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HIV AND COLORECTAL CANCER. NEW INSIGHTS AND REVIEW OF THE LITERATURE

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Abstract – *The HIV-Acquired Immuno-Deficiency Syndrome pandemic led to an extremely reduced life expectancy in the first years of the epidemics. The improvement of the HIV therapy effectiveness, with the introduction of the antiretroviral therapy, led to an extension of the life-length, which can be currently compared to the HIV-negative population's one, and to the appearance of new pathologies, such as colorectal cancer. The likelihood of developing colorectal cancer in HIV-infected people is related to age, persistent inflammation, smoke, and new studies are being conducted to find new soluble markers that could lead to an early diagnosis of colorectal cancer. The aim of this review is to identify key data and factors about colorectal carcinoma in HIV-life people.*

KEYWORDS: *Colorectal cancer, HIV, Colorectal carcinoma, HIV and cancer, CRC.*

INTRODUCTION

The HIV-Acquired Immuno-Deficiency Syndrome (AIDS) pandemic started in 1981 and led to an extremely reduced life expectancy in those years. The improvement of the HIV therapy effectiveness and the introduction of the highly active antiretroviral therapy (ART) led to an elongation of the average life expectancy of people living with HIV (PLWH). On the other hand, this new therapy brought to the appearance of problems related to ageing, which risk is worsened by the HIV virus oncogenic action and by factors linked to recurrent infections and immune depression[1-41]. Moreover, PLWH are at higher risk of cancer than HIV-negative individuals, although rates of classic AIDS-defining malignancies (ADCs) have declined in past decades[42-48]. Currently, there are one million of PLWH in the United States and approximately 40% of these people develop cancer during the course of their disease[4-8,49-51]. In a recent paper, Mortaz et al[52], showed the central role of immunosuppression in cancer development, although they did not find a higher risk of non-infection-associated epithelial cancers like colorectal carcinoma (CRC). CRC is the third most commonly diagnosed neoplasia in the world. Approximately 150,000 new

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cases of CRC are diagnosed annually, with almost 57,000 deaths per year, making CRC a major cause of death worldwide[4-7,49,52-70]. In this report, we review the diagnostic and therapeutic management of colorectal carcinoma in HIV infected patient.

RISK FACTORS AND PATHOGENESIS

There is a strong evidence that many cancers, like Kaposi's sarcoma (KS), are increased in PLWH when compared with the general population but is still unclear whether PLWH are at increased risk for CRC than those without HIV[70]. A study by Berretta et al showed that HIV patients diagnosed with CRC are, for the most part, metastatic at diagnosis, with the liver being the organ most frequently affected by metastasis[60]. Moreover, the same study, according to other reports, highlights that PLWH are affected by CRC at a younger age than general population and with more aggressive forms of the cancer. However, this aggressiveness does not seem to be related to CD4+ T-lymphocyte counts or HIV plasmatic viral load[60, 71]. It is still unclear whether PLWH actually are at higher risk of developing CRC than the general population. Some studies explored the relationship between CRC and HIV, suggesting that PLWH were more likely to be diagnosed with CRC just because of a higher attendance to[53]. Several risk factors for the development of CRC have been identified, including inherited conditions such adenoma, polyposis and inflammatory bowel diseases, especially ulcerative colitis[42, 56, 60, 64]. Even the effects of smoking tobacco on the development of CRC have been extensively studied and several authors found a weak relationship[72, 73]. Current data suggest an association between the risk of developing CRC and excess weight, physical inactivity, alcohol use, cigarette smoking, red meat usage, and reduced vegetable and fruit use[1, 44,54,58,73-78]. Also, no-lifestyle related factors such as personal history of adenoma, positive family history of colon cancer or adenoma, inherited CRC syndromes, and long-standing inflammatory bowel disease have been linked to a higher risk of developing a CRC[42, 61, 77, 79, 80].

