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Initial Experience of Video Capsule Endoscopy After Intestinal Transplantation

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Background. Intestinal transplantation is a procedure which inflicts immunological and infectious complications that affect the transplanted graft, posing both diagnostic and therapeutic challenges. Video capsule endoscopy (VCE) offers easy access to the entire small intestine and presents itself as an interesting option. However, at present, no studies evaluating the usefulness of video capsule endoscopies in this setting have been published. Our aim was to evaluate the usefulness of VCE in detecting complications that arise after intestinal transplantation. **Methods.** We included 7 adult patients with either isolated intestine (n = 1) or multivisceral grafts (n = 6). These patients underwent 12 VCE between 2004 and 2015 at the Sahlgrenska University Hospital. The median age was 42 (21-67) years (4 women/3 men). VCE was used in clinical situations where the conventional diagnostic methods failed to provide answers to the clinical question. **Results.** Indications for the procedure were: suspicion of rejection (n = 4 examinations), gastrointestinal dysmotility (n = 4 examinations), high stomal output (n = 2 examinations), suspicion of lymphoproliferative disease in the transplanted graft (n = 1 examination), and clinical surveillance (n = 1 examination). The median time after transplantation for performing an examination was 740 (26-3059) days. VCE was useful in 83% of the examinations and the results influenced the planned management. The overall agreement between VCE findings and biopsies was moderate ($\kappa = 0.54$, $P = 0.05$) but increased when comparing the presence of inflammation/rejection ($\kappa = 0.79$, $P < 0.001$). **Conclusions.** VCE is a promising diagnostic method after intestinal transplantation. However, larger studies are needed to evaluate its potential risks and gains.

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The early results of intestinal transplantation (ITx) have improved drastically during the last decade owing to refinements in the surgical technique and patient management, including immunosuppression and monitoring.[1] The mainstay of rejection surveillance consists of frequent, protocolized endoscopies (enteroscopies) with random mucosal biopsies, because intestinal acute rejection is frequent and lacks a reliable noninvasive biomarker.[2] Moreover, the diagnosis of other conditions with unclear and often misleading clinical presentations, such as viral enteritis or posttransplant lymphoproliferative disorders, also require endoscopic investigations and biopsies. However, the routine trans-stomal enteroscopies usually only reach the last 20 to 30 cm of the graft, representing less than 10% of the total graft length. Because many transplant-related complications may occur simultaneously, showing patchy distribution or affect only limited segments of the graft, reaching a correct and timely diagnosis may be challenging.

The advent of video capsule endoscopy (VCE) has offered easy access to the entire small intestinal mucosa that hitherto was mostly inaccessible for visual inspection and has expanded the area of examination beyond the most proximal and terminal intestinal graft segments. This makes the intestinal graft unique among the transplantable solid organs because it can now be directly visualized in its entirety. However, the intrinsic technical limitations of VCE, particularly the inability to obtain biopsies, the potential risk for complications, as well as the scarce literature available on its use after ITx leaves its indications and clinical values uncertain.

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The only-case series available in this patient group tested the safety and feasibility of VCE in isolated intestinal graft recipients without a clear clinical indication or any transplant-related complication.[3] Another case report briefly reviewed the results of an uncomplicated VCE in an ITx recipient.[4] To date, the available literature in this special patient population is represented by 6 VCE performed in asymptomatic patients.

In this analysis, we report our experience with 12 VCE performed for diagnostic purposes after ITx and summarize our results and considerations for the future use of this method in clinical settings.

MATERIALS AND METHODS

Between 1998 and 2015, 21 adults received 22 intestine-containing allografts at Sahlgrenska University Hospital in Gothenburg. The rejection surveillance protocol used at our center since 2003 is based on trans-stomal ileoscopies with biopsies. The procedures are performed twice a week during the first month, followed by fewer examinations until the patient is discharged, and thereafter only when clinically indicated. Further details on the posttransplant patient management have been reported elsewhere.[5] This study was a retrospective analysis of prospectively collected data. The regional ethical review board in Gothenburg approved the collection and report of data (no. 319–11).

