REVIEW

A review of urinary fistulae in Crohn's disease

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Introduction: Urinary fistulae develop as abnormal connections between the gastrointestinal (GI) and genitourinary (GU) tracts, and occur in multiple disease processes including diverticulitis, malignancy, and Crohn's disease. Crohn's disease is now the most common cause of fistula formation between the ileum and bladder and the third most common cause of fistulae between the colon and the bladder. Few articles provide a comprehensive review of this process.

Materials and methods: We performed a PubMed search using such terms as "fistula" and "Crohn's disease" and/or "enterovesical fistula." We reviewed references from selected papers and relevant articles were used for information-gathering and cited accordingly.

Introduction

When Crohn et al described regional ileitis in their landmark paper in 1932, they described fistula formation as a hallmark of the disease.¹ Fistulae are

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Address correspondence to Dr. Robert Jansen, One Medical Center Drive, HS 9238, Morgantown, WV 26506 USA **Results:** Fistulae in Crohn's disease generally occur due to preformed abscess formation or bowel perforation from the development of aphthous ulcers. The most common type of urinary fistula is enterovesical, due to the close proximity of the ileum and bladder dome. Computed tomography and cystoscopy are the most common diagnostic tools utilized. Surgical treatment is usually definitive; however medical treatment has been used with some success as well. **Conclusion:** Urinary fistulae represent an uncommon, yet serious problem to patients with Crohn's disease. Patient symptoms and imaging direct the practitioner to proper diagnosis, with direct visualization via cystoscopy confirming the presence of a urinary fistula. Treatment is aimed at relieving symptoms and may be medical or surgical depending on the clinical presentation.

Key Words: fistula, enterovesical fistula, Crohn's disease, fecaluria, pneumaturia

classified depending on the two structures involved. Enteroenteral, enterocutaneous, enterovaginal, enterovesicular, and other less common types of fistulae involving structures adjacent to the intestinal tract may form as a consequence of Crohn's disease. The prevalence of all types of fistula formation in Crohn's disease has been reported at 32%-35%.^{2,3} Enterovesicular fistulae first appeared in the literature in 1888⁴ but were not attributed to Crohn's disease until 1936.⁵ Crohn's disease is now the most common cause of fistula formation between the ileum and bladder and the third most common cause of fistulae between the colon and the bladder (behind diverticulitis and cancer).⁶⁷

Epidemiology

Urinary fistulae due to Crohn's disease have an incidence of 1.7%-12.3% according to multiple studies. Solem et al reviewed 15 studies of urinary fistulae in Crohn's disease, all since 1980, listing incidences of 1.7%-7.7%.⁶ Among urinary fistulae in inflammatory bowel disease, enterovesical fistulae are encountered most commonly. In 2002, Gruner et al reported eight patients with urinary system fistula formation from Crohn's disease in a 400 patient cohort, seven with an enterovesical fistula while one had a colovesical fistula, giving an overall incidence of 2%.8 More recently, a study by Yoon et al analyzed 83 patients who underwent 93 surgical procedures for Crohn'srelated fistulous disease. A total of 122 fistulae were discovered in this study group - 12 of the fistulae were enterovesical and 3 were colovesical - an overall incidence of 12.3%.9 Multiple internal fistulae may be discovered at the time of surgical treatment as well up to 60% of patients with urinary fistulae may have a concomitant ileosigmoid fistula.¹⁰

Independent of etiology, patients are typically in the sixth to eighth decade of life upon presentation;^{11,12} however with the younger presentation of Crohn's disease, development of fistulae in these patients certainly occurs at a younger age.^{8,9,13,14} In one study of 78 patients with urinary fistulae, the median age at diagnosis of Crohn's disease was 27 years (range 10 yrs-76 yrs) and the median age of development of a urinary fistula was 35 years (range 12 yrs-78 yrs); the median interval from Crohn's diagnosis to fistula diagnosis was 2.5 years (range 0-33.9 yrs).⁶ Male to female predominance is approximately 3:1 which is likely due to the protective effect of the uterus which is interposed between the colon and bladder.^{11,12,15} Some studies have shown an increased incidence in women who have undergone hysterectomies and it is suspected that elderly women with atrophic uteruses may be predisposed as well.^{3,15,16,17}

Pathophysiology

Pathogenesis of fistula formation occurs mainly via two separate mechanisms in Crohn's disease. Following adherence of the diseased bowel segment to an adjacent hollow viscous, aphthous ulcers develop and progress to transmural fissures, eventually invading the affected structures.¹⁸ Additionally, fistula can form by preformed abscesses which may locally develop and induce fistula formation. Fistulae may also occur secondary to iatrogenic causes following bowel resection for Crohn's disease, due to abscess formation or anastomotic leakage. Similar conditions such as ulcerative colitis may lead to abscess formation as well, however fistula formation is rare. As ulcerative colitis involves only the mucosa and submucosa of the colonic lining, perforation is extremely uncommon, whereas the transmural processes of Crohn's disease, diverticulitis, and cancer provide a direct mechanism for fistula formation.

