Case Report

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Typhoid Fever in a Non-Endemic Country: Diagnostic and Therapeutic Challenges in a Returning Traveler

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Abstract

Background: Typhoid fever (TF) is a systemic infection caused by *Salmonella enterica* serovar Typhi, typically associated with regions where sanitation and access to clean water are inadequate. Although rare in non-endemic countries, TF remains a diagnostic consideration in travelers returning from endemic areas with febrile illness. **Case report:** We present the case of an 18-year-old female who developed TF following recent travel to Nigeria. The initial clinical presentation, including fever, dysuria, and abdominal pain, led to a misdiagnosis of acute pyelonephritis. Malaria, arboviral infections, acute viral hepatitis, and parasitic diseases were systematically ruled out through clinical evaluation, serological testing, and parasitological analysis. The clinical course was marked by fever, abdominal pain, somnolence, and hematological and hepatic abnormalities. Blood cultures confirmed the diagnosis, with the isolate verified and serotyped by the National Center of Infectious and Parasitic Diseases. Targeted antimicrobial treatment with ceftriaxone and levofloxacin resulted in full recovery, with no evidence of relapse or chronic carriage over a three-month follow-up period. **Conclusions:** This case highlights the critical importance of a structured differential diagnostic approach and microbiological confirmation in febrile patients with relevant travel history. In non-endemic settings, where TF may be underrecognized, early recognition, pathogen identification, and appropriate antimicrobial therapy remain essential to favorable outcomes and public health safety.

Keywords: typhoid fever; returning traveler; *Salmonella enterica* serovar Typhi; non-endemic country; case report

1. Background

TF is an acute systemic infection caused by *Salmonella enterica* serovar Typhi, a Gram-negative, facultative anaerobic bacterium from the family *Enterobacteriaceae*, with humans as the only reservoir. It remains a significant health concern in regions with limited access to safe drinking water and inadequate sanitation infrastructure, such as South Asia, Sub-Saharan Africa, and parts of South America [1,2]. Despite the availability of preventive and therapeutic measures, TF continues to pose a public health challenge due to the moderate efficacy of existing vaccines (~55%) and the growing prevalence of multidrug-resistant (MDR) strains [3]. In non-endemic regions like Bulgaria, TF is encountered primarily among travelers returning from endemic areas and migrants, which necessitates increased diagnostic vigilance among clinicians [1,2]. Typical symptoms include fever, malaise, abdominal pain, constipation, enlargement of liver and spleen, and a characteristic typhoid state manifested by delirium or obtundation. In some cases, rose-colored spots may appear on the chest and abdomen [4]. Diagnosis can be challenging due to its nonspecific clinical manifestation, often leading to misdiagnosis. This case report outlines the diagnostic course and clinical management of a young female patient whose early presentation mimicked a urinary tract infection, resulting in a delayed diagnosis of typhoid fever following her return from West Africa, where she

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had visited family. The aim is to emphasize the critical role of epidemiological history, differential diagnosis, and microbiological confirmation when evaluating febrile patients in non-endemic settings.

2. Case Presentation

An 18-year-old female was admitted to the Department of Internal Medicine at University Hospital "St. Marina" – Varna, Bulgaria, with an initial working diagnosis of acute pyelonephritis. One week prior to admission, she had developed a fever of up to 39°C, diffuse abdominal pain, dysuria, myalgia, arthralgia, and anorexia, with no clinical improvement despite treatment with cefpodoxime.

The patient had returned from Nigeria approximately one month prior, where she had stayed with relatives for four weeks. As a medical student, she traveled during the summer academic break. She had received the yellow fever vaccination, as required for travel to endemic regions, and did not seek additional medical consultation prior to departure.

