CASE STUDY SERIES IN IBD

Hyperbaric Oxygen Therapy for Refractory Perianal Crohn's Disease: A Case Report

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A 19-year-old woman with a history of ileocolonic stricturing Crohn's disease (CD) diagnosed at 7 years of age presented to a tertiary care center for a second opinion regarding severe refractory rectal and perianal disease. Regarding her history of inflammatory bowel disease (IBD), she was started on infliximab and azathioprine at the time of her initial CD diagnosis. At the age of 12 years, she developed obstructive symptoms secondary to a sigmoid stricture that could not be dilated endoscopically. She ultimately required laparoscopic resection of 8 cm of sigmoid colon with colorectal surgery. She was transitioned to vedolizumab (Entyvio, Takeda) at the age of 16 years because of worsening rectal luminal disease with severe ulcerations seen on colonoscopy. More recently, she was transitioned to ustekinumab (Stelara, Janssen) owing to the development of extra-intestinal manifestations of IBD and psoriasis. At the age of 17 years, she developed worsening rectal and perianal disease complicated by a rectal stricture 4 cm from the anal verge that required numerous serial surgical dilations. Owing to the severity of her rectal CD, adalimumab was added to ustekinumab. By the time of referral, she had undergone several examinations under anesthesia (EUAs) with drainage of perianal abscesses with numerous antibiotic courses (ciprofloxacin, amoxicillin clavulanate, metronidazole) as well as seton placements for complex perianal fistula management.

Upon presentation to the clinic, she reported severe daily rectal pain, poor appetite, and fatigue, and required wearing a pad for drainage with twice-daily changes. She denied any fever, significant weight loss, hematochezia, or increased frequency of bowel movements from baseline. She was eating several small frequent meals a day because of obstructive symptoms. She was a freshman in college, and the severe rectal pain limited her daily activities. She had no prior history of tobacco use, denied use of nonsteroidal anti-inflammatory medications, and denied missing doses of her CD medications. Her family history was notable for a brother with celiac disease and a maternal grandmother with systemic lupus erythematosus.

At presentation, her vital signs were normal. Physical examination noted a thin woman resting comfortably with moist mucous membranes and no visible oropharyngeal lesions or skin rashes. On abdominal examination, she had a soft, nondistended abdomen with normal bowel sounds, no tenderness to palpation, and no hepatosplenomegaly. On rectal examination, a single seton extending from the posterior midline anus to the left anterolateral perianal skin was seen, and a narrow stricture was palpated in the distal rectum. Several skin tags were also present. At the time of her clinic visit, she was maintained on adalimumab every 2 weeks and ustekinumab every 4 weeks subcutaneously with most recent trough levels of 6.8 μg/mL and 9.8 μg/mL, respectively. Her laboratory tests demonstrated a hemoglobin of 13.2 g/dL, platelet count of 419 × 10^9/L, creatinine of 0.57 mg/dL, C-reactive protein of 7.3 mg/L, and erythrocyte sedimentation rate of 16 mm/h.

Magnetic resonance imaging (MRI) of the pelvis with intravenous contrast demonstrated previously seen left transsphincteric and intersphincteric perianal abscesses that had decompressed following surgical incision and drainage, without any significant drainable fluid visualized. A known complex branching fistula arising from the 6 o'clock position of the anal canal was seen with an existing seton. Additionally, MRI showed a new transsphincteric fistula arising from the 6 o'clock position coursing through the upper left external anal sphincter and the collapsing abscess cavities, exiting at the left gluteal skin

