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REVIEW ARTICLE

Pseudomelanosis coli, its relation to laxative use and association with colorectal neoplasms: A comprehensive review

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Abstract

Pseudomelanosis coli is historically associated with anthraquinone laxatives and is often used as a surrogate marker for chronic laxative use. The opioid epidemic has seen an increase in laxative use for chronic constipation. Anthraquinone laxatives have demonstrated tumorigenic potential in animal studies due to their apoptotic effects on colonic epithelial cells. Colorectal cancer is associated with significant mortality and morbidity worldwide. Human studies have not shown a significant correlation between anthraquinone laxative use, pseudomelanosis coli, and colorectal carcinoma. The characteristic pigmentation of pseudomelanosis also appears to be absent macroscopically and on histology of neoplastic epithelium. However, there appears to be a slightly higher risk of adenoma development. This has been attributed to a higher polyp detection rate during endoscopy on account of the color contrast between the polyp against a darker background of pseudomelanosis.

Introduction

Pseudomelanosis coli is the dark pigmentation of the colorectal mucosa first described by Cruveilhier in 1829.[1] It is a benign and reversible entity related to anthraquinone laxative use. Wittoesch et al. reported a 0.82–1.13% incidence of pseudomelanosis coli and among these patients, 95% were taking anthraquinone laxatives.[2] Recently, multiple groups have evaluated the relation between anthraquinone laxative use, pseudomelanosis coli, and colorectal neoplasms including colorectal cancer. According to the report by the World Health Organization (WHO), globally colorectal carcinoma is the third most common cancer with 1.8 million new cases and the second most common cause of cancer-related death in 2018.[3] The American Cancer Society estimates 147 950 new colorectal cancer cases and 53 200 cancer-related deaths in 2020.[4] We present a comprehensive review of the latest literature on the relation of pseudomelanosis coli to laxative use and its association with colorectal neoplasms.

Pathophysiology

Extraneous insults like laxative use cause apoptosis of colonic surface epithelial cells. These apoptotic bodies are engulfed by circulating macrophages. Electron microscopy (EM) studies show that these macrophages then migrate to the lamina propria where they undergo intralysosomal degradation to form lipofuscin, which is responsible for the characteristic pigmentation in pseudomelanosis coli.[5] Lipofuscin is nondegradable and cannot be removed via exocytosis, which causes its accumulation in postmitotic cells.[6] The origin of oxidative damage in pseudomelanosis has not been elucidated in the literature. Winterbourne and Weingast suggest that lipofuscin is produced by xanthine oxidase activity on purines.[7] The Western diet, a rich source of purines, is linked to increased prevalence of colorectal cancer.[8]

Relation of pseudomelanosis coli to laxative use

Pseudomelanosis coli is routinely associated with anthraquinone laxative use.[9] This finding was replicated in animal studies. Chronic anthraquinone laxative use in guinea pigs leads to the deposition of pigment-laden macrophages in the lamina propria. Cessation of laxative resulted in the sequential loss of pigmentation from the lamina propria.[10] While anthraquinone derivatives are more commonly associated with pigment deposition, there is evidence to suggest that non-anthraquinone laxatives can also cause pseudomelanosis. Mengs et al. supplemented 14 guinea pigs with anthraquinones and non-anthraquinone laxatives.

Macroscopically, only the anthraquinone group had the characteristic brown-colored colon, which is typical of pseudomelanosis coli. However, EM studies by both groups had a similar degree of apoptotic changes and pigment granule deposition. The exception was non-anthraquinone pigment, which was a lighter color of gray.[11] This can cause a bias in the endoscopist who can miss identifying the lighter pigmentation on endoscopy. Recently, we also have evidence to suggest that not all laxative use culminates in pigment deposition. Byers et al. investigated 38 patients with a histologic diagnosis of pseudomelanosis coli. While apoptotic bodies and lipofuscin deposition were confirmed in all 38 patients, only 16 patients had reported laxative use.[12] In a study of patients with chronic constipation and laxative use, pseudomelanosis was reported in 73.4% of patients consuming anthraquinone laxatives, and in 26.6% of patients not consuming anthraquinone-derived laxatives.[13] Pseudomelanosis is sometimes encountered in colonoscopy without a history of laxative use. In a case series of inflammatory bowel disease (IBD) patients with chronic colitis of greater than 7 years duration and concomitant microscopic melanosis coli, only 20% of the patients had documented laxative use.[14]

