consequently, physicians in Patan, Nepal, endorsed the ceftriaxone–doxycycline combination therapy after experiencing a post-earthquake outbreak of scrub typhus in 2015.⁴ In another cohort from Nepal, 97 patients with undifferentiated fever eventually diagnosed with *R. typhi* infection had no demographic, clinical, or laboratory features distinguishing them from the other diagnoses in the cohort.⁵ Scrub typhus may present with severe diarrhea resembling enteric fever.⁶

Our patient had a dual infection. Physicians typically try to ascribe all symptoms and signs to a single diagnosis, but dual infections occasionally occur. They are typically found among patients with acquired immunodeficiency syndrome,⁷ in cases in which the same vector transmits more than one pathogen,^{8–10} or in food-poisoning outbreaks associated with more than one pathogen.^{11–13} Apart from these situations, mixed infections acquired through different modes of transmissions probably exist (mainly in developing countries) but are under-diagnosed and hence underreported. The diagnosis of concurrent infections is challenging for several reasons. First, naturally and instinctively most physicians suppose there to be a single diagnosis. Second, many infections may have a wide spectrum of clinical manifestations and severities and may be having overlapping signs and symptoms. Third, the confirmation of concurrent infections is dependent on well-equipped microbiology laboratories, which are rare in developing countries. This challenge could be even more difficult with imported diseases that may not be familiar to the local physicians.

There are reports of dual infections, most of them regarding patients with malaria,^{14–17} leptospirosis,^{5,15,18} and dengue fever^{18,19} accompanied with other diseases. Concurrent typhoid fever and other infections were reported from Nepal,^{5,18} India,^{19–21} Bangladesh,²² and Egypt.¹⁵ There are only two case reports of concomitant typhoid and typhus (one murine typhus²² and one scrub typhus²¹), but neither could demonstrate seroconversion, and the diagnosis of typhus relied on the response to doxycycline or on the presence of high immunoglobulin G titers. Other coinfections were reported anecdotally in studies reporting the etiologies of patients

presenting with undifferentiated fever. In Kathmandu, Blacksell et al.¹⁸ found that of 23 patients presenting with *S. typhi* or *S. Paratyphi A* bacteremia, nine also had serologic evidence of scrub typhus, murine typhus, *Leptospira*, or dengue virus. In only one patient with dual infection (*S. typhi*/*R. typhi*), there was evidence of seroconversion. In another study from Nepal, dual infection with *S. Paratyphi*/*R. typhi* was reported in three patients.⁵ In this cohort, all cases of immunoglobulin M-positive murine or scrub typhus were diagnosed initially as enteric fever. In Egypt, Parker et al. studied 1,510 patients presenting with acute febrile illness and found 187 (12%) with concurrent infections, mostly *Leptospira* spp. with either TG *Rickettsia*, *S. typhi*, or *Brucella*. Only one case of concomitant *S. typhi*/*R. typhi* was reported in this cohort. In all the studies reported previously, the acuity of the rickettsial infection could not be confirmed in most cases, because it was based on the detection of IgM antibodies that can persist for months and years after an acute infection.

In our case, given the severe diarrhea on presentation, an enteric infection was promptly suspected and *Salmonella* bacteremia was not a surprising finding. The clinical and laboratory findings, as well as the response to antimicrobial treatment all fitted the diagnosis of typhoid fever. However, the thrombocytopenia was severe and this is rare in typhoid fever. This, along with the clinical deterioration raised the suspicion of another disease and prompted further diagnostic workup. The rapid clinical response to doxycycline, along with positive PCR for SFG *Rickettsia* proved the dual infection with *Rickettsia*.

Serologic cross-reactivity is well known between TG and SFG rickettsia,²³ as well as with *Proteus vulgaris* and *Legionella bozemanii*²⁴ but not with *Salmonella* spp. We could not differentiate the SFG *Rickettsia* species infecting this patient, neither by serology nor by molecular methods, but the clinical and therapeutic approach would have been the same for all rickettsial diseases. The abrogated serological reaction, not reaching a 4-fold increase, could be explained by the corticosteroids administration and by the early administration of adequate antibiotic treatment, as was rarely described in an experimental model of *Rickettsia rickettsii* infection.²⁵ We believe that the patient acquired both diseases while staying in poor conditions in New Delhi, the typhoid being acquired a month previous to presentation with a relapse after an inadequate antibiotic course, and the rickettsial disease acquired just previous to emigration.

To conclude, confirmed dual infection with *S. typhi* and rickettsial disease is very rarely diagnosed and reported. We were able to delineate between these two concurrent infections because of the clinical deterioration and severe thrombocytopenia. The concept of dual infection must be considered in post-travel patients and in immigrants from developing countries presenting with undifferentiated fever.

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