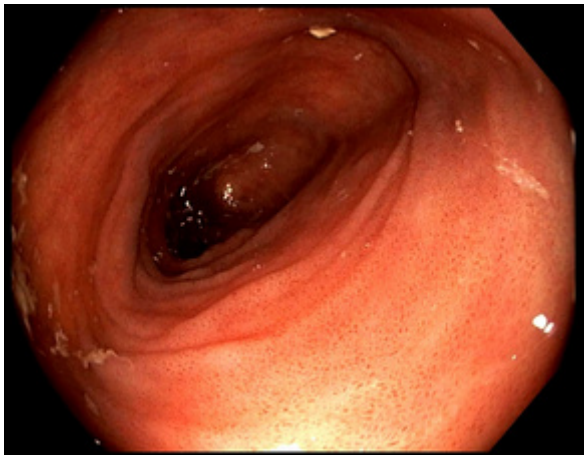
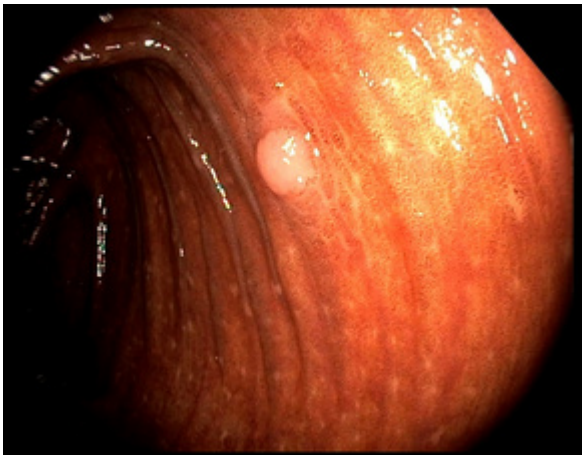
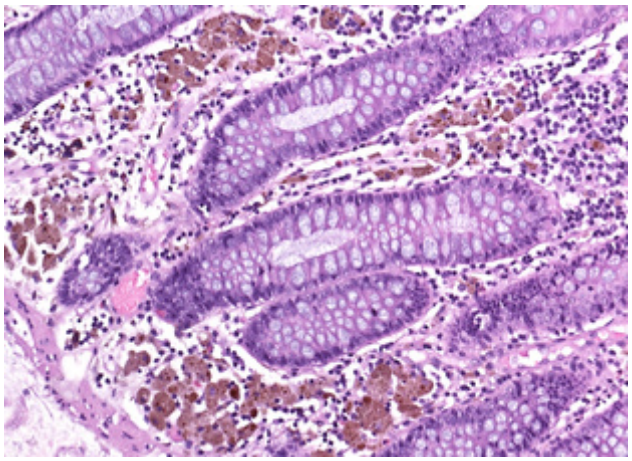
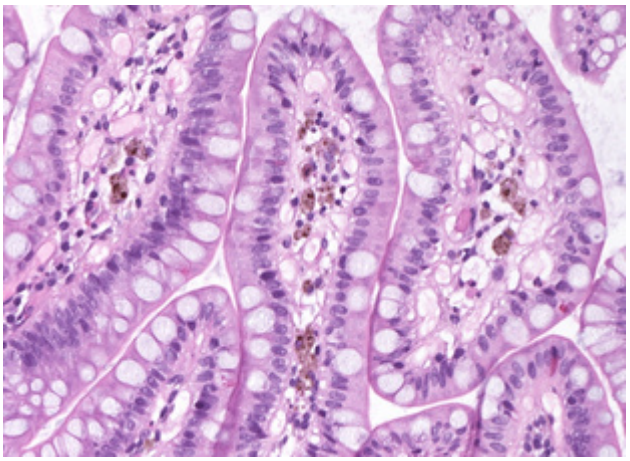
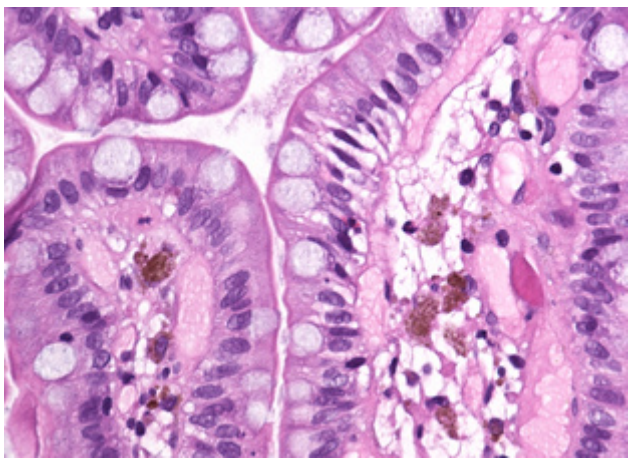
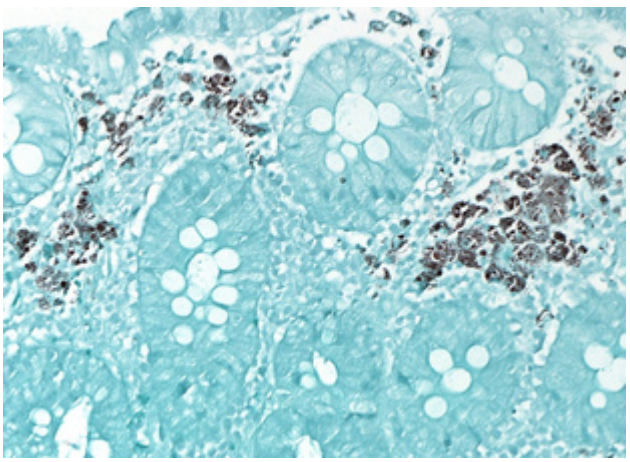
April 2016

