HIV/AIDS and Colorectal Cancer: A Review in the Era of Antiretrovirals

Ryan M. Ford, MD, Matthew M. McMahon, MD, and Mohammad A. Wehbi, MD

Dr. Ford is a gastroenterology fellow in the Department of Medicine in the Digestive Disease Division of Emory University in Atlanta, Georgia, where Dr. McMahon is a medicine resident and Dr. Wehbi serves as Assistant Professor of Medicine.

Address correspondence to:
Dr. Ryan Ford
615 Michael Street
Whitehead Research Building, Suite 201
Division of Digestive Diseases
Emory University
Atlanta, GA 30322;
Tel: 404-727-5596; Fax: 404-727-3660;
E-mail: rmford@emory.edu

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Abstract: Since the discovery of HIV/AIDS and the introduction of antiretroviral therapy, there have been many observations regarding the causes of HIV/AIDS deaths, opportunistic infections, and coexisting diseases such as non–AIDS-defining malignancies. The bulk of the literature worldwide has been epidemiologic and has involved cross-linkage of both HIV/AIDS and cancer registries. Prior retrospective studies have also utilized death certificates. Initial large-scale studies have not identified an increased risk of colon cancer in the HIV/AIDS population, and scrutiny of the literature has elucidated major limitations, most notably the lack of screening data. Only recently have there been studies addressing the rate of colon cancer screening in the HIV/AIDS population. There have also been reports suggesting an elevated risk and earlier age of onset of colonic neoplasia in the HIV/AIDS population. This review summarizes literature from the last two decades regarding HIV/AIDS and colorectal cancer and endeavors to stimulate interest in further investigation of a possible association.

Case Reports

In a 1994 case report from Chicago, Klugman and colleagues described a 25-year-old African-American man with HIV who was found to have advanced colonic adenocarcinoma postmortem.[1] The patient had undergone resection of what was believed to be adenocarcinoma of gastric origin. The authors of this case report cited three other references that also found HIV-positive patients with colon cancer presenting at earlier ages and with more aggressive courses.[2-4] At the time of these reports, Kaposi sarcoma (KS) was the most common HIV-related malignancy of the gastrointestinal (GI) tract.[1] Although KS is linked to human herpes virus 8 and anal/rectal cancer is often secondary to oncogenic human papillomavirus (HPV) infection, the pathogenesis of colonic adenocarcinoma in patients with HIV remains unclear. The connection between colon cancer and HIV may involve more than reduced immune system tumor surveillance, a concept proposed by Burnet in 1970.[5] There is little to no increased risk of colorectal cancer (CRC) in patients who are iatrogenically immunosuppressed following organ transplantation.[6,7]

An Evolving Problem

The following is a review of the literature examining the possible relationship between HIV/AIDS and CRC risk. This is an appropriate topic, as patients with HIV are living longer and dying from cardiovascular disease, liver disease, and non–AIDS-defining cancer (NADC).[8-21] Currently, there are 1 million people in the United States living with HIV.[22] Approximately 40% of all patients with AIDS develop cancer during the course of their disease.[23] In France, 13% of patients with HIV died from NADC in the year 2000,[24,25] contrasted to an incidence of less than 1% of NADC reported in the pre–highly active antiretroviral therapy (HAART) era (1992–1995).[26] At the largest tertiary referral cancer center in India, during the period 2001–2005, 141 of 251 (56.2%) cancer patients with HIV/AIDS had NADC.[27] In the United States, the overall risk and incidence of NADC in HIV-positive patients is increasing.[28-30] In the general US population, CRC ranks as the third leading cause of overall cancer death in both genders and the second leading cause of cancer death in men aged 40–59 years.[31] Presently, 10–15% of HIV patients are likely to be over the age of 50 years.[32] Since the introduction of HAART, patients with HIV have improved survival and life expectancy rates; therefore, they require age-appropriate cancer screening. Guidelines advocate CRC screening for average-risk people to begin at the age of 50 years (or the age of 45 years if the patient is African-American).[33-35]

A Global Issue

After the emergence of case reports of CRC in young patients with HIV, many investigators began to collect data on an epidemiologic scale, often merging HIV/AIDS cohorts with cancer registries and observing trends over several years. Other investigators utilized death records to determine the changing causes of mortality in patients with HIV. These observational studies were conducted on a global scale and involved at least four continents.

