A New Method for Endoscopic Closure of Gastrocolonic Fistula
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Gastrocolonic fistula formation is a rare but serious complication of percutaneous endoscopic gastrostomy (PEG) placement that often requires surgical intervention. The following case study demonstrates a novel and successful endoscopic technique for gastrocolonic fistula closure using a cardiac septal defect closure device in a patient too ill to undergo surgery.

Case study
An 82-year-old woman underwent what was thought to be uneventful PEG tube placement. One year later she presented with diarrhea and feculent vomiting. A CT scan revealed a 1.5 cm gastrocolic fistula tract – and the internal bumper of the feeding tube in the distal transverse colon (Figure 1). Presumably, at the time of G-tube placement, the feeding tube was inadvertently inserted into the stomach through the transverse colon and, over time, the internal bumper eroded through the matured fistula tract and into the colon. The patient was scheduled for surgical repair but developed cardiopulmonary compromise thought to pose an unacceptable peri-operative risk. She was placed on total parenteral nutrition, but had repeated metabolic and infectious complications.

Endoscopic repair of the persistent, mature, non-inflamed fistula tract was attempted a total of four times (Figure 2) before a successful conclusion. The first attempt involved cauterization of the fistula tract followed by hemoclip placement deployed directly over the gastric side of the fistula opening. The old G-tube was removed and a new one placed. Over the next 2 weeks, the colo-cutaneous tract spontaneously closed; however, a contrast study showed persistent fistula patency.

In a second attempt at fistula closure with hemoclips, a sideviewing endoscope was passed per-rectum for optimal visualization of the distal fistula opening. However, hemoclips could not readily be

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deployed at the colonic side of the fistula due to angulation.

The third attempt involved use of an endoloop circumferentially secured adjacent to the fistula edges with hemoclips, followed by tightening of the endoloop after insertion of Surgisis™ directly into the fistula tract. However, two weeks later, a Gastrografin® enema showed persistent patency of the fistula tract.

A novel approach

In the fourth attempt, use of a cardiac septal defect closure device called the Amplatzer®Septal Ocluder was successful. Made from nitinol wire mesh, the occluder is an FDA-approved, self-expandable, double-disk device that was deployed under endoscopic and fluoroscopic guidance across the fistula tract. The proximal disk was then injected with 3cc Dermabond™ to create a watertight seal. However, the device collapsed into the colon after four months and was retrieved via colonoscopy.

A second attempt at a novel approach

Due to the apparent, albeit short-lived, success of the concept using a cardiac septal defect closure device, the decision was made to endoscopically place a similar device. The strategy for this approach involved three distinct stages:

1) Identifying a device that could effectively traverse the fistula and mechanically block free flux of intraluminal contents
2) Anchoring the device to the gastric wall with clips
3) Creating a watertight seal

A cardiac septal defect closure device called a CardioSEAL® septal occluder was chosen and endoscopically placed using a double-channel scope with fluoroscopic guidance in a team effort with an interventional endoscopist and interventional cardiologist. After the device was appropriately positioned across the fistula tract, multiple hemoclips were placed at the edges of the gastric side of the deployed closure device to secure it and prevent migration into the colon (Figure 3). Dermabond® was then injected through the device into the fistula tract through a needle injection catheter.

A contrast gastrogram performed one week later showed that the fistula was no longer patent (Figure 4).

An upper endoscopy performed four months later showed that the device remained in good position, with no evidence of epithelialization over the device membrane.

The patient continues to do well one year after the CardioSEAL device was placed, with tolerance of oral intake and no clinical evidence of fistula patency. This novel approach, currently under patent at Cedars-Sinai, should be considered as an alternative to surgical management for persistent fistulas, especially among those with high operative risk.

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High-Resolution Esophageal Manometry

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Manometry techniques, which record intraluminal pressures simultaneously from several sites along a segment of the gastrointestinal tract, provide an indirect measurement of gastrointestinal contractile activity and bolus movement. Clinicians have performed esophageal manometry for decades to identify disorders of esophageal motor function that produce symptoms like dysphagia and chest pain.

Conventional esophageal manometry systems record and display pressure information from sensors spaced at 3 to 5 cm intervals along a catheter that is placed in the lumen of the esophagus. Pressure data between these widely arranged sensors are not obtained, giving an incomplete picture of esophageal motor function.

Cedars-Sinai clinicians are working to complete the picture of esophageal motor function with a new technique called high-resolution manometry. High-resolution systems record intraluminal pressures at 1 cm intervals over a 35 cm recording segment. These pressure data are transformed into a topographic (color contour) plot that provides a continuous depiction of pressure along the entire esophagus throughout time.

