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REVIEW

Spontaneous free perforation of the small intestine in adults

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Abstract

Spontaneous free perforation of the small intestine is uncommon, especially if there is no prior history of visceral trauma. However, free, even recurrent, perforation may complicate a defined and established clinical disorder, such as Crohn's disease. In addition, free perforation may be the initial clinical presentation of an occult intestinal disorder, such as a lymphoma complicating celiac disease, causing diffuse peritonitis and an acute abdomen. Initial diagnosis of the precise cause may be difficult, but now has been aided by computerized tomographic imaging. The site of perforation may be helpful in defining a cause (*e.g.*, ileal perforation in Crohn's disease, jejunal perforation in celiac disease, complicated by lymphoma or collagenous sprue). Urgent surgical intervention, however, is usually required for precise diagnosis and treatment. During evaluation, an expanding list of other possible causes should be considered, even after surgery, as subsequent management may be affected. Free perforation may not only complicate an established intestinal disorder, but also a new acute process (*e.g.*, caused by different infectious agents) or a longstanding and unrecognized disorder (*e.g.*, congenital, metabolic and vascular causes). Moreover, new endoscopic therapeutic and medical therapies, including use of emerging novel biological agents, have been complicated by intestinal perforation. Recent studies also support the hypothesis that perforation of the small intestine may be genetically-based with different mutations causing altered connective tissue structure, synthesis and repair.

Key words: Free small bowel perforation; Crohn's disease; Non-traumatic perforation; Celiac disease; Small bowel lymphoma; Vasculitis; Collagenous sprue; Biological agents; Monoclonal antibodies

Core tip: Clinical presentation with "an acute abdomen" due to spontaneous "free" perforation usually requires urgent surgical intervention for survival. Often, the clinician is aware of an underlying disorder, but in others, this emergent situation may represent the initial clinical presentation of unrecognized Crohn's disease or, even celiac disease already complicated by a superimposed lymphoma. Other rare causes include medical treatments for a variety of immune-mediated, inflammatory and neoplastic disorders, including some novel biological agents. Evidence also suggests that intestinal perforation could also reflect an occult genetically-based defect causing impaired connective tissue structure, synthesis and repair.

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INTRODUCTION

In adults, perforation of the small intestine may result from obstruction causing gangrene, strangulation of hernias and trauma (Table 1)[1]. Trauma in adults may result

Table 1 Traumatic causes of intestinal perforation

Traumatic causes
Blunt abdominal trauma (*e.g.*, bicycle handlebar injury)
Motor vehicle accident (incl. pelvic fracture)
Ingested foreign bodies (*e.g.*, fishbone, needles, safety pins, magnets)
Endoscopic studies (*e.g.*, endoscopy, ERCP, especially with papillotomy)
Surgical treatment (*e.g.*, laparotomy, especially cholecystectomy, abdominal liposuction)

ERCP: Endoscopic retrograde cholangiopancreatography.

Table 2 Causes of free perforation of the small bowel

Immune-mediated or inflammatory
Crohn's disease (CD)
Celiac disease or gluten-sensitive enteropathy (GSE)
Collagenous sprue
Graft-*vs*-host disease (GVHD)
Infections
Viral: Cytomegalovirus (CMV)
Bacteria: Salmonella paratyphi, mycobacterium tuberculosis
Parasites: Ascaris lumbricoides
Protozoa: Entameba histolytica
Drugs and biological agents
NSAIDs: Indomethacin
Enteric-coated potassium chloride
Chemotherapy (?steroids)
Monoclonal antibodies: Bevicuzimab
Congenital
Meckel's diverticulum
Jejunal or ileal duplications
Metabolic
Homocystinuria
Vascular
Wegener's granulomatosis
Giant cell arteritis
Allergic granulomatous arteritis (*i.e.*, Churg-Strauss syndrome)
Henoch-schonlein purpura
Buerger's disease
Atherosclerotic vascular occlusion
Radiation-induced vascular injury
Neoplasm
Primary (adenocarcinoma, EATCL, angiosarcoma)
Secondary (melanoma, breast, mesothelioma, lung)

NSAIDs: Non-steroidal anti-inflammatory drugs.