VCE has been performed at the Sahlgrenska University Hospital since 2005 and over 800 examinations have been performed over the last 10 years. Seven adult patients transplanted in the period 2004 to 2015 underwent VCE at twelve different occasions, based on various clinical indications. The decision to perform a VCE was taken after other standardized methods such as gastroscopies, ileoscopies, or magnetic resonance imaging (MRI) failed to provide a clear answer to the clinical questions (Figure 1). The age, sex, pretransplant diagnosis, and type of transplantation in these patients are summarized in Table 1. In these patients, 3 different video capsules with similar characteristics were used. One examination was performed with EndoCapsule (Olympus America, Inc, Center Valley, Pennsylvania), 8 with Pillcam SB (Given Imaging, Ltd, Yoqneam, Israel) and 3 with the Mirocam (Intromedic Company Ltd, Seoul, Korea). The capsule battery life varies from 8 (EndoCapsule) to 12 hours (Mirocam, Pillcam SB2).[7] The procedures were performed after a clear liquid diet the day before the examination and an overnight fast combined with bowel preparation with ingestion of 2 liters of polyethylene glycol solution (Laxabon; Recipharm Höganäs AB, Höganäs, Sweden) taken the evening before the examination. In cases where the capsule did not leave the stomach within 3 hours, passage of the capsule to the duodenum with the help of a gastroscope was considered. Administration of patency capsules (Agile patency capsule, Given Imaging Ltd, Yogneam, Israel) were abandoned after 3 examinations if either an urgency for performing the examination existed or the patient did not have a history of mechanical obstruction. Capsule retention was defined as the presence of the capsule in the digestive tract for a minimum of 2 weeks after ingestion or when the capsule was retained in the bowel lumen indefinitely unless a targeted medical, endoscopic, or surgical intervention was initiated.[8]

Statistical Analysis

Data were analyzed using SPSS version 23. Cohen κ analysis was used to examine the agreement between 2 diagnostic methods, that is, VCE and histologic findings from proximal and distal intestinal biopsies. The categorical variables that were compared were the presence of normal/abnormal findings and the presence or absence of inflammation/acute cellular rejection. Values less than 0 as indicating no agreement, 0.00 to 0.20 as slight, 0.21 to 0.40 as fair, 0.41 to 0.60 as moderate, 0.61 to 0.80 as substantial, and 0.81 to 1.00 as almost perfect agreement.[9] *P* values of 0.05 or less were considered significant. One patient was excluded from the analysis because the interpretation of the endoscopic images was impossible due to inadequate bowel cleansing.

RESULTS

The clinical indications for VCE in our group of patients were grouped into acute cellular rejection, gastrointestinal (GI) dysfunction, high stomal output, and other. The indications, the main findings, and the technical details of each procedure are summarized in Table 2.

- *Acute cellular rejection* (n = 4 examinations in 2 patients). Both patients had a biopsy-proven acute cellular rejection before the examination, but the extent and the evolution of the mucosal lesions and improvement after rejection treatment was unknown. One patient with deteriorating intestinal function and clinical condition had 3 VCE performed to evaluate the progression of the mucosal damage. The results from the VCE were helpful in the decision to perform a graft enterectomy and later listing for a retransplantation (**Figure 2, Video, SDC,** http://links.lww.com/TP/B363). The other patient had an acute cellular rejection and developed an early lesion plasma cell lymphoma detected on a liver biopsy which resulted in adjustment of immunosuppression. VCE was performed to evaluate how the endoscopic appearance of acute cellular rejection evolved after this change in the treatment regimen. No progression was however seen and the management remained unchanged. The examination was also followed up with push enteroscopy in 1 case. This patient had severe rejection noted on VCE and was confirmed with biopsies from anterograde push enteroscopy and ileoscopy.
- *GI Dysfunction* (n = 4 examinations in 2 patients). These patients had protracted abdominal discomfort, nausea and vomiting. One of them also had inadequate oral intake and occasionally high stoma outputs. Another examination was performed due to an elevated fecal calprotectin without known cause which necessitated further investigations. The other patient was suffering from recurring subileus episodes and previous investigations with small-bowel follow-through and MRI were normal leading to the suspicion of inflammation as an underlying cause. A fourth VCE was performed to investigate the status of the mucosa in a patient who failed in weaning from parenteral nutrition.
- *High stomal output* (n = 2 examinations in 2 patients). Both patients had high stomal outputs (>1.5 L/d) without known underlying cause, necessitating supplementary intravenous crystalloids solutions.
- *Other* (n = 2 examinations in 2 patients). In 1 patient who was transplanted due to neuroendocrine pancreatic tumors, tumor involvement of the intestines needed to be ruled out. The second patient was clinically well with a satisfactory graft function.

