Obscure Gastrointestinal Bleeding and Video Capsule Retention Due to Enteropathy-Associated T-Cell Lymphoma

Henry C. Ho, MD
Anil B. Nagar, MD
David J. Hass, MD

Section of Digestive Diseases, Yale University, New Haven, Connecticut

Small bowel tumors are a rare cause of occult gastrointestinal (GI) bleeding, at times requiring hospitalization and blood transfusion. Capsule endoscopy is a commonly used tool for investigation of occult GI bleeding. The risk of capsule retention is rare and not commonly seen when capsule endoscopy is performed for the diagnostic evaluation of occult GI bleeding. We report a case of enteropathy-associated T-cell lymphoma (EATL) discovered via examination for occult GI bleeding requiring hospitalization and subsequent capsule retention that necessitated urgent surgical management secondary to bowel obstruction.

Case Report

A 77-year-old man with a medical history significant for chronic obstructive pulmonary disease, diabetes, and mechanical aortic valve replacement maintained on warfarin was admitted to the hospital with fatigue and anemia. Compared with 1 month prior, the patient's hemoglobin level decreased from 9.3 g/dL to 6.8 g/dL. His international normalized ratio was 1.7. The patient denied having frank GI bleeding; however, his stools were positive for fecal occult blood. Warfarin therapy was withdrawn, and an intravenous heparin drip was started. The patient underwent upper and lower endoscopy. No bleeding lesions were observed.

A capsule endoscopy for examination of obscure GI bleeding was then performed. The capsule endoscopy revealed red clots, ulceration, and markedly abnormal tissue estimated to be localized to the midjejunum (Figure 1) at approximately 35 minutes into small bowel transit. The capsule did not pass into the cecum. The presumptive diagnosis of a bleeding jejunal tumor was made. The patient was scheduled for a double-balloon enteroscopy, and a surgical consultation was obtained.

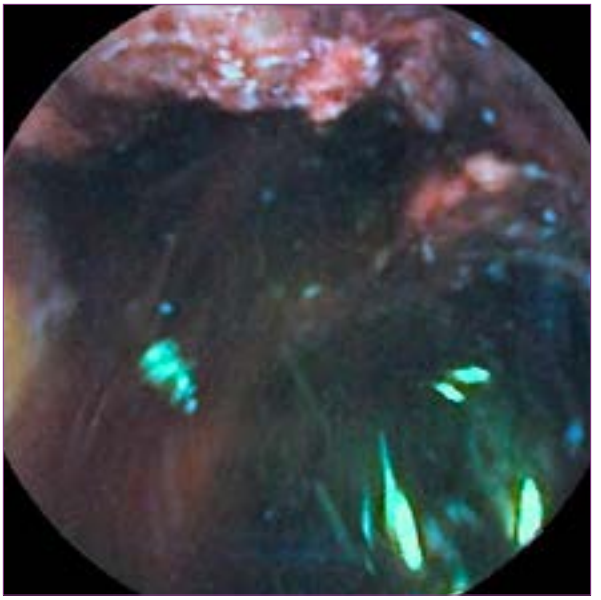

Figure 1. A capsule endoscopy revealed red clots, ulceration, and markedly abnormal tissue estimated to be localized to the midjejunum.

Twelve hours following the introduction of the video capsule, the patient was noted to have severe abdominal pain with a distended abdomen. An urgent computed tomography scan of the abdomen and pelvis with contrast demonstrated focal distension of a segment of proximal jejunum and pneumatosis involving a second loop (Figure 2). An emergent, exploratory laparotomy was performed, which demonstrated a contained perforation with a segment of small bowel with full thickness ischemic necrosis. No discrete mass was identified. Forty inches of small bowel was resected, and the capsule was retrieved. The patient was eventually discharged home on Postoperative Day 23.

