

Melanosis coli

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Abstract: Melanosis coli denotes brownish discoloration of the colonic mucosa found on endoscopy or histopathologic examination. The condition has no specific symptom on its own. It is a fairly frequent incidental finding of colonic biopsies and resection specimens. The pigmentation is caused by apoptotic cells which are ingested by macrophages and subsequently transported into the lamina propria, where lysosomes use them to produce lipofuscin pigment, not melanin as the name suggests. Melanosis coli develops in over 70% of persons who use anthraquinone laxatives (eg cascara sagrada, aloe, senna, rhubarb, and frangula), often within 4 months of use. Long-term use is generally believed to be necessary to cause melanosis coli. The condition is widely regarded as benign and reversible, and disappearance of the pigment generally occurs within a year of stopping laxatives. Although often due to prolonged use of anthraquinone, melanosis can probably result from other factors or exposure to other laxatives. It has been reported as a consequence of longstanding inflammatory bowel disease. Some investigators suggested that increase in apoptosis of colonic mucosa by anthraquinone laxatives increased the risk of colonic cancer. Recent data, including those from large-scale retrospective, prospective and experimental studies, did not show any increased cancer risk.

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What is melanosis coli?

Melanosis coli is a brownish discoloration of the colonic mucosa caused by the accumulation of pigment in macrophages of the lamina propria. It was first described by Cruveilhier in 1829. The term *melanosis coli* was coined by Virchow in 1857, because the pigment was considered to be melanin or a melanin-

like substance. Subsequently, the pigment proved to be more characteristic of lipofuscin, both histochemically and ultrastructurally.^{1,2} The pigmentation is caused by apoptotic cells which are ingested by macrophages and subsequently transported into the lamina propria, where lysosomes use them to produce lipofuscin pigment, not melanin as the name suggests. Some authors therefore prefer the expression “pseudomelanosis coli”.³ Others have suggested renaming the condition as “lipofuscinosis coli” based on clarification of the mechanism of pigment formation.^{4,5}

Clinical, endoscopic and histological features

Melanosis coli can sometimes be detected by endoscopy as an abnormal brown or occasionally black pigmentation of the colonic mucosa. [Fig.1] The reported prevalence of endoscopically visible melanosis coli in proctoscopic studies varies between 0.8% and 9.3%.⁶ The intensity of the discoloration may differ from barely discernible brown coloration to black. Close examination may reveal small (2 mm to 1 cm) raised areas separated by thin unpigmented reticulum (“toad back” appearance).⁷ The condition has no specific symptom on its own; instead, symptoms may be attributed to such accompanying conditions as chronic constipation or diarrhoea. Extensive melanosis coli may mimic ischemic colitis and thus must be considered as a differential diagnosis.⁸

Melanosis coli is a frequently reported incidental finding on colonic biopsies and resection specimens. Histologically, the epithelial cells are unremarkable on light microscopy, but abnormalities of these cells are noted on electron microscopy. The mucosa and submucosa are usually oedematous and contain pigment-laden macrophages, some plasma cells, mast cells and several nerve fibers in different stages of degeneration⁹ [Fig.4 & 5]. In an unselected autopsy series, microscopic melanosis was found in 59.5% of cases.¹⁰ Microscopic melanosis is found more often than endoscopically visible melanosis coli. A histopathological study revealed that among 45 patients with microscopic melanosis coli,

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the pigmentation was macroscopically visible in only 14 cases (31%).¹¹

In humans, and likewise in guinea pigs, macrophages are most abundant in the caecum, decreasing towards the rectum. This explains why the most frequent sites of involvement are the caecum and the appendix, which is the usual distribution pattern of melanosis coli, in the proximal as opposed to the distal colon, though it may affect the whole length of the large bowel. It may also reflect higher luminal concentrations of the offending agent in the proximal compared to distal colon, or differential absorption along the length of the colon.⁷ Mucosal lymphoid aggregates normally display a distinct absence of pigment producing a “starry sky” appearance, especially in the rectosigmoid region [Fig.2]. Interestingly, some focal, usually sessile, colonic mucosal neoplastic lesions, rather than submucosal lesions, may be better appreciated as pigment deposition may be absent or limited [Fig.3]. If detected, removal and further histopathologic analysis of the polyp may be facilitated¹² [Fig.6].