Small and large bowel biopsies in a 75-year old male.

What is your diagnosis?

Diagnosis:

(Pseudo-)Melanosis of small and large bowel.

Comment:

A 75-year-old male with chronic constipation and history of right hemicolectomy due to cecal cancer underwent surveillance colonoscopy. Mild mucosal hyperpigmentation was found in the ileum (Panel A), particularly strong hyperpigmentation in the remaining colon (Panel B, including a small tubular adenoma

which remains unstained).

Histology of small and large bowel showed preserved mucosal architecture and normal cellularity within the tunica propria. In the large bowel, abundant macrophages were found within the tunica propria showing brownish, iron-negative pigment within the cytoplasm (Panel C). These macrophages were also seen in the tunica propria of the small bowel, albeit in lower frequency (Panels D and E). The pigment could be highlighted by Ziehl-Neelsen stain (Panel F). The pigment was absent in the stroma of the small tubular adenoma (not shown). A diagnosis of (pseudo-)melanosis affecting both small and large bowel was made.

Melanosis within the gastrointestinal tract is usually limited to the large bowel, i.e., melanosis coli and is more prominent in the proximal colon, characteristically ending at the ileocecal (Bauhin) valve. Small bowel involvement is exceedingly rare. Histological diagnosis is usually straightforward and Ziehl-Neelsen only necessary in cases that show pigment upon endoscopy, but lack unequivocal proof on H&E-stained slides. Iron staining, e.g. Prussian blue, may be performed to rule out hemosiderin deposits.

The melanosis is pathogenetically linked to chronic use of laxatives containing anthraquinone and persisting faecal stasis. Specifically, anthraquinone inhibits the resorption of water in the colon and damages the endothelium of small vessels. The consequence is increased epithelial apoptosis. Sequestered cell organelles, including mitochondria and endoplasmatic reticulum, are dissolved in lysosomes, ultimatively emerging on the histological level as yellow to brown lipofuscin-like pigment. The pigment is mainly present inside macrophages, which are seen scattered throughout the mucosa, even in the submucosa and rarely also in regional lymph nodes.

Notably, melanosis is absent in neoplastic mucosa, i.e., the stromal macrophages of colorectal adenoma and carcinoma (compare above). The reasons for this feature are largely unclear. According to Regitnig et al. the apoptotic fragments seem to remain in the neoplastic (adenomatous) epithelium and do not reach (at least in higher amounts) the lamina propria. The following factors could be responsible:
(1) neoplastic and hyperplastic colonic lesions have suppressed apoptosis and increased proliferation of epithelial cells relative to normal colonic mucosa,
(2) in contrast to the situation in normal colonic mucosa, apoptotic bodies cannot reach the lamina propria in these lesions, or
(3) lack or low numbers of macrophages ingesting the material derived from apoptotic cells in the lamina propria of these lesions.

On the molecular levels, most adenomas overexpress Bcl-2 oncoprotein, an inhibitor of apoptosis. Hence, in contrast to non-neoplastic colonic mucosa, the absence of melanosis coli in adenomas may be due to impaired transition of apoptotic bodies derived from the epithelium into the lamina propria.

For further reading:

- Regitnig P, Denk H. Lack of Pseudomelanosis coli in colonic adenomas suggests different pathways of apoptotic bodies in normal and neoplastic colonic mucosa. Virchows Arch. 2000; 436: 588-94.
- Batistatou A, Panelos J, Agnantis NJ. Melanosis intestini: case report. Diagn Pathol. 2006; 1:3.
- Freeman HJ. "Melanosis" in the small and large intestine. World J Gastroenterol. 2008; 14: 4296-9.
- Van Weyenberg SJ, Hoentjen F, Thunnissen F, Mulder CJ. Pseudomelanosis coli and adenomatous polyps. J Gastrointestin Liver Dis. 2011; 20: 233.

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