Severe chronic bowel obstruction associated with brown bowel syndrome

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Abstract
A 61-year-old alcoholic male with history of cholecystectomy presented with a 20-year history of recurrent bowel obstruction and a 30lb weight loss. After numerous attempts at conservative management, exploratory laparotomy was performed, which showed no mechanical cause. Despite no clear etiology, the obstruction persisted and intensified. A follow-up computed tomography scan revealed a small bowel obstruction with concurrent megacolon. A total abdominal colectomy was performed, with ileostomy. Grossly, there was intestinal dilation up to 15 cm with prominent brown discoloration of bowel wall. No strictures or other fixed obstruction were identified. Microscopic examination revealed prominent lipofuscin-like pigment deposition, involving the muscularis propria, muscularis mucosae, and vascular smooth muscle. Histochemical staining was positive for periodic acid–Schiff and negative for iron and calcium, consistent with lipofuscin. The gross and histologic findings fit with brown bowel syndrome. Brown bowel syndrome is a very rare condition characterized by lipofuscin deposits predominantly within the smooth muscle of the muscularis mucosae and/or muscularis propria that imparts a brown color to the bowel. It is generally thought to be a smooth muscle mitochondrial myopathy due to chronic vitamin E deficiency secondary to fat malabsorption syndromes, resulting in free radicals causing peroxidation of unsaturated membrane lipids with accumulation of lipofuscin. Brown bowel syndrome may be seen in patients with alcohol abuse, maldigestion, chronic bowel inflammation, and intestinal lymphangiectasia. Our patient’s severe chronic intestinal pseudointestinal obstruction, low levels of certain fat-soluble vitamins (A, D, and E), significant weight loss and history of cholecystectomy with alcohol abuse correlates with brown bowel syndrome clinically.

Keywords
Brown bowel syndrome, chronic bowel obstruction, vitamin E deficiency, alcoholism, cholecystectomy

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Introduction
Brown bowel syndrome (BBS, also known as ceroidosis, ceroid lipofuscinosis, or intestinal lipofuscinosis) is a rare condition first reported in 1963 and is most commonly seen in patients with chronic malabsorption.1 BBS is characterized by a deficiency of vitamins, minerals, and vital proteins usually obtained from the diet. Decreased fat-soluble vitamin (vitamins A, D, E, and K) levels are specifically associated with BBS along with dry skin, fatigue, coagulation problems, infection, and cognitive deficits.2

BBS is generally associated with vitamin E deficiency secondary to fat malabsorption. In patients with a chronic deficiency of vitamin E, oxidation may result in damage to the phospholipid layer of mitochondria, which may further produce lipofuscin-like deposits within the cells.1 BBS is characterized by lipofuscin-like pigment deposits predominantly within the smooth muscle of the muscularis mucosae and/or muscularis propria that imparts a brown color to the bowel. We illustrate a case of BBS associated with severe chronic intestinal pseudo-obstruction.

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A 61-year-old male with history of alcohol abuse (20-year history of 12–24 beers per day), status-post non-complicated cholecystectomy 10 years ago, presented with a 20-year history of recurrent bowel obstruction and 30 lb weight loss. Eight days after cholecystectomy, he developed abdominal pain, bloating, and obstipation, in addition to intermittent diarrhea. Over the following 10 years after his cholecystectomy, he was frequently hospitalized for recurrent “bowel obstructions.” He underwent subsequent colonoscopy and esophagogastroduodenoscopy, which did not reveal any abnormal findings, including any evidence of celiac disease. After numerous unsuccessful attempts at conservative management, exploratory laparotomy was performed, which showed no mechanical cause of the obstructions. Additionally, he showed no neuropathy or neuromuscular dysfunction. Despite no clear etiology for the obstruction, his symptoms persisted and intensified. The patient stopped alcohol abuse completely 1.5–2 years prior due to worsening abdominal pain and discomfort. Fifteen months after his first laparotomy, a computed tomography (CT) scan confirmed a small bowel obstruction, with his small bowel measuring approximately 23 mm in diameter. In addition, the CT scan showed a concurrent megacolon dilated up to 15 cm in diameter (Figure 1(a)). Lab tests were significant for decreased levels of certain fat-soluble vitamins, vitamin A 22 µg/dL (reference range: 32.5–78.0 µg/dL), vitamin D 7 ng/mL (reference range: 20–50 ng/mL), vitamin E 4.3 mg/L (reference range: 5.5–17 mg/L), and vitamin K 2.65 ng/mL (reference range: 0.23–3.2 ng/mL). A gluten-free diet was trialed starting 3 months prior to his second surgery with no improvement in his symptoms and persistent recurring small bowel obstruction. Fifteen months after his first laparoscopy, a total abdominal colectomy with ileostomy was performed.