Goedert and associates conducted a study, reported in 1998, comparing 98,336 people with AIDS and 1,125,098 people with cancer younger than 70 years of age from the United States and Puerto Rico. Looking at the time period from 5 years prior to AIDS diagnosis to 27 months post-AIDS diagnosis, the researchers reported 12 cases of colon cancer. They did not investigate individual risk factors or screening rates. Most of the cases were adult men.[36]

Between 1990 and 1995, Selik and coworkers analyzed patients aged 25–44 who had both HIV and cancer listed on their death certificates. Fifty-five percent of the cancers were KS, and 38% were non-Hodgkin lymphoma. This study suggested an increased risk of rectal cancer, but data on risk factors such as HPV infection were lacking, and the specific type of cancer within the umbrella of rectal cancer was not reported. As death certificate analysis offers information only regarding patients who died with cancer, the incidence of CRC may have been underestimated as well.[37]

Using data collected over 13 years, between 1980 and 1993, Grulich and colleagues linked 3,616 patients with both AIDS and cancer in Australia. The investigators did not observe a significant increase in colon cancer rates, but again there were no data regarding rates of screening.[38] Similarly, but on an even larger scale, Cooksley and associates cross-linked nearly 15,000 patients with HIV/AIDS in Harris County, Texas, with cancer reports spanning from 1975 to 1994. Although the authors in this study suggested that there was an increased risk of colon cancer in women with HIV, 98% of the sample population were men, and the confidence interval was both wide and barely significant. In addition, in line with earlier studies, there was no clear description of screening rates or the type of colon cancer observed.[39]

In 2001, Gallagher and coworkers uncovered 11,371 cancers among 122,993 patients with AIDS 15–69 years of age in New York. Among these patients, AIDS was diagnosed between 1981 and 1994 (pre-HAART) and the analysis looked only at cancer diagnosed 5 years pre- to 5 years post-AIDS diagnosis. This linkage analysis suggested a mildly increased risk of rectal, rectosigmoid, and anal cancer combined. However, the majority of cases were men less than 50 years of age, and there were no data on lifestyle risk factors, HPV infection, the type of tumor identified, or screening rates. In addition, it was not appropriate that anorectal and rectosigmoid cancer cases were combined, as they may have a completely different pathogenesis and tissue origin.[40]

Also in 2001, Frisch and colleagues from the National Cancer Institute in Maryland reported 158 cases (3.5% of NADC cases) of colon/rectal cancer of the 4,422 NADC cases diagnosed 5 years pre- to 27 months post-AIDS diagnosis in 302,834 adults from 11 US cities. The subjects were mostly men 15–69 years of age who were diagnosed with HIV/AIDS between 1978 and 1996. The relative risk of colon cancer was not statistically significant.[41]

Yeguez and associates reported, in 2003, 6 cases of colonic adenocarcinoma diagnosed between 1981 and 1999 in patients with HIV at the University of Miami School of Medicine/Jackson Memorial Medical Center. Several of these patients had taken antiretrovirals, and most of the cases were advanced stage, with early age at diagnosis.[42] During the same year, Demopoulos and coworkers reported 2 cases of CRC out of 57 cancer cases (3.5%) in patients with HIV between 1993 and 1997 at Bellevue Hospital in New York

City. In contrast, 38 of 519 cancer cases (7.3%) were CRC in non-HIV infected patients. The average age of the HIV-positive patients was 48 years compared with 60 years in the control group. Patients with HIV were more likely to smoke or use drugs, and most of them were men.[43]

The following year, in 2004, Bedimo and colleagues collected data from an HIV-positive longitudinal cohort in Birmingham to identify patients diagnosed with cancer between 1989 and 2002. Two cases of colon cancer were discovered in the pre-HAART era and 11 cases from 1997 to 2002 (P=.07). Although CD4 counts did not appear to be predictive of cancer incidence, the authors concluded that the rates of NADC (60 cases total) were rising in the post-HAART era.[44] Several reasons may exist to explain these results: the detection rates may be enhanced or the incidence of CRC may be increasing in this population since the introduction of antiretroviral therapy via either direct effects or other risk factors (such as prolonged survival and advancing age).

