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RAPID COMMUNICATION

Abnormalities of uterine cervix in women with inflammatory bowel disease

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Abstract

AIM: To evaluate the prevalence of abnormalities of the uterine cervix in women with inflammatory bowel disease (IBD) when compared to healthy controls.

METHODS: One hundred and sixteen patients with IBD [64 with Crohn's disease (CD) and 52 with ulcerative colitis (UC)] were matched to 116 healthy controls by age (+/- 2 years) at the time of most recent papanicolaou (Pap) smear. Data collected consisted of age, race, marital status, number of pregnancies, abortions/miscarriages, duration and severity of IBD, Pap smear results within five years of enrollment, and treatment with immunosuppressive drugs. Pap smear results were categorized as normal or abnormal including atypical squamous cells of undetermined significance (ASCUS), low-grade squamous intraepithelial lesion (LGSIL), and high-grade squamous intraepithelial lesion (HGSIL).

RESULTS: The median age at the time of Pap smear was 46 (range: 17-74) years for the IBD group and matched controls (range: 19-72 years). There were more Caucasian subjects than other ethnicities in the IBD patient group (P = 0.025), as well as fewer abortions (P = 0.008), but there was no significant difference regarding marital status. Eighteen percent of IBD patients had abnormal Pap smears compared to 5% of controls (P = 0.004). Subgroup analysis of the IBD patients revealed no significant differences between CD and UC patients in age, ethnicity, marital status, number of abortions, disease severity, family history of IBD, or disease duration. No significant difference was observed in the number of abnormal Pap smears or the use of immunosuppressive medications between CD and UC patients (P = 0.793). No definitive observation could be made regarding HPV status, as this was not routinely investigated during the timeframe of our study.

CONCLUSION: Diagnosis of IBD in women is related to an increased risk of abnormal Pap smear, while type of IBD and exposure to immunosuppressive medications are not. This has significant implications for women with IBD in that Pap smear screening protocols should be conscientiously followed, with appropriate investigation of abnormal results.

Key words: Inflammatory bowel disease; Ulcerative colitis; Crohn's disease; Cervical cancer; Pap smear

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INTRODUCTION

Cervical cancer is responsible for almost 4000 deaths annually in the United States[1]. Due in large part to mass screening protocols with papanicolaou (Pap) smears, mortality from cervical cancer has declined by over 70% in the past 50 years[2]. The importance of mass cervical cytology screening programs in early detection of pre-cancerous and cancerous lesions has been well established. An increase in Pap smear abnormalities has not been documented in patients with either ulcerative colitis (UC) or Crohn's disease (CD), although anecdotal reports have suggested such an association. A previous study of hospitalized patients at Lenox Hill Hospital has reported a higher rate of Pap smear abnormalities in inflammatory bowel disease (IBD) patients (47%) compared to controls (15%)[3].

The purpose of the present study was to compare the rate of cervical abnormalities in non-hospitalized patients with IBD *versus* age-matched controls and to evaluate whether

type of IBD (UC *vs* CD) and use of immunosuppressive medications are related to cervical pathology.

MATERIALS AND METHODS

This was a retrospective cohort study approved by the institutional review board. The study was performed at Lenox Hill Hospital as an interdepartmental collaborative effort amongst gastroenterologists, obstetrician-gynecologists and pathologists. Patients with IBD were identified from an IBD database that spans 30 years, which was established by the Director of Gastroenterology (BIK). Patients were contacted by mail, phone or during office visits and asked to complete questionnaires, which required information regarding age, ethnicity, marital status, type and duration of IBD, severity of illness, number of pregnancies/abortions, family history of IBD, and IBD medications [specifically the use of the immunosuppressive drugs 6-mercaptopurine (6-MP) and azathioprine (AZA), and the anti-TNF drug infliximab)] used at time of PAP smear. They were 18-80 years of age with confirmed IBD and required at least one Pap smear in the previous five years for inclusion in the study. Exclusion criteria were other immunosuppressed states, such as human immunodeficiency virus (HIV), rheumatoid arthritis (RA) and systemic lupus erythematosis (SLE) positivity. Patients signed IRB-approved release forms in order to collect the Pap smear results from their respective gynecologists. If the IBD cases received treatment with 6-MP, AZA, and/or infliximab, the duration of therapy with these drugs was calculated until the time of the Pap smear result available within the time-frame of our study (retrospective 5 years). Data regarding the use of steroids and 5-ASA products were collected using our internal IBD database, supplemented by personal communication. Severity of IBD was determined by subjective patient opinion of the disease, rated as mild, moderate or severe.