Address correspondence to:
Dr. Henry C. Ho, Yale University, 333 Cedar Street, 1080 LMP, New Haven, CT 06520-8019; Tel: 203-785-7012; Fax: 203-737-1755; E-mail: henry.ho@yale.edu

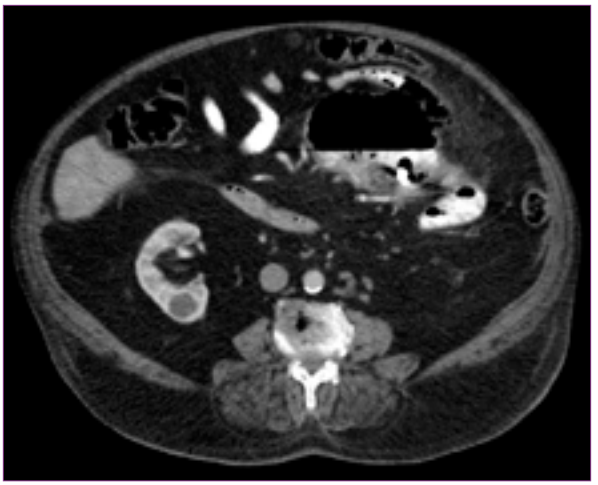

Figure 2. A computed tomography scan of the abdomen and pelvis demonstrated focal distension of a segment of proximal jejunum and pneumatosis involving a second loop.

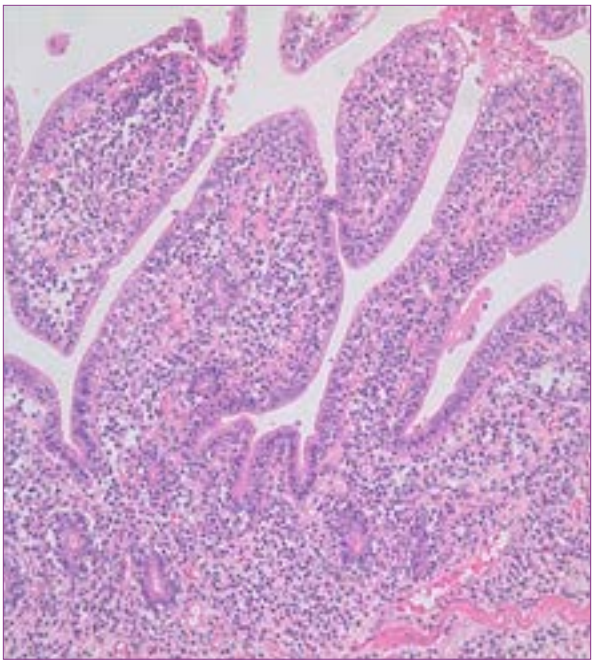

Figure 3. Resected jejunum showed dense lymphocytic infiltrate with ischemic changes (hematoxylin and eosin stain, 400× magnification).

On gross pathologic examination of the resected tissue, there was a 15.5-cm area of small bowel narrowing with denuded mucosa and wall thickening of 0.1 cm. Histologic examination demonstrated a dense lymphocytic infiltrate with ischemic changes extending to the serosal layer (Figure 3). The final immunologic phenotypic profile demonstrated CD3+, CD8+, CD4-, CD56+, CD7+, EBV-, CD20-, and CD30- cells, suggestive of EATL, type II.

Discussion

EATL is an uncommon, intestinal tumor of T lymphocytes. It comprises only 10–25% of all primary small bowel lymphomas. The most common EATL, type I, is highly associated with celiac disease and thus presents with related symptoms. Type II EATL occurs sporadically and more often presents with obstruction or perforation of the small bowel, with no known association with celiac disease.[1] EATL typically involves the small intestine, specifically the proximal jejunum, and, less commonly, intra-abdominal lymph nodes and the colon. Abdominal pain, weight loss, and fatigue are common findings at disease presentation. Patients with untreated gluten-sensitive enteropathy are at increased risk for development of EATL. Accordingly, patients with EATL rarely have a long history of celiac disease.[2]

The general prognosis for EATL is poor, with reported 2-year survival rates of 15–20%. The tumor has rapid growth and a tendency to metastasize.[3] Complications of intestinal perforation due to refractory ulcers occur in many patients; indeed, EATL is often accompanied by mucosal ulceration as the only endoscopic manifestation of lymphoma. The malignant transformation of intraepithelial T cells into a monoclonal population of cells with an abnormal phenotype leads to the spectrum of refractory celiac disease, ulcerative jejunitis, and finally EATL. Treatment typically involves systemic chemotherapy with consideration for hematopoietic stem cell transplant. The high incidence of postsurgical complications—as most cases are diagnosed via laparotomy—often leads to progressive deterioration, particularly in the setting of malnourishment at the time of diagnosis.[4]