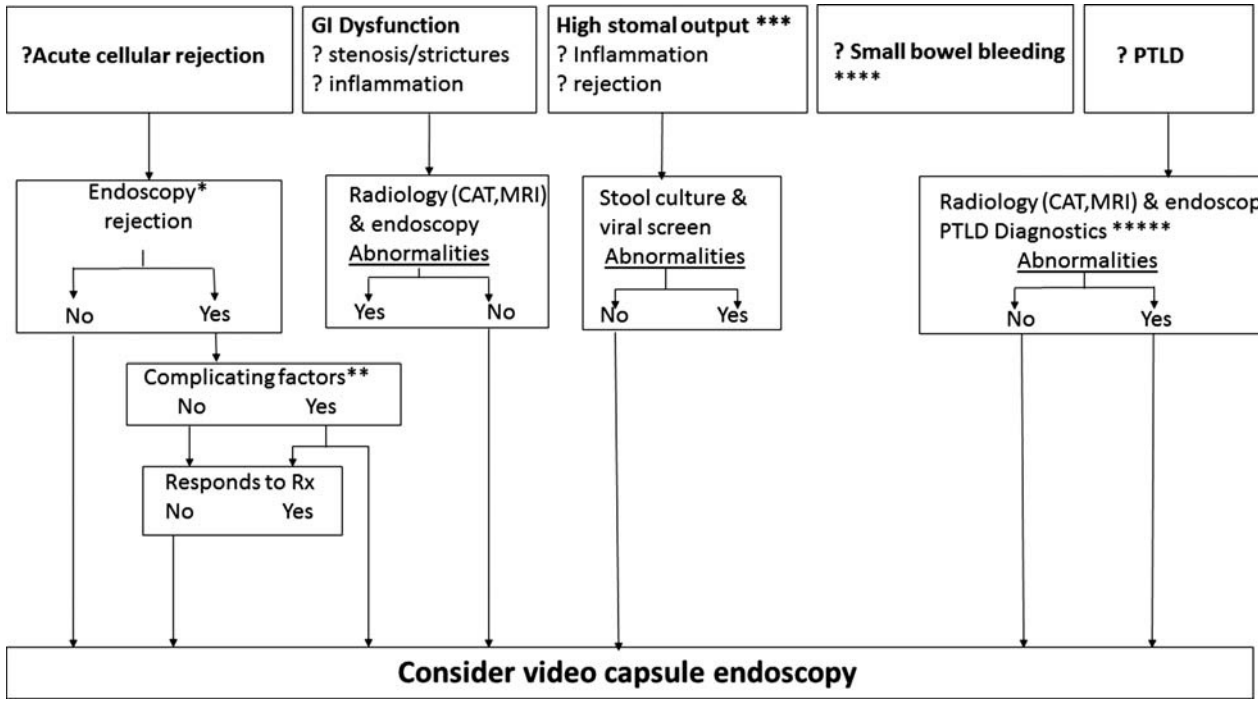

FIGURE 1. Algorithm of our indications for using VCE. VCE was considered after standardized methods failed to answer the clinical question. *Endoscopy, ileoscopy +/– gastroscopy and biopsies. All endoscopies were preceded by stool culture and viral screen **Complicating factors include: concomitant malignancy requiring altered immunosuppressive treatment. Follow-up with VCE was also considered after the completion of a treatment course *** Defined as > 1.5 L/d. ****According to ACG Clinical Guideline.[6] *****PTLD, posttransplant lymphoproliferative disorder. Diagnostic methods for PTLD are described elsewhere.[5]

This examination was performed to evaluate the endoscopic appearance for the surveillance program.

Endoscopic Findings

Endoscopic findings were grouped based on the clinical indication:

