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Nonspecific Proctitis: Association with Human Immunodeficiency Virus Infection in Homosexual Men

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In a cross-sectional study of 140 homosexual men attending a sexually transmissible diseases clinic, the association between the presence of antibody to the human immunodeficiency virus (HIV) and the presence of proctitis, as determined by histologic examination, as well as past or present exposure to other pathogens and details of sexual practices was analyzed. Significant associations with HIV seropositivity were found with the number of lifetime partners, positive treponemal serology, and evidence of previous infection with herpes simplex virus. However the major and unique finding was the strong and independent association between proctitis diagnosed by histologic criteria and seropositivity for HIV. Whether this is cause or effect awaits further elucidation.

Among homosexual men, acquisition of human immunodeficiency virus (HIV) has been associated with multiple sexual partners and with receptive anal intercourse [1–3]. Although proctitis is a well-described phenomenon in homosexual men, and when it is associated with symptoms it is often associated with sexually transmissible agents [4], no pathogenic agent is identified in as many as 26% of patients [5]. We investigated the association of rectal inflammation (proctitis), as determined by histologic examination, in homosexual men attending a sexually transmissible diseases (STD) clinic and the presence of antibodies to HIV.

Patients and Methods

Patients. Subjects were drawn from consecutive homosexual or bisexual males attending the STD Centre, Sydney Hospital, and seen by one of the authors (C.L.) in the period March 1985–1988. They were mostly healthy, were attending for STD

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and HIV screening, and were identified as either homosexual or bisexual on the basis of the sexual history obtained. A self-administered questionnaire was given to each subject to record past medical and STD history and details of sexual practices. For this project, we analyzed the data on 140 of the original 200 enrolled in a study on STD and enteric infections in homosexual men, who had completed questionnaires, undergone rectal biopsies, and turned in the full complement of fecal specimens. A comparison of the study group and the group that was excluded due to incomplete data indicated that there was no significant difference in age, sexual practices, or gastrointestinal symptoms.

Screening tests for STD consisted of cultures for *Neisseria gonorrhoeae* and *Chlamydia trachomatis* from the rectum, urethral meatus, and pharynx and culture for herpes simplex virus (HSV) from the rectum alone. Three rectal biopsies were taken under direct vision from each individual at 15, 10, and 5 cm from the anal verge using flexible colonoscopy biopsy forceps. Clinical features of proctitis such as contact bleeding with rectal mucosal congestion, presence of a mucopurulent exudate, or superficial ulceration were noted. Blood was collected for routine laboratory investigations. Each subject was also asked to deliver fecal samples on 3 separate days over a period of 1–2 weeks.

Laboratory tests. Screening tests for treponemal infections were done using standard methodology: Venereal Diseases Reference Laboratory (VDRL) and *Treponema pallidum* hemagglutination (TPHA) tests. Swabs for culture of *N. gonorrhoeae* were directly innoculated onto modified New York media, and those for culture of *C. trachomatis* and HSV were placed into transport media and subsequently innoculated onto Buffalo green monkey cells and human embryonic fibroblast cells, respectively.

Serologic tests for previous infection with HSV were done using a herpes simplex virus complement fixation test (HSV CFT) and for HIV-I antibody by ELISA (Abbott Laboratories, North Chicago; Wellcozyme, Wellcome Diagnostics, Beckenham, UK). Positive antibody tests were confirmed by Western blot (DuPont, Carlingford, Australia). Lymphocyte subpopulations were quantified using fluorescein-conjugated monoclonal antibodies to Leu-2a, Leu-3a, and Leu-4 (Becton Dickinson, Mountain View, CA) and flow cytometry (FACS 440; Becton Dickinson, Sunnyvale, CA). Total and differential white blood cell counts were done on EDTA-treated blood in a Coulter counter.

