Typhoid Fever Complicated with Bowel Perforation in an HIV Patient

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Abstract

Background

Patients with HIV infection often develop multiple complications and comorbidities, including malignancies and opportunistic infections. The association of HIV infection with typhoid fever remains unclear, though there is a clear risk of typhoid in HIV infected persons. Therefore, the diagnosis of typhoid should be considered in HIV infected individuals, mainly when they present with severe ulcerative diarrhoea.

Case Presentation

A 38-year-old gentleman presented with fever with significant weight loss and anorexia for eight months. He had worked abroad in a middle east country and had recently returned to Sri Lanka. On examination, he was thinly built with a BMI of 18 kg/m^2. The initial full blood count revealed lymphopenia, anaemia and thrombocytopenia. He also had mild hyponatremia. His HIV Ag/Ab combo assay became positive, and he was found to have a low CD4 count. While on antiretroviral therapy, he developed nausea, vomiting and diarrhoea while continuing the preexisting fever followed by severe dyspnoea and epigastric pain and tenderness associated with tachypnoea, tachycardia and hypotension. The urgent chest X-ray revealed gas under the diaphragm. An urgent exploratory laparotomy was done, and he was found to have distal ileal perforation with a typhoid ulcer which was histologically confirmed later. During the postoperative period, the patient developed severe pneumonia, scummed despite all the resuscitation care given.

Conclusion

Fever in HIV patients could be due to HIV itself, opportunistic infections or malignancies. The diagnosis of typhoid should be considered in HIV infected individuals, mainly when they present with severe ulcerative diarrhoea, constipation or bowel perforation. *Salmonella typhi* infection in HIV/AIDS patients may cause life-threatening complications, where the case fatality rate of typhoid significantly increase when present concurrently with HIV, and the mortality further increases with delayed diagnosis.

Background

Human immunodeficiency virus (HIV) infection probably spread from non-human primates to humans sporadically throughout the 1900s. However, only in the 1980s did the virus come to the world's attention when men who had sex with men in urban centres began presenting with advanced and unexplained immunodeficiency. Within two years of the first report of what eventually became known as acquired immune deficiency syndrome (AIDS), scientists discovered the causative virus: HIV [1]. HIV has infected 77.5 million people worldwide, and an estimated 36.7 million people are now living with the virus. Since

the start of the epidemic, 34.7 million people have died from AIDS-related illnesses [2]. In Sri Lanka, an estimated number of 3600 adults and children live with HIV, and 566 cumulative AIDS-related deaths have occurred as of the end of 2019 [3]. Patients with HIV infection often develop multiple complications and comorbidities, including malignancies, infections, non-communicable diseases like chronic obstructive pulmonary disease and cardiovascular diseases and musculoskeletal problems like osteopenia and osteoporosis. Therefore, opportunistic infections should always be considered in evaluating symptomatic patients with advanced HIV/AIDS, although the overall incidence of these infections has decreased [4].

Typhoid fever is an acute systemic infection caused by the bacterium *Salmonella enterica* serovar Typhi. *Salmonella enterica* serovars Paratyphi A, B, and C, cause the clinically similar condition, paratyphoid fever, and both conditions are collectively referred to as enteric fevers [5]. The association of HIV infection with typhoid fever remains unclear; however, there is a clear risk of typhoid and paratyphoid fever in HIV infected persons coming from typhoid-endemic areas. Although it is shown that an increased risk of acquiring typhoid fever among HIV-infected persons was described in Peru, in the United States, typhoid fever has not been widely associated with AIDS [6]. Nevertheless, the diagnosis of typhoid should be considered in HIV infected individuals, mainly when they present with severe ulcerative diarrhoea. Similarly, the occurrence of an atypical typhoid syndrome in persons from typhoid-endemic areas should raise the possibility of a concomitant HIV infection [6]. We present a case of a 38-year-old male diagnosed with HIV and later found to have a typhoid ulcer on the intestine found on surgery due to bowel perforation, surprisingly with negative serology for typhoid, scummed due to acquired immunodeficiency with severe pneumonia.