from blunt injuries (*e.g.*, bicycle handlebars)[2], motor vehicle accidents (especially in the presence of a pelvic fracture), ingested foreign bodies or iatrogenic injuries caused by medical and surgical procedures. Sometimes, a viscous perforation is "contained" because of a retroperitoneal location of the perforation, often with development of a "walled-off" inflammatory mass or abscess. In contrast, a "free" perforation of the small intestine usually presents clinically in a far more dramatic fashion with generalized peritonitis. Even if the usual predisposing causes are not present, urgent surgical intervention is required. Often, in this setting, a precise pre-operative diagnosis may not be possible. Clinicians involved in the care of patients with intestinal disorders, including gastroenterologists and surgeons, may need to exclude other causes of free perforation (Table 2) as further treatment may be required.

Diagnosis prior to surgical intervention may now be substantially aided by the using of modern imaging modalities, particularly computed tomography (CT)[3]. This procedure may be the procedure of choice for evaluation of a suspected perforation, especially since CT imaging has been demonstrated to be accurate in defining a possible site of the perforation.

A number of causes of intestinal perforation have been described. These include immune-mediated, infectious- or medication-related, congenital, metabolic, vascular or neoplastic causes.

IMMUNE-MEDIATED CAUSES

Crohn's disease

Crohn's disease (CD) is typically characterized by a progressive transmural intestinal inflammatory process. As a result, deep ulcers, often associated with abscess formation may develop, as well as single or complex fistulous tracts that often penetrate into the adjacent, usually adherent, intestinal and non-intestinal structures (*e.g.*, bladder), or both. Free spontaneous perforation into the peritoneal cavity is a dramatic event. Fortunately, this complication in the setting of CD is quite rare, but usually requires urgent surgical treatment.

Free perforation in CD was initially described in 1935 as a fatal case of free perforation in ileum[4]. Subsequently, about 100 cases have appeared in the literature. Differing criteria for clinical definition of a free perforation have been noted by some investigators[5,6] as some earlier reports may have included patients with sealed perforations or ruptured abscesses. Studies in large clinical series of patients followed over prolonged periods from both North America and the United Kingdom have confirmed that this complication remains an uncommon, even rare clinical event in CD, consistently estimated to be less than 2%[5-7]. Possibly, this complication is genetically-based as a higher rate of free perforation has been reported in Japanese diagnosed with CD[8]. In contrast, no statistical differences in the incidence of perforation were detected in a comparative study of American and Chinese patients with CD[9].

Interestingly, free perforation may also represent the initial presenting clinical feature of CD[7]. Most small intestinal perforations in CD develop in the ileum[5,7]. Rarely, however, other more proximal sites, such as the jejunum, may be involved[5,7]. Finally, concomitant jejunal and ileal perforations or recurrent and independent perforations during the long-term clinical course of CD may develop[7]. Rather than a specific site-related propensity to develop spontaneous free perforation in CD (*i.e.*, possibly related to the thin wall thickness of the ileum compared to the jejunum), the proportion of jejunal and ileal perforations more likely reflects the overall site distribution of disease involvement within the small intestine (*i.e.*, ileum more than proximal small intestine). Although earlier studies suggested that this subgroup of patients with this CD complication likely have a more protracted long-term clinical course, recent studies have shown that a relatively benign course can be anticipated

with no requirement for ongoing immunosuppression, including corticosteroids[7]. In addition to the inflammatory process *per se*, other disease-related or treatment-related factors may play a role in perforation in CD. Disease-related factors may be either benign or malignant. For example, enterolithiasis may occur rarely in CD[10] and has been recorded as a cause of perforation[11]. Malignant adenocarcinoma or lymphoma may complicate CD and present with small bowel perforation[12]. Application of investigative and therapeutic endoscopic methods in patients with CD may be complicated by perforation. For example, use of wireless capsule and double-balloon endoscopic evaluations may cause small intestinal perforation in CD[13] while perforation has also been recorded after therapeutic balloon dilation of inflammatory and fibrous strictures[14]. In addition, adverse events, including fatal intestinal perforation, have been recorded in CD treated with different medications, including different emerging biological monoclonal antibody agents[15-17].

