Nalidixic acid-resistant Salmonella enterica serotype typhi infection presenting with sub-intestinal obstruction and mesenteric adenitis

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ABSTRACT

الإنثان بالسالمونيلا التعيثية المقاومة لحمض الناليديكسيك تزيد من التركيز المشيط الأدنى لدواء الفلوروكينون بسبب الطفرة الصبغية في المورثة المشفرة لانزيم الحمض النووي و من المحتمل أن تؤدي لتأخر الإستجابة العلاجية و هذا بدوره يغيير مسير المرض مما يسمح بطول مدة المرض و حدوث مضاعفات . في هذه الحالة المسجلة نقدم مريضة من شبه القارة الهندية تم تشخيصها بهذا المرض (الإنثان بالسالمونيلا التعيثية المعوية المقاومة لحمض الناليديكسيك) بمضاعفات الانسداد المعوي مع وصف التشخيص، العلاج ، و بعد ذلك التحسن.

Nalidixic acid-resistant Salmonella typhi (NARST) infections increase minimal inhibitory concentrations of fluoroquinolones, due to chromosomal mutations in the gene encoding DNA gyrase, and can lead to a delayed treatment response. This in turn alters the course of the disease allowing for a protracted period of illness and the occurrence of complications. In this case report, we present a patient from the Indian sub-continent, who was diagnosed with NARST complicated by sub-intestinal obstruction, her diagnosis, treatment, and subsequent recovery.

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The last 2 decades have brought a change in the pattern of typhoid fever due to the emergence of multidrug-resistant strains (MDRS), particularly strains resistant to nalidixic acid.[1] Since an outbreak of nalidixic acid-resistant Salmonella typhi (NARST) in Vietnam in 1993 similar outbreaks have been reported throughout the world from Canada, India, Korea, to Japan.[1-5] In the present paper, we report a patient afflicted with NARST and describe the therapeutic choices in a situation of non-abating fever and a resistant organism.

Case Report. A 30-year-old Bangladeshi housewife mother of 3 children presented to the Accident and Emergency Department of Riyadh Medical Complex, Riyadh, Kingdom of Saudi Arabia, 15 days after returning from her home country complaining of fever associated with aches and pains, rigors and chills, loose motions, and central abdominal pain radiating to the back. The fever was continuously high grade and increasing at night. It started 8 days before presentation and was followed 2 days later by loose motions of watery stools approximately 4 times a day. Thereafter, she complained of abdominal pain located around the umbilicus, continuous, dull, mild to moderate in severity, with no obvious aggravating or relieving factor, radiating to the back and not preventing her from ambulation though she felt weak. There was no significant past medical or surgical history. She had 3 uneventful normal spontaneous vaginal deliveries, regular menses, no history of vaginal discharge, and had been on no medication apart from paracetamol for her recent illness. Her husband was alive and well working as a salesman. There was no reported history of tuberculosis in her family and friends and she was not consuming raw milk. During her vacation in her home country of Bangladesh, she had been well. On physical examination she was a well-built young female, ill looking, with no jaundice, no lymphadenopathy, and no lower limb edema. Her vital signs revealed a temperature of 39.5^{0}C, a blood pressure of 94/60 mm Hg, a pulse of 78 beats/minute and a respiratory rate of 22 breaths/minute. Examination of the cardiovascular system except for the above mentioned relative bradycardia and hypotension was unremarkable. Respiratory system, locomoter system and central nervous system