Two rectal biopsies (from 5 and 10 cm) were routinely handled after formalin fixation, paraffin embedding, sectioning, and hematoxylin-eosin staining. They were examined by an experienced histopathologist (J.M.G.) and graded as follows. Grade I, normal biopsy as defined by the presence of an inflammatory cell infiltrate in the lamina propria within the usual subjective normal limits, that is, a scattered mixed cellular infiltration of plasma cells, lymphocytes, eosinophil leukocytes, mast cells, and macrophages, seen in small numbers and distributed predominantly within the superficial part of the lamina propria. In this grade, no associated inflammatory vascular, epithelial, or crypt injury was present. Grade II, chronic proctitis as defined by an increase in chronic inflammatory cells throughout the lamina propria with minimal vascular, epithelial, and crypt changes. Grade III, acute proctitis or active chronic proctitis as defined by a marked or intense infiltration of acute and chronic inflammatory cells throughout the lamina propria, with vascular, epithelial, and crypt damage as well as possible mucosal ulceration.

This grading was influenced by previous studies of a similar nature [6]. The histologic assessment also allowed for reporting of other diagnostically important changes. These included traumatic changes, the presence of some organisms, foreign body and other granulomas, cases of classic ulcerative, pseudomembranous, and collagenous colitis, and the presence of tumors. The histopathologist was blinded to the clinical history and other laboratory data.

Specimens from each of the 3 days were screened for cysts, ova, and parasites, and specimens from the first 2 days were cultured for bacteria (*Salmonella, Shigella, Aeromonas, Campylobacter,* and *Yersinia,* species and *Clostridium difficile*); organisms were identified by standard methods. The first-day specimens were also examined for viruses by electron microscopy and culture [7].

Statistical analysis. Pearson's χ^2 test with continuity correction and Fisher's exact test, where appropriate, were used to examine the association between the variables collected and proctitis or a positive HIV antibody result. All variables considered statistically or biologically significant were entered into a logistic regression model to evaluate interactions while controlling for possible confounders. Pearson's correlation coefficient (r) was used to examine the collinearity between the variables that were finally entered into the logistic regression model. Therefore, if two variables were found to be highly correlated, one of them was removed from the analysis as both of them were predictive of the same outcome.

Results

All 140 subjects underwent rectal biopsies, but some information was not available for <14% of the subjects.

The mean age of the study group was 34.4 years (range, 21–68). The median number of partners over the subjects' lifetimes was 150 (range, 2–6400) and the mean number of years of homosexual activity was 15.4 (range, 2–40). Sexual practices were divided into "never," "sometimes," and "usually" categories, with most individuals admitting to having ever engaged in oral-genital contact (95%), receptive anal intercourse (91%), and insertive anal intercourse (90%). A lower percentage admitted to other sexual practices: oral-anal contact (53%), use of enemas or dildos (34%), or fisting (8%).

Because the study group was recruited from an STD center, it was not unexpected that the percentage seropositive for HIV was higher than that reported for homosexual or bisexual men by another primary care service in a general practice setting in Sydney (30%) over a similar period of time [8]. Of the 63 individuals (45%) who tested positive for HIV antibody, only 1 presented with Centers for Disease Control class IV disease (overt AIDS), 15 had class III disease (persistent generalized lymphadenopathy), and the rest were class II (asymptomatic) [9, 10]. The T cell helper-to-suppressor ($CD4^+$:$CD8^+$) ratio was within the normal range (1.2–4.1) in

76 patients (54%), while in 46% the ratio was below the normal range for our laboratory. The absolute values of T helper ($CD4^+$) cells were <500 and ≥500 × 10^9/l in 24% (33) and 76% of patients (107), respectively. The majority (56%, 79/140) had absolute T suppressor values ($CD8^+$) within the normal range (230–660 × 10^9/l), but 41% and 2% of patients, respectively, had values above or below these limits. The mean absolute numbers of $CD4^+$ and $CD8^+$ cells were 806 (range, 200–2400 × 10^9/l) and 781 (range, 140–2530 × 10^9/l), respectively.

