

Pseudomelanosis duodeni: Associated with multiple clinical conditions and unpredictable iron stainability – a case series

Authors

D. Giusto, S. Jakate

Institution

Department of Pathology, Rush University Medical Center, Chicago, Illinois, USA

submitted 6 March 2007
accepted after revision
 7 November 2007

Bibliography

DOI 10.1055/s-2007-995472
 Endoscopy 2008; 40:
 165–167 © Georg Thieme
 Verlag KG Stuttgart · New York
 ISSN 0013-726X

Corresponding author

D. Giusto, MD
 Department of Pathology
 Rush University Medical Center
 1750 West Harrison St
 Chicago, IL 60126
 USA
 Fax: +1-312-942 4228
 Deborah_Giusto@rush.edu

Pseudomelanosis duodeni is seen endoscopically as dark spots in the duodenal mucosa and is generally considered to be local deposition of iron from oral iron intake. However, pseudomelanosis duodeni may be identified histologically even before it becomes endoscopically evident; iron stainability within the mucosa is uneven and unpredictable, and multiple clinical conditions other than oral iron intake may be associated. We reviewed 17 adult patients with histologically detected pseudomelanosis duodeni, their en-

doscopic appearances, iron stainability, and clinical findings including oral iron and drug intake. Only 6/17 (35%) had endoscopically apparent dark spots. Perl's iron stain was entirely positive in 18%, partially positive in 64%, and negative in 18% of cases. History of oral iron was present in 76% of patients, but other clinical conditions consistently associated were hypertension in 88%, end stage renal disease in 59%, and diabetes mellitus in 35% of patients.

Introduction

Pseudomelanosis duodeni (pseudomelanosis duodeni) is a rare condition characterized by collection of pigment-laden macrophages in the tips of duodenal villi. The first report of duodenal pigmentation was described by Bisordi & Kleinman [1] in 1976, and since then 42 other cases of pseudomelanosis duodeni have been reported [1–26], mostly in adults (92%) and slightly more commonly in females (1.2 : 1). The pigment, originally interpreted as melanin [1,2,4,8,13], pseudomelanin [3,13], lipomelanin [5] or hemosiderin [7], has now been demonstrated to be mostly ferrous sulfide [12,27] with small amounts of other elements.

Since an iron compound is the principal ingredient, oral iron intake and local iron deposition in the duodenum is considered to be the main clinical association of pseudomelanosis duodeni, although other clinical conditions such as hypertension, end stage renal disease and diabetes mellitus are also described. We evaluated 17 adult patients with a histological diagnosis of pseudomelanosis duodeni from their duodenal biopsies, with regard to corresponding endoscopic appearances, iron stainability, and their clinical profile, including histories of oral iron intake, other medications, and underlying clinical disorders.

Patients and methods

We reviewed pathology and endoscopy databases at Rush University Medical Center, Chicago, Illinois, USA to identify patients who were diagnosed with pseudomelanosis duodeni from duodenal biopsy and/or in endoscopic reports, between 1996 and 2006. We reviewed their medical charts, pharmacy records, and clinical data repository to document all known conditions associated with pseudomelanosis duodeni, any anti-hypertensive medication they were taking at the time, and oral iron intake. As well as review of routine hematoxylin and eosin stain, the duodenal biopsies were also stained for iron (Perl's), copper (rhodanine) and calcium (von Kossa) and reviewed.

Duodenal biopsies from 17 age-matched control patients with a history of oral iron intake, but with no hypertension, end stage renal disease, or diabetes mellitus, were also reviewed.

Results

All 17 patients (aged 34–86 years; 11 women, six men) had pseudomelanosis duodeni histologically but only six of these (35%) had endoscopically visible hyperpigmented brownish-black speckled duodenal mucosa (● Fig. 1); the others had nor-



Fig. 1 Endoscopic view of the proximal duodenum shows fine dark spots typical of pseudomelanosis duodeni.