Melanosis has been rarely recorded in the small intestine, at least, in the most readily visualized areas during routine endoscopic evaluation, including the duodenum or distal ileum. Pigment may extend for a very limited distance into the most distal ileum transitional mucosa in association with melanosis coli.¹²

Treatment of this condition has not been established. Often, a recommendation is made to manage symptomatic constipation with fiber-containing foods or substances with mucilage, including psyllium, along with avoidance of anthraquinone cathartics.

Aetiology

The association between melanosis coli and chronic use of anthraquinone laxatives is firmly established. It was first noted by Bartle in 1928, and substantiated by Bockus in 1933. Many subsequent studies confirmed the association. This is further supported by the development of similar pigmentation in laboratory

animals after administration of anthraquinones.¹³ Several experimental studies in different mammalian species documented the appearance, disappearance and re-appearance of the pigment in colorectal mucosa with repeated cycles of laxative administration.¹² Melanosis develops in over 70% of persons who use anthraquinone laxatives (eg cascara sagrada, aloe, senna, rhubarb, and frangula), often within 4 months of use, with an average of 9 months. There is an earlier age of onset in the females, with a higher detection rate.¹⁴ The condition is widely regarded as benign and reversible, and disappearance of the pigment generally occurs within a year of stopping laxatives.¹⁵ However, melanosis can probably result from other factors or exposure to other laxatives and is not pathognomonic for anthraquinone use.

Nuskoet *al.* performed a prospective case control study at the University of Erlangen to investigate the association of anthranoid laxative use and the development of melanosis coli. A total of 202 patients with newly diagnosed colorectal carcinomas, 114 patients with adenomatous polyps, and 238 patients (controls) with no colorectal neoplasms who had been referred for total colonoscopy were studied. A total of 97 (17.5%) study participants, both cases and controls, admitted to using laxatives. Anthranoid containing laxatives were used by 78 (14.1%) participants. Anthranoid laxative use was significantly associated with macroscopic and microscopic melanosis coli ($p < 0.01$). Nine (12%) patients using anthranoid laxatives showed macroscopic and 31 (40%) microscopic melanosis coli. Eleven (2%) of 476 non-users of such laxatives showed macroscopic, and 68 (14%) microscopic melanosis.¹⁶

Laxatives may be associated with, but need not be the cause of microscopic melanosis. Also, the luminal bacterial flora and faecal material may have a toxic effect on the surface epithelium.¹⁰ Melanosis coli has been reported as a consequence of longstanding inflammatory bowel disease (IBD). Pardi et al found melanosis coli in 25 patients with IBD, most of whom (80%) had no documented laxative use, suggesting that IBD is an independent factor for the deposition of pigment.¹⁷

Pathogenesis

Anthranoid-containing herbal laxatives damage epithelial cells, leading to changes in absorption, secretion and motility.¹⁸ They can induce cell loss, shortening of mucosal crypts and increased cell proliferation.¹⁹ Upon ingestion of anthraquinone containing herbs, an active derivative, rhein, is formed in the large intestine by bacteria, which causes injury to the cells in the lining of the intestine and leads to apoptosis.^{20,21} These cells are either shed into the colonic lumen, or the damaged organelles are sequestered in autolysosomes in macrophages where digestion to residual lipofuscin bodies results. When sufficient cells have been damaged, the distinctive pigmentation of the bowel mucosa develops. Such a sequence of damage has been demonstrated in guinea pigs exposed to anthraquinones. Histologically, the number and size of macrophages within the lamina propria are increased, and the greatest amount of pigment is found in macrophages farthest from the lumen.⁹

It is possible that this relatively selective colonic mucosal involvement may reflect the qualitative or quantitative differences in colonic microbial flora (as opposed to the small intestine). Alternatively, some other structural difference in colonic cells or their response to anthraquinone cathartics may be responsible for the colonic mucosal regionalization of the lipofuscin pigment deposition.¹²

Byers *et al.* investigated the clinical presentation, laxative use and histopathology of 38 patients with a histological diagnosis of melanosis coli and measured the colonic epithelial apoptosis in these cases. They found increased colonic epithelial apoptosis, with majority of cases not associated with laxative use. These results support the proposed role of apoptosis in melanosis coli, and indicate that melanosis coli is a non-specific marker of increased apoptosis with many possible causes, of which the use of laxatives is only one.²²

Is melanosis coli precancerous?