Published in 2005, Burgi and associates identified 133 cases of NADC in a retrospective study of 4,144 HIV-positive patients who had open access to the San Diego military HIV clinic between 1988 and 2003. With a small number of cases identified, the researchers did not find an increased incidence of CRC overall, but they did find an increased risk of CRC in African-Americans with HIV.[23] In the same year, Clifford and coworkers did not observe an increased risk of colon cancer in 7,304 patients in the Swiss HIV cohort followed for 28,836 person-years.[45]

Engels and colleagues from the National Cancer Institute in Maryland used 11 US regions from 1980 to 2002 to identify nearly 376,000 patients with cancer and AIDS, the results of which were published in 2006. Interestingly, other than Hodgkin lymphoma, the authors did not observe a change in risk for NADC over time. An elevated risk for CRC was not observed.[46] Also in 2006, Sackoff and associates performed a linkage of the New York City HIV/AIDS registry and death certificates from 1999 to 2004. There were 50 cases of rectal/anal cancer listed as the cause of death (1.6 deaths per 10,000 persons with AIDS). This finding was perhaps the most comprehensive description of non-HIV–related causes of death among people with AIDS in the United States, and there were no clear reports of colonic adenocarcinoma. In this study, nearly 70% of the patients were men, the median age was 46, and only 18% of the patients were Caucasian.[18,47]

Screening

One of the glaring limitations of the large-scale studies published thus far has been the lack of data on the percentage of patients who underwent appropriate screening for CRC. In addition, the description of lower GI cancer has been limited, with authors often lumping together anal, rectal, rectosigmoid, and colon cancer without any other pathologic description such as tissue type or location. Epidemiologic and population-based studies are only as valuable as the information recorded in their documents. With publications recently advising routine medical screening for patients with HIV, only one study to date has investigated colorectal cancer screening rates in patients with HIV/AIDS. Reinhold and coworkers performed a retrospective study of consecutive HIV patients aged 50 years or older who were referred for flexible sigmoidoscopy between January 2001 and June 2002. Flexible sigmoidoscopy was the preferred modality of screening at the New York Harbor Veterans Affairs (VA) hospital during the study period. Using age- and gender-matched controls, Reinhold and colleagues concluded that HIV-positive patients were less likely to undergo any CRC screening examination (flexible sigmoidoscopy, fecal occult blood test, air contrast barium enema). Men comprised 97% of the patient population. According to multivariate analysis, older age, family history of CRC, more than 10 visits with a primary care physician in the preceding 2 years, and undetectable viral load were the only variables that were significantly associated with having at least one screening examination performed. Interestingly, nearly half of the HIV patients who never had a fecal occult blood test were documented as refusing the test.[48]

The Reinhold study implied that both physician and patient attitudes may play a role in the inadequate screening in this population. Reduced screening certainly may have led to an underestimated incidence of CRC in the HIV population-based studies previously mentioned. If researchers are not looking for CRC in the HIV population, they cannot obtain reliable data to suggest an increased or decreased risk. In response to the Reinhold paper, Berretta and Tirelli published a recommendation to start CRC screening earlier, perhaps at age 45, in patients with HIV, and reported 21 patients who had HIV and advanced CRC diagnosed at a median age of 48.[49]