Age-matched controls (± 2 years) were identified utilizing demographic information from participating gynecologists. Controls were asked to complete questionnaires at the time of routine gynecological office visits. Inclusion and exclusion criteria were identical to the cases, except for presence of IBD. Pap smear results were obtained at the time of inclusion for the controls. For the IBD group, we contacted the patients' gynecologists in person or via telephone and requested Pap smear results and, if available, human papillomavirus (HPV) status for five years prior to the study. For the cases diagnosed with IBD within the past 5 years, we included the Pap smear results that were obtained subsequent to the diagnosis. Pap smear results were considered abnormal with any of the following: atypical squamous cells of undetermined significance (ASCUS), low-grade squamous intraepithelial lesion (LGSIL), high-grade squamous intraepithelial lesion (HGSIL), which includes carcinoma *in-situ*. When the Pap smear was abnormal, we requested any subsequent pathology reports from gynecological procedures, including loop electrosurgical excision procedure (LEEP), cone biopsy, and/or hysterectomy.

Table 1 Patient demographics: IBD *vs* controls

Patient demographics	Total IBD *n* = 116	Controls *n* = 116	*P*
Median age (yr) (range)	46.5 (17-74)	46 (19-72)	
Ethnicity			0.025
Caucasian	93%	85%	
Other (AA, Asian, Hispanic, Indian, Multicultural, West Indian)	7%	15%	
Marital status			0.4
Single	21%	18%	
Married	70%	64%	
Divorced	7%	12%	
Other (widow, unknown)	3%	6%	
Abortions (*n*)			0.008
0	80%	65%	
1	11%	17%	
> 1	9%	18%	
Disease severity[1]			
Mild	56%		
Moderate	31%		
Severe	12%		
Nonresponders	2%		
Family history of IBD[2]			
Yes	37%		
No	61%		
Unknown	3%		
Disease duration in years			
Median (yr) (range)	16 (1-55)		
6MP use			
n	55		
Median (yr) (range)	6 (1-26)		
Imuran use			
n	9		
Median (yr) (range)	3 (1-7)		
Infliximab use			
n	12		
Median (yr) (range)	1 (1-2)		

[1]Combined patient-physician assessment; [2]Includes at least one other first degree or second degree family member with IBD.

Statistical analysis

Demographic and clinical characteristics were obtained for both cases and controls. The statistical analysis plan included the calculation of descriptive statistics, such as percentage and median (range) for categorical and continuous data. Comparisons on non-parametric (categorical) data between the groups were made with the McNemar test for matched samples (IBC *vs* controls) and with the Pearson chi square test with Yates correction for independent samples (UC *vs* CD). $P < 0.05$ was considered statistically significant. SPSS (version 14.0) statistical software was utilized for all analyses.

RESULTS

A total of 116 cases were enrolled in the study. Of these, 91 were recruited *via* mail and 30 were recruited in person. Five cases were excluded utilizing the exclusion criteria. All the 116 age-matched controls were recruited in person. The demographic information is shown in Table 1 (IBD *vs* healthy controls) and Table 2 (subgroup analysis of IBD, CD *vs* UC). The groups were statistically different in

Table 2 Patient demographics: CD *vs* UC

Patient Demographics	CD 64	UC 52	*P*
Median age (yr) (range)	47 (20-72)	45 (17-74)	0.94
Ethnicity			0.666
Caucasian	59	49	
Other (AA, Asian, Hispanic, Indian, Multicultural, West Indian)	5	3	
Marital status			0.914
Single	14	10	
Married	44	38	
Divorced	4	3	
Other (widow, unknown)			
Abortions (*n*)			0.901
0	51	42	
1	8	5	
> 1	5	4	
Disease severity[1]			0.2
Mild	31	33	
Moderate	25	13	
Severe	8	6	
Family history of IBD[2]			0.14
Primary	18	10	
Secondary	10	4	
No family history	34	37	
Disease duration in years			
Median (yr) (range)	19 (1-55)	14 (1-40)	0.147
6MP use			
n	39	16	
Median (yr) (range)	6 (1-26)	6 (1-12)	0.628
Imuran use			
n	6	3	
Median (yr) (range)	4.5 (2-7)	3 (1-4)	0.433
Infliximab use			
n	10	2	
Median (yr) (range)	1 (1-2)	1 (1)	0.392

[1]Combined patient-physician assessment; [2]Includes at least one other first degree or second degree family member with IBD.