Grossly, there was intestinal dilation up to 15 cm with prominent brown discoloration of bowel wall (Figure 1(b)). No strictures or other fixed obstruction were identified. Microscopic examination revealed prominent lipofuscin-like pigment deposition (greater in the ileum) (Figure 2(a)), involving the muscularis propria (Figure 2(b)), muscularis mucosae (Figure 2(c)), and, to a lesser extent, the vascular smooth muscle (Figure 2(d)). Histochemical staining was positive for periodic acid–Schiff, and negative for iron and calcium, consistent with lipofuscin-like pigment deposition. The trichrome immunostaining showed no significant intramuscular fibrosis. The gross and histologic findings were consistent with BBS.

The patient was prescribed vitamin E treatment following surgery and was found to be doing very well in his follow-up visit 1.5 months later. No documented vitamin levels were available for this follow-up visit in his chart. After his total abdominal colectomy, his weight fluctuated quickly. His weight was 53.5 kg before his total abdominal colectomy, and decreased to 48 kg immediately after surgery, and then increased to 54.5 kg when discharged home, and decreased again to 41 kg at his 1.5-month follow-up visit. The patient started eating solid foods without an increase in ostomy output or abdominal symptoms of obstruction.

**Discussion**

The main differential diagnoses of BBS include melanosis coli and hemochromatosis. Melanosis coli, also known as pseudomelanosis coli, is typically seen in patients with history of extended laxative use. Melanosis coli presents with diffuse brown-black discoloration of colonic mucosa seen grossly or on endoscopy, and diffuse deposition of lipofuscin-like pigment in macrophages of lamina propria within mucosa microscopically. Our patient denied any laxative use, and in addition, the lipofuscin-like pigments were in muscle cells and extended deeper into the muscularis propria, which make a diagnosis of melanosis coli less likely.
Hemochromatosis is a condition of iron overload in the body from any cause, including primary (hereditary) etiologies or secondary etiologies (repeated transfusion, oral iron therapy, etc.). Hereditary hemochromatosis is an autosomal recessive, missense mutation of the \( HFE \) gene, located on chromosome 6p, which results in substitution of tyrosine for cysteine at amino acid 282 of the unprocessed protein (C282Y). Grossly, there is dark brown discoloration of liver, heart, endocrine glands, and various other organs. Microscopically, hemosiderin pigment would be granular and golden-yellow to brown which stains positive for iron. Our patient does not have chronic transfusion history or any family history of hemochromatosis. Additionally, the lipofuscin-like pigment in this case stains negatively for iron.

