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Shigellaemia in adult Gambians - a report of 2 cases

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ABSTRACT

Background: Shigellosis is an infection caused by the bacteria *Shigella*. Most commonly, it causes a febrile illness with gastrointestinal symptoms including mucoid, bloody diarrhoea with or without tenesmus. Occasionally it may become septicaemic (shigellaemia) often in the immunocompromised. **Aim:** To document 2 cases of bacteraemia due to *Shigella* in patients with enteric symptoms and clinical signs of immunosuppression. **Findings:** We report two cases of *Shigella* bacteraemia both adult females. The first case was a patient confirmed with HIV 1 infection. The second case had overt clinical signs of advanced immunosuppression but we could not confirm her HIV serostatus. *Shigella flexneri* was isolated from the blood in both cases. Stool cultures were negative in both patients. Molecular diagnostic techniques are now available and have the advantage of being highly sensitive and specific. Regarding outcome, the first case report was in a poor clinical state and was discharged against medical advice while the second case died within 24 hours of admission. **Conclusion:** It is critical that prompt identification of a case of *Shigella* be made by with a high index of suspicion. As part of their management, we propose that patients with febrile gastroenteritis especially in the setting of risk factors like immunosuppression or malnutrition have blood cultures early and empiric therapy initiated while awaiting results. Resistance to commonly used antibiotics is high such that ampicillin is no longer recommended as an empiric treatment. Ciprofloxacin or the third generation cephalosporins are now the drug of choice.

Key words: Shigellosis, shigellaemia, immunosuppression, enteric symptoms, blood culture, empiric antibiotic

INTRODUCTION

Shigellosis or bacillary dysentery is an acute intestinal infection caused by the bacteria *Shigella*.[1] It is an enteric bacteria of the family *enterobacteriaceae*, genus *Shigella*.[2] It is a gram negative, non-motile, non-spore forming bacilli.[1,2,4] *Shigella* has four species and four serogroups. These are *Shigella dysenteriae* - serogroup A, *Shigella flexneri* - serogroup B, *Shigella boydii* - serogroup C, and *Shigella sonnei* - serogroup D.[2,4] Shigellosis is endemic in developing countries and

the most common isolate is *Shigella flexneri.*[4] However, *Shigella dysenteriae* type 1(Sd1) is the most virulent *Shigella* causing a more severe, more prolonged, often fatal disease compared to other shigellae.[4] Sd1 also tend to occur in epidemics while *Shigella sonnei* and *Shigella boydii* are less virulent and cause a milder illness.[4] *Shigella* infections are more prevalent in areas with poor hygiene and overcrowding.[1,2] Transmission is either directly by the faeco-oral route or through contaminated food and water.[1,2,4,5] Occasionally, *Shigella* may become bacteraemic usually in patients who are immunocompromised including HIV/AIDS or may have other underlying condition or disease.[6,7,8]

CASE REPORTS

CASE ONE

Seven weeks after testing positive to HIV 1 infection, a 30 year old female Gambian presented with fever, progressive weight loss, diarrhoea with mucoid bloody stools, dysphagia, cough with white sputum for 2 weeks. She was afebrile (T^{o}=36.9^{o}C) on admission and temperature remained normal throughout the period she was on admission. Results of haematological indices are shown in table 1 below:

No malaria parasite was seen in thick blood film. Stool culture did not grow *Salmonella* or *Shigella.* Blood culture grew *Shigella flexneri* sensitive to gentamicin, ciprofloxacin, cefuroxime sodium, cefotaxime sodium but resistant to ampicillin, cotrimoxazole, chloramphenicol, tetracycline. Urine culture grew *Coliform* species sensitive only to nitrofurantoin. CXR showed no infiltrates. Sputum analysis by Ziehl-Neelson stain showed no acid fast bacilli in 3 samples. HIV serology testing showed that she was HIV 1 positive. CD4 subset count was130 cells/mm^3. CD4 percentage 16%. She was hypokalaemic which was effectively corrected with potassium supplements. She received oral ciprofloxacin 500mg bd for 2 weeks and treated for *Coliform* urinary tract infection with oral nitrofurantoin since this was the only antibiotic to which it was sensitive. She was due to start antiretroviral therapy but her condition remained poor and relatives insisted on taking her home. She was discharged against medical advice.

CASE TWO

A 51 year old female Gambian presented with chronic diarrhoea for 2 months. The stool was watery and very offensive. She also had fever, headache, and weight loss for 2 months, painful vulval and oral sores for 1 month. She was found to be febrile (T^{o}=39^{o}C), very wasted, with florid oropharyngeal candidiasis, multiple, shallow vulval and perineal ulcerations. She was hypotensive. Clinical diagnosis was severe septicaemia in shock with severe herpes genitalis in an immunosuppressed patient. Results of haematological indices are shown in table 2 below.