Association of laxative use and pseudomelanosis coli with colorectal neoplasms

The genotoxic potential of anthraquinone laxatives has been documented in many in vitro studies.[15,16] Animal studies by Mori et al. demonstrated the tumor-inducing potential of anthraquinone derivatives. Twenty-five large bowel carcinomas developed in rats when exposed to a diet containing anthraquinones after 480 days.[17] In a different animal study, it took only 112 days to develop four adenocarcinomas and five adenomas in the large bowel of rats exposed to anthraquinone derivates.[18] In human studies, Siegers et al. reported a three-fold higher risk of colorectal cancer (95% confidence interval [CI], 1.18–4.90) as a result of anthraquinone laxative use.[19] Based on existing literature, The European food and safety authority has labeled anthraquinone derivatives as genotoxic and carcinogenic.[20] The Siegers et al. study is one of the few human studies that have reported a positive correlation between laxative use and colorectal cancer. A prospective case–control study from Germany investigated the risk of anthraquinone laxatives in the development of colorectal adenomas and colorectal carcinomas when compared with patients without colorectal neoplasms. They reported no increased risk for the development of colorectal adenomas or colorectal carcinomas. Even after adjusting for duration of anthraquinone laxative use, age, sex, blood in stools by logistic regression analysis, the odds ratio for colorectal adenomas was 0.84 (0.4–1.7, 95% CI) and for colorectal carcinomas was 0.93 (0.5–1.7, 95% CI).[21] While recent studies show a negative correlation between the development of colorectal cancer and anthraquinone laxative use, further studies are required. Lombardi et al. have published a protocol for a systematic review and meta-analysis to evaluate the association between anthraquinone laxatives and colorectal cancer to guide future research.[22]

Because of its close association with anthraquinone laxative use, pseudomelanosis coli is often used as a surrogate marker for laxative use. Nascimbeni et al. assessed the cause–effect relationship between these risk factors and colorectal cancer by evaluating the frequency of aberrant crypt foci (ACF) in the colonic mucosa of patients with anthraquinone laxative use, pseudomelanosis, and sigmoid adenocarcinoma. The mean ACF frequency was higher in patients with sigmoid cancer but did not vary according to laxative use and pseudomelanosis coli when compared with controls.[23] There are conflicting reports on the association of pseudomelanosis coli and colorectal neoplasms. Koskela et al. when performing autopsies on 200 patients found that pseudomelanosis coli was more prevalent in the proximal part of the colon while colorectal cancer is more common in distal colon and rectum.[24] A retrospective study of 3049 patients who underwent endoscopy reported a 3.13% incidence of pseudomelanosis coli in patients with normal histology. Patients with colorectal adenomas reported an 8.64% incidence of pseudomelanosis coli and colorectal carcinoma was reported in 3.29% of patients. When the same group performed a prospective analysis in 1095 patients, they reported a higher incidence. For patients with a normal colon, pseudomelanosis was reported in 6.9% of patients. In colorectal adenomas, the incidence was 9.8% and 18.6% in colorectal carcinomas.[19] In contrast, a retrospective analysis of 2277 patients by Nusko et al. reported a 2.19 relative risk of adenoma development in patients with pseudomelanosis coli. However, they did not report a statistically significant increase in colorectal carcinoma.[25] The adenomas associated with pseudomelanosis were significantly smaller in size. In patients with pseudomelanosis, the relative risk for tubular adenomas (1.80; 95% CI: 1.26–2.56) and tubulovillous adenomas (2.03; 95% CI: 1.09–3.76) was significantly higher.[26] It is postulated by multiple groups that the detection rate of adenomas and polyps is higher because of the contrast between polyps and mucosal pigmentation. In a retrospective analysis, a large cohort of patients with pseudomelanosis coli over 15 years were included and matched with controls without pseudomelanosis coli on colonoscopy. The polyp detection rate (PDR) was higher in the pseudomelanosis group (33.4%) when compared with the control group (21.8%). In multivariate analysis, the PDR was significantly higher in the pseudomelanosis group (odds ratio [OR] = 1.986, 95% CI: 1.62–2.425, $P < 0.01$). However, the presence of pseudomelanosis coli was associated with a lower incidence of colorectal cancer (0.3% *vs* 3.9%; $P < 0.001$).[27] Likewise, a Chinese study reported similar findings. On retrospective analysis of 12 776 patients undergoing colonoscopy over 3 years, a significant increase in the detection rate of colorectal neoplasm was seen in patients with Pseudomelanosis coli when compared with controls. On multivariate analysis, patients with pseudomelanosis were associated with increased hyperplastic polyp (OR = 1.870, 95% CI = 1.119–3.125; $P = 0.017$ and low grade adenoma (OR = 1.474, 95% CI = 1.027–2.114; $P = 0.035$), but not adenocarcinoma (OR = 1.620, 95% CI = 0.914–2.871; $P = 0.098$).[28]