To our knowledge, there has only been 1 reported case of EATL type II diagnosed with capsule endoscopy. The reported patient had refractory celiac disease, for which there was underlying high suspicion; double-balloon enteroscopy was used for histologic diagnosis.[5] There are also case reports that describe capsule endoscopic findings of EATL following chemotherapy.[6,7]

Obscure GI bleeding accounts for 5% of cases of GI bleeding.[8] In a large portion of these cases, the source is the small bowel. In this case, given the patient's older age, typical causes such as vascular lesions or ulcers would have been suspected rather than a small bowel tumor, which is a common cause of obscure GI bleeding in younger patients.[9] Wireless video capsule endoscopy is a common useful diagnostic tool used when standard conventional upper and lower endoscopy fail to yield a diagnosis.[10] In contrast to enteroscopy, wireless video capsule endoscopy is noninvasive and permits examination of the entire small bowel, which may otherwise be technically difficult.

Furthermore, capsule endoscopy has been shown to be effective in detecting small bowel tumors.[11]

Capsule retention is a reported risk; however, this is a rare complication. In a large review, this risk appeared to be higher in patients with definite or suspected Crohn's disease or neoplastic lesions, although the pretest suspicion for a small bowel tumor in our patient was low.[12] With the development of patency capsules and the possibility of retrieval of retained capsules with double-balloon enteroscopy, the occurrence and clinical consequences of retention are diminished. The most commonly cited incidence of capsule retention in patients with obscure GI bleeding is 0.75%, although the percentage has been reported to be up to 5.8%.[13] Acute obstruction due to capsule retention is rarely reported in the literature.[14]

Conclusion

To our knowledge, this is the first report of a new EATL diagnosis via capsule endoscopy for occult GI bleeding. Furthermore, the development of acute bowel obstruction due to capsule retention at the site of a small bowel tumor is extremely rare. We believe that this case report highlights the importance of maintaining a broad differential for obscure GI bleeding and the utility of capsule endoscopy in the diagnosis of small bowel pathology. Although small bowel tumors are relatively uncommon in elderly patients, they are relatively common in the evaluation of obscure GI bleeding. While transient retention of a video capsule can be expected at a stricture or mass that ultimately requires surgical resection, this case demonstrates the possibility of true obstruction requiring urgent surgery. Consideration for small bowel imaging prior to capsule placement has been reported, although this practice is not typically recommended.[15]

The authors have no conflicts of interest to disclose.

References

1. Ferreri AJ, Zinzani PL, Govi S, Pileri SA. Enteropathy-associated T-cell lymphoma. *Crit Rev Oncol Hematol.* 2011;79(1):84-90.
2. Catassi C, Bearzi I, Holmes GK. Association of celiac disease and intestinal lymphomas and other cancers. *Gastroenterology.* 2005;128(4 suppl 1):S79-S86.
3. Howdle PD, Jalal PK, Holmes GK, Houlston RS. Primary small-bowel malignancy in the UK and its association with coeliac disease. *QJM.* 2003;96(5):345-353.
4. van de Water JM, Cillessen SA, Visser OJ, Verbeek WH, Meijer CJ, Mulder CJ. Enteropathy associated T-cell lymphoma and its precursor lesions. *Best Pract Res Clin Gastroenterol.* 2010;24(1):43-56.
5. Daum S, Wahnschaffe U, Glasenapp R, et al. Capsule endoscopy in refractory celiac disease. *Endoscopy.* 2007;39(5):455-458.
6. Sato Y, Ono M, Sagawa T, et al. Endoscopic findings of enteropathy-type T-cell lymphoma by double-balloon enteroscopy and capsule endoscopy. *Dig Endosc.* 2010;22(3):243-245.
7. Joyce AM, Burns DL, Marcello PW, Tronic B, Scholz FJ. Capsule endoscopy findings in celiac disease associated enteropathy-type intestinal T-cell lymphoma. *Endoscopy.* 2005;37(6):594-596.
8. Szold A, Katz LB, Lewis BS. Surgical approach to occult gastrointestinal bleeding. *Am J Surg.* 1992;163(1):90-92; discussion 2-3.
9. Lewis BS, Kornbluth A, Waye JD. Small bowel tumours: yield of enteroscopy. *Gut.* 1991;32(7):763-765.
10. de Leusse A, Vahedi K, Edery J, et al. Capsule endoscopy or push enteroscopy for first-line exploration of obscure gastrointestinal bleeding? *Gastroenterology.* 2007;132(3):855-862; quiz 1164-1165.
11. Cobrin GM, Pittman RH, Lewis BS. Increased diagnostic yield of small bowel tumors with capsule endoscopy. *Cancer.* 2006;107(1):22-27.
12. Liao Z, Gao R, Xu C, Li ZS. Indications and detection, completion, and retention rates of small-bowel capsule endoscopy: a systematic review. *Gastrointest Endosc.* 2010;71(2):280-286.
13. Pennazio M, Santucci R, Rondonotti E, et al. Outcome of patients with obscure gastrointestinal bleeding after capsule endoscopy: report of 100 consecutive cases. *Gastroenterology.* 2004;126(3):643-653.
14. Cave D, Legnani P, de Franchis R, Lewis BS. ICCE consensus for capsule retention. *Endoscopy.* 2005;37(10):1065-1067.
15. Voderholzer WA, Beinhoelzl J, Rogalla P, et al. Small bowel involvement in Crohn's disease: a prospective comparison of wireless capsule endoscopy and computed tomography enteroclysis. *Gut.* 2005;54(3):369-373.

