Chronic \textit{Shigella flexneri} Infection Preceding Development of Acquired Immunodeficiency Syndrome

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\textit{Shigella} sp. is known to be an important cause of diarrhea in homosexual men, although chronic infection is infrequently recognized. We describe recurrent and relapsing symptomatic infection due to \textit{Shigella flexneri} in a human immunodeficiency virus-infected homosexual man who subsequently developed acquired immunodeficiency syndrome. Patients with acquired immunodeficiency syndrome may be prone to developing chronic shigellosis because of impaired intestinal cell-mediated immunity.

Infection due to \textit{Shigella} sp. usually results in a self-limited illness characterized by fever, abdominal pain, and diarrhea with stools containing mucus and blood. Fecal excretion of \textit{Shigella} sp. in untreated patients generally lasts 1 to 4 weeks. Chronic shigellosis or long-term fecal carriage of the organism is infrequently recognized. We report a case of recurrent and relapsing symptomatic infection due to \textit{Shigella flexneri} in a human immunodeficiency virus (HIV)-seropositive patient, who subsequently developed acquired immunodeficiency syndrome (AIDS).

Case report. HIV antibody was first detected in a 39-year-old male homosexual in October 1986. Two months later, he developed fever, abdominal pain, and watery diarrhea. Stool cultures grew ampicillin-resistant \textit{S. flexneri} type 1b on two occasions. Examination of feces for ova and parasites revealed cysts and trophozoites of \textit{Entamoeba histolytica} and \textit{Endolimax nana}. Treatment with co-trimoxazole and metronidazole resulted in improvement of symptoms and eradication of the enteric pathogens. Fever and diarrhea recurred in March 1987. This time stool cultures yielded an ampicillin-susceptible strain of \textit{S. flexneri} type 4a (Table 1). The patient was treated with ampicillin for 6 weeks, with resolution of symptoms and negative stool cultures. However, in the next 7 months, he suffered two symptomatic relapses associated with the recovery of \textit{S. flexneri} type 4a. Each relapse was successfully treated with a prolonged course of ampicillin. In November 1987, he underwent colonoscopy because of a recurrence of watery diarrhea and weight loss. Colonic biopsies revealed chronic inflammation without histopathologic evidence of fungal, mycobacterial, viral, or protozoan infection. After the endoscopy, \textit{S. flexneri} type 4a resistant to ampicillin was isolated from stool cultures. Treatment with norfloxacin resulted in rapid clinical improvement and negative stool cultures. Stool cultures have remained negative after 10 months of follow-up. In January 1988, he was hospitalized with \textit{Pneumocystis carinii} pneumonia, from which he recovered after treatment with pentamidine isethionate. At this time, his T-lymphocyte helper/suppressor cell ratio was severely depressed (0.2). This represented his first opportunistic infection fulfilling Centers for Disease Control criteria for AIDS.

Susceptibility testing of the \textit{Shigella} isolates was done with a commercially available microdilution panel (MicroScan; Travenol Laboratories Inc., Mahwah, N.J.). MICs of ampicillin were determined by standard macrodilution procedures according to National Committee for Clinical Laboratory Standards guidelines (12). Total genomic DNA of each \textit{Shigella} isolate was extracted as described by Bradbury et al. (2). DNA fragments were generated by digestion to completion with the restriction endonucleases \textit{ClaI}, \textit{PvuII}, and \textit{HindIII} (Boehringer GmbH, Mannheim, Federal Republic of Germany) as specified by the supplier. The digests were electrophoresed on a 0.7% agarose gel in Tris-borate-EDTA buffer, stained with ethidium bromide, and photographed under UV illumination. Restriction endo-

\begin{table}
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\caption{Dates of isolation, serotypes, and antimicrobial susceptibility of \textit{Shigella} isolates from an HIV-seropositive patient}
\begin{tabular}{|c|c|c|c|c|c|c|c|}
\hline
Isolate no. & Mo of isolation\textsuperscript{a} & \textit{S. flexneri} serotype & Am & Pi & Ch & T/S & Nx & Te & Gm \\
\hline
1 & January & 1b & 128 & <8 & >16 & <0.5/9.5 & <16 & >8 & <1 \\
2 & January & 1b & 512 & 16 & >16 & <0.5/9.5 & <16 & >8 & <1 \\
3 & March & 4a & 512 & <8 & >16 & <0.5/9.5 & <16 & >8 & <1 \\
4 & June & 4a & 2 & <8 & >16 & <0.5/9.5 & <16 & >8 & <1 \\
5 & September & 4a & 2 & <8 & <16 & <0.5/9.5 & <16 & >8 & <1 \\
6 & November & 4a & 1,024 & 64 & <16 & <0.5/9.5 & <16 & >8 & <1 \\
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\textsuperscript{a} All isolates were obtained in 1987.