Upon admission, the patient was in moderately impaired general condition, febrile up to 39°C, somnolent, but responsive. Physical examination revealed a dry, coated tongue; absence of rash or lymphadenopathy; and soft, non-tender abdomen without hepatosplenomegaly. There were no signs of respiratory or neurological involvement. Laboratory tests indicated anemia, thrombocytopenia, and leukopenia with marked neutrophilia, elevated liver enzymes, hypoalbuminemia, and hypoproteinemia. Inflammatory markers (CRP, ferritin) were significantly elevated. Electrolyte disturbances included hyponatremia and hypokalemia (Table 1). Urinalysis showed proteinuria, leukocyturia, and erythrocyturia. Imaging studies (abdominal ultrasound and chest X-ray) revealed no abnormalities. Serological tests for acute viral hepatitis, Epstein–Barr virus (EBV), cytomegalovirus (CMV), influenza virus, and vector-borne diseases were negative. No pathogenic microorganisms were isolated from blood, stool, or urine cultures. Thick and thin blood smears (three samples) were negative for *Plasmodium* spp. Blood cultures grew *Salmonella enterica* serovar Typhi, which was confirmed and serotyped by the National Center of Infectious and Parasitic Diseases (NCIPD), and showed susceptibility to amoxicillin/clavulanic acid, ampicillin, aztreonam, cefotaxime, ceftazidime, ceftriaxone, levofloxacin, meropenem, and piperacillin/tazobactam.

Table 1. Laboratory test results during hospitalization.

Test[1–20]	14.11	26.11	Reference range
Hb, g/l[1]	100.0	116.0	120–160
RBCc, x10[12]/l[2]	3.94	4.25	3.8–5.2
Leucocytes, x10[9]/l[3]	3.68	5.74	4.0–10.0
Neutrophils, %[4]	70.7	55.7	40–75
Basophils, %[5]	0.4	0.8	0–1
Monocytes, %[6]	3.6	4.4	2–8
Eosinophils, %[7]	0.0	0.1	0–5
Lymphocytes, %[8]	25.3	35.8	20–45
Plt, x10[9]/l[9]	58	163	150–400
Urea, mmol/l[10]	13.3	8.2	2.5–8.3
Creatinine, μmol/l[11]	99	89	44–97
Total protein, g/l[12]	51.0	69.5	64–83
Albumin, g/l[13]	25.0	34.0	35–52
ALT, U/l[14]	680.0	108.0	<40
AST, U/l[15]	2586.0	85.0	<40
GGT, U/l[16]	140.0	41.0	<38
CRP, mg/l[17]	174.0	16.09	<5
Na, mmol/l[18]	129.0	135.0	135–145
K, mmol/l[19]	3.3	3.7	3.5–5.1

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Cl, mmol/l[20]	95.0	101.0	98–107

Legend: [1] Hemoglobin. [2] Red blood cells. 3.[3] Leucocytes. [4] Neutrophils. [5] Basophils. [6] Monocytes. [7] Eosinophils. [8] Lymphocytes. [9] Platelets. [10] Urea. [11] Creatinine. [12] Total protein. [13] Albumin. [14] Alanine aminotransferase (ALT). [15] Aspartate aminotransferase (AST). [16] Gamma-glutamyltransferase (GGT). [17] C-reactive protein (CRP). [18] Sodium (Na). [19] Potassium (K).

Following consultation with an infectious diseases specialist, the patient was transferred to the Infectious Diseases Clinic for further diagnostic evaluation and management, where she presented with persistent fever, accompanied by abdominal pain, loss of appetite, pronounced weakness, and a generally reduced level of activity and interaction, consistent with a developing typhoid state. Surgical pathology was ruled out. A ten-day course of etiological therapy was administered according to the antibiotic susceptibility profile of the isolated pathogen (Ceftriaxone at a dose of 2 × 2.0 g/day IV and Levofloxacin 1 × 500 mg/day IV), in addition to pathogenetic and symptomatic treatment including glucose-saline infusions, plasma transfusion, dexamethasone, H_2-receptor antagonists for stress ulcer prophylaxis, hepatoprotective agents, antipyretics, and a laxative. This therapeutic approach led to rapid infection control and complete clinical recovery. The patient was discharged in good condition after obtaining negative blood, urine, and stool cultures. At both the first- and third-month post-discharge, she remained in good general health, with no clinical or laboratory evidence of relapse or chronic carrier.