- *Acute cellular rejection* (n = 4 examinations, 2 patients): Different stages of inflammation were detected, predominantly in the distal portion of the small intestine but also in the proximal part. Severe inflammation appeared to be associated with impairment of the intestinal peristalsis as noted on the VCE and also by a prolonged capsule passage time, since capsule passage time exceeded capsule battery life in all patients. Ulcerations and active/postinflammatory stenoses were located on the proximal portion of the intestine in 2 patients (n = 3 examinations).
- *GI Dysfunction* (n = 4 examinations, 3 patients): Multiple stenoses and ulcerations were present in the proximal portion of the small intestine in 2 patients (Figure 3). One patient had an inflammatory lesion in the mid portion of the small intestine which on the following ileoscopies showed similar features distally with biopsies revealing presence of ACR. In 1 patient with nausea, vomiting, difficulties with oral intake and a past history of strictures as well as ulcerations in the small intestinal graft the VCE revealed normal findings.
- *High stomal output* (n = 2 examinations, 2 patients): One patient who had high stomal output and normal inflammatory tests was examined and showed completely normal findings. In the other patient the VCE resulted in poor image quality due to inadequate bowel cleansing.
- *Other* (n = 2 examinations, 2 patients): One patient had generalized edema of all the segments in the small intestine and the other patient had a proximal edema and a single erosion in the proximal intestine.

VCE revealed pathologic findings, varying from asymptomatic focal ulcerations to widespread edema, inflammation and strictures. Four out of the twelve capsule endoscopies were completed within 9 hours. The investigation was incomplete in 7 cases as the capsule endoscope did not progress along the entire small intestine during the battery time and remained in the GI tract beyond this period (>8-12 h). As delayed gastric emptying was common in these patients, and in order to save battery time the capsule was advanced beyond the pylorus with a gastroscope in 5 cases. The time needed to excrete the capsule (witnessed by either patient or medical staff) varied from 5 hours to 12 days. In total, 1 patient had symptoms attributable to the capsule. Capsule retention occurred twice in the same patient. The first retention episode led to ileus that needed surgical intervention

TABLE 1.

Demographics and clinical presentation

Patient ID	Age, y	Sex	Diagnosis[a]	Graft type
1	40	M	IF, trauma	Multivisceral
2	48	M	IF, MVT	Multivisceral
3	21	F	IF, CIPO	Multivisceral
4	44	M	NEPT	Multivisceral
5	42	F	IF, SBS	Isolated small bowel
6	34	F	IF, CIPO	Multivisceral
7	67	F	IF, CIPO	Multivisceral

[a] IF, intestinal failure; MVT, mesenteric vein thrombosis; CIPO, chronic intestinal pseudo-obstruction; NEPT, neuroendocrine pancreatic tumor; SBS, short bowel syndrome; F, female; M, male.

TABLE 2.

Endoscopic and histologic features in small bowel transplanted patients

ID	Days after Tx	Indication	VCE findings	Passage time	Successful?	Biopsies[a]	Medication
1	1090	GI dysfunction	Multiple sections with ulcerations, normal in between	9 h	Yes	Ulcerations with inflammation. No signs of ACR	MID[b]
2	191	GI dysfunction	Ulcerations. Multiple nonobstructive strictures, continuous moderate inflammation	>12 h	Yes	Ulcerations and suspicion of ACR	MID
2	399	ACR?	Ulcerations, strictures, short sections with mild inflammation	>12 h	Yes	Mild chronic inflammation	MID
2	2538	GI dysfunction	Normal appearance of intestine	5 h	Yes	Normal	Opioids
3	1143	High stomal output	Poor preparation, inconclusive	>8 h	No	Normal	Opioids
3	1899	GI dysfunction	Poor preparation, inconclusive	>12 h	No	Not performed	Opioids
4	3059	Tumor?	Mild edema continuous throughout intestine. No tumors visible	5.5 h	Yes	Normal	No
5	26	ACR?	Distal from anastomosis: ulcerations and continuous mild/moderate/severe inflammation	>12 h	Yes	ACR, severe	Opioids
5	258	ACR?	Distal segment of small intestines with edema, ulcerations and continuous inflammation	>12 h	Yes	ACR, extensive ischemia	Opioids
5	310	ACR?	Continuous severe inflammation from proximal intestine, dilated, dehaustrated intestine with minimal peristalsis	>12 h	Yes	ACR, chronic rejection	Opioids
6	100	Surveillance	Proximal section with patches of mild edema and 1 erosion	<6 h	Yes	Normal	No
7	1436	High stomal output	Normal appearance of intestines	5.5 h	Yes	Normal	MID

The examination was deemed successful if the capsule had adequate imaging and was passed within the battery life of the capsule or if the images resulted in an explanation/alteration in management.

[a] Biopsies from gastroscopies and ileoscopies.

[b] MID, motility inhibiting drugs include; felodipine, loperamide, metoclopramide, hyoscyamine.

