

Seymour Katz, M.D., Series Editor

# Abnormal Cervical Cytology and Inflammatory Bowel Disease: Impact of Immunosuppression

by Ngozi Okoro, Sunanda Kane

## BACKGROUND

**C**ervical cancer is the second most common cancer in women worldwide, and responsible for almost 4,000 deaths annually in the United States. Human Papilloma Virus (HPV) is a necessary, but not sufficient, cause for the development of cervical cancer.

Inflammatory bowel disease (IBD) constitutes several chronic inflammatory diseases that may require immunosuppressant therapy to control symptoms and disease activity. Immunosuppressant use is associated with a higher risk of opportunistic infections and neoplasia, including those involving the female genital tract. Early work hypothesized that IBD, an immune-related condition treated with immune modulating medications, could increase susceptibility to cervical cancer (1). What has more recently come to clinical attention is the relationship between corticosteroids, the immunomodulators 6-MP and azathioprine and biologic agents, and abnormal cervical cytology of any type. With the advent of an effective, safe HPV vaccine, understanding who may be at increased risk and may require more aggressive screening is important.

## IBD AND ABNORMAL CERVICAL CYTOLOGY

The first study published in the era of biologics was by Bhatia, et al in 2006 (2). They demonstrated that the

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presence of IBD is correlated with abnormal cervical pathology: over a five year time period, more than 18% of patients with IBD had abnormal pap smears compared to 5% in the matched control group ( $P = 0.004$ ). They noted no statistically significant difference between ulcerative colitis (UC) and Crohn's disease (CD) in the rate of cervical pathology nor any associations between Pap smear abnormalities and treatments commonly used for IBD patients.

In 2008 this author along with others found a higher incidence of abnormal Pap smears in women with IBD compared to healthy controls from a similar population (3). In addition, there were a significantly higher number of advanced lesions compared to controls. This increase was more likely to occur in women taking immunomodulators compared with those treated with other medications.

Hutfless, et al published data from the Kaiser population of Northern California looking at a different endpoint—development of cervical cancer (4). While not statistically significant, women with IBD were 45% more likely to receive a diagnosis of cervical cancer than women without IBD. They also noted that women with IBD received four percent more Pap smears than women without IBD—which may account for the reported prevalence of cervical abnormalities. Exposure to 5-ASA products, corticosteroids and immune modulators carried elevated risks of cancer. No cancer case was seen with the use of infliximab.

Work done more recently and presented in abstract form show conflicting results.

Lees, et al tried to answer the question as to whether the increased incidence of abnormal cervical smears so far reported in women with IBD was as a result of immunosuppressant therapy or disease phenotype (5). They conducted a case-control study in a single tertiary institution in Scotland. Surprisingly, they noted no difference in rates of abnormal smears between patients with IBD and controls, and no impact whatsoever of immunosuppressant therapy and cervical dysplasia or neoplasia. They argue that women with IBD are not at increased risk of abnormal cervical smears unless they smoke, irrespective of disease activity, location or therapy.

Singh, et al performed a similar study although using a population-based cohort from the Canadian province of Manitoba (6). Their findings also did not support an association between IBD or IBD treated by immunosuppressants and the risk of developing cervical abnormalities. However, in this study smoking could not be accounted for, and the exposure and dose of immunosuppressants could not be ascertained.

In a smaller study at the University of Alabama in Birmingham, Lyles, et al compared women with IBD who had been treated with immunomodulators and those who had not (7). In their small study, they concluded that the increased risk of cervical dysplasia or cancer had to do with a longer duration of treatment with 6MP/azathioprine in patients with a prior history of HPV.

### HPV VACCINE AND SCREENING

These findings have clinical relevance with the introduction of the first vaccine for cervical cancer (8). The quadrivalent human papillomavirus vaccine (Gardasil®) is given in a three dose series over a six-month period. It is indicated for the prevention of disease caused by HPV types 16 and 18, associated with approximately 70% of cervical cancers, as well as 6 and 11, both associated with genital warts. It is recommended for women nine-to-26 years of age prior to initiation of sexual activity, as well as for those already engaged in intercourse. The Centers for Disease Control are also recommending administration to women with a history of HPV infection or an abnormal Pap smear, although the data do not indicate that the vaccine will have a therapeutic effect on existing cervical lesions. Women

with IBD especially on immunosuppressants, therefore, regardless of sexual activity history, should be considered candidates for the vaccine.

Current recommendations published by the American College of Gynecologists (ACOG) suggest yearly cytological screening for women younger than 30, and screenings every two-to-three years for older women who have three consecutive negative Pap smears. In addition, women who are at greater risk for cervical dysplasia as a result of immunosuppression should be screened at least annually for cervical cancer with Pap smears. Since the purpose of screening tests like the Pap smear is to prevent development of invasive cancers by identifying and treating individuals at high-risk, women with IBD and more importantly those on immune suppressants should be considered candidates for inclusion among American College of Obstetricians and Gynecologists guidelines for more frequent cancer screening for immunocompromised patients.

It is obvious that the data are conflicting. Several explanations could account for these differences: some of the studies were done among small populations of patients, the endpoints of the studies were different, in those patients on immunosuppressant therapy, no full assessment of the level of immunosuppression was performed; the studies did not adjust for combination therapy or for disease severity. In addition, patient compliance could be a factor that would affect whether a patient or a single Pap test is classified as exposed or unexposed. Another important consideration is that the Pap test is a screening exam and not a diagnostic test to evaluate for cervical disease.

Many questions arise if we believe that there is an increased risk of cervical dysplasia and cancer in those patients found to have abnormal cervical pathology in the setting of IBD on azathioprine/6-MP. According to current guidelines, such patients should be tested for HPV and serotyped, as serotypes 16 and 18 are clearly associated with the development of cancer and require closer monitoring. If HPV infection is found without dysplasia, then cessation of immune suppression may not be mandated. Other risk factors for dysplasia include sexual promiscuity, cigarette smoking and the use of oral contraceptives. Patients with Crohn's disease tend to smoke more than the normal population

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and thus smoking cessation should be part of the treatment plan.

In the event that HPV is found with dysplasia or cellular atypia, the indication for azathioprine/6-MP should be re-assessed. Minimizing immunosuppression would be important in preventing progression of the cervical lesion or its recurrence and alternatives discussed. It is unclear if methotrexate carries the same risk for viral replication as 6MP/azathioprine. If no other reasonable options exist, decreasing the dose to the lowest amount possible would be imperative. In both scenarios, the patient should be managed in conjunction with a gynecologist.

In summary, based on available data, no definite conclusions about the increased risk of cervical cancer in patients with IBD with or without immunomodulator therapy can be made. For now, we would encourage regular screening according to current recommended guidelines as well as vaccination for HPV. ■

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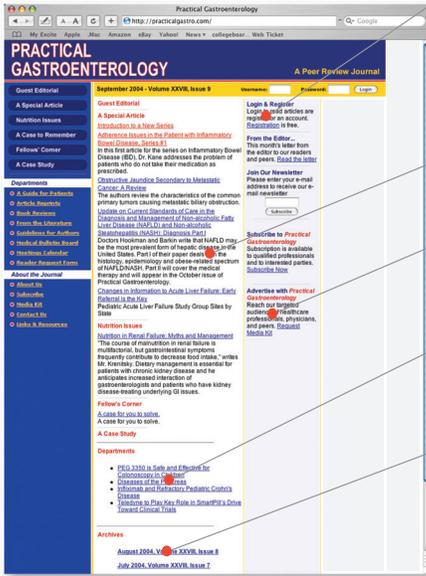
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