

Review Article

Pseudomelanosis duodeni: a short review

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Abstract: Pseudomelanosis duodeni is characterized by the presence of brownish or blackish pigmentation in the duodenal mucosa identified during endoscopy. Although the pathogenesis is uncertain, it was generally believed that it is sequelae of luminal absorption of iron and sulfide chemicals, which is subsequently deposited in the lamina propria. It is often associated with hemodialysis and oral intake of iron supplements. Histologically it is characterized by dark brown pigmentation accumulated within macrophages in the lamina propria, particularly at the tips of villi. Histological differential diagnosis includes hemosiderosis/hemochromatosis, brown bowel syndrome and malignant melanoma, which could be differentiated using special stains and immunohistochemical markers. Pseudomelanosis duodeni per se does not lead to any clinical symptom; however, it indeed evokes anxiety and confusion for clinicians and pathologists because of its rarity, peculiar endoscopic features, and concerns for malignancy.

Keywords: Pseudomelanosis duodeni

Introduction and definition

Pseudomelanosis duodeni is a rare condition first described in 1976 by Bisordi and Kleinman [1]. It is characterized by the presence of brownish or blackish pigmentation in the duodenal mucosa identified during endoscopy. Pigments may be composed of melanin like substances, iron, sulphate, and other chemicals. Melanosis was described most commonly in the colon, which is generally believed to be a sequela of the extended use of laxatives; but it also affects the duodenum, jejunum, and ileum [2, 3]. Duodenum is the most reported extracolonic site, while jejunal and ileal involvements are rarely reported [2]. Different from the melanosis coli, the pathogenesis of pseudomelanosis duodeni remains unclear. The term “pseudomelanosis” is used when the pigment does not consist of melanin, as the term “melanosis” would imply; however the pigment is similar in morphology on the routine hematoxylin and eosin stain. While pseudomelanosis duodeni is a rare condition, it could pose a diagnostic dilemma due to peculiar endoscopic findings, which could be confused with hemosiderosis or neoplastic process, particularly malignant mel-

anoma. Here, we have performed a systemic review of pseudomelanosis duodeni including clinical, endoscopic and histological features, proposed pathogenesis and clinical significance.

Endoscopic features of pseudomelanosis duodeni

Endoscopically, pseudomelanosis duodeni is characterized by speckled pigmentation of the duodenal mucosa (**Figure 1A**). The color of the duodenal pigments varies from brown to black, often with a spotty distribution (**Figure 1B** and **1C**). The pigment is usually more prominent in the second portion of the duodenum with extension as far as the endoscope could reach. In contrast, duodenal bulb (the first portion of the duodenum) is involved to a lesser extent. Kang et al reported that pigment deposition could extend to distal stomach occasionally [4]. Follow up endoscopic findings vary from patient to patient. A repeat endoscopic examination may show a complete disappearance of duodenal pigmentation while it may also demonstrate a persistent pigmentation with minimal improvement [4].

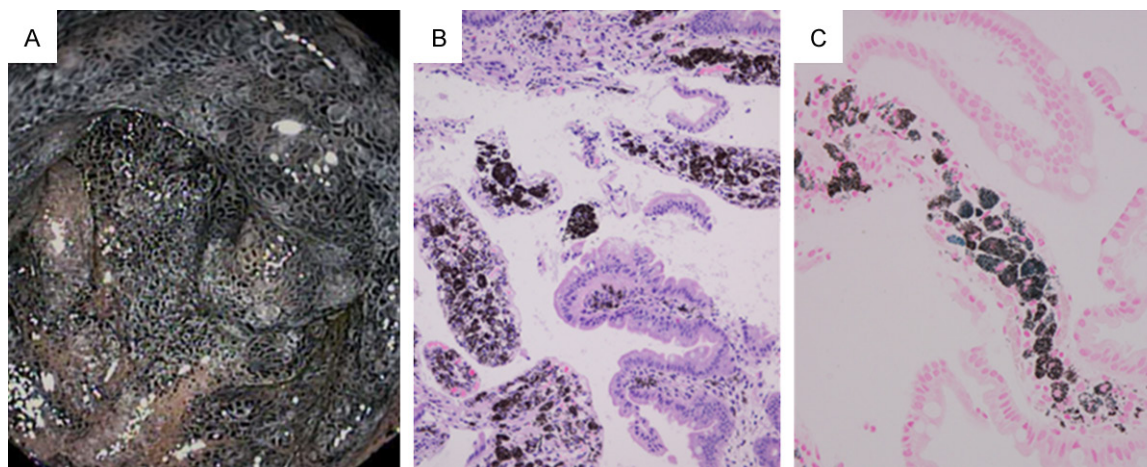


Figure 1. Endoscopic and histological features of pseudomelanosis duodeni: A: Endoscopically, the duodenal mucosa shows brown to black speckled pigmentation. B: Histology shows pigment deposition in the lamina propria. The pigment is more prominent in the tips of duodenal mucosal villi. The villous structure is well maintained. C: An iron stain shows patchy iron positivity of the pigments.

