Bowel Perforation Resulting in Necrotizing Soft-Tissue Infection of the Abdomen, Flank, and Lower Extremities

Disha Kumar,¹ Nicolás W. Cortés-Penfield,² Hanine El-Haddad,^{2,3} and Daniel M. Musher^{2,4}

Abstract

Background: Fournier's gangrene is a necrotizing soft-tissue infection (NSTI) that often originates from a break in bowel integrity and affects the perineum, anus, or genitalia. Although the pathogenesis is similar, NSTI caused by a break in bowel integrity less commonly presents as infection of other sites.

Objective: To characterize NSTIs originating from bowel perforation and presenting as infection of the abdominal wall, flank, or thigh but that largely spare the perineum, anus, and genitalia.

Methods: We describe a characteristic case and summarize findings from 67 reported cases.

Results: The causes of bowel injury included trauma (29%), perforated appendicitis (23%), perforated diverticulitis (16%), and perforation of a gastrointestinal tract cancer (16%). The symptomatic prodrome is indolent and nondescript. Most patients have polymicrobial infections and require antibiotic therapy combined with serial surgical debridements. Because the presentation differs from that of typical Fournier's gangrene, recognition of NSTI was delayed in the reported cases, and the associated bowel perforation often was overlooked, leading to delayed surgical treatment. As a result, the mortality rate was >33%, far exceeding that of typical Fournier's gangrene. Delays in diagnosis or surgical intervention predict a poor outcome.

Conclusions: An NSTI resulting from bowel perforation can present in an atypical fashion carrying significant morbidity and mortality rates. Delayed diagnosis and treatment of this condition is associated with a poor outcome.

Keywords: bowel injury; bowel perforation; Fournier's gangrene; necrotizing fasciitis; necrotizing soft-tissue infection

INFECTIONS that compromise the vascular supply and cause necrosis of skin, subcutaneous tissue, fascia, and muscle are known broadly as necrotizing soft-tissue infections (NSTIs) [1–10]. Such infections of the male genitalia were first described by Fournier in 1883, and the entity was named eponymously [11,12]. Later investigators extended the definition of Fournier's gangrene (FG) to NSTI involving the perineum, anus, genitalia, or some combination [13,14]. The pathogenesis in most cases of FG involves escape of bowel flora as a result of perforation or translocation of the bowel wall, followed by spread through soft tissues and along fascial planes [3,4,10,11,15]. Thus, FG usually is polymicrobial, with enteric gram-negative bacilli and anaerobic bacteria predominating. In a proportion of cases, infection is caused by groupable streptococci or *Staphylococcus aureus*.

These cases may emanate from the bowel; however, invasion of the skin and soft tissues also may result from recognized or unrecognized breaks in the skin [15,17–19].

Fournier's gangrene most frequently affects men aged 50 to 60 years, many of whom have diabetes mellitus. Fournier's gangrene has been associated with colorectal disease, genitourinary disease, and trauma [20]. These infections evolve rapidly, are invasive, and have a high mortality rate. Early recognition and surgical intervention are essential determinants of the outcome; delays exceeding 24 hours from the time of hospital admission to surgery have been associated with a greater than nine-fold increase in the relative risk of death [1]. Troublingly, in a recent review of NSTI cases, the disease was misdiagnosed initially in >70% of patients, and the overall mortality rate exceeded 20%—no better than the

¹School of Medicine, Baylor College of Medicine, Houston, Texas.

²Section of Infectious Diseases, Department of Medicine, Baylor College of Medicine, Houston, Texas.

³Division of Infectious Diseases, University of Kentucky College of Medicine, Lexington, Kentucky.

⁴Medical Care Line, Section of Infectious Diseases, Michael E. DeBakey Veterans Affairs Medical Center, Houston, Texas.

rate of death reported in Meleney's first manuscript characterizing NSTI almost a century ago [2,16].

