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DIAGNOSTIC DILEMMA
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A Fall in Ghana

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PRESENTATION

A fall marked the beginning of a perilous medical journey for a 34-year-old man. He had traveled from the United States, where he lives with his family, to Accra, Ghana for business purposes and was well until the ninth day of his trip, when he fell and twisted his lower back. Although he was able to stand immediately afterwards, the back pain worsened as the morning progressed and was then compounded by malaise, leading him to spend the remainder of the day in bed. He had no neurologic deficits or loss of bowel or bladder continence.

That evening, the patient developed a fever of 102.1° F (38.9° C) with chills and progressive malaise. His health status began to rapidly deteriorate, and he was evacuated to the United States the following day. En route he developed hypoxia, which was corrected with supplemental oxygen. Tachycardia and hypotension responded to intravenous fluid. Upon arrival, he was evaluated at a community hospital, where he received empiric ceftriaxone. He was determined to be in critical condition and was transferred urgently to the intensive care unit (ICU) of the National Naval Medical Center in Bethesda, Md for further management.

Previously healthy, the patient had an unremarkable medical history. A systems review revealed no further complaints, and he had been fully compliant with his malaria prophylaxis. Throughout his stay in Ghana, he had no contact with sick people, animal exposure, or insect bites. He did not leave the luxury hotel complex and only ate approved prepared meals, except for 1 dinner on day 3, which took place at a high-end restaurant with colleagues. His vaccinations were current.

ASSESSMENT

Upon admission to the ICU, the patient's temperature was 102.9° F (39.4° C). He was tachypneic, with a respiratory rate of 47 breaths per minute and an oxygen saturation of 96% on 100% oxygen via a non-rebreather mask. His heart rate was 116 beats per minute with a blood pressure of 90/50 mm Hg. He was somnolent but appropriately conversant. Lung examination revealed accessory respiratory muscle use, diffuse rales, and bibasilar lung crackles. Cardiac, abdominal, and neurological exams were unremarkable. Scleral icterus was noted, but the patient had no rash or skin lesions. Initial laboratory results were significant for thrombocytopenia, coagulopathy, renal insufficiency, and hepatitis (Table 1).

The patient's progressive respiratory failure required intubation and mechanical ventilation. Continuous infusion of norepinephrine was initiated for persistent hypotension despite adequate volume resuscitation. Pulse contour analysis of a good-quality invasive radial arterial pulse tracing showed a cardiac index of 5.1 and a systemic vascular resistance of 631 $dyn \cdot sec \cdot cm^{-5}$. Computed tomography of the chest disclosed no evidence of pulmonary embolism. Bilateral diffuse infiltrates with dense alveolar consolidations in the dependent areas were consistent with a diagnosis of adult respiratory distress syndrome (Figure 1).

Empiric antibiotic coverage with doxycycline, meropenem, levofloxacin, vancomycin, atovaquone/proguanil, oseltamivir, and quinine was administered. Bronchoscopy with bronchoalveolar lavage showed normal airways and turbid lavage fluid with a white blood cell count of 960×10^3 cells/mm^3 and a normal differential cell count. Gram-staining of the bronchoalveolar lavage fluid showed no organisms. A peripheral malaria smear was negative, as was a Binax NOW immunochromatographic assay. Further microbiologic studies are summarized in Table 2. Abdominal and pelvic computed tomography indicated nonspecific dif-

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Table 1 Laboratory Evaluation