Though contingent on the segment of bowel affected by disease, the most common origin of urinary fistula formation is the ileum due to its proximity to the dome of the bladder. Of the 78 patients in Solem's review, 46 (64%) had urinary fistulae originating from the ileum, 15 (21%) from the colon and 6 (8%) from the rectum; 7% suffered from multiple urinary fistulae.⁶ Although rare, potential processes also include rectovesical,^{3,17,19,20} rectourethral,^{3,21} vesicocutaneous,²² urethrocutaneous,²³⁻²⁴ ileoureteral,³ enterourachovesical,²⁵ anourethral,²⁶ and ileal pouch-vesical fistulae.²⁷

Diagnosis

Despite the fact that fistulae arise from diseased bowel, presenting symptoms are usually of a genitourinary origin, as low intravesicular pressure favors the flow of air and bowel contents into the bladder.¹¹ The most common presenting symptoms are pneumaturia, recurrent urinary tract infections (UTIs), frequency/ dysuria, and fecaluria. Pneumaturia may be seen in 50%-94% of patients, and up to 86% report recurrent UTIs.^{3,6,12,16} E. coli is the predominant infective organism, and Enterococcus faecalis, Enterobacter, Pseudomonas, and Klebsiella are also commonly isolated from urine specimens.8,28 Frequency and dysuria are associated with UTIs, and fecaluria has an incidence of 28%-78%.^{6,12} Other less common presenting symptoms include fever, abdominal pain, hematuria, urorrhea, or septicemia.3,6,12,15,17

The two tests which have the highest sensitivity and are most commonly used in diagnosing enterovesical fistulae are computed tomography and cystoscopy. Computed tomography (CT) is the most commonly used modality currently and has been cited as a useful, noninvasive diagnostic modality in detecting urinary fistulae, specifically enterovesical fistulae and has become the primary imaging modality used when enterovesicular fistula are suspected. Common findings include visualization of inflamed bowel



Figure 1. Computerized tomography showing an increased soft tissue density in the right hemipelvis with thickening of the terminal ileum.

adjacent or adherent to the bladder, or air within the urinary tract, Figure 1. Along with a sensitivity and specificity of 68.4% and 91.3% respectively,²⁹ diagnostic yield has been reported to be anywhere from 52%-80%.^{6,9,15,29} Comparing CT to other imaging modalities such as ultrasound or barium studies, Maconi et al reported similar detection rates, stipulating that increasing diagnostic accuracy would follow disease severity.²⁹ Cystoscopy is useful in not only detecting the presence of a fistula, but ruling out the rare bladder malignancy which may induce similar symptoms. Typically, an entero- or colovesical fistula appears as a fistulous opening with inflamed mucosa. As the fistula matures, bullous edema and mucosal papillomatous hyperplasia will surround the tract.¹¹ Necrotic tissue or granulation tissue may be seen adjacent to the tract as well as the presence of mucus or fecal matter in the bladder or passage of debris, pus, or air.^{11,16} In a review of 45 patients, Solem et al reported direct visualization of a fistula in 69%, feculent debris and/ or pus in 44%, and bullous edema in 29%.⁶ Diagnostic yield is as high as 82.5%;¹⁹ however, due to the chance of edema obscuring a fistulous tract, up to 50% of patients may not be diagnosed.¹¹ Performing

a fluoroscopic cystogram at the time of cystoscopy can show dye entering the gastrointestinal tract if, indeed, a fistula is present, Figure 2. Other tests which have been described in the literature include intravenous pyelography, coloring agents, charcoal, and the Bourne test. Intravenous pyelography or computed tomography with delayed-phase imaging is primarily helpful in diagnosing uretero-enteric fistulae.³ Indocyanine green can be administered orally or rectally, with a positive result obtained via colorometric urinalysis. Sou et al reported 92% accuracy using this test in patients with clinically occult fistulae.³⁰ Rectal administration of methylene blue has been studied; however, as the agent is absorbed by the rectum and excreted by the kidneys, this test is highly inaccurate. Oral charcoal has the advantage of being inexpensive and easily administered at home with subsequent urinalysis at 24 hours. Sensitivity approaches 100%; however, it does not elucidate the location of the fistula.¹¹ The Bourne test, which consists of radiographic analysis of voided urine after barium enema administration, was used prior to the implementation of CT scan with a sensitivity as high as 50% and detection of contrast in the urine with an amount as low as 0.001 mL of barium could be detected after centrifugation.³¹



Figure 2. Fluoroscopic imaging showing dye entering the cecum and ascending colon from the fistulous site in the bladder. Dye in the right renal collecting system is shown from a previous retrograde pyelogram, revealing hydronephrosis.