Whereas NSTI of the perineum, anus or genitalia—typical FG—is a well-characterized entity, infection resulting from a break in bowel integrity may spread instead through other soft tissues and along fascial planes and present as NSTI of the abdominal wall, flank, or thigh. The pathogenesis of these infections is similar to that of FG; however, they may spare the perineum, anus, and genitalia. This atypical presentation may cause delayed recognition and treatment, resulting in a mortality rate greater than that in FG [21].

In this paper, we examine cases of NSTI resulting from a bowel perforation that involved primarily areas other than those described for FG and that were not characterized as typical FG. Previous case reports and small case series have described 67 cases of NSTIs of the abdominal wall, flank, and lower extremities in the context of bowel injury. The present article adds an additional case to the literature and reviews previously published cases to describe this entity more clearly.

Case Presentation

A 58-year old previously healthy man presented to the emergency department with excruciating pain in the back and the left upper leg. He had come in four days previously with a one-week history of back pain radiating to the left leg associated with fecal incontinence, intermittent loose bloody stools, and urinary urgency, which had become complicated by numbness and weakness in the leg in the prior few days. He denied fever or chills. During the initial encounter, he did not appear acutely ill; his vital signs were normal, and rectal examination did not reveal blood. His hemoglobin concentration was 7.14 mmol/L (11.5 g/dL), the white blood cell (WBC) count was $26 \times 10^9/L$, urinalysis showed pyuria, and magnetic resonance imaging of the patient's spine was normal. He was discharged with a diagnosis of urinary tract infection and a prescription for oral cefpodoxime.

Over the next four days, his symptoms did not improve, and on the day of admission, his back and leg pain had worsened acutely. He did not have any history of diabetes, cancer, inflammatory bowel disease, or diverticulosis. On the second admission, he appeared acutely ill and was hypotensive. His left leg was tender and had crepitus extending from the left hip to the knee. His abdomen was not tender, and the genitalia were normal. He had the following laboratory results: hemoglobin 5.52 mmol/L (8.9 g/dL), WBC count 12.1×10^9 cells/L, serum sodium concentration 132 mmol/L, serum lactic acid concentration 7.1 mmol/L, serum glucose concentration 10.99 mmol/L (198 mg/dL), serum creatinine concentration 205.88 μ mol/L (2.7 mg/dL), and serum albumin concentration 14.0 g/L (1.4 g/dL). Computed tomography (CT) demonstrated extensive subcutaneous gas extending from the left lower pelvis to the left buttock and thigh and an enhancing fistulous tract from the rectum into an inflammatory fluid collection on the left side of the pelvis.

The patient was started on an antibiotic regimen of cefepime, vancomycin, and metronidazole. He was taken promptly to surgery, where he underwent extensive debridement of necrotic tissue in the left leg and pelvis and drainage of a large pelvic abscess; a toothpick was found perforating the rectal wall. Surgical cultures yielded two strains of *Escherichia coli*, non-groupable β -hemolytic streptococci,

and *Prevotella loescheii*. The patient required diverting colostomy, disarticulation of the left hip, six further operative debridements of the pelvis, and an extended course of ceftriaxone and clindamycin. He eventually survived.

Methods

Study design

We searched the English-language literature via PubMed for case reports and case series describing NSTIs primarily involving the abdominal wall, flank, or lower extremities with evidence of bowel perforation. Search terms included “necrotizing fasciitis” or “necrotising fasciitis” and “bowel” or “perforation.” Articles available as full text in PubMed Central, ResearchGate, or our institution's library were included in the final analysis; to these, we added the case presented above. We excluded cases that were identified as FG by the article authors, as well as cases in which there was no evidence of bowel perforation.

Outcomes

Extracted data included the initial history and physical examination findings, laboratory values, diagnosis, management, and outcome of the NSTI.

Analysis

We conducted descriptive and statistical analyses in Microsoft Excel, with p values calculated using the Fisher exact and Wilcoxon rank sum tests. P values <0.05 were considered significant.