Case Presentation

A 38-year-old gentleman presented to our ward with a history of fever with significant weight loss and loss of appetite for eight months. His fever was initially low grade intermittent, and he had responded to paracetamol. However, later his fever became high grade, associated with profuse sweating and generalized body weakness. He had lost about 20 kg of weight throughout these eight months, and his skin had darkened, so his appearance had become difficult for his family members to recognize him on arrival. Also, there was an associated severe loss of appetite and reflux symptoms with occasional vomiting and epigastric pain. He also had myalgia and exertional dyspnoea.

Nevertheless, he denied any cough, altered bowel habits, altered urinary habits, long term backache, hair loss, any rashes, joint pains, any history of altered behaviour or personality changes or any bleeding manifestations. He had worked abroad in a middle east country as a construction site supervisor for the past five years and had returned to Sri Lanka just one month ago. There was no family history of malignancies or any contact history of tuberculosis. He was married, having two children but had several high-risk sexual encounters while working abroad. He was an occasional drinker and a non-smoker. He had consumed food from outside while working abroad. He had sought medical treatment for the above symptoms previously and was given treatment for reflux symptoms but had no proper medical follow up.

On examination, he was a tanned, thinly built, anxious man with many stretch marks at creases with a BMI of 18 kg/m^2. He was febrile (100.8°F) and mildly pallor. He had did not have any rashes, lymphadenopathy, ankle oedema, clubbing or peripheral stigmata of infective endocarditis. Oral hygiene was good, and the throat was healthy-looking. His vitals were stable with a heart rate of 96 beats per minute and a respiratory rate of 16 cycles per minute with a peripheral oxygen saturation of 98%. On auscultation, there was no any audible murmurs or any added sounds over the lungs. The blood pressure was normal, without any postural drop. On abdominal examination, there was mild epigastric tenderness but no hepatosplenomegaly. His neurological examination was normal, including the fundal examination.

His initial full blood count revealed a white cell count of 7.02 × 10^9 / L, neutrophils 6.67 × 10^9 / L, lymphocytes 0.28 × 10^9 / L, eosinophils 0.01 × 10^9 / L, a haemoglobin level of 10.2 g/dL, mean corpuscular volume 84.9 fL, and a platelet count of 120 × 10^3 / µL. The C-reactive protein (CRP) level was 25 mg/L, and the erythrocyte sedimentation rate (ESR) was 80 mm/h. The findings on the blood picture were compatible with chronic inflammation/infection. Liver functions and coagulation profile were normal. His sodium level was 130 mmol/L, and his potassium level was 4.5 mmol/L. His initial blood and urine cultures were negative for any growth. His initial chest X-ray and abdominal ultrasound were unremarkable. His Mantoux test was negative, and sputum for acid-fast bacilli was also negative. The random serum cortisol level was 100 µg/dL. His Hepatitis A, B, and C antigen and antibody levels were below the cut off value for the population, and the Melioidosis antibody level was also negative. However, his HIV Ag/Ab combo assay, P24 antigen, became positive, and he was found to have a CD4 count of 473 cells/mm^3.

Then we sent cytomegalovirus (CMV), and Toxoplasma IgM and IgG, Tuberculous interferon-gamma release assay, standard agglutination test where all were turned out to be negative. Eye screening for CMV was negative. We also performed a high-resolution CT (HRCT) of the chest to exclude *Pneumocystis carinii*, and it was also turned out to be normal. Finally, the patient was counselled about his HIV status, the family was also counselled after taking permission from the patient, and family members were tested to be negative.

The patient was started with treatments for HIV with Efavirenz 600 mg daily, Emtricitabine 200 mg daily and Tenofovir 300mg daily. In addition, highly Active Antiretroviral Therapy (HAART) was started under cover of intravenous Meropenem 1 g 8 hourly, Doxycycline 100 mg daily and Cotrimoxazole 960 mg daily as prophylaxis for pneumocystis pneumonia.

After three days of starting the above retroviral therapy, the patient developed nausea, vomiting and loose stools while continuing the preexisting fever. We gave him supportive treatment for loose stools, and it settled after two days. Four days later, the patient complained of severe shortness of breath and epigastric pain in the morning. His respiratory rate was 40 cycles per minute, and his lungs were clear on auscultation. The heart rate was 120 beats per minute, and the blood pressure was 90/60 mmHg. His epigastric area was tender, bowel sounds were sluggish, and the patient had not opened his bowel for one day. The urgent blood gas analysis revealed respiratory alkalosis with lactic acidosis.

