A 21-Year-Old Returned Traveller with Typhoid Fever Complicated By a Multifactorial Anemia and Splenic Infarction

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Abstract

Typhoid fever is a rare disease in North America. We present the case of a 21-year-old female who developed invasive *Salmonella typhi* infection after returning from rural Pakistan. The patient presented with classic signs of enteric infection including high fever, diarrhea, and a tongue coated in white patches. The patient developed hematologic complications of anemia and splenic infarction. Investigations, imaging studies and treatment are discussed. The case outlines both common and uncommon complications of typhoid fever and reminds the clinician of its importance in the differential of fever in the returning traveller. Four key point to consider are:

1. Fever in a returning traveler has a broad differential diagnosis, but concurrent abdominal symptoms should result in blood cultures to assess for gram-negative bacteria. 2. Ceftriaxone, azithromycin, or fluoroquinolones are the treatments of choice for *Salmonella typhi,* although clinicians should be aware of increasing resistance to the latter and base treatment on sensitivity testing. 3. Anemia during typhoid fever can be multifactorial and include elements of gastrointestinal blood loss, hemolysis and transient marrow suppression. 4. Spleen involvement can lead to complications such as splenic infarction or abscess formation.

Résumé

La fièvre typhoïde est une affection rare en Amérique de Nord. Nous présentons le cas d'une femme de 21 ans ayant développé une infection envahissante due à *Salmonella typhi* à son retour du Pakistan rural. La patiente présentait les signes classiques d'une infection intestinale, notamment une fièvre élevée, de la diarrhée et une langue recouverte de plaques blanches. Puis, la patiente a présenté des complications hématologiques : anémie et infarctus splénique. Nous discutons ici des investigations et des examens d'imagerie effectués, ainsi que du traitement appliqué. Le cas donne un aperçu des complications courantes et inhabituelles de la fièvre typhoïde et rappelle au clinicien leur importance dans la reconnaissance des fièvres chez la personne qui rentre de voyage. Il y a quatre points principaux à considérer :

1. La présence de fièvre chez une personne qui rentre de voyage ouvre la porte à un large éventail de diagnostics différentiels, mais la concomitance de symptômes abdominaux devrait mener à des hémocultures pour évaluer la présence de bactéries à Gram négatif. 2. La ceftriaxone, l'azithromycine et les fluoroquinolones sont les traitements de choix contre *Salmonella typhi*. Toutefois, les cliniciens doivent être conscients que la résistance à ces dernières est en hausse et leur choix de traitement devrait être basé sur une analyse de sensibilité. 3. L'anémie accompagnant la fièvre typhoïde peut être multifactorielle et comporter des pertes sanguines gastro-intestinales, des hémolyses et une dépression médullaire passagère. 4. Une atteinte à la rate peut causer des complications comme un infarctus splénique et la formation d'abcès.

Case Presentation

The patient was a 21-year-old female who had visited friends and relatives in rural Pakistan. She had received standard childhood immunizations, but did not seek any specific travel vaccinations or advice. She was previously otherwise healthy. During her trip, she was exposed to numerous infectious risk factors including eating street food, drinking unpasteurized milk, contact with farm animals, wooded areas, and freshwater lakes. She was not exposed to animal bites, IV drug use, nor sexual activity while abroad. She first became ill 19 days into her vacation, experiencing daily bilious vomiting and fevers as high as 39.5°C. These symptoms subsided for one day after being given antibiotics of an unknown type by a relative, but subsequently returned with the additional development of non-bloody diarrhea. She spent a total of 26 days abroad and presented to the emergency department 6 days after returning to Canada. Thus, she presented having been ill for approximately 2 weeks.

At presentation, she had diffuse myalgia, headache, and periumbilical pain. Her triage vital signs showed a temperature of 38.6°C, a heart rate of 110 beats/min, and a blood pressure of 101/58 mm Hg. The physical examination was significant for buccal ulcers, a tongue coated in white patches, and epigastric tenderness. Her investigations showed anemia, mild haemolysis and abnormal liver enzymes (see Table 1 for abnormal results). An abdominal ultrasound showed the presence of splenomegaly at 13.7 cm. Her initial blood cultures grew gram-negative bacilli after 14 hours. This was subsequently identified to be *Salmonella typhi* . She was admitted and empiric ceftriaxone was started.