Results

Epidemiology and clinical presentation

Sixty-four reports described 68 cases of NSTIs resulting from bowel perforation, including our own (see Supplemental File 1 for references). Thirty-one patients (46%) were female, and the median age was 62 years (range 26–89 years). Table 1 summarizes the anatomic location of the NSTI, predisposing risk factors, the nature of the bowel trauma, presenting symptoms, and initial physical examination findings.

Among patients with NSTIs resulting from bowel perforation, the most common sites of the presenting infection were the thigh and lower extremity (n = 34; 50%), abdominal wall (n = 29; 43%), and flank/retroperitoneum (n = 22; 32%); the total exceeds 100% because multiple areas often were involved. In five cases (7%), involvement of the perineum and scrotum was noted also, although the primary site was the abdominal wall, flank, or lower extremity; and the authors in these cases had not diagnosed FG. Common causes of bowel injury were iatrogenic or surgical trauma (n = 20; 29%), perforated appendicitis (n = 15; 23%), perforated diverticulitis (n = 11; 16%), and perforation of malignant disease involving the gastrointestinal tract (n = 11; 16%). Three patients (4%) with NSTIs had bowel perforation attributable to inflammatory bowel disease. Underlying medical co-morbidities that might have predisposed to NSTIs included diabetes mellitus in 7 patients (10%), malignant disease in 21 patients (31%), chronic corticosteroid use in 7 patients (10%), and use of bevacizumab in 2 patients (3%). Also, NSTIs followed chemotherapy in

TABLE 1. CHARACTERISTICS OF 68 PATIENTS WITH NECROTIZING SOFT-TISSUE INFECTION RESULTING FROM BOWEL PERFORATION

	No. patients (%)
Anatomic locations of involvement	
Thigh or lower extremity	34 (50)
Abdominal wall	29 (43)
Flank or retroperitoneum	22 (32)
Other	5 (7)
Medical co-morbidities	
Malignant disease	21 (31)
Previously diagnosed diverticular disease	9 (13)
Diabetes mellitus	7 (10)
Recent abdominal surgery	5 (7)
Inflammatory bowel disease	3 (4)
Chronic renal disease	2 (3)
Chronic liver disease	2 (3)
Etiology of bowel perforation	
Trauma (iatrogenic or foreign body)	20 (29)
Perforated appendicitis	15 (23)
Perforated malignancy	11 (16)
Perforated diverticulitis	11 (16)
Fistula	4 (6)
Other	7 (10)
Presenting symptoms	
Pain	64 (94)
Fever	37 (54)
Diarrhea	14 (21)
Nausea/vomiting	11 (16)
Altered mentation	10 (15)
Physical examination findings	
Tachycardia	31 (46)
Abdominal tenderness	27 (40)
Erythema	26 (38)
Crepitus	19 (28)
Hypotension	19 (28)
Peritoneal signs	11 (16)
Tachypnea	10 (15)

three cases (4%), radiotherapy in three cases (4%), and combined chemotherapy and radiotherapy in two cases (3%).

The initial presenting symptoms and physical findings were largely nonspecific. Patients reported a median of six days of symptoms before presenting to a healthcare provider (range 1–90 days). The most common presenting symptoms were pain (n=64; 94%) and fever (n=37; 54%). A minority of reports commented on the presence of diarrhea, nausea and vomiting, or altered mentation; when mentioned, each symptom was present about half the time (n=22; 50%; n=18; 61%; and n=23; 43%). The most common reported abnormalities on physical examination were tachycardia (n=31; 46%), hypotension (n=19; 28%), abdominal tenderness (n=27; 40%), local erythema (n=26; 38%), and crepitus (n=19; 28%). Signs of peritonitis were documented in only 11 patients (16%).

Laboratory testing and imaging

Laboratory data were reported inconsistently; results are presented as a proportion of cases in which data were avail-

able. Leukocytosis was observed in 76% of patients and leukopenia in 13% (n=55). The median WBC count was 19.45×10^9 cells/L (mean 20.344×10^9 cells/L; range 0.2 – 54.4×10^9 cells/L; n=48). Anemia was present in 70% (n=20) and hyponatremia in 56% of patients (n=9). Serum glucose concentrations were uniformly elevated in the eight cases in which these values were reported. C-reactive protein was elevated 96% of the time (n=25).