The clinical utility of high-resolution manometry was made clear in the case of a 23-year-old woman who presented with a complaint of dysphagia to solids for six months after a Nissen fundoplication. She also complained of a gurgle emanating from the chest and occasional regurgitation when swallowing liquids. She had no other complaints, no allergies and was taking no medications. Her physical exam was normal. An endoscopy revealed only an intact fundoplication, and biopsies of the esophagus were normal. The TSH, fasting glucose, ANA and ESR were normal.

A normal esophageal manometry is seen in Figure 1, displayed as a conventional tracing (A) and a high-resolution contour (B). The patient’s manometry is seen in Figure 2. The high-resolution color contour clearly elucidated the pathophysiological process in this patient. Failure of the GE junction to open indicated that the fundoplication was not done correctly, and was likely the cause of the patient’s dysphagia. The gurgling sound and regurgitation occurred because the swallowed bolus was compressed against the unopened GE junction, and squirted back (escaped) into the proximal esophagus when peristalsis failed. Based on the results of her high resolution manometry testing, the patient’s fundoplication was revised in a

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Recent Advances in the Understanding of Inflammatory Bowel Disease Genetics

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This is a remarkable time in which to be a clinician treating inflammatory bowel disease (IBD). We are on the cusp of an exciting new era of many novel treatments for IBD that build on the success of the anti-TNF therapeutics. Additionally, significant progress is being made in our understanding of the pathogenesis of IBD, and no greater progress has been made than in the field of IBD genetics. These advances have been made possible, in part, through the development of high throughput and relatively inexpensive genotyping methods.

**Less expensive genotyping enables research progress**

In 2001, when the first gene for Crohn’s disease was discovered (NOD2 or CARD15), genotyping was a painstaking and costly business. Financial restraints meant that studies were of limited power and only a few targeted genes could be analyzed (and incompletely at that). Today, “chip-based” (see Figure 1) technology allows genotyping to be performed at a fraction of a cent per genotype. The cost decrease has allowed large-scale studies of thousands of subjects (both cases and controls) to be performed, looking at many thousands of polymorphisms across the genome. Called genome-wide association scans (GWAS), these studies have become the state-of-the-art for genetically complex diseases such as IBD.

**Linking TNFSF15 gene to Crohn’s**

The first IBD-related GWAS, published in 2005, examined 72,000 single-nucleotide polymorphisms (SNPs) and identified an association between genetic variation in the TNF superfamily 15 (TNFSF15) gene and Crohn’s disease in a Japanese cohort, as well as ulcerative colitis in two British cohorts. Cedars-Sinai researchers have confirmed the association of TNFSF15 with Crohn’s and have identified a particular association between polymorphisms in this gene and Jewish individuals with Crohn’s disease (IRB #1096).

Further research performed at Cedars-Sinai confirmed the role of TL1A, a protein encoded by TNFSF15, as a critical regulator of gastrointestinal mucosal inflammation (IRB #2673, 3358). A number of biotechnology companies are now looking at antibodies to this molecule as a possible therapy for IBD and other inflammatory conditions – a potential first “bench-to bedside” benefit of the vast amounts of genetic research in IBD. To date, TNFSF15 remains the only gene identified that increases the risk of Crohn’s in both Caucasian and Asian populations.

**Research consortium furthers discovery of genes**

Subsequent GWASs have been performed with considerable success identifying IBD-related genes. Cedars-Sinai was a founding member of the North American consortium that identified a single variant within the interleukin 23 receptor (IL23R) as a susceptibility SNP for both Crohn’s disease and ulcerative colitis. Further work at Cedars-Sinai identified a number of risk haplotypes within this gene that increase the risk of Crohn’s, and found that the overall contribution of this gene to Crohn’s risk is significantly greater than initial studies suggested. (IRB #1096)

The consortium also identified variants within the IRGM gene that increase the risk of Crohn’s disease. IRGM encodes a protein involved in autophagy, a process whereby intracellular debris and toxins are removed. The critical role of autophagy in Crohn’s pathogenesis was first highlighted when another autophagy gene, ATG16L, was identified in an earlier GWAS from Germany. These findings highlight one of the benefits of the GWASs: the identification of pathways and processes not previously identified as relevant to IBD pathogenesis.

In another effort, the North American consortium pooled data with a British consortium and a Franco-Belgian group to perform a meta-analysis of their three GWASs (IRB #1096). This study of more than 3,000 cases and nearly 5,000 controls confirmed 11 previously identified susceptibility loci and identified 21 new loci associated with Crohn’s disease. The new loci include the chemokine receptor 6 (CCR6) and IL12B, as well as STAT3 and JAK2 (involved in the IL23 pathway). Despite the identification of more than 30 susceptibility loci for Crohn’s, less than 20 percent of the genetic risk has been explained, suggesting there are many more genes yet to be discovered.