Review

Veronica N. Baptista, MD
David R. Cave, MD, PhD

Division of Gastroenterology
Department of Medicine
UMass Memorial Medical Center
Worcester, Massachusetts

Since its introduction into practice in 2001, video capsule endoscopy (VCE) has been considered part of the algorithm in the workup for obscure gastrointestinal bleeding (OGIB). VCE is also routinely used for evaluation of other indications, such as iron-deficiency anemia (IDA), suspected Crohn's disease, small bowel tumors, and other enteric disorders, including celiac disease in select patients. Multiple studies have looked at the diagnostic yield and outcome of VCE in the diagnosis of small bowel tumors.

Small bowel neoplasms account for 1–3% of all gastrointestinal malignancies. The incidence of these neoplasms appears to be stable, with the exception of carcinoids, which have increased 4-fold over the past few decades, and smaller increases of adenocarcinomas and lymphomas.[1] Multiple studies have looked into the incidence of small bowel tumors noted on VCE performed for various indications. The highest rate of diagnostic yield for small bowel tumor on VCE was 15.4% for

Address correspondence to:
Dr. David R. Cave, UMass Memorial Medical Center, 55 Lake Avenue North, Worcester, MA 01655; Tel: 508-856-8399; Fax: 508-856-3981; E-mail: David.Cave@umassmemorial.org

the indication of unexplained weight loss,[2] followed by 3.8–9% for OGIB[2-4] and 3.5% for IDA.[5] In a meta-analysis of over 1,349 VCEs, the incidence rate of small bowel tumors was 7.9% for all indications and 5.8% for nonbleeding indications.[4]

Small bowel tumors were single in 89.5% of cases and multiple in 10.5% of cases.[6] Approximately 60% of all small bowel tumors found on VCE were malignant.[2,7] The most common malignant small bowel tumors were adenocarcinoma (20–35%), carcinoid (15–32%), melanoma (9%), lymphoma, including T-cell lymphoma (9%), and sarcoma (7%). The most common benign tumors were gastrointestinal stromal tumor (GIST; 32–51%), hemangioma (11%), harmartoma (11%), and adenoma (6%). Fifty-two percent to 70% of malignant tumors were located in the jejunum, 22–27% were located in the ileum, and 7–8% were located in the duodenum.[6,7] These small bowel tumors appear on VCE as typical masses or polyps in 70–80% of cases. Other features can include mucosal ulceration, nodularity, active bleeding with no clear source, and/or stenosis.[8]

The tools that may be applied to the diagnosis of small bowel tumors vary with the presentation of the lesion. A significant proportion of small bowel tumors present as surgical emergencies and require radiologic imaging followed by surgical intervention. Patients presenting with abdominal pain, change in bowel habits, and/or OGIB present a broader challenge. The size and site of the tumor play roles in its detection. For patients with pain alone, computed tomography (CT) or CT enterography is indicated. Few centers now employ enteroclysis or small bowel series. For patients with OGIB, the initial diagnostic test chosen is likely to be VCE, but the limitations of VCE should be understood. Specifically, it is a useful tool but far from perfect.