Of the subjects, 87% had serologic evidence (HSV CFT) of exposure to HSV, either type 1 or 2. However, in 7% (10/126), HSV-2 was isolated from rectal swabs. Twenty-eight percent had serologic evidence of previous exposure to a treponemal infection, with reactive TPHA in association with either a nonreactive or weakly reactive VDRL. Twenty-two percent of the study group (25/113) had anal warts on clinical examination. The prevalence of rectal chlamydial infection was extremely low in this study, with only one case; that patient's rectal biopsy was normal. *N. gonorrhoeae* was not cultured from any of the rectal swabs.

Inflammatory changes were noted in the rectal biopsies in 34 patients (24%) and in 17 (12%) were clinically apparent at sigmoidoscopy. These changes were generally mild and consisted of contact bleeding with rectal mucosal congestion; occasionally a follicular appearance or the presence of mucopurulent exudate was also noted. None of the patients had ulcerated mucosa on macroscopic examination via the sigmoidoscope. Almost all patients with proctitis were rated histologic grade II with chronic inflammatory cells. Only one patient had grade III or acute changes, and the proctitis was not associated with any particular pathogen.

Potentially pathogenic viruses were carried by 13% (16/123): rotavirus in 6, enterovirus in 3 cases, and echovirus type 7, coronavirus, and adenovirus in 2 each. Bacterial pathogens were identified in 3% (4/122): *Yersinia enterocolitica* in 3 and *Shigella flexneri* in 1. Interestingly, although 34 (26%) of 133 reported occasional and nonspecific gastrointestinal symptoms on direct questioning, there was no association between the detection of any of these organisms and gastrointestinal symptoms or proctitis. In the case of the latter, the only exception was with rectal HSV isolation.

Factors associated with proctitis. Table 1 shows the relationship between sexual practices, HIV antibody, T cell subset measurements, HSV isolation from a rectal swab, TPHA, HSV CFT, and proctitis. χ^2 analysis revealed proctitis to be significantly associated with: HIV antibody ($P < .001$), $CD4^+$ count <500 × 10^9/l ($P = .01$), $CD4^+$:$CD8^+$ ratio <1.2 ($P < .05$), rectal HSV isolation ($P = .02$), and anal warts ($P = .02$).

All the factors significantly associated with proctitis on χ^2 analysis were entered into a logistic regression model together with receptive anal intercourse, use of enemas or dildos, HSV CFT and TPHA results, rectal HSV isolation, and presence of anal warts. The latter were included because of the likelihood of syphilis, anorectal herpes, and trauma from anal intercourse and pleasuring devices playing a contributory role in proctitis. HIV seropositivity (odds ratio [OR], 6.5; 95% confidence interval [CI], 2.3–18.6), rectal HSV isolation (OR, 5.2; 95% CI, 1.2–23.5), and anal warts (OR, 4.9; 95% CI, 1.6–15.1) remained highly significant, with P values of <.001, .01, and .02, respectively. Because of collinearity between $CD4^+$ absolute number and HIV seropositivity ($r = .68$), the significant association between the former and proctitis was lost when HIV antibody result was included in the model.

Table 1. Association of sexual practices, human immunodeficiency virus (HIV) antibody result, T cell subset measurements, *Treponema pallidum* hemagglutination (TPHA) test, herpes simplex virus complement fixation test (HSV CFT), rectal HSV isolation, and detection of anal warts with proctitis in 140 homosexual men.

Variable	Histologically confirmed proctitis		P (χ^2)	P (logistic regression)	Adjusted odds ratio (95% confidence interval)
	Absent	Present			
Lifetime partners >150*	59/106 (55.7)	21/34 (61.8)	NS	.98	1.2 (0.4–3.6)
Receptive anal intercourse	83/89 (93.3)	25/30 (83.3)	NS	.63	0.8 (0.5–2.6)
Use of enemas or dildos	30/94 (31.9)	13/31 (41.9)	NS	.50	1.3 (0.6–2.3)
HIV antibody positive	38/106 (35.9)	25/34 (73.5)	<.001	<.001	6.5 (2.3–18.6)
$CD4^+$ cells <500 × 10^9/l	19/106 (17.9)	14/34 (41.2)	.01	.14†	
$CD4^+$:$CD8^+$ ratio <1.2	52/106 (49.1)	24/34 (70.6)	<.05	.91	1.2 (0.3–5.1)
TPHA reactive	29/104 (27.9)	12/34 (35.3)	NS	.72	1.5 (0.4–4.8)
HSV CFT titer ≥4	85/98 (86.7)	30/33 (90.9)	NS	.99	1.0 (0.2–5.1)
HSV isolated from rectal swab	4/102 (3.9)	6/34 (17.6)	<.05	<.01	5.2 (1.2–23.5)
Anal warts detected	14/105 (13.3)	11/33 (33.3)	<.05	.02	4.9 (1.6–15.1)

