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Enteric fever and COVID-19 co-infection in a teenager returning from Pakistan

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We obtained written consent to publish this case report from the patient and his parent.

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HIGHLIGHT

As SARS-CoV-2 has become widespread around the globe, co-infection with other endemic infectious diseases will occur. Here we present the first reported case of enteric fever and COVID-19 co-infection, in a teenager returning from travel to Pakistan and describe his clinical course.

INTRODUCTION

In March 2020, the World Health Organization declared the COVID-19 outbreak, caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), a global pandemic. As SARS-CoV-2 spreads worldwide, some patients will be concurrently infected with the SARS-CoV-2 virus and other ubiquitous or endemic pathogens. Co-infections with SARS-CoV-2 have been reported with various respiratory infections, as well as tropical disease such as malaria[1].

Enteric fever is a systemic illness caused by the Gram negative bacilli *Salmonella enterica* subspecies *enterica* serovars Typhi (*S.* Typhi) and Paratyphi (*S.* Paratyphi) A, B, or C which are usually transmitted through contaminated water. Enteric fever is most prevalent in South Asia, the Middle East and Sub-Saharan Africa, with highest risk in children and young adults. A notable risk factor for typhoid fever in high income countries is traveler visiting friends and relatives (VFR)[2]. As a large global city whose population is more than half foreign born, a significant number of travel associated infections, including enteric fever, are diagnosed in children in Toronto each year[2]. We conducted a literature search using the terms COVID-19 or Coronavirus or SARS-CoV-2 and *Salmonella* or Typhoid or Typhi or Enteric Fever as key words on December 1st 2020 using Embase, Medline and PubMed databases and only one publication discussed both topics. This letter discussed the likelihood of having these two epidemics collide and the challenges for healthcare systems as well as frontline clinicians in distinguishing the two conditions, or co-infection based only on clinical presentations[3]. Here we describe, to our knowledge, the first documented case of travel acquired enteric fever and SARS-CoV-2 co-infection, in a teenager.

CASE SUMMARY

A 14-year-old male Canadian visited friends and relatives in a rural area in Khyber Pakhtunkhwa province, Pakistan. He did not seek pre-travel care, nor did he receive any pre-travel immunizations. He ate local food and drank well water. The patient experienced chronic diarrhea while in Pakistan, for which he received a prolonged course of oral metronidazole.

The patient returned to Canada in July 2020. Eight days after returning to Canada, the patient developed fever up to 40.9°C and diarrhea. After 5 days of fever, watery diarrhea, and an episode of non-bloody, non-bilious emesis, he presented to the Emergency Department (ED) of a community hospital in Toronto. Investigations revealed leukocytosis, polycythemia, thrombocytopenia, hyponatremia, transaminitis and elevated creatinine (Table 1). Malaria rapid antigen test and initial smears were negative. A nasopharyngeal swab was sent for SARS-CoV-2 PCR. Chest X-ray was unremarkable. Blood cultures were drawn, IV fluids were administered, and he was discharged home without antibiotics with blood cultures pending. The next day, on day 6 of illness, he was seen in the hospital's pediatric follow-up clinic and remained stable. Repeat blood cultures and malaria screen were collected, and he was again discharged home. At 12 hours of incubation, the second blood culture set became positive with Gram-negative bacilli seen on microscopy. The patient was notified via telephone on day 7 of illness and instructed to present to the local children's hospital. Shortly afterwards his SARS-CoV-2 nasopharyngeal swab was reported as positive.

The patient presented to The Hospital for Sick Children (HSC), a large tertiary pediatric hospital in Toronto, on day 7 of illness as directed by the community physician. In addition to his previously identified gastrointestinal symptoms, he also reported a two-day history of sore throat and intermittent cough, beginning 13 days after returning to Canada. Review of systems revealed pre-syncopal episodes, frontal headaches, dizziness and myalgias associated with fevers. He denied any anosmia, loss of taste, abdominal pain, chest pain, or rashes.

On presentation to HSC, he was febrile at 39.4 °C and tachycardic to 108 bpm. Blood pressure was 124/56 mmHg, respiratory rate was 18, and oxygen saturation was 99% on room air. He

appeared in no acute distress and physical exam was effectively unremarkable other than tachycardia and cool extremities. Laboratory investigations are listed in Table 1. Blood cultures and malaria rapid antigen and smears were repeated, and stool multiplex PCR for gastrointestinal pathogens and culture were performed.