If VCE is unrevealing, then anterograde and/or retrograde deep enteroscopy of the small bowel should be considered. Surgical intervention, laparoscopy, or laparotomy is the best single diagnostic modality whereby it is possible to "run the bowel" between clamps or fingers to palpate the lesion. However, even this approach can miss small or soft lesions. Obviously, the invasive nature of surgery makes it one of the last options in the diagnostic algorithm.

Lesions may be missed, especially in the duodenum, where the capsule moves quickly. In a small study by Baichi and colleagues that looked at 10 confirmed small bowel tumors that had prior VCEs, the miss rate was 30%.[9] The 3 missed cases were: normal findings on VCE that turned out to be a GIST in the proximal jejunum that was noted as an abdominal mass on CT, a missed inflammatory fibroid polyp in the duodenum, and a missed distal ileal adenocarcinoma that caused symptomatic capsule retention requiring urgent laparotomy.[9] VCE only showed normal proximal images but incomplete distal examination due to retention. In a meta-analysis of 24 studies involving 530 VCEs, the miss rate for VCE in detecting small bowel tumor was 18.9%, which is significantly lower than the 63.2% miss rate for comparative methods such as push enteroscopy, radiologic small bowel series, or colonoscopy with ileoscopy.[4] Radiologic imaging detected only 35% of the small bowel tumors found on VCE.[10] VCE was also better at detecting smaller tumors that were a mean of 14.3 mm (range, 2–35 mm) compared with radiologic studies detecting a mean tumor size of 48.7 mm (range, 10–110 mm).[2]

It is worth considering why tumors might be missed by VCE. There are several possibilities. First, there may be no mucosal representation, as with a GIST that is predominantly intraperitoneal. Second, the tumor may only be seen on a few frames with a minimal view of the tumor. This may occur with midsize (2–3 cm) tumors in which the capsule is diverted in such a way that the field of view, which is approximately 150° for the 3 available capsules, catches only a lateral glimpse of the tumor. Third, the tumor may be submucosal, and it may be difficult to determine whether the tumor is another organ protruding into the lumen or a true mass. Various visual clues have been described regarding how this distinction may be made, including flattening overlying fold(s), surface ulceration, or erosion. However, none of these observations are foolproof, and the use of computer-assisted tomographic enterography, magnetic resonance enterography, or deep enteroscopy is a reasonable arbitration strategy. Finally, tumors may simply be missed.[11,12]

Capsule retention has been the main complication of VCE, with a reported rate of up to 20% in high-risk patients. Patients at risk include those with a history of small bowel obstruction, small bowel Crohn's disease, nonsteroidal anti-inflammatory drug–induced enteropathy with diaphragm-like strictures, radiation enteritis, extensive postsurgical adhesions, surgical anastomoses, and small bowel tumors. In the case report by Ho and colleagues,[13] acute obstruction from capsule retention developed and required emergency laparotomy. The patient was subsequently found to have a rare small bowel tumor: enteropathy-associated T-cell lymphoma. Whether the capsule caused the perforation or the perforation was part of the natural history of the tumor is unclear. The focal ischemia and absence of a palpable mass that may have retained the capsule suggest the latter scenario.

In a multicenter European study that only looked at small bowel tumors, the retention rate was 9.7% (12 cases out of 124 patients) at the site of the tumor. There was no difference in the occurrence of retention according to type of OGIB, location, or histologic type

of tumor. Among tumors associated with capsule retention, 41.6% had a negative small bowel enteroclysis prior to VCE.[6] In another study, it was noted that the most common tumors causing retention were adenocarcinoma (50%) and lymphoma (25%).[7] Most of these retentions were asymptomatic, and acute obstruction was not observed in a large series; only 1 acute obstruction was described among the 10 cases reported by Baichi and colleagues[9] and other case reports.[14]

Although capsule retention may be the most dreaded complication of VCE, the procedure should be viewed in a positive light because it is associated with a prompt diagnosis and subsequent surgical treatment, of which the overwhelming majority are elective. The case described by Ho and colleagues[13] is a rarity from the point of view of precipitating obstruction. Obstruction requires a stricture that is slightly less than the diameter of the capsule, so as to provide a tight fit. The majority of strictures are either larger than 11 mm (in which case, the capsule passes without symptoms) or smaller (in which case, the capsule is retained above the stricture and bounces around like a ping pong ball, causing no tissue injury). We are familiar with 2 patients who have retained capsules for 5 years without symptoms.