Treatment

There are two schools of thought pertaining to treatment of inflammatory bowel disease (IBD)-related urinary fistulae – medical therapy versus surgical therapy. Neither are curative of IBD itself, rather the goals of treatment are to induce disease remission and relieve symptoms related to the fistulae. Medical treatment against urinary fistulae may be reserved for patients who are poor surgical candidates or who have mild symptoms without evidence of urinary obstruction. Though there is sparse literature directing treatment specifically against urinary fistulae, studies involving general fistulous disease give insight into possible medical treatments. Antibiotics such as ciprofloxacin and metronidazole have been shown to be effective in remitting Crohn's disease and facilitating closure of perianal fistulae,^{32,33} one metaanalysis showed efficacy of antibiotics in reducing the number of open draining fistulae by at least 50% from baseline.³⁴ Immunoregulators such as azathioprine and 6-mercaptopurine (6-MP) have been shown to be effective in the treatment of fistulae as well. A Cochrane meta-analysis analyzing the efficacy of 6-MP and azathioprine showed a fistula closure rate of 55%, compared to 29% in placebo; however, this difference was not statistically significant.^{34,35} Despite its usefulness mainly in short intervals for Crohn's flare-ups, glucocorticoids may prove useful in the treatment of fistulae in combination with antibiotics or immunoregulators.^{6,13,36} Second-line therapies for fistulous disease include tacrolimus, infliximab, and adalimumab. Literature on the aforementioned agents is limited, and results are mixed. Tacrolimus has been shown to improve fistulous disease, but effectiveness in closing fistulae has yet to be determined.^{37,38} Though the data is limited, one randomized control trial cited a 43% improvement rate compared to 8% in the placebo group; however, no fistula closure was noted in either group.³⁷ Infliximab and adalimumab, both tumor necrosis factor alpha antagonists, have shown promise in treating enterocutaneous fistulae, thus may be useful in treatment protocols aimed at urinary fistulae.^{39,40} The case series by Teitelbaum et al put forth some evidence showing the effects of infliximab in pediatric patients with enterovesical fistulae secondary to Crohn's disease. Of the five patients followed in their series, three of the patients were able to postpone surgical intervention, with two of the five patients becoming asymptomatic after treatment with infliximab and maintenance therapy with 6-MP.41 Another case report by Game et al demonstrates resolution of enterovesicular fistula and no recurrence over 30 month follow up with

the introduction of infliximab after failure of fistula closure with management of total parenteral nutrition, aminosalicylates, prednisone, and azathioprine.⁴² Adalimumab may be efficacious in patients who have failed infliximab therapy or are infliximab-naïve.⁴³

Surgery is almost inevitable in patients with Crohn's disease; following diagnosis, almost 75% of patients will require surgery in the next 20 years.⁴⁴ While some authors argue that surgery is not necessary in cases of enterovesical fistulae,^{12,45} others argue that due to the rarity of spontaneous fistula closure and potential for septic complications, presence of an enterovesical fistula necessitates surgical intervention.^{11,46} Potential complications and indications for intervention include urosepsis, recurrent UTIs, intraabdominal abscess, bowel obstruction, acute abdomen, failure of medical therapy, and malnutrition.^{8,13} Though surgical management varies depending on the location of urinary fistulae, Crohn's-related enterovesical fistulae are treated by resection of the affected bowel with or without primary bladder repair. Once the diseased bowel segment is peeled off the bladder, the bladder may be closed with absorbable suture.^{3,8,13,46} The bladder defect may also be left open with bladder drainage^{19,47} or oversewn with an interpositional omental flap.^{19,23,48} Bowel resection can be performed in one or two stages. A one-stage procedure involves immediate bowel reanastamosis and is generally preferred due to low morbidity; a two-stage procedure, usually reserved for cases with associated abscess and severe inflammation, results in temporary fecal diversion with later closure.8,11,20 Following resection, recurrence of enterovesical fistulae are rare, with multiple studies reporting no recurrence.^{8,19,20,48} Yamamoto et al reported recurrence in 3 of 23 patients; however, all 3 had severe postoperative sepsis. Postoperative complications occur in up to 6.4% and include bowel obstruction, pelvic abscess, wound infection, urine leak, and enterocutaneous fistula.^{19,20} Fistulae occurring elsewhere in the urinary tract are generally treated surgically as well. Talamini described surgically treating patients with rectourethral fistulae, rectovesical fistulae, and ureteroileal fistulae with bowel resection and primary closure of the urinary tract. Fazio advised using a transanal rectal advancement flap in the repair of rectourethral fistulae.²¹ El Khader et al described a patient with a small ureteroileal fistula managed successfully with a temporary ureteral stent in conjunction with corticosteroid therapy.49

Conclusion

Urinary fistulae represent an uncommon, yet serious problem to patients with Crohn's disease. A wide

array of diagnostic tools is at one's disposal, with CT and cystoscopy most commonly used as well as most effective. Although surgery remains the definitive treatment for enterovesical fistula, recent advancements in medical therapy for fistula formation in Crohn's disease have allowed patients to postpone surgery for extended periods of time and allow some to avoid it indefinitely. These advancements have allowed patients that are poor surgical candidates who suffer from enterovesical fistula to remain largely asymptomatic with a significant reduction in morbidity. Though no studies have been devoted specifically to urinary fistulae, surgical and medical treatments used for fistulous disease have been successful in ameliorating symptoms and, in some cases, providing closure of fistulae.

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