Fifty-one case reports included the results of tissue or blood cultures or both. Polymicrobial infections predominated (84% of patients). Gram-negative bacilli were isolated most frequently (n=43; 84%), followed by gram-positive organisms (n=35; 69%), obligate anaerobes (n=24; 47%), and *Candida* (n=4; 8%). The most common organisms isolated were *E. coli* (50%), *Enterococcus* spp. (22%), *Bacteroides* spp. (23%), and *Pseudomonas aeruginosa* (19%). Of the eight monomicrobial infections, three were caused by *Streptococcus* spp. (one Group G, one unspecified β -hemolytic streptococcus, and one *S. milleri* group) and one case each of *Pediococcus pentasaceus*, *Hemophilus influenzae*, *E. coli*, *Klebsiella pneumoniae*, and *Bacteroides thetaiotamicron*.

Plain radiography, described in 31 cases, showed subcutaneous gas in 22 (71%), bowel distention or ileus in three cases (10%), and no abnormalities in six cases (19%). Five of these six patients with no abnormalities on radiography had a subsequent CT scan that showed evidence of NSTI; the sixth patient was taken to surgery on the basis of clinical suspicion. Results of ultrasound examination were reported in seven cases. Abscess with or without subcutaneous gas was detected in three cases (43%), edema in one case (14%), and no evidence of NSTI in three cases (43%). Of the three patients with a normal scan, subsequent CT diagnosed NSTI in one; the other two were taken to surgery on the basis of clinical suspicion. The CT results were reported in 43 cases, revealing evidence of NSTI in 42 (98%), with findings of subcutaneous gas in 35 (81%) and abscess in 24 cases (56%). The one patient in whom CT failed to detect NSTI underwent surgical exploration that confirmed the clinical suspicion of NSTI.

Treatment

Sixty-six patients (97%) underwent surgical debridement; of these, 38 (56%) required more than two debridements. The case reports specifying the number of debridements reported a mean of 2.5 (n=57; median 2, range 1–20). Two patients did not undergo surgical debridement. Surgery was recommended for both; however, either the patient or the medical decision-maker declined, and both patients died. Of the 20 cases for which the length of the hospital stay was reported, the mean was 45 days (median 35 days; range 11–112 days). There were 37 cases reporting which antibiotics were given to the patient. The average number of antibiotic classes given during a patient's hospital stay was 2.7, with 97% of the antibiotic regimens (n=36) including anaerobic coverage. Among these cases, the most frequently used antibiotic classes were metronidazole (n=20), penicillins (n=15), aminoglycosides (n=13), clindamycin (n=13), carbapenems (n=10), cephalosporins (n=9), and glycopeptides (n=8).

Twenty-eight (42%) of the case reports described a missed opportunity for early diagnosis and management of the disease (Table 2), which we defined as a delay of more than 12 hours from presentation to initial debridement. The most common

TABLE 2. MISSED OPPORTUNITIES IN THE DIAGNOSIS AND MANAGEMENT OF NECROTIZING SOFT-TISSUE INFECTIONS RESULTING FROM BOWEL PERFORATION (N=28)

<i>Missed opportunities</i>	<i>No. of patients (%)</i>
Delay from admission to debridement ^a	9 (32)
Initial misdiagnosis of infection as limited to skin and soft tissues	6 (21)
Initial misdiagnosis of systemic infection not requiring surgical management	5 (18)
Initial misdiagnosis of noninfectious condition (i.e., venous thromboembolism, renal colic)	8 (29)

^aDelay from admission to debridement defined as >12 h.

forms of missed opportunity were delay in surgery after admission (n=9), initial diagnosis of limited skin and soft tissue infections not requiring surgical management (n=6), initial diagnosis of a systemic infection not requiring surgical management (n=5), and initial diagnosis of a non-infectious condition such as venous thromboembolism or renal colic (n=8). The mortality rate was higher among patients with a missed opportunity than in those without (13 fatalities among 27 patients [48%] with vs. 10 fatalities among 39 patients [26%] without missed opportunities; $p=0.07$), particularly in those who had a delay in surgery (six fatalities among eight patients with a delay in surgery [75%] vs. 17 fatalities among 58 patients with timely surgery [29%]; $p=0.02$).