examination were normal. Abdominal examination revealed a diffuse mild abdominal tenderness with no rebound, tender hepatomegaly with a smooth edge, span of 16 cm. Rectal examination was normal. Laboratory investigations showed a complete blood count with white blood cells 8.5 x 10^3 and neutrophils 78%, hemoglobin 11.6 g/dl, hematocrit 33.6%, mean cell volume 83.4 fl, mean cell hemoglobin 28.9 pg, mean cell hemoglobin concentration 34.7 g/dl and platelet count of 99 x 10^3. Peripheral blood film showed thrombocytopenia. The erythrocyte sedimentation rate was 90 mm in the first hour. Coagulation profile showed a prothrombin time of 12.8 seconds, a partial thromboplastin time of 23.9 seconds and an international normalized ratio of 1.12. Urea and electrolytes showed a urea of 2.3 mmol/l, creatinine 69 µmol/l, glucose of 6.1 mmol/l, sodium 132, and potassium 3.3 mmol/l. Amylase 58 u/l, uric acid 153 mmol/l, calcium 2.05 mmol/l, phosphate 1.2 mmol/l, and magnesium 0.86 mmol/l. Liver function tests revealed an aspartate aminotransferase of 178 u/l, alanine transferase 109 u/l, alkaline phosphatase 214 u/l, total bilirubin of 24.62 µmol/l, direct bilirubin 17 µmol/l, and total protein 69 g/l and albumin 30 g/l. Cardiac enzymes showed a lactate dehydrogenase level of 872 u/l, and creatinine phosphokinase of 204 u/l. On lipid profile, the total cholesterol was 2.78 mmol/l, and triglycerides 4.14g/dl. Hepatitis B antigen screen, hepatitis C antibody, hepatitis A IgM, and human immunodeficiency virus screen were negative. Hepatitis A total IgG was positive indicating earlier exposure, C-reactive protein was 70.8. Brucella titers for abortus and melitensis were negative. Malaria films thin and thick were negative twice. Salmonella O antibodies were positive 1:320 H antibodies 1:320 and AH antibodies and BH antibodies negative. Bone marrow aspiration and biopsy showed only normal hematopoietic tissue. Urinalysis and culture, stool analysis, culture and stool for ova and parasites were negative repeatedly. Urine human chorionic gonadotrophin was negative indicating absence of pregnancy. An electrocardiogram and a chest radiograph were unremarkable. On the first day of hospitalization her temperature reached 40°C, and she was commenced on ceftriaxone 2 grams intravenously (iv) daily, ciprofloxacin 500 mgs orally twice daily, and mefloquine 1250 mg orally Stat dose. The latter was administered to combat a possible malaria falciparum infection, which was effectively ruled out later. A surgical consult was made, while blood and bone marrow cultures were awaited, because of the suspicion of sub-acute intestinal obstruction, based upon her abdominal pain and obvious distension. Supine and erect x-rays of the abdomen revealed distended small bowel loops, with multiple fluid levels, but no perforation (**Figure 1**). Ultrasound of the abdomen revealed a diffuse enlarged fatty liver with a span of 20 cm and a small thick walled gallbladder. On the second day of admission she remained febrile with a range between 38.5-40.5°C. A CT of the abdomen showed multiple mesenteric and para-aortic enlarged lymph nodes, largest measuring 1.5x1.5 cm, hepatomegaly and enlarged small bowel loops (**Figure 2**). Subsequently, she was started on anti-tuberculous medication including isoniazid, rifampicin, and pyrazinamide as well as pyridoxine. Mantoux test was negative, and she remained highly febrile when on the 6th day of hospitalization Salmonella typhi was cultured from a blood culture taken on the second day of admission. The organism was reported to be sensitive to ciprofloxacin, cefotaxime, ceftazidime, Augmentin,

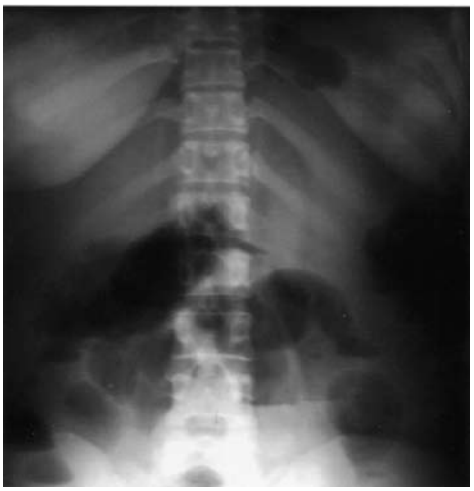

Figure 1 - Abdominal radiograph showing dilated small bowel.

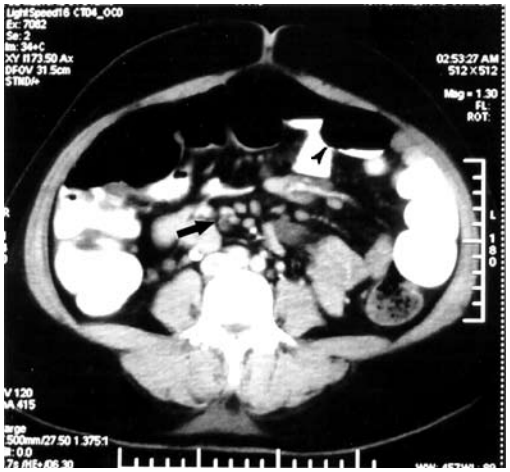

Figure 2 - Computed tomography of the abdomen with contrast showing mesenteric, lymphadenopathy (large arrow) and dilated loops of small bowel (small arrow).

piperacillin, imipenem, and meropenem. Repeated blood cultures following the 4th day of admission were reported as negative. Anti-tuberculous medication was discontinued, and ciprofloxacin dose increased to 750 mg orally twice daily, dexamethasone 230 mg iv stat was added followed by dexamethasone 70 mg iv every 6 hours for 2 days and ranitidine 50 mg iv every 8 hours. On the 7th day of hospitalization, the organism was reported by the microbiology laboratory to be nalidixic acid resistant and she started on azithromycin 1 gram orally daily for 5 days in addition to her other medications. On the 14th day she became afebrile, and the abdominal distension had regressed and the pain had abated. She was discharged on the 15th day in good health on ciprofloxacin 750 mg orally twice daily to be continued for a week. On a visit to the outpatient department 2 weeks later she was in good health.