Then we urgently took an urgent chest X-ray of the patient and found air under the diaphragm. The patient was urgently referred to the surgical team, and an urgent exploratory laparotomy was done. During the laparotomy, the surgical team had found peritoneal free fluid and found to have distal ileal perforation with a longitudinal white deep ulcer suggestive of a typhoid ulcer. The perforated segment was brought out as a stoma, and a tube drain was placed.

After the surgery, he was given continuous ventilatory care and was covered with intravenous meropenem, metronidazole and teicoplanin. The cotrimoxazole dose was increased up to 960 mg 6 hourly, and Tamiflu was added, although influenza nasal swab screening was negative. After two days, his chest X-ray revealed bilateral patchy inflammatory shadows. His platelet count gradually dropped to 119×10^3 / µL, and blood picture findings suggested microangiopathic hemolytic anaemia. His coagulation profile was also deranged with prolonged PT/INR (1.9) and APTT (59 s). He gradually became hemodynamically unstable and was supported with inotropes.

The histology report of the resected specimen revealed marked enlargement of Payer's patches and lymphoid tissue in the appendix and ascending colon, leading to mucosal elevation along the ileum. Distal ileum and proximal colon showed multiple variably sized punched out lesions with a slightly elevated margin, oedematous hyperaemic mucosal patches with haemorrhagic spots and shallow perforated ulcers. Microscopy revealed neutrophils, histiocytes with cytoplasmic bacteria, nuclear debris and haemorrhage within the colonic lamina propria associated with a lymphocytic infiltrate. The findings were suggestive of a perforated Typhoid ulcer.

Despite all the resuscitation care given, the patient scummed four days after the surgery. The cause of death was given as acquired immunodeficiency with perforated small bowel typhoid ulcer with severe pneumonia.

Discussion

HIV infection is one of the leading causes of morbidity and mortality worldwide, with most of the disease concentrated in sub-Saharan Africa. As the infection often takes hold in adults who are in the prime of their economic productivity, HIV infection has dramatically altered the economies of many countries [1]. Regardless of its multisystem involvement, more than 20 % of patients with HIV infection remain undiagnosed. Although the overall incidence of many opportunistic infections has decreased with effective chemoprophylaxis and combination antiretroviral therapy, prompt recognition and appropriate management are imperative to decrease mortality related to these conditions [4]. The relationship between HIV infection and typhoid has been unclear. Studies done in typhoid endemic areas have demonstrated an increased risk of typhoid and paratyphoid fever in HIV infected persons [6]. In contrast, a study done in Tanzania showed an apparent protective effect of HIV against Salmonella as those results were explained by using trimethoprim-sulfamethoxazole prophylaxis, which could protect against typhoid fever [7].

The diagnosis of HIV infection remains a challenge since many patients may have an asymptomatic infection after exposure, where it takes 2 to 4 weeks from the exposure to the onset of the symptoms. In acute retroviral syndrome, symptoms like fatigue, muscle pain, skin rash, headache, sore throat and swollen lymph nodes may appear acutely. Although none of these symptoms is specific to HIV, their increased severity and prolonged duration indicate a poor prognosis [8]. However, fever is the most common symptom of HIV infection, which present in 80–90% of patients [9]. Chronic HIV infection can be characterized by either with or without AIDS and can progress to advanced HIV infection. In chronic HIV infection without AIDS, the predominant features include oral thrush, vaginal candidiasis, oral hairy leukoplakia, herpes zoster and peripheral neuropathy. Chronic HIV infection with AIDS is defined as a CD4 cell count < 200 cells/μL or the presence of any AIDS-defining condition regardless of the CD4 cell count. The AIDS-defining conditions include recurrent pneumonia, chronic intestinal cryptosporidiosis, Kaposi sarcoma, Burkitt lymphoma, tuberculosis, pneumocystis jirovecii pneumonia and progressive multifocal leukoencephalopathy. Advanced HIV infection is defined as a CD4 cell count < 50 cells/μL [10]. Our patient had chronic low-grade intermittent fever with significant weight loss and anorexia for eight months, where his fever became high grade, associated with profuse sweating and generalized body weakness. He also had myalgia and exertional dyspnoea; however, there was no lymphadenopathy, and the oral hygiene was good. All these symptoms were non-specific though the diagnosis of an infection or an inflammatory condition were most likely. He also had a travel history to the middle east; therefore, it is essential to consider such social factors in the diagnosis of HIV, although the prevalence of HIV in the middle east is relatively low [2].