BBS is a very rare condition and generally thought to be due to chronic vitamin E deficiency, usually as a result of deficient enteral uptake of fat-soluble tocopherol in malabsorption syndromes, such as celiac disease, post-gastric and jejunoeileal bypass surgeries. BBS may also be associated with, or preceded by, several other diseases or conditions such as alcohol abuse, vegan diet, malnutrition (e.g. chronic pancreatitis, liver disease, cholestasis), chronic inflammation (e.g. Crohn’s disease, ulcerative enteritis, Whipple disease), and intestinal lymphangiectasia. There is predominantly circular muscle hypertrophy with ceroid lipofuscin-like deposits. Microscopically, the deposits are seen predominantly within the smooth muscle cells of the muscularis propria, muscularis mucosae, and surrounding blood vessels, which gives the typical gross appearance of “brown bowel.” The deposits can sometimes result in dysmotility of the gastrointestinal (GI) tract due to ineffective peristalsis. The hypothesis is that a deficiency of the antioxidant vitamin E results in oxidative stress buildup within the smooth muscle cells, damaging the mitochondria of the affected cells. This mitochondria-related myopathy likely results in gastrointestinal dysmotility and ileus of the small bowel, a common presentation of the condition.

The lipofuscin-like pigment stains positive for lipid stains (e.g. Sudan III and Oil Red O), acid fast coloration with carbol fuchsin, PAS, and can also auto-fluoresce under ultraviolet light. Lipofuscin-like pigment in BBS is not very well characterized. It is similar to the lipofuscin which exists physiologically in certain tissues and its concentration increases as we age. Lipofuscin accumulates in the setting of increased oxidative stress and reduced antioxidizing ability of the aging host cell. Lipofuscin is composed of yellow-brown pigment granules which consist of lipid-containing residues of lysosomal digestion, resulting from oxidation of
membrane lipids and proteins by free radicals and acting as potent free radicals intracellularly.\textsuperscript{12,13}

Some reports have suggested that BBS could be a smooth muscle mitochondrial myopathy and is speculated to be caused by lipofuscin-like pigment deposition with a resulting disorder in energy production, possibly related to an excess of free radicals, ultimately causing atrophy and atonia of the smooth muscle. The proposed mechanism explains multiple findings, including general muscular dystrophy, weight loss, signs of vitamin deficiency, abdominal pain, bowel atonia, dysmotility, intussusception, and pseudo-obstruction.\textsuperscript{2,3} However, there is some disagreement as to whether the bowel dysmotility is a cause of or a result of the lipofuscin-like pigment deposition.

Our patient had undergone a previous cholecystectomy, and it would be appropriate to consider whether or not the absence of bile acids in the gastrointestinal tract contributed to the development of his vitamin E deficiency. Studies are scant on establishing an association between patients who received a cholecystectomy and the development of vitamin E deficiency. A study by Wanieck et al.\textsuperscript{14} describes an inverse relationship between circulating vitamin E levels and the development of gallstones, which suggests that his vitamin E deficiency may have preceded his cholecystectomy. Our patient’s chronic bowel obstruction, low levels of certain fat-soluble vitamins (A, D, and E), significant weight loss, and history of cholecystectomy with alcohol abuse correlates with BBS clinically.

Long-term vitamin supplementation treatment has been reported to improve the malabsorption syndrome, prevent further lipofuscin-like pigment accumulation, and subsequent complications, but may or may not reduce already deposited pigment in muscle cells. It has been shown that long-term vitamin E supplementation resulted in a regression of the lipofuscin deposits in concert with the improvement of enteric absorption function.\textsuperscript{15} It is important to have clinical suspicion for BBS and be able to recognize BBS early, so the patient can be treated with vitamin E supplement and avoid persistent and intensified symptoms, as well as surgical intervention. For advanced cases, such as our patient with frequently recurrent bowel obstruction and failed numerous conservative management, surgery is an appropriate treatment option.\textsuperscript{16}

**Conclusion**

BBS is generally thought to be a smooth muscle mitochondrial myopathy due to chronic vitamin E deficiency secondary to fat malabsorption syndromes, resulting in free radicals causing peroxidation of unsaturated membrane lipids with accumulation of lipofuscin. Our patient’s severe chronic intestinal pseudo-obstruction, low levels of certain fat-soluble vitamins (A, D, and E), significant weight loss, and history of cholecystectomy with alcohol abuse correlate with BBS clinically.

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