Stool culture did not grow *Salmonella* or *Shigella*. Blood culture grew *Shigella flexneri* sensitive to gentamicin, ciprofloxacin, cefotaxime sodium, cefuroxime sodium but resistant to co-trimoxazole, chloramphenicol, tetracycline. These results were received posthumously. HIV serology was not done due to her moribund clinical condition and short hospital stay. She received rapid intravenous rehydration for shock, intravenous ceftriaxone, oral fluconazole, intravenous potassium chloride supplements in normal saline and oral acyclovir. Her condition deteriorated progressively and she died the following day after admission.

DISCUSSION

Human immunodeficiency virus (HIV) infection is characterized terminally by severe immunosuppression (AIDS) with susceptibility to various opportunistic infections and neoplasms.[1] Infection due to encapsulated and enteric bacteria occurs at increased frequency in HIV.[3] This is due to a defect in both cell mediated and humoral immunity that occurs early and progressively in HIV.[3] Shigellosis is an infection caused by bacteria of the genus *Shigella.*[1,2] Source of infection is the faecal matter of infected persons, convalescent and subclinical cases. Transmission is by faeco-oral route either directly through person to person or hand-to-mouth or indirectly through contaminated water, food or fomites in the setting of poor hygiene.[1,2,5,8] Houseflies are good vectors[1] hence the mnemonic of '4Fs' (food, fingers, faeces and flies) used for transmission.[9] *Shigella* gastroenteritis though an uncommon disease among HIV seropositives, *Shigella* bacteraemia can occur.[10,11,12] HIV infection is a significant risk factor for acquiring shigellosis.[6,8,18] Factors that are involved in HIV patients acquiring *Shigella* or other enteric bacteria may be related to HIV-induced altered mucosal immunity and HIV-associated achlorhydria.[4] Among men who sleep with men increased susceptibility to shigellosis might be related to social adaptation and behavioural practices making *Shigella* infection a sexually transmitted disease in this subgroup who may also be HIV infected.[13] The first patient presented with

an acute febrile illness with enteric symptoms and bloody diarrhoea which raised the suspicion of *Shigella* or other causes of bloody stool discussed below. Before blood culture results were received she was rehydrated with intravenous fluids and started on ciprofloxacin which was continued for 2 weeks but never really improved. The addition of antiretroviral drugs might have made the outcome more favourable. The second patient presented with features of advanced immunosuppression. She had chronic diarrhoea with watery, non mucoid, non bloody stool and not the typical mucoid, bloody stool more representative of bacillary dysentry. Her condition was complicated by a shock state which could result from either hypovolaemia or endotoxaemia or both which are well known complications of *Shigella* septicaemia.[14] Blood culture grew *Shigella* - a result received posthumously. She was managed for septicaemia in shock. Intravenous normal saline was administered rapidly to treat shock but only received two doses of ceftriaxone as she progressively deteriorated and died the following day. While bloody mucoid stools are suggestive of *Shigella*, other differential diagnosis must be borne in mind. These include bacterial, protozoan or viral causes. Bacteria or protozoan commonly associated with bloody stool are *Campylobacter jejuni*, enteroinvasive *Escherichia coli* (EIEC), *Salmonella, Yersinia enterocolitica, Entamoeba histolytica* and *Schistosoma mansoni.*[5,15] Direct microscopy of fresh stool should be an initial discriminatory investigation modality to rule out *Entamoeba histolytica* and *Schistosoma mansoni*.[5] Erythrophagocytic trophozoites in stool in the absence of polymorphonuclear leucocytes are indicative of *Entamoeba histolytica,* whereas sheets of polymorphonuclear leucocytes are characteristic of *Shigella.*[5,15] The egg of *Schistoma mansoni* is characterized and identifiable by its terminal spine.[15] Culture of *Shigella* in either stool or blood is confirmatory of the diagnosis and distinguishes it from other bacterial causes mentioned above.[5,15]

Table 1: Haematological indices of the patient (case 1)

Investigation	Results	Normal ranges[27]
Haemoglobin	11.8 g/dl	12.5-16.5 g/dl (Women)
Total white cell count	2.8	4-11 x10^9/L
Neutrophil count	63.7%	37-85%
Lymphocyte count	28.4%	10-50%
Monocyte count	7.9%	0-12%
Platelet count	265	142-424 x10^9/L

Table 2: Haematological indices of the patient (case 2)

Investigation	Results	Normal ranges[27]
Haemoglobin	12.0	12.5-16.5 g/dl (Women)
Total white cell count	5.8	4-11 x10^9/L
Neutrophil count	88.0%	37-85%
Lymphocyte count	9.3%	10-50%
Monocyte count	2.7%	0-12%
Platelet count	160	142-424 x10^9/L