Histological features of pseudomelanosis duodeni

The term melanosis in the gastrointestinal tract describes the accumulation of pigment in the lamina propria of mucosa [5]. Pigments could be either fine or coarse granules, which are usually found inside the lysosomes of macrophages located in the lamina propria of duodenum, particularly at the tip of villi (**Figure 1B**). It has been assumed that these deposits to be melanin-like substances, hemosiderin, lipomelanin and lipofuscin [4, 6]. Prior studies described the pigment by light microscope as golden to yellowish brown, mainly within macrophages in the lamina propria. A small proportion of pigments could be located in the extracellular space [4]. Kang et al [4] has observed three staining patterns:

- (1) The pigment was positive with the Prussian blue iron stain (**Figure 1C**) and negative with the Masson-Fontana method for melanin deposit in contrast.
- (2) The pigment was negative with Prussian blue iron stain, and positive with the Masson-Fontana method, which becomes negative after bleaching.
- (3) The pigment is positive by both the Masson-Fontana method and the Prussian blue iron stain, after bleaching, the pigment became negative with the Masson-Fontana method but

the iron stain remained positive. So far, all studies have shown that the pigments are negative for bile based on Fauchet staining method and auto fluorescence (lipofuscin) [4]. The pigments are generally negative for PAS stain. The endoscopic and histological differential diagnosis includes true melanin due to metastatic malignant melanoma, brown bowel syndrome, and hemosiderosis/hemochromatosis. Hemosiderosis is iron deposits secondary to mucosal hemorrhage, iron pill deposition, primary hemochromatosis or secondary hemochromatosis. Iron pigments in hemosiderosis can be seen in stromal cells, epithelium or both, often present as light brown pigments. Prussian blue iron stain would highlight diffuse strong iron stain of all pigments in hemosiderosis which is different from pseudomelanosis duodeni only partial and relatively weak iron positivity. True melanosis is a deposition of melanin produced by melanocytes, associated with metastatic melanoma. Malignant melanoma cells often show marked cytological atypia with enlarged hyperchromatic nuclei, prominent nucleoli and frequent mitosis. The Masson-Fontana stain would highlight melanin pigments. Melanin pigments do not stain with Prussian blue. Immunohistochemical stains would be helpful to distinguish malignant melanoma from pseudomelanosis duodeni. Malignant melanoma cells are positive for S100, HMB-45, MelanA/Mart1, tyrosinase and microphthalmia transcription factor (MITF); while the histiocytes in pseudomelanosis duodeni are positive for CD168 and

CD68. In addition, Immunohistochemical stain for Ki67 is also helpful. Melanoma cells often demonstrate high proliferative index; in contrast, Ki67 labeling for histiocytes in pseudomelanosis duodeni is usually negative.

Ultrastructural findings of pseudomelanosis duodeni

Siderits et al performed an electron microscopic examination on a case of pseudomelanosis duodeni [7]. It was shown that the pigments were membrane-bound, electron dense bodies located within macrophage lysosomes. The pigments appear to be amorphous, smooth-to-angular, crystalline representing iron particles (6-8 nm) as well as ferritin (9-12 nm). Other studies have demonstrated different patterns of electron dense materials including angular membrane bound electron dense structures and rounded or irregularly shaped electron dense structures [4]. In some areas, these structures are slightly angular and seemed to be contained within lysosomal bodies [4].

Chemical composition of pigments in pseudomelanosis duodeni

Since the first description of duodenal melanosis by Bisordi and Kleinman [1], the earlier studies considered the pigment to be melanin since the pigments stain positive with the Masson-Fontana method. However the Masson-Fontana method is not specific for melanin. It is well known that other reducing substances would also stain by this method. Further studies by Sharp et al [8] indicated that the pigments are not identical with melanosis. Kang et al [5] has performed electron probe X-ray analysis on the pigments from six patients with pseudomelanosis duodeni. It was found that iron was present in all cases analyzed, while sulphur was present in five samples. In addition, all specimens showed peaks of copper and osmium. As mentioned earlier, a Prussian blue stain for iron could be either entirely negative or patchy positive even though all pseudomelanosis duodeni contains iron component as demonstrated by electron probe X-ray studies. The possible explanation for this discrepancy is likely due to iron in the duodenal pigments occurs in the sulphide form, which does not react with Prussian blue iron staining reagents as reported before [9]. An extended study by Yamase and colleagues further confirmed that all pseudomela-