Melanosis coli has long been considered to be a harmless discolouration of the large bowel. However, mutagenic effects have been reported for some anthranoid laxatives *in vitro*.^{23,24} Some evidence has been found in animal experiments that dantrone, a synthetic anthranoid laxative, may induce colorectal tumours.²⁵

Siegers *et al.* conducted a prospective study in 1095 patients who underwent endoscopy between October 1989 and March 1991. In patients with no abnormal changes, a pseudomelanosis coli frequency of 6.9% was detected. In patients with inflammatory diseases, pseudomelanosis coli incidence amounted to 2.3%, and in those with diverticulosis to 9.1%. In patients with adenoma the incidence was increased to 9.8% and in those with carcinoma it was 18.6% ($p=0.0008$). Statistical evaluation of these data indicates a significantly higher incidence of pseudomelanosis coli in patients with tumours of the large bowel.²⁶ Other studies, however, have either failed to confirm this or found an increased risk for colorectal adenomas but not for cancer.²⁷

Some investigators have suggested that increase in apoptosis of colonic mucosa by anthraquinone laxatives increased the risk of colonic cancer. *In vitro* and animal studies have shown a potential role of anthranoid laxatives in both the initiation and promotion of tumorigenesis. Studies in humans have also suggested tumour promoting activities for these laxatives. However, recent data, including those from large-scale retrospective, prospective and experimental studies, did not show any increased cancer risk. It is widely accepted that increase in the incidence of adenomas is probably due to easier detection of small adenomas against the black background²⁸[Fig.3].

Nusko *et al.* performed a prospective case control study to investigate the risk of anthranoid laxative use for the development of colorectal adenomas or

carcinomas. They found no statistically significant risk of anthranoid use for the development of colorectal adenomas (unadjusted odds ratio 1.0; 95% CI 0.5-1.9) or carcinomas (unadjusted odds ratio 1.0; 95% CI 0.6-1.8). Also, there were no differences between the patient and control groups for the duration of intake. Macroscopic and high grade microscopic melanosis coli were not significant risk factors for the development of adenomas or carcinomas. They concluded that neither anthranoid laxative use, even in the long term, nor macroscopic or marked microscopic melanosis coli were associated with any significant risk for the development of colorectal adenoma or carcinoma.¹⁶

Other permanent damage

There is also concern about the possibility that stimulant laxatives may induce permanent enteric nerve or muscle damage with the use of anthraquinone laxatives. In part, this may be due to the development of melanosis coli. However, its functional significance is unknown, it does not extend to the muscle layers or enteric plexuses, and it is completely reversible when the use of such laxatives is stopped. The preponderance of the evidence suggests that long-term use of anthraquinone laxatives is not associated with morphologic changes of colonic muscle or enteric neuronal structures.²⁹

Role of complementary and alternative medicine in melanosis coli

The use of complementary and alternative medicine (CAM) has been on the rise in the past few decades. CAM use appears to be more common among those with functional bowel disorders. Patients with chronic and refractory gastrointestinal disorders tend to use CAM more frequently: herbal products being the most commonly used. Overall, 10% of herbal therapy is used for digestive symptoms. Indeed, up to 30% of patients with chronic liver disease and 40% of patients with irritable bowel syndrome claim to have used some form of herbal medication. An estimated 51% of patients with gastrointestinal disorders have tried some form of

CAM.³⁰ Several studies have shown that female gender is most predictive of CAM use. Patients are more likely to use CAM as an adjunct to conventional medicine than instead of conventional medicine, and only 48% of patients taking CAM provide this information to their physician. Interestingly, doctors may not question patients about CAM usage.³¹