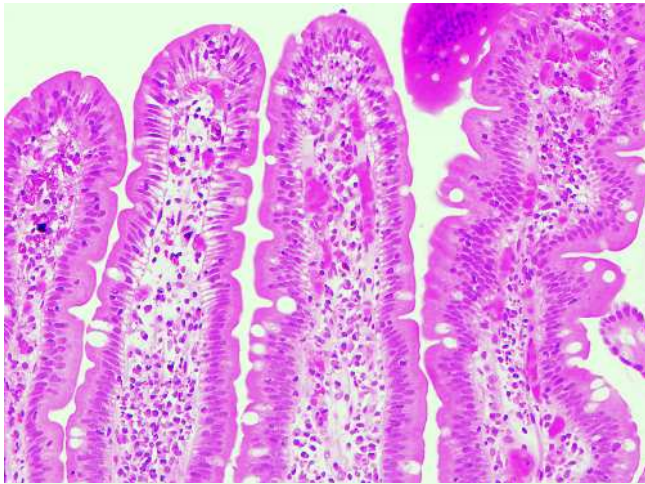


Fig. 2 Duodenal villi showing brownish-black pigment located within the apical portion of the villi (hematoxylin-eosin stain; × 200).

mal-appearing duodenum. There were no cases where endoscopic hyperpigmentation was not supported by histological evidence of pseudomelanosis duodeni.

Routine histologic sections demonstrated aggregates of pigment-laden macrophages in the apical portion of the villi (● **Fig. 2**). Perl's stain for iron was negative in 3/17 (18%), only partially positive in 11/17 (64%) and entirely positive in 3/17 (18%) cases (● **Fig. 3**). Staining for copper was negative. There was focal staining for calcium in 4/17 (24%) cases. No iron staining was seen in the 17 control patients with oral iron intake.

Several clinical conditions known to be associated with pseudomelanosis duodeni were shared by the patients, with hypertension being the most common: 15/17 (88%) patients had hypertension, 13/17 (76%) were receiving oral iron therapy, 10/17 (59%) had end stage renal disease, and 6/17 (35%) had diabetes mellitus (● **Table 1**). Various classes of antihypertensive medication, including beta blockers, thiazides, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers and alpha blockers were being taken by the hypertensive patients. Hydrochlorothiazide, atenolol, lisinopril/quinapril and irbesartan were some of the commonest medications.

Discussion



As seen in our patients, oral iron intake is not the sole condition associated with pseudomelanosis duodeni. In fact, the majority of patients taking oral iron but without other associated clinical conditions do not develop pseudomelanosis duodeni as was apparent in our control population. There is a stronger association with hypertension than with oral iron and there are noteworthy associations with end stage renal disease and diabetes mellitus. Often more than one of these conditions are present in patients displaying pseudomelanosis duodeni.

The source of the pigment and the mechanism by which the duodenal mucosa is selectively vulnerable to pigment deposition are unclear and have yet to be delineated [9]. It has been suggested that the ferrous sulfide pigment that is present in pseudomelanosis duodeni is derived from gastrointestinal bleeding [6] or related to oral iron intake [7]. In studying the composition of the pigment, Fernando [19] used electron probe X-ray analysis of epithelial cells and macrophages at different levels of the intestine to demonstrate that absorbed iron has been coupled with sulfur in pseudomelanosis duodeni. He proposed that this coupling leads to difficulty in iron transport and results in accumulation of ferrous sulfide in macrophages of the duodenal lamina propria. Normally, macrophage transport of iron via the blood stream to stores in various anatomic sites does not require linkage to sulfur. The source of sulfur is not clear; however, certain medications such as antihypertensive drugs have been implicated. It is noted that the majority of patients with pseudomelanosis duodeni have received antihypertensive medications. Some authors [22,23] have proposed that antihypertensive medications may be the source of sulfur since some of the medications, such as furosemide and hydrochlorothiazide, contain a sulfur moiety. However, the significance of this is unclear, as several patients with pseudomelanosis duodeni were on medications that do not contain sulfur moieties.