Several studies showed that tobacco smoking has a dose- and time-dependent association with the development of CRC, leading to a 20% increased risk of CRC in current smokers compared to never smokers[73]. Some authors support the idea that the incidence of CRC is similar between PLWH and the general population, but very few studies reported about existing differences in CRC mortality rate between people with and without HIV infection[65, 69, 81, 82]. CRC can arise from one or a combination of different genetic mechanisms such as chromosomal instability, acquisition of mutations in the adenomatous polyposis, mutational activation of the *KRAS* oncogene, inactivation of the *TP53* tumor suppressor gene[83-86]. Chromosomal instability is associated with 65%-70% of sporadic CRCs, due to mutational upregulation or downregulation of mitotic checkpoint such as *hRod*, *hZwilch*, *hZw10*[87]. Several studies showed that hypermethylation of specific promotor regions is associated with *BRAF* mutations[74, 85, 88]. *TP53* targets cell cycle inhibitors such as *14-3-3* and pro-apoptotic factors, and it is dysfunctional in the majority of human tumors. A specific subgroup of the patient population is formed by those people affected by a hereditary CRC syndrome, accounting for 5-10% of all patients. The most common syndrome is caused by a mutation in one of the DNA mismatch-repair genes: *MLH1, MSH2, MSH6, PMS2* or *EPCAM*[89].

Some studies showed that also microRNAs might have a role in CRC. MicroRNAs are small (20-25 nucleotides), single-stranded, non-coding RNAs that negatively regulate gene expression. MicroRNAs expression is frequently altered in cancers, with reports of downregulation in CRC. Several authors demonstrated that microRNAs might also work as potential biomarkers for therapeutic outcomes and predictors of the response to specific therapies[90-96]. The mechanism through which HIV increases the risk of the mutation ratio is not completely understood but it seems to be a multifactorial event. Several studies on PLWH found that the only factor associated with increased risk of colorectal adenoma was age, whereas CD4 count, HIV-RNA, and HPV infection were not associated with carcinogenesis[33]. However, previous studies suggested a possible relation between HIV infection and an increased risk of colorectal adenoma (CRA). These studies showed a high incidence of adenoma in HIV-infected patients, with patients with low CD4+ T-cell count being at higher risk[58,83,97]. On the other hand, CRC risk is likely more complicated than a drop in CD4 count. Although CD4+ T cells are important in tumor surveillance, it is possible that immune reconstitution leads to chronic cytokine activation and possible damage to DNA via oxidative stress[85, 88, 98]. Some systematic reviews and meta-analysis observed a rate of CRC-related mortality twice as higher in PLWH than HIV-negative individuals[99]. Moreover, some authors have found that patients with HIV have more advanced stage disease at presentation than uninfected individual[100]. However, this report must be considered only preliminary because it is based on 3 studies that did not meet conventional criteria for statistical significance. It is also possible that HIV drugs have a direct role in oncogenesis[8].

DIAGNOSIS

CRC can be associated with a spectrum of symptoms, including: blood in stools, change in bowel movement pattern and abdominal pain. Other symptoms include fatigue, anemia-related symptoms such as pale appearance and shortness of breath, and weight loss.

Biomarkers

Nowadays, several biomarkers as blood and fecal tests, such as searching for hemoglobin in stools (Fecal Occult Blood Test, FOBT, and Fecal Immunochemical Test, FIT), serum carcinoembryonic antigen (CEA) and fecal calprotectin are available for the evaluation of symptomatic patients. Testing for fecal occult blood (FOB) is the most common method of CRC screening throughout the world, and several studies have demonstrated that CRC screening with FOBT or FIT in average-risk populations significantly reduces CRC mortality. FOBT is able to detect most of the early CRCs and many advanced adenomas. FOBT is easily performed, widely available, and it is inexpensive, but this methodology shows several limitations, like a low sensitivity and the inability to differ human blood from animal myoglobin ingested with a meal and not digested. FIT was introduced into the scientific panorama to overcome these limits. As a matter of fact, FIT is more specific and sensitive than the traditional test, using an antibody targeting human hemoglobin[54, 101, 102].

The use of CEA is limited to surveillance after CRC resection, it is not used as a screening biomarker [79,103]. New biomarkers have been recently proposed for intestinal inflammation and other intestinal disorders. Among them, fecal calprotectin, which levels have been found to be significantly elevated in patients with inflammatory and neoplastic conditions[104]. However, some authors showed that no significant differences in calprotectin values exist between patients with CRC compared with controls. The sensitivity and specificity of calprotectin for the diagnosis of CRC are 36% and 71%, respectively[105-108].