Anthraquinone compounds are present in many over-the-counter laxatives, including herbal medicines. In addition, laxatives are frequently used as slimming agents, usually in the form of herbal teas. With a sufficient dose and duration of laxative ingestion, the entire colon may be involved as melanosis coli can develop in as short as 6 weeks.³² Aloe vera extracts, administered externally or internally, are advertised as over-the-counter treatment for conditions such as burns, wounds, common cold, gout, rheumatoid arthritis, atherosclerosis, and even AIDS and cancer. Kunkel *et al.* reported an elderly man with long term intake of aloe vera juice as a wellness drink, presenting with chronic diarrhoea and melanosis coli. Like other herbal laxatives, aloe vera contains anthraquinones whose laxative effect is well established but obviously not known to the user and many health care professionals.³³

The photos used in this paper came from a 51-year-old woman who consulted the author for dyspepsia and bleeding per rectum. Clinical examination was unremarkable. Gastroscopy was normal, while colonoscopy found severe melanosis coli throughout the whole colon, and a single flat polyp of 2-3 mm in the rectum. She also has internal haemorrhoids. She admitted to taking about 20 capsules a day of over-the-counter preparations for various indications. One of them contains Rhubarb and Cascara, besides 7 other herbal ingredients. She takes 2 capsules of this "K-1 capsule" on a regular basis. Indication on the label was "traditionally used to improve digestion, relief stomach discomfort and mild constipation".

Although melanosis coli is a harmless discoloration of colonic mucosa resulting from complementary or

alternative medicine, it is believed that this association with herbals was often overlooked, not suspected by patients nor enquired by doctors. Therefore, it should be emphasized to patients that “natural” or “alternative” is not equal to “safe” or “without unwanted consequences”.³³

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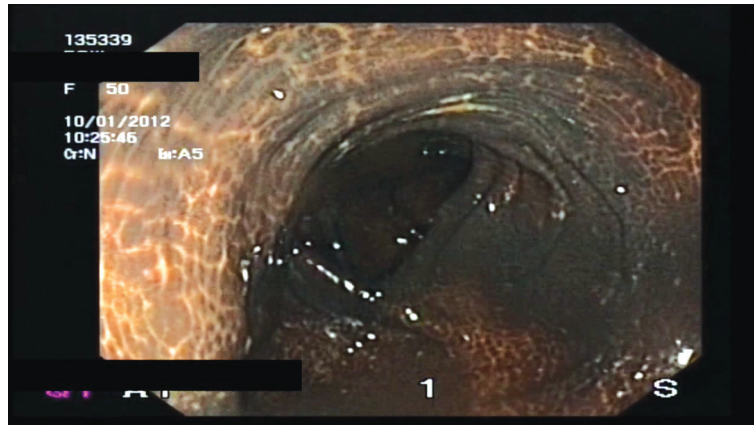


Fig 1: Colonoscopy showing diffuse dark brown and black pigmentation throughout the colon, consistent with the presence of melanosis coli. Please note the typical snake skin appearance.



Fig 2: This is an earlier colonoscopy of the same patient. Melanosis coli was present but less intense. Note the “starry sky” appearance.



Fig 3: A single sessile flat polyp in the rectum, easily visualized from the rest of the mucosa as it is not pigmented. Please see microscopic appearance in Fig 6.