Worldwide, *Shigella flexneri* is the commonest serogroup isolated from blood cultures in most studies. [10,16-18] It is therefore not surprising that blood culture in both patients grew *S.flexneri.* However, other *Shigellae* could also cause bacteraemia.[7,14] Shigellaemia only (that is stool culture is negative but blood culture positive) is associated with a higher mortality rate than those who have both shigellaemia and a positive stool culture.[11] An earlier study from this unit on bacteraemia which included both immunocompetent and HIV patients showed that blood culture positivity was a risk factor for death.[12] This might partly account for the poor response to treatment in these two cases reported. Other prognostically important factors determining outcome in shigellosis include age above 50, infancy, malnutrition in both children and adults.[5]

Additionally, infection with *Shigella dysenteria* type 1(Sd1) could be severe and may be fatal.[5] Other factors that affect prognosis include time of presentation with those presenting early more likely to have better outcome.

Furthermore, treating *Shigella* strain that is antibiotic resistant is likely to give a poor outcome. Supportive management must be optimal to improve outcome. Outcome of *Shigella* infections is a product of interactions between these multiple factors. Late presentation and advanced immunosuppression may have contributed to the poor outcome in our patients despite the administration of drug sensitive antibiotics. We suggest blood cultures are obtained routinely from patients with signs of immunosuppression with febrile gastroenteritis. The culture medium that grew *Shigella* in both cases was MacConkey agar. The sensitivity of conventional culture methods for detection of *Shigella* is low especially in developing countries where there is easy availability of antibiotics. New molecular approaches such as PCR, 16s rRNA sequencing, quantitative and next generation PCR which have been shown to be highly sensitive and specific are now readily available and can be applied for the detection of *Shigella.*[19,20] Haematological findings in shigellosis are inconsistent. The total white blood cell count may show leucocytosis (with increased number of band cells), leucopaenia or may be normal. There may even be a leukemoid reaction.[21,22] The differential white blood cell count often times exhibit increased neutrophil count though normal count could be seen. Both patients exhibited this diversity in haematological indices. The first case showed a leucopaenia with normal differential white blood cell count while the second case showed relative neutrophilia with normal white blood cell count. The marked variation in white blood cell count in patients shigellosis makes this test to be of low utility in differential diagnosis of shigellosis.[23,24]

Antibiotics administration seems to be the mainstay of therapy of *Shigella* bacteraemia. Empiric therapy should be initiated immediately coupled with intense supportive management while awaiting results. Using an effective antibiotic has multiple benefits. Antibiotics lessen the risk of serious complications and death. It also shortens the duration of symptoms and course of illness. Antibiotics also speed up the elimination of shigella from the body.[21] The choice of antibiotics depend on susceptibility pattern. The following antibiotics are used to treat shigella: Beta lactams: Ampicillin, third generation cephalosporins (ceftriaxone, cefixime). Quinolones: Ciprofloxacin, ofloxacin, norfloxacin and nalidixic acid. Macrolides: Azithromycin. Others: trimethoprim –sulphamethoxazole (TMP-SMX) , furazolidine. tetracycline.[21] Globally, emerging drug resistance has narrowed antibiotic options that can be used as empiric treatment. Hence sulphonamides, tetracyclines, ampicillin and trimethoprim –sulphamethoxazole (TMP-SMX) are not recommended for empiric therapy.[20,25,26] Parenteral ceftriaxone or fluoroquinolone (e,g ciprofloxacin), azithromycin or oral cefixime are the drugs of choice where ampicillin and trimethoprim – sulphamethoxazole (TMP-SMX) resistance is present.[20] Antibiotic therapy is usually administered for 5 days.[20] General supportive care should be given to these patients. Their fluid and electrolyte status should be quickly assessed and replacement should be instituted without delay. Oral rehydration therapy may be adequate for the mildly dehydrated patient who is not vomiting. Intravenous fluid replacement is necessary for the severely dehydrated and those in hypovolaemic shock. Electrolyte imbalance, especially hypokalaemia, is frequent as seen in the first case presentation; potassium deficit should be promptly corrected.[20]

CONCLUSION

Shigellosis among HIV-infected population could become bacteraemic with significant morbidity and could be fatal. Clinicians and health care providers need to suspect this diagnosis in the immunosuppressed with pyrexia and diarrhoea with or without blood. Early treatment and optimal management of associated complications of shigellosis could make all the difference between life and death with significant morbidity and death arising from delayed treatment. We suggest blood cultures are obtained routinely from patients with signs of immunosuppression with febrile gastroenteritis. Empiric therapy should be initiated immediately coupled with intense supportive management while awaiting blood culture results. Definitive treatment should always be tailored to the result of antibiotic sensitivity.

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