In a 3-center Australian study that looked at the outcome of small bowel tumors resected surgically, surgery was curative in 52% (12 cases), including 3 carcinoids, 2 GISTs, and 1 adenocarcinoma, with no tumor recurrence at 26–51 months of follow-up.[10] Among the other benign tumors that were resected, there was also no recurrence of OGIB at 3–51 months of follow-up.

VCE has an established role in the diagnostic workup of OGIB. In addition, it has been widely used for the evaluation of small bowel mucosal diseases such as Crohn's disease and celiac disease. Recent studies also support the use of VCE in the diagnosis and management of small bowel tumors. Despite concern about capsule retention, studies have shown the retention rate to be acceptable with no significant change in outcome, as patients ultimately underwent surgery for definitive therapy. Thus, VCE can facilitate early diagnosis and treatment of small bowel tumors, which may subsequently translate into better prognosis.

Dr. Baptista has no conflicts of interest to disclose. Dr. Cave receives consulting and research funding from Olympus and Capsule Vision.

References

1. Pan SY, Morrison H. Epidemiology of cancer of the small intestine. *World J Gastrointest Oncol.* 2011;3(3):33-42.
2. Cheung DY, Lee IS, Chang DK, et al. Capsule endoscopy in small bowel tumors: a multicenter Korean study. *J Gastroenterol Hepatol.* 2010;25(6):1079-1086.
3. Cobrin GM, Pittman RH, Lewis BS. Increased diagnostic yield of small bowel tumors with capsule endoscopy. *Cancer.* 2006;107(1):22-27.
4. Lewis BS, Eisen GM, Friedman S. A pooled analysis to evaluate results of capsule endoscopy trials. *Endoscopy.* 2005;37(10):960-965.
5. Koulaouzidis A, Rondonotti E, Giannakou A, Plevris JN. Diagnostic yield of small-bowel capsule endoscopy in patients with iron-deficiency anemia: a systematic review. *Gastrointest Endosc.* 2012;76(5):983-992.
6. Rondonotti E, Pennazio M, Toth E, et al. Small-bowel neoplasms in patients undergoing video capsule endoscopy: a multicenter European study. *Endoscopy.* 2008;40(6):488-495.
7. Schwartz GD, Barkin JS. Small-bowel tumors detected by wireless capsule endoscopy. *Dig Dis Sci.* 2007;52(4):1026-1030.
8. Urbain D, De Looze D, Demedts I, et al. Video capsule endoscopy in small-bowel malignancy: a multicenter Belgian study. *Endoscopy.* 2006;38(4):408-411.
9. Baichi MM, Arifuddin RM, Mantry PS. Small-bowel masses found and missed on capsule endoscopy for obscure bleeding. *Scand J Gastroenterol.* 2007;42(9):1127-1132.
10. Bailey AA, Debinski HS, Appleyard MN, et al. Diagnosis and outcome of small bowel tumors found by capsule endoscopy: a three-center Australian experience. *Am J Gastroenterol.* 2006;101(10):2237-2243.
11. Ross A, Mehdizadeh S, Tokar J, et al. Double balloon enteroscopy detects small bowel mass lesions missed by capsule endoscopy. *Dig Dis Sci.* 2008;53(8):2140-2143.
12. Zheng Y, Hawkins L, Wolff J, Goloubeva O, Goldberg E. Detection of lesions during capsule endoscopy: physician performance is disappointing. *Am J Gastroenterol.* 2012;107(4):554-560.
13. Ho HC, Nagar AB, Hass DJ. Obscure gastrointestinal bleeding and video capsule retention due to enteropathy-associated T-cell lymphoma. *Gastroenterol Hepatol (N Y).* 2013;9(8):536-538.
14. De Palma GD, Masone S, Persico M, et al. Capsule impaction presenting as acute small bowel perforation: a case series. *J Med Case Rep.* 2012;6(1):121-124.