Since clinical features are non-specific in HIV infection, blood investigations play a vital role in the diagnosis. The full blood count is an affordable, routinely performed test, even in resource-limited settings with essential clues for the diagnosis. Leucopenia is a common finding in HIV infection predominantly due to lymphopenia and neutropenia, and haemoglobin concentration is also low. The causes for these findings are multifactorial, including immune activation and release of cytokines, effects of antiretroviral therapy and opportunistic infections, which lead to decreased bone marrow production and increased peripheral destruction of cells [11]. In our patient, the initial full blood count revealed a normal white cell count, 7.02×10^9 / L (4.09–11.00), and a normal neutrophil count, 6.67×10^9 / L (1.78–6.95). However, the lymphocyte count, 0.28×10^9 / L (1.34–3.92), and the eosinophil count, 0.01×10^9 / L (0.05–0.55), were low, along with a low haemoglobin level of 10.2 g/dL (13.4–16.7) [12].

ESR is not a helpful test in diagnosing HIV, although initially considered an indicator of disease progression, later studies disagreed or demonstrated only a negligible fall in CD4 count with rising ESR. At the same time, ESR does not predict acute illness in HIV, and when measured, it is not uncommon to discover values in triple figures in otherwise asymptomatic individuals with normal CD4 counts [13]. However, HIV-infected individuals show a significant increase in CRP over time and the level of CRP is associated with HIV disease progression independent of CD4 lymphocyte count and HIV/RNA level [14]. Our patient had a CRP level of 25 mg/L and an ESR of 80 mm/h, both values compatible with characteristic findings in HIV infection though not having any diagnostic value. Our patient also had

hyponatremia with an average potassium level. Hyponatremia in HIV disease and AIDS occur in 20–80% of hospitalized patients. A syndrome of inappropriate ADH secretion, volume depletion, and adrenal insufficiency, as well as some drugs, are the most common causes of hyponatremia in HIV-infected patients [15].

HIV infection is confirmed either by detecting HIV-specific antibodies in serum or plasma or by demonstrating the presence of the virus by nucleic acid detection using polymerase chain reaction (PCR), p24 antigen testing or, rarely these days, by growing virus in cell culture. However, antibody testing is most commonly used to diagnose HIV infection [16]. The most recent advances in EIA technology have produced 'combination assays', which allow for the simultaneous detection of p24 HIV antigen and HIV antibodies. This approach has further shortened the interval between HIV infection and detectable HIV antigen/antibodies [17]. The diagnosis of HIV was made in our patient by Ag/Ab combo assay, where p24 antigen became positive. However, his CD4 count was 473 cells/$mm^{3,}$ lower than the standard value of 500–1200 cells/mm^3. How it only when the CD4 count is less than 350 cells/mm^3 it is considered as the risk for several infectious complications begins to rise, including varicella-zoster infection, severe bacterial infections and tuberculosis [1].

Fever in HIV patients is due to multiple factors. First, infection with HIV can cause fever, as is the case in 40–90% of patients with HIV primo-infection. Second, immunodeficiency in advanced HIV infection puts patients at high risk for opportunistic infections and malignancies [18]. Therefore in a febrile patient with HIV, it is essential to investigate for opportunistic infections. A few common AIDS-defining opportunistic infections include tuberculosis, *Candida* infections, *Pneumocystis* pneumonia, *Toxoplasma gondii* encephalitis, and *Cytomegalovirus* retinitis [19]. We investigated our patient for *Cytomegalovirus*, *Toxoplasma*, and *Tuberculous* infections, where all became negative. We also performed an HRCT chest to exclude *Pneumocystis carinii* infection, and it also turned out to be negative.