Twenty-three of the 68 patients (34%) died. Survivors and non-survivors were similar in age (62 vs. 58 years; $p=0.48$) and in most clinical characteristics (Table 3). Survivors were more likely than non-survivors to have had at least 72 hours of symptoms prior to presentation (95% vs. 72%; $p=0.03$) and were more likely to present with erythema (49% vs. 9%; $p=0.001$). Whereas mean WBC counts tended to be higher among survivors than non-survivors (21.53×10^9 cells/L vs. 6.82×10^9 cells/L; $p=0.165$), there were no significant differences between these groups in the incidence of leukocytosis (WBC $>10.0 \times 10^9$ cells/L) or leukopenia (WBC $<3 \times 10^9$ cells/L).

Discussion

In the present case series, we describe NSTI of the abdominal wall, flank, or lower extremities that generally spares the anus, genitalia, and perineum but occurs in association with recognized bowel perforation. This clinical syndrome might be regarded as an atypical presentation of FG, but it appears to be epidemiologically distinct from typical FG and carries a higher burden of mortality and morbidity. Compared, for example, with the cohort of 80 patients with FG described by Eskitascioglu et al. [20], our patients had a greater proportion of women (46% vs. 5%; $p<0.001$), a lower proportion of patients with diabetes mellitus (10% vs. 43%; $p<0.001$), and a greater proportion of patients with a history of malignant disease (31% vs. 4%; $p<0.001$). The mortality rate was significantly higher in patients in our case series (34% vs. 4%; $p<0.001$) [20] and

was higher than the 16% rate reported in a review of more than 1,700 cases of FG [11].

We hypothesize that the higher mortality rate in this case series was attributable to the atypical presentation of NSTI. Physicians are well-trained to recognize FG and therefore to consider NSTI and a possible break in bowel integrity in patients who present with severe and progressive cellulitis of the perineum. In contrast, cellulitis presenting in the abdominal wall, flank, or thigh may be less likely to lead to consideration of NSTI and to consideration of a possible bowel injury. These factors might explain the frequent delays in definitive surgical treatment of NSTI resulting from bowel injury and the high associated mortality rate when the presentation is not that of typical FG.

Common risk factors identified in our series were gastrointestinal malignant disease, diverticular disease, diabetes mellitus, recent abdominal surgery, inflammatory bowel disease, and the use of corticosteroids or other immunosuppressive drugs. The etiologies of bowel perforation and resulting NSTI were diverse, although traumatic (including iatrogenic) injuries and perforation secondary to appendicitis, diverticulitis, and gastrointestinal malignant disease occurred most commonly. Two patients in this case series developed NSTI while receiving bevacizumab, which is associated with a higher risk of bowel perforation [22–25]. The overall incidence of NSTI among patients with these risk factors certainly is low. However, given the relatively high proportion of our patients with a history of malignant disease (31%) and recent abdominal surgery (7%), providers should consider NSTI in patients with these co-morbid conditions who present with severe abdominal pain and fever.

The initial symptoms and physical findings of NSTI were nonspecific, hindering timely diagnosis. The course of the disease was surprisingly indolent, with patients reporting a mean of 14 days from the onset of symptoms to the time they sought medical care. Interestingly, survivors were more likely than non-survivors to have had at least 72 hours of symptoms prior to presentation (95% vs. 72%; $p=0.03$) and were more likely to present with erythema (49% vs. 9%; $p=0.001$). Survivors may have had a more indolent and thus less life-threatening form of NSTI; alternatively, survivors may have presented for care in an earlier stage of disease. Importantly, peritoneal signs were reported in only 16% of all cases, showing that the absence of peritonitis in no way opposes the clinical diagnosis of NSTI.