ACR, acute cellular rejection.

5 days after the examination. In the second episode the patient underwent graft enterectomy due to severe treatment refractory rejection. The capsule was found in the explanted intestine. In most patients with prolonged capsule passage time a continuous use of opioids (5 of 6 examinations) or motility inhibiting drugs: felodipine, loperamide, metoclopramide, hyoscyamine (3 of 4 examinations) was present.

Correlation Between VCE and Biopsies

The overall agreement between VCE finding and biopsies obtained from gastroscopies and ileoscopies revealed a moderately strong agreement ($\kappa = 0.54$, $P = 0.05$) when differentiating between normal/abnormal appearance. A substantial agreement ($\kappa = 0.79$, $P < 0.001$) was seen when comparing the presence or absence of inflammation/acute cellular rejection between VCE and biopsies.

DISCUSSION

Our results show that VCE was helpful in answering the clinical question in 83% (10/12) of the examinations. Many examinations were incomplete, but still rendered sufficient imaging to be helpful in patient management. The correlation between VCE findings and biopsies from gastroscopies and ileoscopies was significant. The wide variety of indications for VCE illustrates the possibilities of this investigation. The challenges encountered with this examination are the sensitivity and the specificity to detect lesions after small-bowel transplantation.

Visual inspection of the intestinal mucosa through frequent ileoscopies combined with random mucosal biopsies is the main strategy for monitoring intestinal allograft rejection.[10] The low sensitivity and specificity (43% and 67%, respectively) of endoscopy as the only diagnostic tool in diagnosing intestinal acute rejection does not support it as the single investigation for rejection surveillance[11] especially considering conditions that have a similar endoscopic picture eg enteritis yet with different treatments.[10] However, in our series we noticed a correlation between the findings from the VCE and the biopsies obtained from the distal and proximal portion of the small intestine. Unfortunately, the biopsies were not captured with deep enteroscopy making the correlation more difficult to assess. One general conclusion that can be drawn though is that similar findings seemed to appear both within and outside the range of the endoscopes. The question therefore remains: what is the role of VCE in these patients? The clinical benefits derived from most examinations illustrates its potential as a useful tool in the diagnostic management of this group of patients. In our experience, the greatest gain can be seen in patients with acute cellular rejection that do not respond to conventional treatment or as a useful surveillance protocol for posttransplant lymphoproliferative disorder in immunologically challenged patients currently receiving or that have recently completed treatment for acute cellular rejection. We also see a role in investigating patients with diffuse GI symptoms, since an organic cause may explain their symptoms. Another potential indication include suspicion of ileal rejection in patients with additional colon grafts or in patients where the native colon is reconnected to the transplanted intestine.

The endoscopic features in the small intestine after immunosuppressive treatment are unknown. Chronic medication with several drugs may cause mucosal lesions with the most

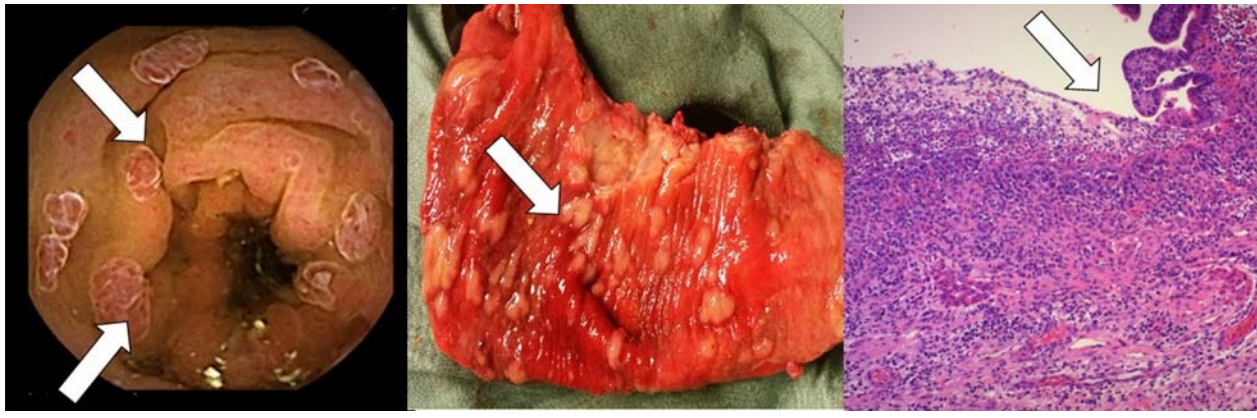

FIGURE 2. Extensive mucosal loss and scattered islands of epithelium (arrow) in a patient with exfoliative ACR refractory to treatment. Endoscopic image (left) and the macroscopic aspect at graft enterectomy (middle). Microscopic histological view of the surgical specimen (right) show rejection with extensive denudation of the surface epithelium (arrow) with loss of crypts.