The WHO guidelines on HIV antiretroviral therapy revised recently in 2018. According to that, dolutegravir (DTG)-based regimen is recommended as the preferred first-line regimen for people living with HIV initiating antiretroviral therapy and DTG in combination with an optimized nucleoside reverse-transcriptase inhibitor backbone, which includes abacavir (ABC), emtricitabine (FTC), lamivudine (3TC) and zidovudine (AZT) is the preferred second-line regimen [20]. However, according to the guideline published by the Ministry of Health, Sri Lanka in 2014, the first-line regimen for adult and adolescents includes the combination of tenofovir (TDF), 3TC (or FTC) and efavirenz (EFV) or AZT, 3TC and EFV [21]. Therefore after the initial diagnosis of HIV, our patient was treated with EFV, FTC, and TDF, which is a standard first-line antiretroviral therapy in Sri Lanka. However, there was no evidence of pneumocystis infection; he was covered with meropenem, doxycycline and cotrimoxazole as prophylaxis.

There is an association between HIV infection and an increased likelihood of bacteraemia and mortality as a higher incidence of bacteraemia have been reported in immunocompromised patients. HIV-positive patients have been found to have an increased risk of non-typhoid salmonella bacteraemia with organisms *Salmonella typhimurium* and *enteritidis* compared to HIV-negative patients though the

relationship between HIV and typhoid has been unclear [6, 22]. However, the diagnosis of typhoid should be considered in HIV infected individuals, mainly when they present with severe ulcerative diarrhoea. [6]. The incidence of non-typhoid salmonellosis has been estimated to be 10 to 100 fold greater in HIV infected individuals compared to the general population [23]. Nontyphoidal Salmonella bacteremia causes a significant public health problem and represents an important cause of morbidity and mortality in HIV-infected patients, representing around 10% of HIV infected individuals. Factors such as handwashing habit, contact with pet animals, consumption of raw or improperly cooked meat, milk, and vegetables have been indicated as potential sources of Salmonella infection [24]. Thus recurrent Salmonella septicemia is considered an AIDS-defining illness [25].

Typhoid is an infectious disease that presents with non-specific symptoms. Patients complain of enterocolitis after 12 hours to 48 hours of inoculation. Often, they initially present with nausea, vomiting that progresses to diffuse abdominal pain, bloating, anorexia, and diarrhoea, which can vary from mild to severe diarrhoea with or without blood, followed by a short asymptomatic phase that gives way to bacteremia and fever with flu-like symptoms [26]. Symptoms of enterocolitis generally last a few days and are self-limited without the need for medical intervention except in the old and very young. Immunocompromised patients with HIV, particularly those with low CD4 counts, more commonly present with severe diarrhoea and tend to have more metastatic severe infections [27]. Classic typhoid fever follows a “step-ladder” pattern, and abdominal distress is frequently seen. Due to the hypertrophy of Payer patches, constipation may predominate over diarrhoea in some cases [26].

When typhoid is complicated by ileal perforation, tenderness, rigidity, and guarding of the abdomen may be present. Visible rose spots (rose-coloured macules on the abdomen) are associated with typhoid fever but rarely occur. The patient looks pale, mildly distressed, and dehydrated with sunken eyes, dry skin, and lethargy. Some patients have jaundice, pale stool, and dark urine when the patient has associated gallstones and other biliary pathology. Enlarged spleen on palpation may also be present [28]. Our patient developed nausea, vomiting and diarrhoea after three days of antiretroviral therapy while continuing the preexisting fever followed by severe dyspnoea and epigastric pain in the following day associated with tachypnoea, tachycardia and hypotension. He also had preceding constipation. Therefore his clinical features were compatible with the characteristic features of enterocolitis and ileal perforation following typhoid fever. An urgent chest X-ray confirmed the bowel perforation by air under the diaphragm, where the surgical team found distal ileal perforation with a longitudinal white deep ulcer suggestive of a typhoid ulcer.