3. Discussion

Travel to developing regions is associated with an increased risk of acquiring infectious diseases, with travelers visiting friends and relatives (VFR) representing a particularly vulnerable subgroup. They often face extended stays, greater exposure to local conditions, and lower rates of pre-travel medical advice, making them more likely to underestimate infectious risks [5,6]. In returning travelers, fever persisting for more than five days necessitates a systematic diagnostic approach, with epidemiological history serving as a key component. In the present case, the patient—a VFR traveler—was initially misdiagnosed with acute pyelonephritis based on the presence of fever, abdominal pain, and anorexia; however, the absence of supporting features such as lumbar pain or positive urine cultures necessitated diagnostic reconsideration.

Malaria remains a major concern in travelers returning from endemic regions [7]; however, in the present case, repeated negative blood smears effectively ruled out this diagnosis. According to CDC guidelines, when malaria is excluded in patients returning from sub-Saharan Africa, the differential diagnosis should include arthropod-borne viral infections (e.g., dengue, yellow fever), invasive meningococcal disease, salmonellosis (including typhoid and paratyphoid fever), and parasitic diseases such as schistosomiasis and trypanosomiasis [8]. Based on these considerations, the diagnostic work-up was extended to include arboviral and parasitic infections. Dengue, schistosomiasis, and amebiasis, as well as EBV, CMV, and hepatotropic viruses, were all excluded based on clinical presentation and laboratory findings. The patient's persistent fever, typhoid state with obnubilation, abdominal pain, and abnormal hematological and hepatic profiles, combined with positive blood cultures for *Salmonella enterica* serovar Typhi, led to the final diagnosis of TF. Microbiological confirmation by blood culture remains the gold standard for the diagnosis of TF. In this case, the isolated strain was further serotyped by NCIPD to confirm its identity and epidemiological relevance. Although modern diagnostic tools such as RT-PCR offer high sensitivity, their availability is limited in many settings, including Bulgaria [1].

Antimicrobial therapy should be guided by local patterns of antimicrobial resistance. In this case, the patient was treated with ceftriaxone and levofloxacin, as confirmed by the susceptibility profile of the isolated strain. The increasing prevalence of MDR and extensively drug-resistant (XDR) *Salmonella Typhi* strains represents a significant global health concern, particularly in regions such as South Asia and sub-Saharan Africa. As of 2023, more than 120 cases of XDR *Salmonella Typhi* have been reported in the United States, including cases in patients without recent international travel

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history, underscoring the need for continued epidemiological vigilance even in non-endemic settings [9]. Initial antimicrobial therapy should be guided by regional resistance patterns, with carbapenems and azithromycin recommended as first-line agents in areas with high prevalence of XDR *Salmonella Typhi.* Early initiation of therapy is critical to prevent complications and reduce mortality [10].

Despite the absence of complications or relapse during follow-up, the potential for chronic carriage remains an important consideration. Studies suggest that relapse occurs in up to 10% of cases, while 1-4% of patients may develop chronic carrier states [9]. The effectiveness of early diagnosis and timely antimicrobial treatment in preventing relapse and chronic carriage was demonstrated in our patient, who showed no clinical or microbiological evidence of either during the three-month follow-up period.

This case highlights the importance of a structured diagnostic approach, microbiological confirmation, and tailored therapy in the management of travelers returning with febrile illness. The role of national reference laboratories in serotyping, molecular analysis, and antimicrobial resistance monitoring is indispensable for accurate diagnosis, appropriate treatment, and epidemiological control.

4. Conclusion

Our clinical case highlights the diagnostic and therapeutic challenges of managing TF in non-endemic countries. Its clinical significance remains underestimated, often resulting in delayed diagnosis and a higher risk of complications. A thorough epidemiological history, particularly recent travel to endemic regions, is crucial in guiding diagnostic decisions. Travelers to such areas are at higher risk of infectious diseases, necessitating enhanced clinician awareness and familiarity with region-specific pathologies.

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