The pediatric infectious disease (ID) team was consulted. He was admitted to hospital given high suspicion for enteric fever and started on IV meropenem (1g every 8 hours) while awaiting speciation and antibiotic susceptibilities due to recent high rates of extensively drug resistant (XDR) typhoid in Pakistan [4]. Admission investigations revealed biochemical evidence of inflammation and coagulopathy including elevated CRP, LDH, triglycerides, D-Dimer, INR, ferritin, and creatinine kinase (CPK) (Table 1). ECG showed normal sinus rhythm. His blood culture confirmed *S.* Typhi infection (susceptible to ampicillin [minimum inhibitory concentration (MIC) of ≤ 2 μg/ml], ceftriaxone [MIC ≤ 0.5 μg/ml] and trimethoprim-sulfamethoxazole [MIC ≤ 20 μg/ml] but resistant to ciprofloxacin [MIC > 2 μg/ml]). His stool PCR was positive for *Salmonella* sp., and stool cultures confirmed *S.* Typhi. Repeat malaria blood smears were negative from three samples collected 24 hours apart. On day 3 of antibiotics, therapy was narrowed to IV ampicillin guided by susceptibility results and the patient defervesced on day seven of therapy. Given that enteric fever infection can rarely cause endocarditis and myocarditis and COVID-19 has been associated with myocarditis and coronary artery dilatation, an echocardiogram was performed; this showed no significant abnormality. Given the normal ECG and echo and normal troponin I on eight samples, we monitored but did not diagnose a myocarditis in this case.

The rheumatology service was consulted due to elevated inflammatory markers (Table 1) in the setting of COVID-19 for consideration of IVIG. Given the co-infection with *S.* Typhi and SARS-CoV-2, it was unclear whether hyperinflammation was secondary to bacteremia, acute COVID-19 or Multisystem Inflammatory Syndrome in Children (MIS-C). Ultimately IVIG was not given due to improvement in the inflammatory markers starting on day 4 of antibiotics and normal initial and repeat echocardiogram. The patient did not receive any SARS-CoV-2 directed therapy.

Due to significant biochemical hyperinflammation in the context of COVID-19, immobility and body habitus (BMI of 26.3 kg/m^2) with normal limb ultrasound ruling out deep vein thrombosis, anticoagulation was given (prophylactic enoxaparin) under the recommendation of the thrombosis team. This was complicated by liver dysfunction as indicated by elevated INR and hypoalbuminemia resulting in Vitamin K Supplementation.

On day 3 of admission, the patient developed tachypnea, hypoxia with the lowest saturation of 87% requiring low flow O_2 supplementation up to 3 L/min. He did not progress to severe respiratory distress. Chest X-ray showed streaky opacities in the retrocardiac region thought to represent atelectasis or bronchovascular crowding. He weaned off O_2 in less than 8 hours and was clinically diagnosed with fluid overload rather than progressive COVID-19 pneumonia. The patient defervesced after 7 days of appropriate antibiotics. He recovered clinically and was discharged home after 10 days on amoxicillin 1g TID to complete a 21-day treatment course and follow-up with ID as an outpatient.

On assessment in ID clinic two weeks after discharge, he had remained afebrile and had resolution of respiratory, gastrointestinal and constitutional symptoms with improving laboratory values (Table 1). He was counselled regarding MIS-C, to monitor for fevers, seek medical attention if febrile or appears unwell, and to inform health care workers of recent COVID-19 infection.

DISCUSSION

To our knowledge, this is the first documented case of *S.* Typhi and SARS-CoV-2 co-infection. Both disease entities can have similar clinical presentation of fever, respiratory and gastrointestinal symptoms and laboratory findings showing inflammatory changes, independently. Clinicians should be mindful that rarely two serious infections can happen concurrently and thus a broad differential should be maintained, particularly when there is pertinent epidemiology. While it is not possible to draw general conclusions from a single patient, and patients with either of these conditions can present with a wide range of severity, it is notable that the teenager presented here with enteric fever and concurrent COVID-19 was

sicker, and had more biochemical abnormalities, than typical for a child with either of these infections individually.