Discussion. Enteric fever is an inclusive term for a systemic infection caused by Salmonella enterica, including serotype typhi, and paratyphi.[6] The former also known as "typhus abdominalis," or "typhoid fever," where "typhus" denotes clouding of the mind, is nowadays a predominantly travel associated disease and domestic outbreaks can usually be pinpointed to an immigrant source.[6-8] The greatest travel risk appears to arise from travel to the Indian subcontinent from which our patient arrived.[6] Faced with a highly febrile patient from the above mentioned location necessitates the inclusion of malaria in the differential diagnosis, not only because the diseases of typhoid fever and malaria have similarities and can coexist in the same patient, but also because malaria falciparum is a deadly illness. In fact, the term "typho-malaria" was coined formerly, only to be debunked by Sir William Osler, whose clinical description of typhoid fever remains unsurpassed until this day.[9] In view of the considerations mentioned above, our patient received a course of mefloquine over night, before results of blood films were obtained. Reliance on fever patterns to differentiate typhoid fever and malaria, as Sir Osler did, is in no doubt valid, but needs time for observation and is in our view not advisable, in ill patients, who may or may not have had prior antibiotic therapy, which potentially could distort the pattern of fever observed. Clinically our patient demonstrated high fever associated with relative bradycardia and abdominal tenderness and a normal leukocyte count with a predominance of neutrophils and a high serum C-reactive protein concentration. C-reactive protein, which is produced by the liver, has been shown to be highest in Salmonella typhi culture positive patients.[10] A tentative diagnosis of typhoid fever was made, and the patient was commenced on ceftriaxone and ciprofloxacin. The former is a first line therapy and the latter can be given in sensitive strains though starting both was probably over treatment from our side.[6] Bone marrow aspiration and biopsy was performed while results of other cultures were being awaited, since enteric fever is the only bacterial infection of humans for which bone marrow examination is routinely recommended.[11] It is particularly helpful with increasing duration of illness, which increases the ratio of bone marrow-to-blood bacterial concentrations.[11] Widal test nowadays is regarded clinically not useful but an H titer of >64 in our case 320 in a non-immunized patient indicates acute infection.[2,12] The differential diagnosis in this kind of patient is wide and is extended by her presentation with sub-acute intestinal obstruction. When CT abdomen revealed mesenteric adenitis the differential diagnosis could be narrowed down with one series reporting Yersinia enterocolitica, non-typhoidal Salmonella, tuberculosis, and typhoid fever as the possible infectious causes of our patient's condition.[13] Mesenteric adenitis is known to occur in typhoid fever, can be marked and associated with a high fever, just as in our case.[14] Other complications of typhoid fever include intestinal perforation, psoas abscess and hepatitis.[2,15,16] Though liver involvement in the disease process was also apparent in our patient, it did not develop into a fulminant hepatitis and abated over the course of hospitalization. Eventually, blood culture secured the diagnosis. However, despite an initially reported sensitive organism, there was no clinical response to therapy and our patient remained highly febrile though her general well being improved following dexamethasone administration, a strategy devised in Indonesia, which reportedly decreases mortality substantially.[2] The nalidixic acid screening test was ordered, which detects increased fluoroquinolone resistance, and was found to be positive.[17] Hence, the therapy was altered according to established guidelines, and the azithromycin added to the regimen.[2] It is well known that patients with NARST infections have in general a poor outcome, and have associated longer duration of fever at presentation, a higher frequency of hepatomegaly, and higher levels of aspartate aminotransferase 121 u/l mean (66-235) versus 73 u/l in susceptible isolates.[18] There are calls to revise the breakpoint of ciprofloxacin for Salmonella typhi, since treatment failures have occurred and we wholeheartedly join them after we needed to add azithromycin to our regimen to finally achieve the clinical response of normothermia and general well being.[19]

Education of travelers regarding hygiene precautions and eventually more effective vaccines against the new multidrug resistant strains, in addition to proper

sanitation in developing countries can protect people from this potentially fatal illness.[6] Patients presenting to Saudi Arabian hospitals after returning from the Indian subcontinent, complaining of high grade fever and abdominal pain should be investigated for typhoid fever, since prompt diagnosis and treatment is rewarding and prevents a public health concern.

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