Invasive techniques

Several diagnostic interventions such as colonoscopy, barium enema, flexible sigmoidoscopy and CT-colonography have been used to detect CRC.
Colonoscopy offers the opportunity to examine the entire colon and collect tissue biopsies just using an endoscope. It is the gold standard for the diagnosis of CRC and it has a high diagnostic accuracy, permitting to identify cancer, pre-malignant adenomas and other symptomatic colon disorders[109,110]. However, colonoscopy is an invasive procedure and it may not be possible to perform a complete examination in a proportion of patients because of their poor tolerance or inadequate bowel preparation[43,79]. Capsule endoscopy is useful in diagnosing adenomas and CRC. The first-generation capsule endoscopy was found to be able to detect polyps ≥6 mm[62,103].
Barium-enema is a radiological investigation of the colon-rectum with no need for anesthetic use and with a lower incidence of serious complications. However, there is limited evidence about the diagnostic accuracy, and it is reported to be less sensitive than colonoscopy[111]. CT colonography uses low-dose CT scanning to obtain an interior view of the colon. This technique is the most recent radiological investigation, and images are obtained after laxative preparation and insufflation of the large bowel with carbon dioxide. After the acquisition, images undergo reconstruction techniques and then analyzed[103].

Classification of CRC

CRC may remain asymptomatic for years before diagnosis, thus screening is essential for early diagnosis. On the other hand, CRC may also cause fatigue, weakness and anemia since its development. CRC can spread to other parts of the body in two ways: through a direct extension into adjacent structures or with metastatic cells circulating through lymphatic vessels and bloodstream. According with several studies, the most commonly used system to describe the extent of CRC is the tumor-nodes-metastasis (TNM) classification released by the American Joint Commission on Cancer[83, 109, 112, 113]. The WHO histological classification of tumors of the colon and rectum divided epithelial cancers in adenoma, carcinoma (adenocarcinoma, mucinous adenocarcinoma, signet-ring cell carcinoma, small cell carcinoma, squamous cell carcinoma), carcinoid and non-epithelial tumors as lipoma or sarcoma. Actually, CRC is not a single disease, but a variety of disorders that can be classified into different subtypes, characterized by specific molecular and morphological alterations. A major feature of CRC is genetic instability caused by two different mechanisms: chromosomal instability and hypermutated microsatellite instability[88].

Studies performed during pre-ART era suggested an increased prevalence of colon adenomas in the HIV-positive population. However, in the post-ART era these data were not confirmed. As a matter of fact, the most recent evidence shows that there is no significant difference in incidence between PLWH and general population. On the other hand, there is a significant difference in stage of diagnosis, with PLWH being diagnosed in later stages of CRC than the general population[58, 114].

THERAPIES

Treatments of CRC include surgery, radiotherapy and chemotherapy.

Surgery is the mainstay curative treatment for patients with non-metastasized CRC. Laparoscopic surgery is used for primary disease, while laparotomy is to be chosen in the case of a more advanced, but still localized, disease. In advanced cases of rectal cancer, neoadjuvant treatment can reduce tumor load and even tumor stage and might even be necessary to optimize the chances for a successful resection[115].

Chemotherapy or radiotherapy are often used to treat CRC. There is no accepted neoadjuvant treatment for colon cancer. However, for rectal cancer, neoadjuvant radiotherapy or chemoradiotherapy are recommended for intermediate-stage and advanced-stage cancers. Neoadjuvant radiotherapy (or chemoradiotherapy) can be proposed for patients with unfavorable T3, that invade > 5mm into fat, rectal tumors. However, the treatment for CRC reduces cellular immunity and it can expose the HIV patients at risk of opportunistic infections, therefore the knowledge of HIV status before to starting treatment is essential[116-121]. Both chemotherapy and radiotherapy are well known to cause immunosuppression of both adaptive and innate cell-mediated immunity by depleting immune cell subsets. When administered to immunocompetent individuals, chemotherapy causes a profound decline in CD4+ T-cell counts. In PLWH the prolonged CD4+ T-cell suppression induced by chemotherapy could negatively influence the course of HIV-1 disease[43].

CONCLUSIONS

The relative risk of CRC in PLWH remains uncertain and there is no evidence of significant difference in incidence when compared with the general population or HIV-negative people. Several studies show that PLWH are usually diagnosed with CRC at a younger age than general population, supposedly because of an inherent increase in susceptibility to CRC in HIV/AIDS patients. CRC has a high incidence and mortality, independently from HIV serological status. Because of that, it is a major worldwide public health problem. Early diagnosis is crucial.

Whenever it is possible, advanced tumors must be treated with combined treatments of surgery, chemo and radiotherapy.

Conflict of Interest:

The Authors declare that they have no conflict of interests.

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