Over the next 11 days, the patient experienced daily fevers ranging from 38.7 to 40.5°C before defervescing. *Salmonella typhi* was also identified in both her urine and feces. The detected *Salmonella typhi* was sensitive to ampicillin and ciprofloxacin, and she was stepped down to oral ciprofloxacin once she began to tolerate an oral diet. The infectious disease service advised treatment for a total of 3 weeks.

By day 3 of admission, free hemoglobin was no longer evident and her haptoglobin had normalized. However, her hemoglobin continued to trend downwards. Initially, there was no reticulocyte response. On day 9, the patient experienced palpitations and had a hemoglobin of 69 g/L. She was transfused with one unit of packed red blood cells and her hemoglobin stabilized for the remainder of the hospitalization. The day before she showed defervescence and clinical improvement, her reticulocyte count had increased to 92×10^9/L.

Due to ongoing epigastric pain, the patient had an abdominal computed tomography (CT) and ultrasound on day 4 of admission. These studies revealed a 2 cm wedge shaped infarct at the lateral border of the spleen (Figure 1). Three subsequent ultrasounds during her admission confirmed a stable splenic infarct.

The patient stayed in hospital for an additional week due to hospital acquired pneumonia. She was discharged home on day 21.

Discussion

The clinical presentation of *Salmonella typhi* is relatively non-specific, and thus a broad differential must be considered in fever in a returning traveller. Consideration must be given to both regional pathogens and exposure to risk factors. The differential here is broad and includes parasites (malaria, giardia, amoebic

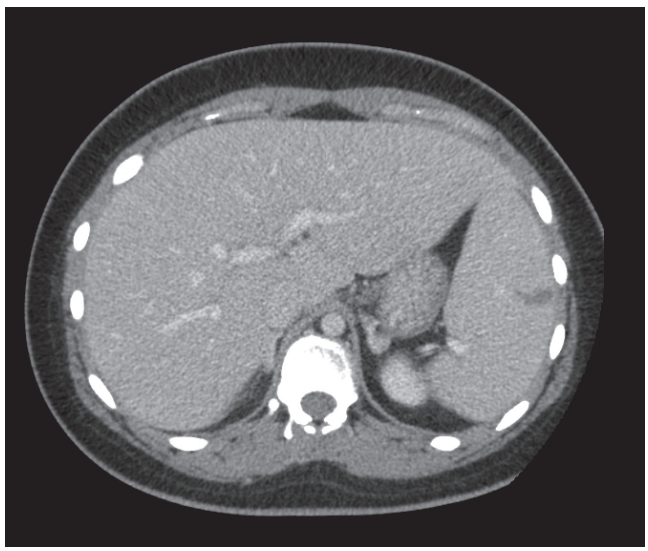

Figure 1. Computed tomography scan showing the splenic infarct.

Table 1. Patient Blood-Work on Presentation. Only Abnormal Lab Values are Shown

Parameter	Patient value	Normal range	Unit
Haemoglobin	109	123-157	g/L
Lactate dehydrogenase	912	95-195	IU/L
Free haemoglobin	present		IU/L
Haptoglobin	reduced		IU/L
Aspartate aminotransferase	316	0-35	IU/L
Alanine transaminase	319	3-36	IU/L
gamma-glutamyl transpeptidase	621	5-36	IU/L
Alkaline phosphatase	400	35-100	IU/L
Lipase	287	<160	IU/L

abscess), bacteria (*Salmonella typhi, Salmonella paratyphi*, enteric gram-negative bacilli, leptospora, rickettsia, brucella), and viruses (dengue, hepatitis, human immunodeficiency virus) amongst other organisms.