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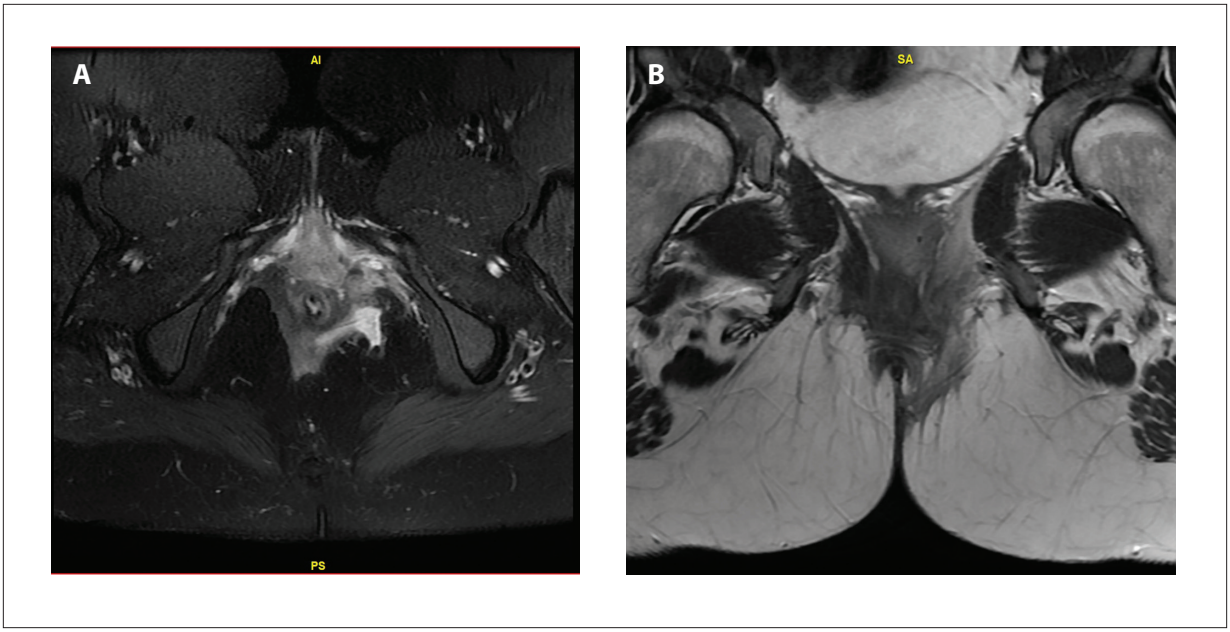

Figure. Pelvic magnetic resonance imaging of the patient with Crohn's disease demonstrating a complex, transsphincteric fistula. The fistula tract is shown **(A)** first coursing horizontally and cephalad traversing the upper left external anal sphincter and **(B)** then inferiorly through the ischioanal fat to exit at the left gluteal skin.

(Figure). Enhancing granulation tissue was demonstrated along the fistulous tract.

Her colonoscopy demonstrated a benign-appearing stenosis measuring 2 cm in length at the rectum in addition to mild stenosis measuring 1 cm in length at the splenic flexure. Pathology from the rectal and splenic strictures demonstrated focal mild active chronic colitis with nonnecrotizing granulomas, without evidence of dysplasia. The terminal ileum and remaining mucosa in the colon appeared normal endoscopically. Biopsies from the ileum demonstrated mild chronic ileitis, and biopsies from the transverse and ascending colon were notable for mild active chronic colitis. She also underwent an esophagogastroduodenoscopy, which demonstrated a normal examined esophagus, stomach, and duodenum. Pathology demonstrated normal small bowel mucosa without diagnostic abnormality and no evidence of Whipple disease, celiac sprue, or *Giardia*. Gastric biopsies were negative for *Helicobacter pylori*.

Topical tacrolimus was discussed as an option for her perianal fistulizing CD; however, she was not able to tolerate the suppositories owing to severe rectal pain limiting administration. After multidisciplinary review in the setting of her refractory rectal and perianal disease on combination biologic therapy, she was referred for hyperbaric oxygen therapy (HBOT). She underwent a total of 20 sessions of HBOT with significant improvement in her symptoms, including decreased rectal drainage, improved appetite, and overall enhanced quality of life in college. Additionally, she underwent repeat surgical dilation of the rectal stricture with a Hegar dilator without any complications. She had subsequent improvement in her postprandial abdominal pain and ability to tolerate a less restrictive diet. Subsequent pelvic MRI performed after completion of HBOT demonstrated stability of the intersphincteric and transsphincteric fistulas without any new abscess, fluid collection, or perianal fistula development. She is scheduled for a follow-up EUA for consideration of potential seton removal for the perianal fistulas.