NOTE. Data are no. with variable/no. tested (%). Denominators do not always total 140 because some information was not available for all subjects. NS = not significant.

* Median for study group.

† Because of collinearity between $CD4^+$ absolute number and HIV antibody positive ($r = .68$), significant association between former and proctitis was lost when HIV antibody result was included in logistic regression model.

Factors associated with HIV seropositivity. The association between sexual practices, T cell subset measurements, proctitis, and HSV CFT, TPHA, and HIV antibody results was examined using χ^2 analysis (table 2). There was a highly significant association between histologically confirmed proctitis ($P < .001$) or evidence of past exposure to treponemal infection ($P < .01$) and less significant associations with past exposure to HSV infection ($P < .05$) and number of lifetime partners ($P < .05$). Not unexpectedly, there were significant associations between HIV antibody result and $CD4^+$ and $CD8^+$ absolute numbers and $CD4^+$:$CD8^+$ ratio, with P values of <.01, .001, and <.001, respectively.

When the variables found significant by χ^2 analysis and receptive anal intercourse data were entered into a logistic regression model with HIV antibody result on the basis of their known association with HIV seropositivity, proctitis (OR, 8.2; 95% CI, 2.1–31.8), reactive TPHA (OR, 3.6; 95% CI, 1.4–9.2), and positive HSV CFT (OR, 5.3; 95% CI, 0.9–31.2) emerged as independently associated with HIV seropositivity, with P values of <.001, .003, and .04, respectively. As described by others, number of lifetime partners (OR, 5.5; 95%, CI, 1.8–17.0), $CD8^+$ absolute numbers (OR, 3.2; 95% CI, 1.1–9.6), and $CD4^+$:$CD8^+$ ratio (OR, 22.1; 95% CI, 6.7–73.7) were also independently associated with HIV seropositivity, with P values of .01, <.01, and <.001 respectively. Because of high collinearity between $CD4^+$ absolute number and $CD4^+$:$CD8^+$ ratio ($r = .62$), the significant association between the former and HIV antibody result was lost when they were both included in the model. Both were predictive of HIV seropositivity.

Discussion

We examined first the associations of different variables with proctitis and then the associations of these same variables with the presence of HIV antibody. As expected, significant associations with HIV seropositivity were found for the number of lifetime sex partners, reactive treponemal serology, and evidence of previous infection with HSV. These results are consistent with those of other investigations [1–3, 5]. However, the major unexpected finding was the strong association between proctitis diagnosed by histologic criteria and seropositivity for HIV-1. This effect persisted after controlling for a number of potential interactions and confounders such as sexual practices, immunologic status, reactive TPHA, positive HSV CFT, and rectal HSV isolation.

Whether recurrent rectal inflammation as described preceded the acquisition of HIV is unclear, since the study design was cross-sectional in nature. Conventional explanations for the association between genital ulcer disease and acquisition of HIV usually rely on disruption of the mucosal integrity of the genital (or gastrointestinal) tract [11, 12]. Although these explanations appear possible in this group, as conditions associated with a disruption of epithelial integrity (presence of anal warts and rectal HSV) were significantly associated with the detection of histologic features of proctitis, proctitis alone and not these factors was significantly associated with HIV antibody status. In fact, on the basis of clinical and histologic features, there was no mucosal ulceration in any patient in this group. It is possible that not all cases of transmission of HIV are reliant on mucosal ulceration. For example, the presence of inflammatory cells so

Table 2. Association of sexual practices, T cell subset measurements, and *Treponema pallidum* hemagglutination (TPHA) test and herpes simplex virus complement fixation test (HSV CFT) results with human immunodeficiency virus (HIV) antibody result in 140 homosexual men.