**Next steps in genetic research**

The challenges for IBD researchers are considerable. The majority of genes in Caucasians are yet to be identified, and genes that predispose to non-Caucasian IBD have, with the exception of TNFSF15, not yet been found. Furthermore, researchers now need to decipher the functional consequences of these variants that may highlight novel therapeutic targets for IBD. Finally, genetic studies need to be performed in well-phenotyped cohorts of patients to allow the identification of genetic markers that predict disease behavior and response to therapy in IBD.

The IBD Center at Cedars-Sinai, under the direction of Stephan Targan, MD, is at the forefront of pushing back the boundaries in all of these areas.

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**Figure 1:** A genotyping “chip” for performing a GWAS. Each dot represents one single nucleotide polymorphism (SNP) and the different collars represent different alleles. Each chip typically genotypes between 370,000 and 1,000,000 SNPs on an individual. Hundreds of cases and controls are genotyped in this way and the frequency of the SNPs is compared in the cases to the controls to see if there is any association with the disease in question.
minimally invasive procedure. After surgery, she no longer complained of dysphagia, regurgitation or a gurgling in the chest.

Figure 1: Normal Esophageal Motor Function. The recording in 1A was made with a high-resolution manometry catheter and recording system, but is displayed to look like a conventional esophageal manometry. Nine of 36 recording channels are displayed to mimic a conventional manometry tracing. Channels were selected to record simultaneously from the pharynx to the stomach. With conventional manometry systems it would not be possible to record simultaneously from the upper and lower esophageal sphincters. Pressure is on the Y-axis, and time is on the X-axis. The numbers to the right of the graphic indicate sensor spacing relative to the nares. The tracing labeled UES is from the upper esophageal sphincter, and that labeled LES is from the lower esophageal sphincter. WS indicates the timing of a wet swallow. The esophageal peristaltic pressure wave and relaxation of the UES and LES are seen in this recording. The high-resolution color contour obtained from the same data is seen in 1B. Sensor location is on the Y-axis, and time is on the X-axis. The color bar to the right depicts the relationship between color and pressure. Resting UES and LES pressures are seen as horizontal bands of color that are several cm wide. Their hues indicate pressures that are greater than in the adjacent pharynx, esophagus or stomach. Opening of the UES and LES relaxation are portrayed as color change to hues that represent a lower pressure: UES pressure approximates that in the esophagus, and LES pressure approximates that in the stomach. The peristaltic pressure wave is depicted as a diagonal band of color running from the UES to the LES. Its amplitude diminishes transiently over a segment of the proximal esophagus (asterisk). This is the transition zone over which the esophageal musculature changes from striated to smooth muscle. Pressure in the swallowed bolus (intrabolus pressure) is depicted as a small, simultaneous rise in intraesophageal pressure that is seen as an abrupt change in color to a lighter blue (arrowhead). Intraesophageal pressure drops after the peristaltic pressure wave passes (return to a darker blue color), indicating bolus clearance from the esophagus.

Figure 2: Dysphagia after a Nissen Fundoplication. The manometry is displayed in line mode as a conventional manometry (A). A wet swallow (WS) produces contraction in the proximal smooth muscle esophagus that appears to give way to simultaneous repetitive pressure waves in the distal esophagus. The LES does not relax appropriately. In the UES there is a pressure wave that is not associated with pharyngeal motor activity. It correlates temporally with the esophageal pressure wave at 32 cm from the nares. The asterisk was placed to indicate the timing of a gurgling noise coming from the patient’s chest. The HRM color contour helps interpret this complex manometry (B). The wet swallow produced peristalsis in the striated and proximal smooth muscle esophagus. Peristalsis in the proximal smooth muscle segment generated high amplitude isobaric pressure waves in the more distal esophagus (arrowhead). This isobaric pressure wave is seen in the line tracing as the first component of the double-peaked pressure waves at 32 and 37 cm from the nares. This isobaric pressure arises from squeezing of the bolus against a GE junction that does not open. Next, peristalsis fails. This is seen as a narrow, vertical band of green between proximal and distal smooth muscle contractions (timing marked by vertical arrow). The gurgle (timing indicated by the asterisk) occurs when peristalsis fails, pressure in the bolus ahead of the peristaltic pressure wave decreases (vertical arrow), and there is a simultaneous pressure rise in the proximal esophagus; i.e. there is a shift in color from dark to light blue or aqua (asterisk). These pressure changes indicate that the distal esophagus is being decompressed by bolus escape into the proximal esophagus. Retrograde movement of the bolus produces the gurgle. The LES pressure peak seen during the gurgle represents UES contraction at the time pressure went up in the proximal esophagus.

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