Discussion

Perianal CD represents a spectrum of disease that includes perianal fistulas, abscesses, or anorectal strictures, and occurs in up to 25% to 35% of patients with CD.[1,2] Symptoms may include rectal pain, urgency, hematochezia, rectal discharge, and systemic symptoms including fever. Patients with obstructive symptoms in the setting of an anorectal stricture may present with nausea, vomiting, postprandial abdominal pain, and a restricted diet. Patients with a fistula involving the bladder may experience fecaluria and pneumaturia. Risk factors for the development of perianal fistulizing CD include younger age at diagnosis, rectal involvement, longer duration of

Table. Parks Classification of Perianal Fistulas

Parks classification	Description
Type 1	Intersphincteric fistula
Type 2	Transsphincteric fistula
Type 3	Suprasphincteric fistula
Type 4	Extrasphincteric fistula

disease, prolonged corticosteroid use, and the presence of extraintestinal manifestations.[3,4] Although most cases present concomitantly with or after the diagnosis of luminal CD, perianal fistulas may precede the diagnosis of luminal disease in some patients.

The digital rectal examination is a key component of the physical examination in any patient presenting with CD and suspected perianal complications. Findings of warmth, erythema, and a palpable fluctuant mass indicate a diagnosis of a perianal abscess. Additionally, close inspection for perianal fistulas should be performed and include specific location, relationship to the external anal sphincter, and the presence of purulent drainage. Narrowing of the anal canal on palpation suggests the presence of an anorectal stricture. The examination should be tailored to patient symptoms; for women, an assessment of the anterior perineum should be performed upon concern for gynecologic involvement, such as the presence of a rectovaginal fistula.

Perianal fistulas in CD are broadly categorized as simple or complex for risk stratification and subsequent management.[5] Simple fistulas have a single external opening without an associated abscess or stricture. In contrast, complex fistulas involve the muscle layers, may have multiple external openings, and may be associated with an abscess or stricture. These fistulas may also penetrate nearby organs such as the vagina, bladder, or bowel. Another categorization system is the Parks classification, which organizes fistulas into 4 types based on the relationship to the external and internal anal sphincters as well as overall anatomy (Table).[6] The Parks classification system is useful for surgical planning. Rectal endoscopic ultrasound (EUS) and MRI with intravenous contrast are the preferred imaging modalities for the evaluation of a suspected perianal fistula or abscess in CD.[7] Cross-sectional imaging with MRI or computed tomography enterography is also important for the evaluation of anorectal strictures to assess the degree of luminal narrowing and stricture length, the presence of prestenotic dilation, and the relationship of the stricture to anastomotic sites in patients with previous surgical resections.

For perianal fistulas, EUA is used to further evaluate the perianal anatomy prior to any potential procedural or surgical intervention. Additionally, colonoscopy is an important component of the workup to evaluate for the presence of active luminal CD with associated endoscopic mucosal ulceration, erythema, or active inflammation seen on pathology. Additionally, CD-related strictures should be biopsied to evaluate for potential malignancy.[8] Patients who have asymptomatic anorectal strictures typically do not require intervention. In contrast, patients with obstructive symptoms are treated with serial endoscopic balloon dilation or surgical dilation.[9] Additionally, patients may perform subsequent dilations at home; however, this is often limited by rectal pain, and patients must be appropriately counseled to avoid overdilation, which may cause sphincter injury and subsequent incontinence.

A 2-week course of antibiotics (eg, ciprofloxacin, metronidazole) in addition to an anti–tumor necrosis factor (TNF) agent (eg, infliximab, adalimumab, certolizumab pegol [Cimzia, UCB]) or anti-integrin or anti-interleukin (IL)-12/23 agent (eg, vedolizumab, ustekinumab) targeted at the underlying CD luminal inflammation is the preferred management for most simple perianal fistulas.[10] The newer anti–IL-23 agents (eg, risankizumab [Skyrizi, AbbVie]) presumably will also demonstrate efficacy for perianal fistulas. In general, antibiotics should be initiated prior to immunosuppressive therapy. Thiopurines (eg, azathioprine, 6-mercaptopurine) may be added to biologics for fistulizing CD, although the onset of action of these medications is slow. Anti-TNF agents demonstrate the most robust data for fistulizing perianal disease and are used as first-line medical therapy. Anti-integrin and anti–IL-12/23 inhibitors may be used in patients with suboptimal response to anti-TNF agents.[11-13] After induction, the biologic agent is used for maintenance therapy to reduce subsequent CD complications and maintain remission. In severe refractory cases, such as the patient in this case report, combination biologic therapy may be required. Several studies have demonstrated increased rates of fistula closure associated with higher therapeutic levels of biologics (≥10.1 µg/mL for infliximab and >9.0 µg/mL for adalimumab).[14,15]