The characteristic pigmentation that aids the endoscopist in the diagnosis of pseudomelanosis coli appears to be absent in colorectal neoplasms. In a study of 511 patients with colon cancer, concomitant diagnosis of pseudomelanosis coli was found in 5.9% of cases. In these cases, the colonic mucosa demonstrated a lack of pigmentation in the proliferative or neoplastic epithelium. The lack of pigmentation was so conspicuous that it led the authors to postulate that the absence of pigment-laden

macrophages can be considered a marker for abnormally proliferating epithelium.[29] Similarly, a retrospective analysis of 436 patients undergoing colorectal surgery that analyzed sections of cancer also reported an absence of pigmentation inside tumors.[30] Not just carcinomas, hyperplastic polyps and adenomas also demonstrated a characteristic loss of pigmentation.[31,32] Regitnig et al. studied this absence of pigmentation in colonic neoplasia. In the epithelial layer of colorectal adenomas, they found seven apoptotic bodies per 100 epithelial cells when compared with 1.7 apoptotic bodies in melanotic mucosa. In the lamina propria, there were a higher number of apoptotic bodies, 2.5 per high power field (HPF), in the melanotic mucosa when compared with 0.2 per HPF in adenomas.[33]

Although PC is associated with increased tumor detection, the cause–effect relationship between pseudomelanosis coli and colon cancer remains uncertain. Besides laxative use, several environmental, genetic, and lifestyle-related factors are implicated in the pathogenesis of colorectal cancer.[34] The effect of these factors on the development of PC and consequently the risk of colorectal cancer is unknown. Molecular pathologic epidemiology, a concept consolidated by Ogino et al., can investigate those factors in relation to PC and colorectal tumors.[35] While traditional epidemiological research investigates the risk of cancer in relation to risk factors, molecular pathology epidemiology evaluates the somatic molecular changes in relation to exposure and its effects tumor behavior.[36] It is a new, evolving field of epidemiology that can help direct future research in cancer epidemiology.

Conclusion

Pseudomelanosis coli is most commonly associated with anthraquinone laxative use. However, the use of non-anthraquinone laxatives and chronic inflammatory conditions inducing apoptosis of colonic epithelium can also cause pigment deposition in the colonic mucosa. While there is some evidence to support the carcinogenic potential of chronic laxative use, the association of anthraquinone laxative use and pseudomelanosis coli with the development of colorectal cancer is not widely reported. This is supported by the characteristic lack of pigmentation in colonic neoplasms. However, there seems to be a higher rate of detection of colonic adenomas and colonic polyps in patients with pseudomelanosis. This has been attributed to better visualization of these abnormal growths by the endoscopist against a contrasting background as opposed to pseudomelanosis coli serving as a nidus for abnormal epithelial proliferation.

Ethical Statement. The manuscript represents the original work of the authors and is compliant with internationally-accepted standards of research practice and reporting.

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