typical being the mucosal lesions after NSAID use.[12] Mycophenolate mofetyl is a frequently used immunosuppressant drug that has common GI side effects, such as abdominal pain, nausea, bloating, diarrhea, and colitis. Capsule endoscopy examinations conducted in symptomatic renal transplant recipients revealed abnormal intestinal findings in 16 out of 18 cases (89%) and although a detailed endoscopic description was absent, erosions and ulcerations were mentioned.[13] Although none of the patients in our series received Mycophenolate mofetyl at the time of VCE the effect of concomitant medication on the intestinal mucosa is yet unclear and needs to be further clarified in both asymptomatic and symptomatic patients (eg, acute cellular rejection). However, this setup may often require elaborate logistics while the endoscopic mucosal biopsies incur a certain risk for bleeding and perforation.

When reviewing the symptoms necessitating a VCE, abdominal pain was common in our cohort. Studies have described an increased diagnostic yield with abdominal pain and other associated symptoms or an underlying Crohn disease.[14] In our cohort intestinal strictures were seen among patients with abdominal pain, and because our cohort has extensive comorbidity and many potential causes of pathology in the small intestine, the decision to perform VCE may

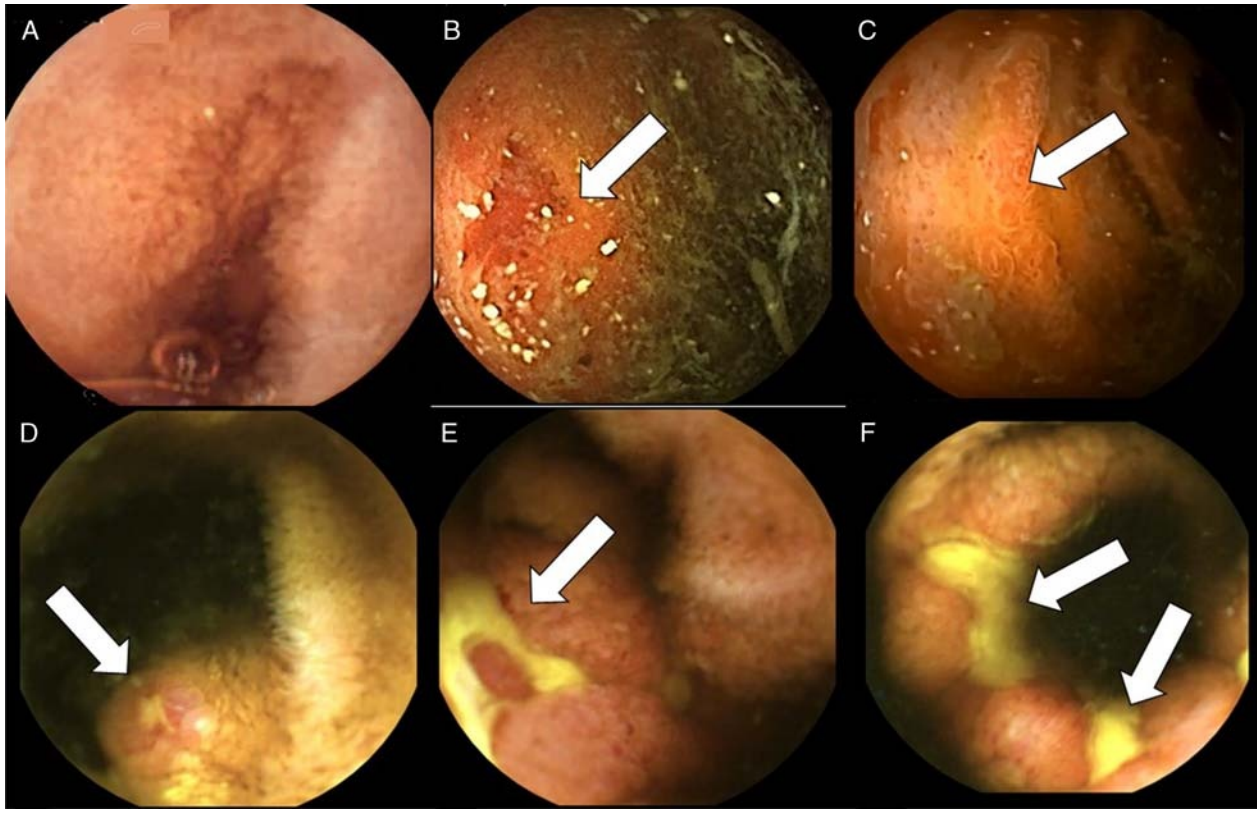

FIGURE 3. A, Normal appearance of the small intestine. B, Edematous mucosa with villous atrophy and erosions with spontaneous hemorrhage (arrow). C, Intestinal inflammation is seen (arrow) along with villous atrophy and edema. D-F, Different ulcerations with varying depth and inflammation. D, Shallow lesion is seen (arrow) and E and F, the deep ulcerations (arrow).

be warranted with a low threshold to exclude other causes. The role of VCE in patients with malabsorption is not yet established. Multiple studies on celiac disease have been performed and the diagnostic yield increased when extensive disease was present.[15] In our patient with intestinal malabsorption no abnormalities were found yet might not exclude minor mucosal changes. The presence of high stomal output is a challenge that often raises the suspicion of rejection. In our patient, the findings were normal which is in accordance with a previous study.[16] Malignancies are another challenge in this patient population and several patients' contract posttransplant lymphoproliferative disorders.[5] In a recent study, the detection rate of small-bowel tumors was superior with VCE compared with other methods.[17] However, we did not encounter any small bowel malignancies throughout our study period.