nosis duodeni pigments contained iron, but it displayed a spectrum of histochemical characteristics depending on the amount of sulphur component in the pigments [10]. The duodenal pigment definitely differs from melanin because melanin does not contain any iron component. The duodenal pigment in pseudomelanosis duodeni also is different from the pigment in melanosis coli of the colon. The pigments in melanosis coli are usually a mixture of lipofuscin and melanin with no significant iron component.

Clinical features and associated diseases

Pseudomelanosis duodeni is associated with various clinical conditions and medications including hypertension, renal disease, oral iron intake [11-13], diabetes mellitus, folate deficiency, and gastrointestinal bleeding [2]. Pseudomelanosis in the upper gastrointestinal tract was also associated with ingestion of hydralazine, and in some cases, this pigmentation disappeared within three months after the discontinuation of hydralazine administration [4]. Pseudomelanosis duodeni was found to be more common in older women [5], although it also has been reported in an eight years-old child with chronic renal failure. Apparently it can occur in children like adult patients especially if there is longstanding disease [14].

Pseudomelanosis duodeni is a clinically rare condition, which is often an incidental endoscopic finding with no significant clinical symptom. Unlike pseudomelanosis coli, pseudomelanosis duodeni does not have an apparent association with anthraquinone containing laxatives. Unlike iron pill duodenitis or gastritis, which could generate tissue injury, inflammation, reactive changes and fibrosis, pseudomelanosis duodeni is not associated with fibrosis or cellular injury. Furthermore, there is no evidence indicating that pseudomelanosis duodeni is any neoplastic precursor or associated with other progressive pathology. Treatment is discontinuation of medication associated with this condition.

The lack of cytological atypia is reassuring that pseudomelanosis duodeni is a benign process. CD68 and CD168 immunohistochemical stains would confirm the histocytic nature of pigmented cells. In contrast, metastatic melanoma often shows marked cytological atypia with

increased nuclear cytoplasmic ratio, enlarged hyperchromic nuclei, prominent nucleoli, and frequent mitoses. Melan A, S100, HMB45, and SOX-10 immunohistochemical stains are of great help in confirming the diagnosis of malignant melanoma. Other disorders with accumulation of pigments within macrophages include brown bowel syndrome, hemosiderosis/hemochromatosis, barium granuloma, and chronic granulomatous diseases. Prussian blue iron stain would highlight a diffuse iron reaction in hemochromatosis/hemosiderosis. Brown bowel syndrome is due to long term chronic malabsorption leading to a liposoluble vitamin E deficiency. Vitamin E deficiency could lead to formation of lipofuscin aggregates, i.e. brown bowel syndrome. The pigments with brown bowel syndrome are featured with yellow auto-fluorescence.

Pathogenesis

The pathogenesis of pseudomelanosis duodeni still remains unclear. Kang et al [4] thought that the iron component more likely comes from luminal absorption. Impairment of subsequent transport would then result in its accumulation [4]. Frequent association of pseudomelanosis duodeni with hemodialysis supports this hypothesis because patients on hemodialysis are always on iron supplements. The source of sulphate, however, is unclear. Kang and colleagues thought it might be derived from the food [4]. While the pigment has been identified as ferrous sulfide, another study hypothesized that coupling of absorbed iron with sulfur from antihypertensive drugs such as hydralazine could be associated with the accumulation of the pigment deposits in the macrophage [6, 13, 15, 16]. The proximal duodenum which is the most reported extracolonic site with pseudomelanosis duodeni is also the site of maximal iron absorption, further supporting the above hypothesis [17]. Defect in macrophage metabolism may also contribute to iron sulfide storage. It has been shown that the pigment is partially associated with impaired macrophage metabolism of drugs containing cyclic compounds such as indoles phenols and skatoles [12].

In summary, pseudomelanosis duodeni is a rare condition and may be differentiated from several entities including hemosiderosis/hemochromatosis, brown bowel syndrome, and malignant melanoma. Special stains and immu-

nohistochemical studies are of great help to differentiate it from its mimickers. Pseudomelanosis duodeni per se does not lead to any clinical symptom or adverse consequences; however, it indeed evokes anxiety and confusion for clinicians and pathologists because of its rarity, peculiar endoscopic features and concerns for malignancy.

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Pseudomelanosis duodeni: a short review

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