\textsuperscript{b} Am, Ampicillin; Pi, Piperacillin; Ch, Chloramphenicol; T/S, Trimethoprim-Sulfamethoxazole; Nx, Norfloxacin; Te, Tetracycline; Gm, Gentamicin.

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nuclease analysis of the total DNA content confirmed that all of the *S. flexneri* type 4a isolates had identical restriction patterns, which were distinct from those of the *S. flexneri* type 1b isolates (Fig. 1). Agarose gel electrophoresis of undigested plasmid extracts also demonstrated that the plasmid profiles of the *S. flexneri* type 4a isolates were identical to one another but distinct from those of the *S. flexneri* type 1b isolates (data not shown).

**Discussion.** Chronic diarrhea and weight loss occur frequently in patients with AIDS. These symptoms may be attributed to enteric infection, neoplasia, or an enteropathy associated with malabsorption, but often no known cause is identified. A variety of infectious agents, including cytomegalovirus, *Mycobacterium avium-M. intracellulare*, *Cryptosporidium* sp., and *Isospora belli*, are now known to be important gastrointestinal pathogens in these patients (4). In addition, HIV has recently been detected in bowel biopsy specimens from AIDS patients with chronic diarrhea (13). Recurrent or relapsing *Salmonella* (3, 8) and *Campylobacter* (14) infections, often associated with bacteremia, have also been described in patients with AIDS. Interestingly, despite the observation that *Shigella* sp. is a relatively common cause of enteric infection in homosexual men (15), it has infrequently been recognized as a significant isolate in HIV-infected patients. A few cases of *S. flexneri* bacteremia have been reported in patients with AIDS (1, 6, 11, 17), and a homosexual man without AIDS but known to be infected with HIV had a 3-month history of watery diarrhea due to a multiresistant strain of *S. flexneri* (5). This report is the first describing chronic *Shigella* infection, persisting for almost a year, in an HIV-infected homosexual man who subsequently developed AIDS. It is not known whether this patient was ever bacteremic, because blood cultures were not obtained. Molecular techniques, including analysis of plasmid and total chromosomal DNA content, confirmed that this patient’s recurrent *Shigella* infection was due to an initial reinfection with a different strain and then several relapses with the same strain of *S. flexneri*. It is likely that after prolonged use of ampicillin the *S. flexneri* type 4a isolate became ampicillin resistant by acquiring a transposon specifying β-lactamase production (7).

For *Shigella* sp. to cause colitis or dysentery, it is necessary for organisms to penetrate intestinal epithelial cells and replicate within intestinal mucosa. The development of local enteric immunity, particularly intestinal antibody-dependent cell-mediated immune mechanisms, appears to be of primary importance for host defense in *Shigella* infections (10). The role of specific coproantibodies is less certain; although humoral antibodies typically develop in response to shigellosis, these do not appear to be protective. Deficiencies in intestinal mucosal T-lymphocyte cell populations have been described in homosexual men with the syndrome of persistent generalized lymphadenopathy and with AIDS (16). Thus, as with several other enteric pathogens, *Shigella* infections in patients with AIDS may be prolonged or complicated by bacteremia or relapses. These complications may be due to impaired cell-mediated and/or humoral immunity interfering with colonic epithelial cellular defense mechanisms.

It is apparent that the list of agents capable of causing severe enteric infection in patients with AIDS has been expanding as experience with this disease increases. The evaluation of HIV-infected patients with chronic diarrhea must therefore include a diligent search for agents of bacterial, viral, and protozoan pathogens. As this case illustrates, shigellosis is a serious but treatable infection in patients with AIDS and may precede or accompany other opportunistic infections.

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LITERATURE CITED