While there are 22 million cases of typhoid fever annually, it is rare in high-income settings with only a few hundred cases reported annually in Canada and the United States.[1]

Typhoid fever typically presents with fever and malaise, with a 7–14 day incubation period after ingestion of the gram-negative bacilli, most commonly from contaminated food or water. The bacteria penetrate the mucosa of the small intestine and enter the Peyer's patches where they are phagocytosed by macrophages, surviving intracellularly. The salmonella-infected macrophages subsequently distribute via the lymphatics to reticuloendothelial tissues such as the liver, spleen, lymph nodes and bone marrow.[2]

Classical features of typhoid fever include prolonged fever, headache, myalgias, non-productive cough, and gastrointestinal symptoms such as abdominal pain, nausea, vomiting, and diarrhea or constipation. Physical examination findings may include a tongue coated in white patches, rose spots rash, relative bradycardia, splenomegaly, and abdominal tenderness. Laboratory investigations may demonstrate a gram-negative bacteremia and mild transaminitis. Common complications include gastrointestinal bleeding, intestinal perforation, encephalopathy, and hepato-splenic abscesses.[1] Our patient's presentation was classic, including 3 of 4 identified specific clinical markers for typhoid fever,[3] having experienced high fever, loose bowel movements, and coated tongue, but no bradycardia.

Although fluroquinolones are the most effective agents for susceptible S. typhi, increasing rates of resistance have led to the use of third generation cephalosporins or azithromycin for empiric therapy. Defervescence usually occurs after approximately one week of therapy. If a fully susceptible organism is identified, therapy should be stepped down to ciprofloxacin, as was the case in our patient.[1,4,5]

The etiology of the anemia was likely multi-factorial, involving gastrointestinal bleeding, haemolysis, and bone marrow suppression. Gastrointestinal bleeding can develop from Peyer's patch necrosis and occurs in up to 10% of hospitalized patients.[1] Intestinal perforation is a feared complication of typhoid fever which can present insidiously with worsening anemia and abdominal pain or more classically, with an acute abdomen. Imaging studies did not reveal frank perforation in our patient. However, it is conceivable that she was experiencing clinically silent gastrointestinal bleeding.

The patient's splenomegaly secondary to infection likely contributed an extravascular haemolytic component. The free hemoglobin and abnormal haptoglobin pointed to a concurrent intravascular haemolytic event. However, this was likely mild due to a normal bilirubin. The *lactate dehydrogenase* elevation could be the result of both mild haemolysis and acute liver disease. There is *in vitro* evidence that *Salmonella typhi* responds to host neuroendocrine stress hormones by releasing haemolysin E, which could have contributed to the patient's haemolytic picture.[6]

In a small cohort study, G6PD deficiency has been proposed as a risk factor for haemolysis during typhoid fever.[7] The hematological workup of our patient did not reveal glucose-6-phosphate dehydrogenase (G6PD) deficiency, autoimmune mediated haemolysis, spherocytosis, or beta thalassemia. We did not perform an alpha thalassemia genetic test. Thus, it is still possible that our patient harbours an intrinsic haemoglobinopathy that predisposed her to haemolysis during *Salmonella typhi* infection.

While the patient's anemia worsened during the initial stages of her hospital admission, her early reticulocyte counts did not respond with an increase. At least one report of a small cohort of typhoid fever patients showed that Salmonella typhi can infiltrate the bone marrow and cause isolated anemia or mixed cytopenias.[8] In this report, 28 of 36 patients experienced disturbances in at least one blood cell line. When our patient's

clinical symptoms of fever and diarrhea began to improve, her reticulocyte count also began to respond. Her *Salmonella typhi* infection may have initially caused an element of bone marrow suppression, negating the expected rise in reticulocytes. From a clinical standpoint, bone marrow biopsies may be too invasive for the majority of typhoid fever patients.

Splenic complications are uncommon in typhoid infections. The differential for the lesion found on our patient's spleen included abscess and infarction, which have both been previously reported.[9,10] In our patient, a non-evolving infarction was confirmed by multiple imaging studies. Other causes of splenic infarct including haemoglobinopathy, hematologic malignancy, embolic disorders and trauma were unlikely in this patient given the investigations and history of presenting illness. However, in the absence of genetic testing for alpha thalassemia, we are unable to rule out the possibility of the splenic infarct arising from an underlying haemoglobinopathy, as opposed to exclusively from the typhoid fever. Regardless, this case highlights the importance of monitoring the spleen for complications in invasive *S. typhi* infections.

Declaration

The authors declare no competing interests.

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All four persons named contributed equally to the development of this manuscript and qualify as authors.

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