The approach to typhoid patients should be clinical. Patients residing in areas with poor sanitation or impure drinking water or a history of travel from endemic areas presenting with febrile illness for more than three days along with gastrointestinal manifestations (pain, constipation, or diarrhoea) are highly suspicious. Diagnosis in the first week is difficult, but various laboratory studies assist in making the diagnosis [29]. However, the definitive diagnosis requires isolation of *Salmonella typhi* from blood, bone marrow, stool, or urine cultures [30]. Other investigations such as the Widal test, skin snip test, polymerase chain reaction (PCR) assay and Enzyme-Linked Immunosorbent Assay (ELISA) test can also be done [26].

However, since our patient presented with bowel perforation, there was no opportunity to perform these diagnostic tests. The histology of the resected specimen had findings suggestive of a perforated Typhoid ulcer. Ulcerations in typhoid generally occur in the terminal ileum, cecum and the ascending colon, and rarely in the left side of the colon [31]. Overall, the histological picture of typhoid perforation was found to be one of chronic but discrete inflammation around the perforation site, with relatively mild-to-moderate mucosal changes. The pathogenesis of intestinal perforation in patients with typhoid fever is poorly understood concerning the host and bacterial factors involved. It is generally believed that perforation occurs in the Peyer patches of the distal ileum. Typhoid perforation has an inflammatory nature, showing that the inflammatory infiltrate consists predominantly of macrophages and T lymphocytes and that it is most severe in the deeper tissues [32].

Salmonella typhi infection in HIV/AIDS patients may cause life-threatening complications like septic shock, meningitis, and local abscess formation. They are severely ill are more prone to mortality. Disease severity may be affected by access to health care and treatment delays [27]. Regarding risk factors for worse prognosis and complications of *Salmonella* infection, co-infections and acute renal failure are the most frequent, where the case fatality rate of typhoid significantly increase when present concurrently with HIV [33]. Our patient developed severe pneumonia in the background of immunodeficiency in the postoperative period, where he scummed despite the resuscitation efforts. Though there was no aetiological diagnosis for pneumonia, he had been covered with broad-spectrum antibiotics. HIV patients with pulmonary infections requiring intensive care, *Pneumocystis* pneumonia and mechanical ventilation are associated with higher mortality. At the same time, not having an aetiological diagnosis is independently associated with higher mortality [34].

Conclusion

The relationship between HIV infection and typhoid has been unclear, though an increased risk of typhoid and paratyphoid fever in HIV infected persons. The diagnosis of HIV infection remains a challenge since many patients may have asymptomatic infection, and even the symptoms occurring are non-specific. Blood investigations play a vital role in the diagnosis of HIV, and the diagnosis is confirmed either by detecting HIV-specific antibodies in serum or plasma or by demonstrating the presence of the virus by nucleic acid detection. Fever in HIV patients could be due to HIV itself, opportunistic infections or malignancies. The diagnosis of typhoid should be considered in HIV infected individuals, mainly when they present with severe ulcerative diarrhoea where the patients may present with gastrointestinal symptoms and diarrhoea with or without blood, followed by fever with flu-like symptoms. HIV patients with typhoid can also present as constipation or ileal perforation. *Salmonella typhi* infection in HIV/AIDS patients may cause life-threatening complications, where the case fatality rate of typhoid significantly increase when present concurrently with HIV. HIV patients with pulmonary infections requiring intensive care, *Pneumocystis* pneumonia and mechanical ventilation are associated with higher mortality, especially when not having an aetiological diagnosis.

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Informed written consent was obtained from the relatives of the patient for publication of this case report.

Availability of data and materials

The authors confirm that the data supporting the findings of this study are available within the article.

Competing interests

The authors declare that they have no competing interests.

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Authors' Contributions

All authors involved in the management of the patient and generating the concept. All authors made an intellectual contribution and wrote the paper. All authors read and approved the final manuscript.

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Abbreviations

HIV
Human Immunodeficiency Virus; BMI:Body Mass Index; HRCT:High Resolutions Computed Tomography; PT:Prothrombin Time; INR:International Normalized Ratio; APTT:Activated Partial Thromboplastin Time; ADH:Antidiuretic Hormone; Ag/Ab:Antigen/Antibody; WHO:World Health Organization

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