Variables	Reference Range	Values on Admission	Values on Hospital Day 1	Values upon Discharge
Hematology				
WBCs ($\times 10^3$ cells/mm^3)	4.5-11	7.1	6.4	10
Neutrophils (%)		94.4		
Lymphocytes (%)		3.8		
Monocytes (%)		1.7		
Basophils (%)		0.1		
Eosinophils (%)		0.0		
Hematocrit (%)	41-53	31.5	27	26.7
Hemoglobin (g/dL)	13.5-17.5	10.5	9.1	8.9
Platelets ($\times 10^3$/mm^3)	150-350	121,000	84,000	597,000
PTT (sec)	22.1-35.1	43.3		
PT (sec)	11.1-13.1	20.4		
INR		1.8		1.0
D-dimer (μg/mL)	$<$0.5	9.36		
Chemistry				
Sodium (mEq/L)	136-145	140	143	145
Potassium (mEq/L)	3.5-5	3.7	4.1	4.5
Chloride (mEq/L)	98-106	110	117	110
Carbon dioxide (mEq/L)	21-30	23	23	26
Urea nitrogen (mg/dL)	10-20	23	32	21
Creatinine (mg/dL)	0.8-1.2	1.2	1.5	1
Total bilirubin (mg/dL)	0.3-1	3	5.5	1
Direct bilirubin (mg/dL)	0.1-0.3		4.5	
Total protein (g/dL)	5.5-8	5	5	5.5
Albumin (g/dL)	3.5-5.5	2.7	2.4	2.8
AST (U/L)	0-35	46	115	54
ALT (U/L)	0-35	43	109	47
ALP (U/L)	30-120	48	84	72
Amylase (U/L)	60-180		101	191
Lipase (U/L)	0-160		132	113
Calcium (mg/dL)	9.0-10.5	7.4		8.1
Lactate (mmol/L)	0.6-1.7	1.3		
CK (U/L)	60-400	806	646	
CK-MB (ng/mL)	0-7	8	7	
Troponin-I (ng/mL)	0-0.4	0.04	0.04	
TSH (μU/mL)	0.5-4.7		1.7	
Cortisol (μg/dL)	5-25		34.7	
Immunology				
ANA	Negative	Negative		
ANCA	Negative	Negative		
Anti-GBM Ab	Negative	Negative		

WBCs = white blood cells; PTT = partial thromboplastin time; PT = prothrombin time; INR = international normalized ratio; AST = aspartate aminotransferase; ALT = alanine aminotransferase; ALP = alkaline phosphatase; CK = creatine kinase; CK-MB = creatine kinase, MB fraction; TSH = thyroid-stimulating hormone; ANA = antinuclear antibody; ANCA = antineutrophil cytoplasmic antibodies; Anti-GBM Ab = anti-glomerular basement membrane antibodies.

fuse bowel-wall thickening and mesenteric lymphadenopathy; a complete abdominal ultrasound examination was unremarkable. Computed tomography of the head was normal. A lumbar puncture yielded normal results.

DIAGNOSIS

Acute febrile illness and rapidly progressive cardiopulmonary failure in a previously healthy 34-year-old man generated a broad differential diagnosis focusing on infectious causes (Table 3). Annually, 4 million travelers become ill enough to seek health care abroad or upon returning home.[1] The GeoSentinel database, a network of 30 specialized clinics on 6 continents, provides information regarding the association between travel destination and the probability of clinical diagnoses.[1] Malaria is the most frequent cause of systemic febrile illness among sick travelers; several reports note adult respiratory distress syndrome as a complication. Furthermore, rickettsial infections can be complicated by adult respiratory distress syndrome. Typhoid fever is a pri-

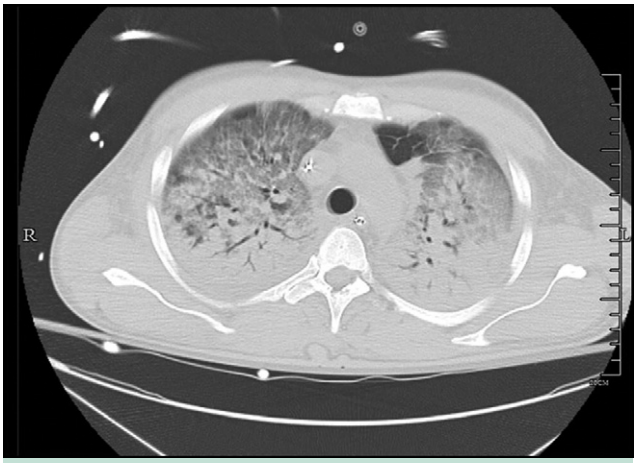

Figure 1 Computed tomography of the chest showed bilateral diffuse infiltrates with dense alveolar consolidations in the dependent areas.

mary contributor to systemic febrile illness among travelers returning from South Central Asia, and less commonly, from Africa.