CELIAC DISEASE OR GLUTEN-SENSITIVE ENTEROPATHY

Glute-sensitive enteropathy (GSE) is an immune-mediated disorder that causes histopathological changes in the small intestine that respond to treatment with a gluten-free diet. Malignant disease, usually lymphoma, may be the presenting clinical feature of un-recognized GSE as well as it's closely allied disorder, dermatitis herpetiformis[18], or alternatively, malignant lymphoma may complicate the long-term clinical course of GSE[19]. Ulceration in the small bowel may also occur, although ulceration in this setting may be actually due to a difficult-to-diagnose intestinal lymphoma rather than so-called benign non-granulomatous ulcerative jejunoileitis[18]. Rarely, ulceration with free perforation may occur in celiac or sprue-like intestinal disease[20]. In most, the site of perforation was the jejunum, other more distal intestinal sites, including the colon, was involved with a perforating lymphoma[20]. In some, a gluten-free diet response was also documented, however, perforation with lymphoma was also detected in refractory GSE after a gluten-free diet response had been defined[20]. In others, rapid clinical deterioration from a perforated lymphoma prohibited precise diagnosis of GSE and evidence for improvement on a gluten-free diet could not be documented[20]. In all, however, free perforation caused by the superimposed or associated lymphoma had a high mortality[20]. In this clinical setting, the appearance of lymphoma was not predictable and could occur, despite strict compliance to a gluten-free diet[20].

COLLAGENOUS SPRUE

Another disorder, collagenous sprue, has been reported to complicate GSE[21]. This disorder is characterized by a pathologically distinctive lesion in the small intestinal mucosa characterized by a patchy or diffusely thickened sub-epithelial collagen band in flattened small intestine[22]. This histopathological marker is usually associated with the appearance of sloughed epithelial cells in the intestinal lumen and protein-losing enteropathy may occur[22]. Lymphoma associated with or complicating collagenous sprue has also been described, often but not exclusively, in an advanced state with extensive lymphoma[23-25]. Finally, collagenous sprue may result in free small intestinal perforation without clear histopathological evidence of a frank lymphoma[26].

INTESTINAL GRAFT-*VS*-HOST DISEASE

Acute intestinal graft-*vs*-host disease (GVHD) involving the intestinal tract has been estimated in an Italian study to occur in approximately 30%-50% of allogenic bone-marrow transplant recipients: 10%-20% have emergent events, including perforation associated with a very high mortality[27]. After stem-cell transplantation, intestinal perforation has also been recorded with thrombotic microangiopathy[28] and post-transplant lymphoproliferative disorder[29]. Of note, after bone marrow or hematopoietic stem cell transplantation and subsequent development of GVHD, free air appearing within the peritoneal cavity, caused by pneumatosis cystoides intestinalis, has also been reported to mimic an intestinal perforation[30,31].

INFECTIOUS CAUSES

Cytomegalovirus

Cytomegalovirus (CMV) has been recorded as a cause of perforation in several reports, usually in immunologically compromised individuals. An isolated ileal perforation associated with CMV was noted in a 31-year-old female with lupus enteritis[32]. She required emergency laparotomy, resection and ganciclovir therapy. In a separate report, 2 patients receiving chemotherapy for non-Hodgkin's lymphoma developed an occlusive vasculitis with small intestinal perforations thought be due to a superimposed CMV infection[33]. Multiple small bowel perforations due to CMV infection have also been recorded in patients with the acquired immunodeficiency syndrome[34].

Other infections

A host of other bacterial, parasitic and protozoan infectious agents may also cause small bowel perforation. Some include enteric pathogens (*e.g.*, salmonella[35]). Another bacterial agent, Tropheryma whipplei, the recognized agent that causes Whipple's disease, may be indirectly involved in the development of intestinal perforation. In about 10% of successfully treated patients, inflammation reappears after the initial improvement. In some of these, however, polymerase chain reaction for the organism is negative during this "re-inflammation" phase. This had been labeled IRIS or the "immune reconstitution inflammatory syndrome" and may respond

to corticosteroids, rather than antimicrobials. Rarely, this unusual syndrome has been reported to be complicated by small intestinal perforation[36]. Other bacterial agents, including tuberculosis, have become increasingly recognized as a cause, especially with rising incidence of human immunodeficiency virus (HIV)[37]. Occasionally, free perforation may occur, even during anti-tuberculous therapy for extra-pulmonary tuberculosis[38]. Unfortunately, even with surgical treatment, however, mortality may still result[39].