The iron stainability of the pigment seen in our patients was variable and unpredictable, as seen in some earlier case reports. Pounder et al. [6], speculated that the reason for this variability in iron staining is that iron sulfide is auto-oxidized to iron oxide; this was also supported by Yamase et al. [9]. Iron sulfide is known to give a negative reaction whereas iron oxide gives a positive reaction for iron staining with a common stain (Perl's prussian blue). Four cases showed focal staining for calcium.

When Pounder et al. [6] performed electron-probe X-ray analysis on the pigment in pseudomelanosis duodeni, trace amounts of calcium, potassium, aluminum, magnesium, and silica were present.

Another interesting finding is that only 35% of our patient cases had endoscopic evidence of pseudomelanosis duodeni, whereas all the previous reports in the literature describe brownish-black duodenal pigmentation on endoscopy. Thus histological deposi-

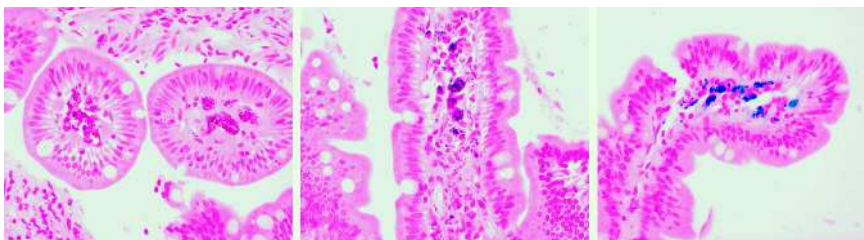


Fig. 3 Three cases of pseudomelanosis duodeni showing (from left to right) negative, focal, and complete iron staining (blue coloration, Perl's iron stain; × 400).

Table 1 Summary of endoscopic appearance of the duodenal mucosa, associated clinical conditions and the result of iron staining in all 17 patients.

Patient no.	Age, years; sex	Endoscopic appearance	Hypertension	End stage renal disease	Oral iron	Diabetes mellitus	Iron staining
1	86; F	Hyperpigmented	+	-	-	-	Positive
2	65; F	Hyperpigmented	+	+	+	-	Partial
3	63; F	Normal	+	-	-	+	Partial
4	68; F	Normal	+	-	-	-	Partial
5	60; M	Hyperpigmented	+	+	+	-	Negative
6	63; F	Normal	+	-	+	+	Positive
7	66; F	Hyperpigmented	+	+	+	+	Partial
8	70; M	Normal	+	+	-	-	Partial
9	34; F	Normal	-	+	+	-	Partial
10	52; M	Hyperpigmented	-	+	+	+	Partial
11	59; M	Normal	+	-	+	+	Negative
12	53; F	Normal	+	+	+	-	Partial
13	65; M	Normal	+	-	+	-	Partial
14	52; M	Normal	+	+	+	-	Negative
15	49; F	Hyperpigmented	+	+	+	-	Partial
16	58; F	Normal	+	-	+	-	Positive
17	67; F	Normal	+	+	+	+	Partial

F, female; M, male; +, present; -, absent

tion might be apparent sooner than endoscopic detection is possible.

The diagnostic and prognostic significance of pseudomelanosis duodeni has yet to be determined and the appropriate follow-up, if any, is unclear. Unlike iron or other heavy metal deposits elsewhere in the body, which may generate a fibroinflammatory reaction, pseudomelanosis duodeni has not been documented to cause any fibrosis, stricture, or erosive duodenitis, or to have a predictable progression. No therapeutic chelating or follow-up protocol is recommended in the literature. Our study illustrates multiple and distinct associated clinical conditions, endoscopic underdetection, and variable stainability for iron, in a sizable group of patients.