In the case presented here, blood cultures obtained at the community hospital became positive for Gram-negative rods and grew *Salmonella paratyphi*, serogroup C. A diagnosis of typhoid fever associated with adult respiratory distress syndrome and multiple organ dysfunction syndrome was made.

Typhoid fever is an acute systemic disease caused by ingestion of food or water contaminated with *Salmonella enterica*, serotype Typhi or Paratyphi. Typically, after an asymptomatic period of 7-14 days (range, 3-60 days), the onset of bacteremia is marked by fever and malaise.[2] Patients typically present with influenza-like symptoms and few physical signs.[3]

It is estimated that 21 million cases of typhoid fever arise annually worldwide; 90% occur in Asia.[2] In the US, about 500 cases per year are reported, and 75% are associated with foreign travel.[4] There is a wide spectrum of clinical manifestations. Severe typhoid fever is defined as fever plus delirium, stupor, coma (in Greek, typhus means "fog"), or shock and is associated with fatality rates of 44-56%.[5]

Many complications of typhoid fever have been described (Table 4). Although cough is a common symptom, occurring in 11-86% of cases, pulmonary complications of typhoid fever are rare, documented in only 1-6% of cases.[6] Reported pulmonary manifestations include bronchitis, pneumonia, lung abscess, pleural effusion, and empyema, yet sputum cultures are usually negative.[4,6] Adult respiratory distress syndrome is a very rare complication of typhoid fever, which is surprising, given the bacteremia and endotoxinemia associated with the disease. To our knowledge, only 5 cases are reported in the literature.[7] However, in a report on 5 fatal cases of typhoid fever, features of adult respiratory distress syndrome were discovered on autopsy in 3 cases, suggesting that the disorder might be underreported.[8]

The standard diagnostic method is blood culture, positive in 60-80% of patients. Bone marrow cultures are more sensitive, with ≥85% of infected patients testing positive. Stool culture sensitivity is about 30%. Serologic testing, the Widal's test, is controversial due to varying sensitivity, specificity, and predictive values in different geographic areas.[9]

MANAGEMENT

Randomized controlled trials indicate that fluoroquinolones are the most effective typhoid fever treatment.[9] In severe typhoid fever, fluoroquinolones should initially be given intravenously, and treatment should last for at least 10 days. Furthermore, patients with delirium, stupor or coma, and shock might benefit from the prompt administration of dexamethasone. In a randomized double-blind trial involving 38 patients in Indonesia with severe typhoid fever, mortality was decreased from 50% to 10% ($P = .003$) when high-dose dexamethasone was administered (3 mg/kg over 30 minutes, followed by 1 mg/kg every 6 hours for 8 doses).[3] Lower dosages of steroids were not found to be effective.[5] Chronic biliary carriage might occur in 2-5% of

Table 2 Microbiology Studies

Test	Result
Legionella antigen, urine	Negative
Streptococcus antigen, urine	Negative
Blood Cultures	
On admission (at community hospital)	Gram negative bacteria
First day (4 draws out of 4)	Negative
Second day (2 draws out of 2)	Negative
Third day (4 draws out of 4)	Negative
Stool Cultures	No growth
	Negative for ova and parasites
Clostridium difficile toxin	Negative
Lumbar puncture	No growth
BAL	
Bacterial culture	No growth
Viral culture	No growth
Fungal culture	No growth
AFB smear and culture	Negative
Influenza, CMV, RSV antigen	Negative
Serologies	
Leptospira	Negative
Hepatitis A, B, C	Negative
EBV	Negative
CMV	Negative
Brucella	Negative
HIV	Negative

BAL = bronchoalveolar lavage; AFB = acid-fast bacillus; CMV = cytomegalovirus; RSV = respiratory syncytial virus; EBV = Epstein-Barr virus; HIV = human immunodeficiency virus.