The time needed for the capsule to transit the entire small bowel and enter the colon as reported by large patient series ranges between 3 and 7 hours while the rate of incomplete examinations vary between 20 and 30%.[18,19] We observed a much slower progression through the GI tract with only 6 of 12 complete examinations. This is likely due to a combination of factors such as the denervation of the transplanted splanchnic organs, postoperative adhesions, motility inhibiting drugs and a decreased peristalsis due to underlying pathology. These findings are in line with the limited existing literature as only 3 of the 6 cases previously reported excreted the capsule within 8 hours.[3,4] The most feared complication of VCE is capsule retention as this carries the risk of intestinal obstruction. Capsule retention occurred twice in a patient with ongoing advanced (exfoliative) rejection which can be compared with 10% reported in patients with Crohn disease.[20] The use of opioids and other agents that inhibit GI motility in transplanted patients has been problematic. We did not stop these medications before the examinations because of a prior inability to wean off of opioids despite multiple attempts. A more rigid protocol with exclusion of motility inhibiting drugs and attempt to wean off opioids is likely to be beneficial to improve the function of the GI tract and the diagnostic potential of the VCE.

Further trials to document the mucosal/endoscopic patterns associated with various transplant-related conditions would be needed. We think that a systematic use of VCE in consecutive patients and relating the findings to symptoms, complications, and clinical course is necessary to evaluate individual findings. Hence, the absence of endoscopic features in clinically well patients will determine the relevance of these findings because a lot of pathology can be seen in asymptomatic individuals. Although the technique has been available at our hospital since 2005, we have been selective with the use of VCE and reserved it for cases were extensive standard endoscopy and radiology investigations including MRI could not deliver a diagnosis. In 1 case, VCE was followed up with deep enteroscopy, which confirmed the suspicion from VCE. A combination of VCE and deep enteroscopy may represent an alternative approach in selected cases to acquire more information. However, because this approach is invasive and with a complication rate of 1% to 3% (abdominal pain, perforation, pancreatitis, GI hemorrhage) as well as a failure rate of 20% to 30%, particularly due to adhesions from prior surgery, its use should be considered thoroughly.[21] Perhaps, an additional role of VCE is to replace the standardized protocol biopsies in a subset of patients with normal gastric emptying. Nonetheless, today, this approach is restricted by the limited experience of this technique in the transplanted patients.

In conclusion, VCE appears to be a useful diagnostic method for several conditions developing after ITx. However, larger studies investigating patients in a prospective fashion are needed to evaluate its clinical value as well as its risk to determine its clinical indications in the setting of small ITx.

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