Small intestinal perforations have also been recorded with fungal infections (*e.g.*, histoplasmosis[40]), parasitic infections (*e.g.*, roundworm[41]) and infections with protozoan agents (*e.g.*, *Entamoeba histolytica*[42]). Usually, with amebiasis, deep necrotizing ulcers occur in the colon, but in at least one report[42], small intestinal ulceration with a free perforation was documented.

MEDICATION-RELATED CAUSES

Ulceration and, less commonly, perforation in the small intestine may occur with a number of medications[43,44]. Often, these may be provided for a concomitant or a related disorder. For example, non-steroidal anti-inflammatory drugs (NSAIDs)[45] are often used in patients with ankylosing spondylitis or other arthropathy associated with inflammatory bowel disease. Sometimes, these agents have been associated with a wide range of small intestinal pathological changes, including ulceration and stricture formation that, in some instances, may be even difficult to distinguish from an underlying intestinal disorder, such as CD. Enteric-coated potassium chloride has been associated with small intestinal ulcerations and perforation, even with slow release forms[46-48]. Antineoplastic and immunosuppressive agents as well as radiation have been recognized for decades to cause small intestinal mucosal as well as colonic injury during treatment for malignant disorders[49-51]. Neutropenic enterocolitis is a well recognized clinical syndrome associated with disease-induced or chemotherapy-induced neutropenia and this entity may be complicated by hemorrhage and perforation[52]. Co-administration of other medications, such as corticosteroids, have also been implicated in intestinal perforation[53,54]. Some agents, such as methotrexate[55], may also cause mucosal flattening associated with a reduced mitotic index (different from the increased mitotic index in celiac disease), possibly related to folate depletion. Treatment with some newer or more novel chemotherapeutic agents has also been complicated with small intestinal perforation. Combination chemotherapy with etoposide and cisplatin was associated with small bowel perforation in a patient with extrapulmonary small-cell carcinoma of the small bowel[56]. Gefitinib, an epidermal growth factor receptor tyrosine kinase inhibitor, was used to treat an elderly female with non-small cell lung cancer and she developed an ileal perforation during the acute phase of irradiation[57]. A female with metastatic non-small cell lung cancer developed a bowel perforation with enterocutaneous fistula after treatment with erlotinib[58].

In recent years, reports of intestinal perforation associated with some emerging monoclonal antibody agents have also appeared. Bevacizumab, an inhibitor of vascular endothelial growth factor, has been used in the treatment of metastatic malignancies, particularly colon, ovary and non-small cell carcinoma of the lung. A few reports of intestinal perforation were recorded[59-61] followed by a recent estimate of 3% perforation rate in a series of bevacizumab-treated patients with non-squamous non-small cell lung cancer[62]. Another biological agent, interleukin-2 (IL-2) used in high dose resulted in remission in some patients with metastatic melanoma and renal cell carcinoma with about half of these experiencing complete remission. In a large National Cancer Institute series from Bethesda, intestinal perforation was recorded in 0.44% of almost 1800 treated patients[63]. Ipilimumab, a monoclonal antibody to cytotoxic T-lymphocyte-associated antigen 4, used in treatment of metastatic melanoma may induce a severe enterocolitis. Rarely, perforation of this enterocolitis has been reported[64]. A risk of perforation was also noted in patients receiving IL-2 after therapy with ipilimumab[65]. In addition, rituximab, a novel monoclonal antibody agent used as a therapeutic option to deplete B-lymphocyte populations, was used to reportedly treat multiple distal ileal perforations in a patient with Wegener's granulomatosis[66]. A number of reports, noted above, have also recorded rare cases of free perforation in CD following anti-tumor necrosis factor (TNF) monoclonal antibody treatment[15-17]. Cases treated with either infliximab or adalimumab have been documented[15-17]. In one patient, free perforation developed after the initial dose of infliximab[16]. In another treated with adalimumab, an ileal perforation was reported to be fatal[17]. In a case-control study from Amsterdam, a higher occurrence of free perforation in CD treated with TNF was evident compared to CD not treated with TNF[15].