References

- Bisordi W, Kleinman M. Melanosis duodeni. *Gastrointest Endosc* 1976; 23: 37-38
- Breslaw L. Melanosis of the duodenal mucosa. *Gastrointest Endosc* 1980; 26: 45-46
- Cowen M, Humphries T. Pseudomelanosis of the duodenum. *Gastrointest Endosc* 1980; 26: 107-108
- Ganju S, Adomavicius J, Salgia K et al. The endoscopic picture of melanosis in the duodenum. *Gastrointest Endosc* 1980; 26: 44-46
- Sharp J, Insalaco S, Johnson L. Melanosis of the duodenum associated with a gastric ulcer and folic acid deficiency. *Gastroenterology* 1980; 78: 366-369
- Pounder D, Ghadially F, Mukherjee T. Ultrastructure and electron-probe X-ray analysis of the pigment in melanosis duodeni. *J Submicrosc Cytol* 1982; 14: 389-400
- Steckman M, Bozymski E. Hemosiderosis of the duodenum. *Gastrointest Endosc* 1983; 29: 329-327
- Fisher S, Kahn E, Ellis D. Melanosis duodeni in a child with congenital hepatic fibrosis and renal failure. *J Pediatr Gastroenterol Nutr* 1983; 2: 567-569
- Yamase H, Norris M, Gillies C. Pseudomelanosis duodeni: a clinicopathologic entity. *Gastrointest Endosc* 1985; 31: 83-86
- Pounder D. The pigment of duodenal melanosis is ferrous sulfide [letter]. *Gastrointest Endosc* 1983; 29: 257
- Gupta T, Weinstock J. Duodenal pseudomelanosis associated with chronic renal failure. *Gastrointest Endosc* 1986; 32: 358-360
- Ghadially F, Walley V. Pigments of the gastrointestinal tract: a comparison of light microscopic and electron microscopic findings. *Ultrastruct Pathol* 1995; 19: 213-219
- Castellano G, Canga F, Lopez I. Pseudomelanosis of the duodenum. *J Clin Gastroenterol* 1988; 10: 150-154
- Lee H, O'Donnell D, Keren D. Characteristics of melanosis duodeni: incorporation of endoscopy, pathology, and etiology. *Endoscopy* 1987; 19: 107-109
- Lin H, Tsay S, Chiang H. Pseudomelanosis duodeni. *J Clin Gastroenterol* 1988; 10: 155-159
- Rex D, Jersild R. Further characterization of the pigment in pseudomelanosis duodeni in three patients. *Gastroenterology* 1988; 95: 177-182
- Kuo YC, Wu CS. Duodenal melanosis. *J Clin Gastroenterol* 1988; 10: 160-164
- Kang JY, Wu AY, Chia JL et al. Clinical and ultrastructural studies in duodenal pseudomelanosis. *Gut* 1988; 28: 1673-81
- Fernando S. Pseudomelanosis duodeni: a case report with electron-probe X-ray analysis. *Pathology* 1990; 22: 169-172
- El-Newihi H, Lynch C, Mihas A. Case reports: pseudomelanosis duodeni: association with systemic hypertension. *Am J Med Sci* 1995; 310: 111-114
- Wang K, Lin HJ, Perng CL et al. Pseudomelanosis duodeni: report of eight cases. *J Formos Med Assoc* 1995; 94: 632-634
- Leong S. Pseudomelanosis duodeni and the controversial pigment clinical study of 4 cases. *Ann Acad Med Sing* 1992; 21: 394-398
- Pueblitz S, Squires R, Timmons C. Pseudomelanosis duodeni in an adolescent male: case report and review of the literature. *Pediatr Pathol Lab Med* 1997; 17: 115-123
- Arguedas M, Lazenby A, Wilcox C. Pseudomelanosis duodeni. *Gastrointest Endosc* 2000; 52: 753
- Weinstock L, Katzman K, Wang H. Pseudomelanosis of stomach, duodenum and jejunum. *Gastrointest Endosc* 2003; 58: 578
- Cantu J, Adler D. Pseudomelanosis duodeni. *Endoscopy* 2005; 37: 789
- West B. Pseudomelanosis duodeni. *J Clin Gastroenterol* 1988; 10: 127-129