Table 3 PAP results in IBD patients *vs* controls

Pap results	IBD total	Controls	*p*
Normal	95	110	
Abnormal	21	6	
ASCUS[1]	11	2	
LGSIL[2]	6	3	
HGSIL[3]	4	1	
Total	116	116	
Abnormals (%)	18.1	5.2	0.004

[1]Atypical Squamous Cells of Undetermined Significance; [2]Low-grade squamous intraepithelial lesions; [3]High-grade suamous intraepithelial lesions (including carcinoma *in sit*u).

Table 4 PAP results in IBD subgroups: CD *vs* UC

Pap results	CD	UC	*p*
Normal	50	45	
Abnormal	14	7	
ASCUS[1]	7	4	
LGSIL[2]	4	1	
HGSIL[3]	3	2	
Total	64	52	
Abnormals (%)	22	13	0.793

[1]Atypical Squamous Cells of Undetermined Significance; [2]Low-grade squamous intraepithelial lesions; [3]High-grade suamous intraepithelial lesions (including carcinoma *in situ*).

Table 5 HPV Data in IBD patients *vs* controls (for abnormal Pap results)[1]

HPV status	IBD total	CD	UC	Controls
Positive (high risk)	5	5	0	2
Positive (low risk)	3	0	3	0
Negative	4	4	0	2
Unknown	9	5	4	2
Total	21	14	7	6

[1]HPV data were available in a small subset of abnormal Pap results and in none of the normal Paps.

ethnicity, with more Caucasian subjects in the IBD group ($P = 0.025$). There were no significant differences between the two groups with respect to marital status ($P = 0.4$). The control group had a significantly higher number of abortions ($P = 0.008$). More than half of patients within the IBD subgroups had self-reported mild disease (33/52 with UC and 31/64 with CD). One third of the patients with IBD had family clustering of the disease, with at least one other first- or second-degree relative diagnosed with IBD. There were no significant differences between the UC and CD groups with respect to age ($P = 0.94$), ethnicity ($P = 0.66$), marital status ($P = 0.90$), number of abortions ($P = 0.20$), disease severity ($P = 0.14$), family history of IBD ($P = 0.14$), duration of disease ($P = 0.147$) and length of drug therapy, including 6-MP ($P = 0.62$), AZA ($P = 0.43$), infliximab ($P = 0.39$), corticosteroids and 5-aminosalicylate (5-ASA) products.

The main results of the study are presented in Tables 3 and 4. Table 3 shows IBD *versus* controls. Within the IBD group, 18% (21/116) of Pap smears were abnormal compared with 5% (6/116) in healthy controls ($P = 0.004$). The Pap smear abnormalities found in IBD patients were ASCUS: 9.5% (11/116), LGSIL: 5.2% (6/116) and HGSIL: 3.4% (4/116). The control group had 1.7% (2/116), 2.6% (3/116) and 0.9% (1/116) Pap smear abnormalities, respectively. The subgroup analysis of IBD patients shown in Table 4 indicated that 14/50 patients with CD (22%) and 7/45 patients with UC (13%) had abnormal Pap smears. This was not a significant difference ($P = 0.793$).

Table 5 represents the HPV status of abnormal Pap smear results for patients in the IBD and control groups. HPV was positive in 11 of the IBD patients (8 CD and 3 UC) and 2 of the controls, while 4 IBD patients with CD were negative for HPV. There were 9 IBD patients (5 CD and 4 UC) with unknown HPV status. The scarcity of HPV data (more than 50% of abnormal Pap results in both IBD and control groups available and none for the normal Pap outcomes) represents the changing standards of gynecological practice during the last 6 years, the time frame used in this study. Although HPV status could have been extrapolated from the pathology slides, our study

did not include consent for the destruction of Pap smear slides. As a result, no further statistical analysis could be applied and no definitive conclusion could be reached regarding presence of HPV and abnormal Pap results in this study.

Table 6 presents the association between the major medications prescribed for patients with CD and UC and Pap smear outcomes. There was no significant association between the groups with abnormal Pap smears who were on these medications and the groups with abnormal Pap smears who were not on these medications ($P > 0.38$).