Variable	HIV antibody		P (χ^2)	P (logistic regression)	Adjusted odds ratio (95% confidence interval)
	Negative	Positive			
Age >34 years	39/76 (51.3)	28/62 (45.2)	NS	.74	0.4 (0.2–2.3)
Lifetime partners >150*	37/77 (48.1)	43/63 (63.3)	<.05	<.01	5.5 (1.8–17.0)
Homosexual activity >15 years	31/68 (45.6)	27/56 (48.2)	NS	.64	1.5 (0.4–5.5)
Receptive anal intercourse	24/65 (36.9)	30/54 (55.6)	NS	.57	1.3 (0.4–4.3)
Use of enemas or dildos	19/69 (27.5)	24/56 (42.9)	NS	.66	1.2 (0.4–4.1)
$CD4^+$ cells <500 × 10^9/l	9/77 (11.7)	24/63 (38.1)	<.01	.23†	
$CD8^+$ cells >781 × 10^9/l‡	22/77 (28.6)	36/63 (57.1)	≤.001	<.01	3.2 (1.1–9.6)
$CD4^+$:$CD8^+$ ratio <1.2	21/77 (27.3)	55/63 (87.3)	≤.001	<.001	22.1 (6.7–73.7)
Histologically confirmed proctitis	9/77 (11.7)	25/63 (39.7)	≤.001	<.001	8.2 (2.1–31.8)
TPHA reactive	15/76 (19.7)	26/62 (41.9)	<.01	<.01	3.6 (1.4–9.2)
HSV CFT titer ≥4	57/70 (81.4)	58/61 (95.1)	<.05	<.05	5.3 (0.9–31.2)
HSV isolated from rectal swab	4/76 (5.3)	6/60 (10.0)	NS	.71	1.6 (0.3–7.9)
Anal warts detected	11/76 (14.5)	14/62 (22.6)	NS	.63	1.0 (0.1–15.4)

NOTE. Data are no. with variable/no. tested (%). Denominators do not always total 140 because some information was not available for all subjects. NS = not significant.

* Median for study group.

† Because of collinearity between $CD4^+$ absolute number and $CD4^+$:$CD8^+$ ratio ($r = .62$), significant association between former and HIV antibody result was lost when both were included in logistic regression model. Both were predictive of HIV antibody result.

‡ Mean for study group.

closely adjacent to infectious virus may be relevant, since it is known that activated lymphocytes are more susceptible to infection [13], and in recurrent herpes, an inflammatory infiltrate of activated $CD4^+$ lymphocytes and macrophages is found subjacent to the epithelium [14]. The assay we used, which detected antibody to both HSV-1 and HSV-2, should in future be replaced by a specific HSV-2 antibody assay, as others have found significant associations between prior HSV-2 infection and acquisition of HIV [5]. As enteric organisms (other than HSV-2) did not appear to be significantly associated with histologically diagnosed proctitis, other mechanisms contributing to inflammatory changes may need to be investigated. For example, granulomas around foreign body debris were occasionally noted in the histologic sections of biopsies taken from the distal rectum (unpublished data) and may represent localized reactions to oil-based lubricants commonly used by homosexual men during anal intercourse.

An alternative explanation for our results could be that the presence of HIV directly or indirectly modified the inflammatory response in the rectal mucosa. We were unable to exclude direct infection of the rectal mucosal cells with HIV; in other studies, this has occasionally been demonstrated in bowel biopsies by molecular techniques [15]. Although the gastrointestinal tract appears to be a major target organ late in HIV infection, as indicated by tumors, opportunistic infections, and malabsorption, much remains to be learned about the gastrointestinal mucosal response to HIV. Indeed, the mucosal immune response to bowel infections in general has not yet been clarified.

In summary, our data suggest a strong association between proctitis diagnosed on histologic criteria and seropositivity for HIV. Prospective studies are needed to elucidate this relationship.

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