His fever and upper respiratory tract symptoms began 8 and 13 days after returning to Canada respectively. Given the estimated median incubation period of SARS-CoV-2 is approximately 5 days with 14 days reaching the 97th percentile, and the lack of a confirmed contact with a SARS-CoV-2 contact, it is not possible to say with certainty where the patient was infected with SARS-CoV-2[5]. With SARS-CoV-2 transmission occurring worldwide, it is highly likely that there will be more cases of concurrent COVID-19 and enteric fever, particularly in South Asia where risk of enteric fever is highest. This case also serves as a reminder to consider pre-travel immunization with a typhoid vaccine for travelers to endemic regions and advocate for immunization in endemic regions. In light of ongoing travel restrictions, the incidence of imported tropical infections such as enteric fever has decreased in non-endemic regions, however front-line clinicians must continue to have a high index of suspicion of imported infections in a returning traveller with fever. Description of additional cases with concurrent infections will help to better define the range of clinical illness in these patients as well as the true prevalence of co-infection, which are likely going undetected or underreported.

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AUTHOR'S CONTRIBUTIONS

S.I.A., S.I., E.A.C., S.K.M. conceived and drafted the manuscript. S.I.A. and S.I. performed the literature review. All authors contributed to manuscript revision, approved the final version of the manuscript and act as guarantors of the work.

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Table 1. Laboratory values in an enteric fever and COVID-19 co-infection case.

Laboratories	Ref. values	Units	Outside hospital ED (Day #5)	HSC ED (Day #7)	Admission Lab Tests (Day #8)	Peak/Trough	Discharge (Day #16)	Follow-up (Day #33)
WBC	4.8-10.8	x10^9/L	4.8 (N)	4.8 (N)	4.33 (N)	4.33 (N)	6.61 (N)	7.91 (N)
Hemoglobin	120-160	g/L	167 (H)	150 (H)	132 (N)	167 (H)	132g/L (N)	134g/L (N)
Platelet	150-500	x10^9 g/L	127 (L)	105(L)	90 (L)	90 (L)	163 (N)	262 (N)
Na+	136-144	mmol/L	130(L)	132 (L)	133 (L)	132 (L)	135 (N)	137 (N)
ALT	0-40	U/L	42 (H)	56 (H)	48 (H)	149 (H)	129 (H)	37 (H)
GGT	</=17	U/L	N/A	N/A	35 (H)	53 (H)	53 (H)	42 (H)
Creatinine	62-106	μmol/L	113 (H)	83(H)	62 (N)	113 (H)	44 (N)	47 (N)
ESR	2-34	mm/hr	28 (N)	48 (H)	19 (H)	36 (H)	36 (H)	23 (N)
CRP	0.1-1	mg/L	82.1(H)	87 (H)	92 (H)	109.6 (H)	22.1 (H)	2.1 (H)
INR	0.8-1.2		N/A	N/A	1.5 (H)	1.5(H)	1.2 (N)	1.0 (N)
PTT	24-36	seconds	N/A	N/A	26 (N)	35 (N)	33(N)	28 (N)
Albumin	37-50	g/L	N/A	N/A	32 (L)	31(L)	31 (L)	N/A
Triglyceride	<1.02	mmol/L	N/A	N/A	1.3 (H)	2.01 (H)	1.41 (H)	2.70 (H)
Ferritin	12.7-82.8	μg/L	N/A	N/A	1,365.1 (H)	1,780.6 (H)	570.9 (H)	77.3 (H)
D-Dimer	<0.50	μg/ml	N/A	11.86 (H)	12.22 (H)	12.47(H)	N/A	N/A
VWF	0.41-1.58	IU/ml	N/A	N/A	5.01 (H)	N/A	N/A	N/A
CPK	60-355	U/L	N/A	N/A	2628 (H)	2628 (H)	366 (H)	377 (H)
Troponin I	<30.9	ng/L	N/A	N/A	25.6 (H)	25.6 (H)	<10.0 (N)	<10.0 (N)
ProBNP	<35	pmol/L	N/A	N/A	9.7 (N)	N/A	N/A	N/A
LDH	360-730	U/L	N/A	N/A	2028 (H)	3016 (H)	1660 (H)	757 (H)
Fibrinogen	1.9-4.3	g/L	N/A	N/A	4.0 (N)	4.0 (N)	3.9 (N)	3.8 (N)

N (normal), H (high), L (low), N/A (non-available).
Day # refers to day of illness.