Table 6 Incidence of abnormal pap results in 116 IBD patients after treatment

Pap results	Normal pap *n* (%)	Abnormal pap *n* (%)	Total (*n*)	*P*
Corticosteroids	49 (80)	12 (20)	61	0.747
No corticosteroids	43 (83)	9 (17)	52	
5-ASA[1]	88 (82)	20 (19)	108	0.934
No 5-ASA[1]	4 (80)	1 (20)	5	
Immunosuppressives[2] and Anti-TNF α[3]	54 (79)	14 (21)	68	0.381
No immunosuppressives[2] and no Anti-TNF α[3]	42 (86)	7 (14)	49	

[1]5-aminosalicylates (sulfasalazine, mesalamine, olsalazine, *etc*); [2]Monoclonal antibody to Tumor Necrosis Factor α (infliximab); [3]6-mp and/or azathioprine.

DISCUSSION

The obstetrical-gynecological issues related to fertility, pregnancy, influence of drug therapy and fistulae are known entities in patients with IBD[4], but little is known about the link between IBD and uterine cervical pathology. Other immunosuppressed disease states such as HIV[5,6], SLE[7,8], and organ transplantation[9-11] have been shown to carry increased risk for developing abnormalities of the uterine cervix leading to cervical carcinoma and it is crucial to follow the recommended screening guidelines in these patient populations. In a previous study of hospitalized IBD patients, a much higher rate of cervical abnormalities is found in patients with IBD (47%) compared with non-IBD controls (15%)[3], for which the severity of IBD symptoms leading to the hospitalization may be responsible. Furthermore, little has been reported regarding immunosuppressive medications and the risk of cervical abnormalities, but a recent study showed that infliximab use does not increase the risk of abnormal Pap smears[12].

The results obtained through this study of 232 women demonstrate that the presence of inflammatory bowel disease is correlated with abnormal cervical histology. The group with IBD (116) and the healthy control group (116) were well matched demographically and by gynecological history, except for the higher number of Caucasians and the lower number of abortions in the IBD group. This significantly different gynecological history would have theoretically led to an outcome such that the IBD group with a lower rate of abortions should have shown a lower rate of abnormalities on Pap smear. However, the results of our study indicate that despite this significant difference in abortion rate, the IBD group still shows a significantly higher rate of Pap smear abnormalities.

Within the IBD group, the patients with CD and UC were well matched by duration and severity of disease and medication use. Our data indicate that IBD, a group of autoimmune diseases with or without immunosuppression, also carries a higher risk for developing cervical abnormalities, as more than 18% of patients in IBD group had abnormal pap smears compared to 5% in the matched control group ($P = 0.004$) over the 5-year time period. Subgroup analysis between CD and UC revealed no statistically significant difference ($P = 0.793$) in the rate of cervical pathology. Furthermore, there were no significant associations between Pap smear abnormalities and treatments with commonly used medications for IBD patients. Specifically, oral or intravenous steroids ($P = 0.747$), 5-ASA products ($P = 0.934$), and various combinations of infliximab, azathioprine, and 6-MP ($P = 0.384$) did not significantly contribute to cervical abnormalities in IBD patients. These data provide preliminary support to the conclusion that IBD may be a significant variable for developing an abnormal Pap smear.

Due to the nature of a retrospective design we have identified limitations of our study. We relied on previous Pap smear results obtained from multiple institutions, leading to interobserver variability in the interpretation of the smears. Furthermore, clinical information was obtained from patients' questionnaires, which made the assessment of disease severity and medication use difficult due to recall bias. By relating IBD severity to the timing of Pap smears, we might have been able to determine the causal effect of diarrhea on Pap smear results, but again due to the retrospective nature, this was not possible. In addition, during the time frame of our study, only a small percentage of cases and controls had HPV data available, precluding the ability to make a correlation with this contributing factor.

Despite the limitations of the study design, our data show a significant correlation between IBD and cervical abnormalities, which is not influenced by the use of immunosuppressive medications. The precise mechanism for this correlation is unknown. Other autoimmune diseases, such as rheumatoid arthritis, may also have this correlation and further research into uterine cervical abnormalities with other immunosuppressed disease states is needed. Based on our results, we recommend the standard cervical cancer screening for all IBD female patients with strict follow-up of those with abnormal findings.

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