The first prospective controlled study targeted at the examination of increased risk of colorectal tumors in patients with HIV was published in 2006. Bini and colleagues from the New York Harbor VA enrolled 165 patients with HIV who were 50 years of age or older, asymptomatic, and referred for average-risk screening from 1998 to 2003 to undergo flexible sigmoidoscopy, the standard modality used at the facility at the time. Patients were excluded if they had a positive fecal occult blood test, flexible sigmoidoscopy, or air contrast barium enema within the last 5 years, or a colonoscopy within the

last 10 years. An abnormal flexible sigmoidoscopy led to a full colonoscopy. The study findings showed that patients with HIV were at greater risk for colonic neoplasia, both proximal and distal. The HIV patients were more likely to be younger, more likely to be an ethnic/racial minority, more likely to smoke, and less likely to be taking aspirin than controls. In addition, the doctors were not blinded to HIV status, which possibly introduced ascertainment bias. Multivariate analysis showed that duration of HIV infection and CD4 count were independent predictors of distal lesions.[22]

In 2007, Wasserberg and colleagues at the Keck School of Medicine in southern California studied 12 patients diagnosed between 1994 and 2003 with both HIV and CRC. In this case-controlled design, the investigators reported that HIV-positive patients were more likely to be young (median age, 41 years) at the time of diagnosis and more likely to present at a more advanced stage (90% at stage III or IV) of CRC.[50]

Proposed Mechanisms

In regard to CD4 counts, there have been more data suggesting the lack of a relationship between CD4 count and CRC risk than the presence of one.[9,18,23,44,47] Interestingly, the recent study by Bini and associates noted that duration of HIV infection and CD4 count were independent predictors of distal colonic lesions.[22] Looking at data from 82,217 patients in the pre-HAART era, Mbulaiteye and coworkers performed one of the largest studies using CD4 counts to assess the relationship between immune status and cancer risk. Published in 2003, this study found no relationship between CD4 count and the risk of NADC; however, CRC risk was not evaluated.[51]

If an elevated CRC risk exists in the HIV population, it is likely more complicated than a drop in CD4 count.[36] Burgi and colleagues found predictors of NADC to include age over 40, a longer duration of HIV infection, and a history of opportunistic infection.[23] Although CD4+ T cells are important in coordinating with CD8+ T cells and other cell types in tumor surveillance, it is possible that immune reconstitution in the post-HAART era leads to chronic cytokine activation and possible damage to DNA via oxidative stress.[9] It is also possible that HIV medications themselves have a direct role in oncogenesis.[52-54] Underlying genetics, co-infections, and lifestyle exposure to unknown antigens can never be underestimated, and scientists continue to investigate the interaction of HIV and its proteins with host machinery on a molecular level. It is clear that patients with HIV appear to have a different malignancy profile than patients who are iatrogenically immunosuppressed after organ transplantation; however, studies addressing CRC are scarce. Serraino and colleagues recently reported an increased risk of colon cancer in solid organ transplant recipients (11 cases in 2,875 patients) as compared to HIV-positive patients (1 case in 8,074 patients) in southern Europe. However, the transplant patients were older (median age of 46 vs median age of 31 in HIV-positive patients), and there were no descriptions of tumor type or screening rates.[7] In addition, in a recent meta-analysis, Grulich and associates suggested a small increased risk of CRC in renal transplant recipients, as opposed to no increased risk of CRC in HIV-positive patients.[6] In this meta-analysis, the HIV studies that were included were heterogeneous (underscoring what is outlined in this review) and there were no data on age, demographics, tumor type, or screening rates.

Future Direction

With many questions unanswered regarding the relationship between HIV and CRC, there are many directions in which further research may be headed. As physicians and patients become better educated regarding the causes of death associated with HIV, cancer screening may also improve in this population. With adequate screening in the HIV population, better data will be obtained for observing a reliable increased or decreased risk of CRC. In addition, it may be possible to observe which modality of CRC screening appears to be most appropriate. If a higher risk of CRC were confirmed, studies on appropriate follow-up of polyps/neoplasia would be important. Finally, it would be important to prospectively investigate prognosis and treatment options/outcomes in patients with HIV who are diagnosed with CRC.

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