Table 3 Differential Diagnosis of Fever and Rapidly Progressive Cardiopulmonary Failure

Bacterial Infection
Severe community-acquired pneumonia
Meningitis, endocarditis
Rickettsial disease (babesiois, ehrlichiosis, Rocky Mountain spotted fever, scrub typhus, Mediterranean spotted fever)
Q-Fever (*Coxiella burnetii*)
Brucellosis
Plague (*Yersinia pestis*)
Tularemia (*Francisella tularensis*)
Typhoid fever/salmonellosis
Leptospirosis (*Leptospira interrogans*)
Anthrax
Mycobacterial infections
Viral Infections
Viral pneumonia (influenza, CMV, EBV, VZV, SARS)
Hantavirus
Dengue fever and yellow fever
Hemorrhagic fever (Lassa, Marburg, or Ebola viruses)
Fungal infections
Coccidiomycosis
Cryptococcus
Histoplasmosis
Blastomycosis
Parasitic infections
Malaria
Leishmaniasis
Schistosomiasis
Strongyloides
Noninfectious causes:
Inflammatory
Rapid-onset interstitial pneumonia (acute interstitial pneumonia, acute hypersensitivity pneumonitis)
Acute eosinophilic pneumonia
ARDS due other causes (inhalation injury, drug overdose, trauma)
Rheumatologic disorders
Wegener granulomatosis, Churg-Strauss disease, Goodpasture's syndrome
Systemic lupus erythematosus, antiphospholipid syndrome
Other
Malignancy, lymphoma, lymphoproliferative disease, leukemia
Pulmonary embolism, aortic dissection, acute myocardial infarction
Adrenal insufficiency, thyroid storm

CMV = cytomegalovirus; EBV = Epstein-Barr virus; VZV = varicella zoster virus; SARS = severe acute respiratory syndrome; ARDS = acute respiratory distress syndrome.

cases even after treatment and can last as long as a year. In that situation, antibiotic therapy might be necessary; cholecystectomy also might be necessary if gallstones are present.

The cumulative efficacy at 3 years for Ty21a, an attenuated live vaccine, and the Vi typhoid vaccine, which is based on the purified capsular polysaccharide, are similar at 51% and 55% respectively, but, as was the case with our patient, who received the polysaccharide vaccine, the agents do not guarantee protection.[10]

Our patient was treated with a 14-day course of levofloxacin. He did not have neuropsychiatric symptoms, and his shock resolved within 24 hours, so he was not treated with dexamethasone. He remained in the ICU for 11 days, was extubated on day 6, and was discharged to rehabilitation on hospital day 16. By discharge, all of his laboratory

Table 4 Manifestations and Complications of Typhoid Fever

Organ System	Prevalence	Risk Factors
Abdominal	10-25%	
Gastrointestinal hemorrhage	10%	HIV, IVDU, pyogenic infection, hemoglobinopathy
Gastrointestinal perforation	1-3%	
Hepatitis, cholecystitis	20%	
Pancreatitis	20%	
Hepatic or splenic abscesses	1-5%	
Cardiovascular	1-5%	
Myocarditis, Endocarditis	1-5%	Existing valvular abnormalities
Pericarditis, arteritis	1%	
Neuropsychiatric	3-35%	
Cerebral edema, seizures Encephalopathy Meningitis Cerebral abscess, ventriculitis Guillain-Barré-syndrome		Pulmonary infections, meningitis, ventriculitis, trauma, surgery, osteomyelitis of the skull
Respiratory	1-6%	
Bronchitis, Pneumonia, Empyema ARDS		Past pulmonary infection, sickle cell disease, HIV, alcohol abuse
Hematologic	Common	
Anemia, DIC, thrombocytopenia	Common	
Hemophagocytic syndrome	<1%	
Renal	5-10%	
Glomerulonephritis Acute renal failure		Hepatitis
Others		
Focal abscess	<1%	
Pharyngitis	<1%	
Osteomyelitis	<1%	Sickle cell disease
Arthritis	<1%	
Genitourinary system, orchitis	<1%	Urinary tract pathology

HIV = human immunodeficiency virus; IVDU = intravenous drug use; ARDS = acute respiratory distress syndrome; DIC = disseminated intravascular coagulation.

Adapted from: Huang DB, DuPont HL. Problem pathogens: extra-intestinal complications of Salmonella enterica serotype Typhi infection. *Lancet Infect Dis*. 2005;5:341-348.

abnormalities had resolved, and a repeated stool culture showed no evidence of *Salmonella paratyphi*. In summary, typhoid fever should be considered as a possible diagnosis in patients with an acute febrile illness and rapidly progressive cardiopulmonary failure, especially for patients who have traveled from endemic regions.

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