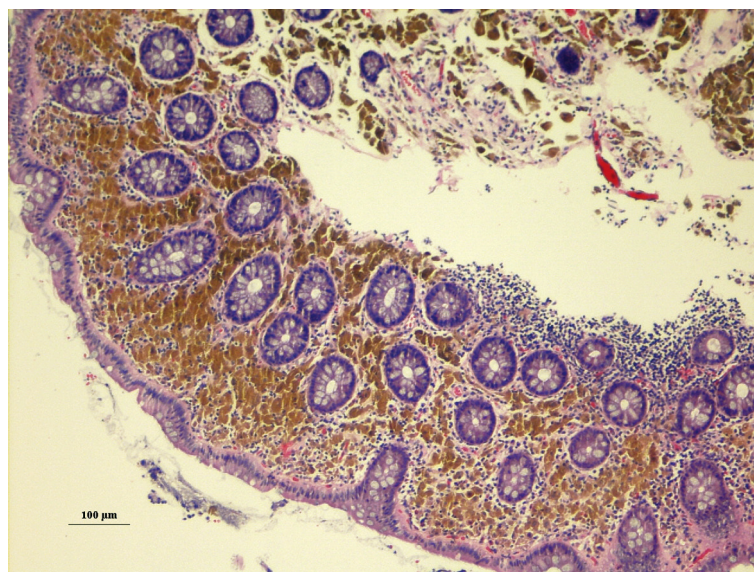


Fig 4: Photomicrograph (H&E, 200x) showing colonic mucosa beneath which are seen glands surrounded by brownish pigment laden macrophages, amidst scattered inflammatory cells.

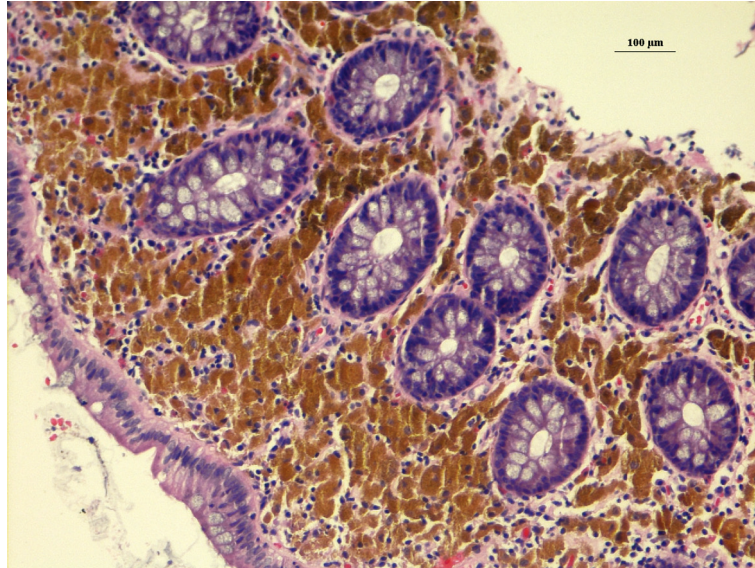


Fig 5: Photomicrograph (H&E, 400x) showing sheets and clusters of brownish pigment laden macrophages extending along the lamina propria and around the glands, and few inflammatory cells.

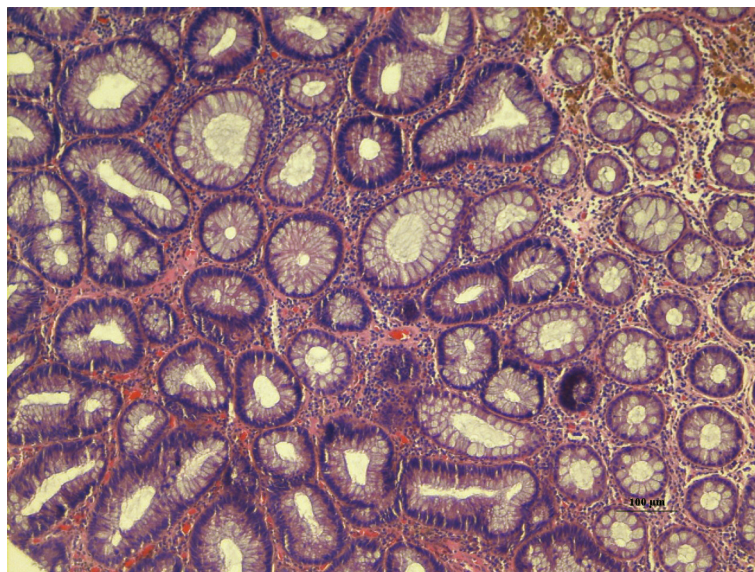


Fig 6: Photomicrograph (H&E, 200x) of tubular adenoma, showing increased crowding of glands lined by cells with basal nuclei and abundant cytoplasm, but with no evidence of atypia. Focal chronic inflammatory cells are present. The pigment laden macrophages are absent in the adenoma, and may be seen at the periphery where the rest of the mucosa continues on.