MALIGNANT CAUSES

As noted earlier, malignant small intestinal disorders may complicate celiac disease and present with free perforation. Most have been defined as T-cell type lymphomas or enteropathy-associated T-cell lymphomas[18-20]. Other types include adenocarcinomas and carcinoid tumors[67]. A number of very rare primary malignancies may also affect the small bowel. Angiosarcoma, for example, has been reported to even initially present with a small bowel perforation, especially in the elderly[68]. Additional multicenter reports of enteropathy-associated T-cell lymphoma by an Asia Lymphoma Study Group also estimated that bowel perforation was a common presenting feature, about 34%[69]. Of 1062 patients reported from the Mayo Clinic with lymphoma involving the gastrointestinal tract, 9% developed a perforation. More than half, or 55%, developed a perforation after

chemotherapy was initiated and large B-cell lymphomas were the most common type associated with perforation, estimated to be almost 60%[70]. In Chinese patients with primary small intestinal lymphomas from Taiwan, perforation was a common presenting clinical feature, particularly in diffuse large-cell and immunoblastic lymphomas, estimated at 23%[71]. A further study of lymphoma in Chinese from Beijing revealed primary intestinal T-cell and NK-cell lymphomas were heterogeneous but not usually associated with celiac disease[72]. Instead, most were NK-cell type with a poor prognosis showing molecular evidence for a prior Epstein-Barr virus infection[73].

The small intestine may also perforate due to involvement with a secondary rather than primary malignancy, or metastatic disease, usually from an extra-abdominal site, including lymphoma[74]. Often, metastatic tumors in the ileocecal region appear to have been developed through a hematogenous route from the primary lesion[75]. Other extra-intestinal causes of metastatic disease causing small intestinal perforation recently noted include rhabdomyosarcoma[73], squamous cell carcinoma from the tongue[75], breast carcinoma[76], lung cancer[73] and pleural mesothelioma[77]. Cutaneous malignant melanoma has also been reported to cause intestinal perforation, even after years of apparently tumor-free follow-up[78].

MISCELLANEOUS CAUSES

Congenital diverticulae in the small intestine may present or be complicated with an intestinal perforation. These include perforated Meckel's diverticulae[79] as well as jejunal[80] and ileal duplications[81]. These may be isolated congenital diverticulae that initially only appear for the first time in the elderly[82]. Interestingly, in several independent reports, gastrointestinal stromal tumors (GISTs) complicated the diverticulum or duplication and were responsible for a superimposed focal intestinal perforation[79-81].

A number of unusual mesenteric vascular causes have been described as a cause of small intestinal perforation. Some include: giant cell arteritis, even as an isolated form of the disease[83], Churg-Strauss syndrome (or allergic granulomatous angiitis)[84-86] and other forms of eosinophilic enteritis[87,88], Wegener's granulomatosis characterized by a necrotizing vasculitis with granulomatous changes of the upper and lower respiratory tract and associated glomerulonephritis[89,90] and Buerger's disease involving multiple sites within the small intestine[91].

Finally, an intriguing patient with a concomitant metabolic disorder has been recorded with spontaneous small intestinal perforation[92]. In an adult with documented homocystinuria, spontaneous jejunal perforation presented emergently and efforts were made to exclude all known other causes of perforation. The investigators hypothesized that connective tissue weakness in homocystinuria may be due to homocysteine interference with recombinant human fibrillin-1 fragments or cross-linking of collagen through permanent degradation of disulfide bridges and lysine amino acid residues in proteins. DNA analysis showed three mutations in the cystathionine beta-synthetase gene, including two new mutations. This particular case may have special significance because it raises the possibility that other cases, even those with an apparent well-defined cause, may have an underlying genetically-based predisposition to intestinal perforation, possibly due to a mutation causing impaired connective tissue structure, synthesis or repair.

CONCLUSION

A diverse group of causes of small intestinal perforation have now been recorded in the literature and the list of possible causes is slowly increasing. Once traumatic and some of the more common causes have been excluded, clinical attention may be focused on other small intestinal disorders, such as CD and GSE, that may be initially presenting with peritonitis and an acute abdomen. Urgent surgical intervention will most often be needed, however, consideration to other rare causes may help in subsequent management, especially if the cause is not immediately apparent during initial urgent diagnostic evaluation or following surgical treatment.

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