In contrast, complex fistulas usually require multidisciplinary management with gastroenterology, colorectal surgery, and radiology. Treatment may include both medical therapies, discussed previously, as well as surgical intervention, depending on patient comorbidities, anatomic location of the fistula, and prior surgical history. Patients with a perianal abscess require drainage, and patients with a perianal fistula typically require seton

placement by colorectal surgery with EUA. Treatment response to medical and surgical management should be assessed with repeat imaging with MRI or EUS, as well as endoscopy for evaluation of mucosal healing in patients with rectal inflammation. The optimal timing of seton removal is a multidisciplinary decision based on patient symptoms, the severity of perianal CD, as well as response of luminal inflammation to medical therapy. In general, seton removal is considered after the control of mucosal inflammation, achievement of therapeutic biologic trough levels, and resolution of the local infection.[16] Additional surgical options for severe perianal fistulizing CD may include ligation of intersphincteric fistula tracts, fistulotomies, or endorectal advancement flaps.[17] Risks of surgery include fecal incontinence, especially with significant external anal sphincter involvement of disease. Lastly, for severe refractory fistulizing CD, fecal diversion or proctectomy is a surgical option.[18]

A recent systematic review and meta-analysis of 118 patients treated with HBOT for perianal fistulizing CD demonstrated clinical response and remission rates of 75% (95% CI, 66%-83%) and 55% (95% CI, 44%-65%), respectively.

Patients with refractory disease, unresponsive to the previously discussed medical and surgical management, may require other treatment modalities such as local injection of mesenchymal stem cells for a chronic nonhealing perianal fistula, or HBOT.[19,20] Studies evaluating mesenchymal stem cell therapy in perianal CD demonstrate heterogeneity in cell type used, mode of delivery, and dose.[21,22] A phase 3, double-blind, randomized controlled trial evaluating mesenchymal stem cells for perianal fistulizing CD reported clinical remission with fistula closure in 56% of patients in the treatment group compared with 40% of patients in the control group.[23] A recent systematic review and meta-analysis of 118 patients treated with HBOT for perianal fistulizing CD demonstrated clinical response and remission rates of 75% (95% CI, 66%-83%) and 55% (95% CI, 44%-65%), respectively.[24] Limitations of HBOT and stem cell therapies include lack of widespread availability except at tertiary referral centers and the absence of uniform coverage by health insurance.

Conclusion

Perianal CD presents with significant clinical heterogeneity and is associated with an increased rate of hospitalizations, diminished quality of life, and greater health care costs.[25] Initial evaluation includes a careful history and physical examination, imaging with pelvic MRI or EUS to define the fistula anatomy followed by EUA, as well as colonoscopy to assess the presence and extent of luminal disease activity and to biopsy anorectal strictures. Management requires a multidisciplinary approach with gastroenterology, colorectal surgery, and radiology. Treatment includes biologic medical therapy (eg, anti-TNF agents) to target luminal inflammation combined with surgical intervention for abscess drainage, dilation of anorectal fibrotic strictures, or seton placement for perianal fistulas when appropriate. For the subset of patients with refractory perianal CD, HBOT and local injection of mesenchymal stem cells are additional treatment options.[26] Further research is needed to determine the efficacy and safety of these novel therapies and standardize treatments.

Disclosures

Dr Tome has no relevant conflicts of interest to disclose. Dr Kane serves as a consultant to Boehringer Ingelheim, Bristol Myers Squibb, Gilead Sciences, InveniAI, Janssen, Predicta Med, Seres Therapeutics, Takeda, and TechLab. In addition, Dr Kane serves as the editor for the IBD section of UpToDate.

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