The limitations of our analysis include inconsistent reporting of clinical variables in case reports. As the authors of each case report included data they deemed to be relevant, our study may overestimate or underestimate the true rates of presenting symptoms, examination findings, and abnormal laboratory values within the case series. Moreover, there presumably were cases that were not reported. In addition, our retrospective literature review included cases published over more than four decades (1975–2017). Thus, improvements in early diagnosis of intra-abdominal pathology (e.g., with the adoption of CT) and advances in medical care of the critically ill patient may have led our analysis to overestimate the mortality rate of this condition in the present day.

Conclusions

Necrotizing soft-tissue infections of the abdominal wall, flank, or lower extremities may result from a break in bowel

TABLE 3. CHARACTERISTICS OF SURVIVORS VS NON-SURVIVORS OF NECROTIZING SOFT-TISSUE INFECTIONS RESULTING FROM BOWEL PERFORATION^a

	Percent among Survivors	Percent among Non-Survivors	P Value
Clinical characteristics			
Male gender	53	57	NS
Malignant disease	31	30	NS
Diverticular disease	13	13	NS
Diabetes mellitus	9	13	NS
Recent abdominal surgery	7	9	NS
Inflammatory bowel disease	7	0	NS
Chronic renal disease	2	4	NS
Chronic liver disease	2	4	NS
Potential cause of bowel perforation			
Trauma (iatrogenic or foreign body)	26	26	NS
Perforated appendicitis	22	17	NS
Perforated malignancy	18	22	NS
Perforated diverticulitis	17	13	NS
Other	15	22	NS
Presenting symptoms			
Pain (N=44 and N=20)	100	100	NS
Fever (N=39 and N=18)	67	61	NS
Diarrhea (N=16 and N=10)	56	20	NS
Nausea/vomiting (N=9 and N=9)	67	56	NS
Altered mentation (N=12 and N=11)	25	64	NS
At least 72 h of symptoms prior to presentation (N=37 and N=18)	95	72	0.03
Physical examination findings			
Tachycardia (N=29 and N=13)	76	69	NS
Abdominal tenderness (N=25 and N=18)	64	61	NS
Crepitus	42	30	NS
Erythema	49	9	0.001
Hypotension (systolic blood pressure <13.3 kPa [<100 mm Hg])	31	26	NS
Peritoneal signs (N=24 and N=13)	33	23	NS
Tachypnea (ventilatory rate ≥ 22)	20	4	NS
Laboratory findings			
Leukocytosis (WBC $>10.0 \times 10^9$ cells/L) (N=29 and N=16)	86	63	NS
Leukopenia (WBC $<3.0 \times 10^9$ cells/L) (N=32 and N=16)	6	19	NS
Polymicrobial infection (N=34 and N=17)	85	100	NS
Gram-negative organisms present (N=34 and N=17)	88	100	NS
Gram-positive organisms present (N=34 and N=17)	68	71	NS
Anaerobic organisms present (N=34 and N=17)	44	53	NS
Fungi present (N=34 and N=17)	6	18	NS
Management			
Missed opportunity identified	33	56	NS (0.07)
Delay in initial surgery >12 h	5	26	0.02
Mean no. of operations	2.8	1.4	<0.001

^aFor each variable, percentages are calculated from the proportion of case reports in which the relevant data were provided. N=45 for survivors and N=23 for non-survivors unless otherwise stated.

WBC = white blood cell count.

integrity attributable to trauma, cancer, appendicitis, diverticulitis, or other causes. The initial clinical presentation may be nondescript and the patient's initial symptomatic prodrome misleadingly mild and indolent. Although the pathogenesis is similar to that of FG, the presentation is atypical. Moreover, the epidemiology appears to be distinct with a greater proportion of female patients, fewer patients who have diabetes, and a high incidence of underlying gastrointestinal malignant disease. The management of patients with NSTI secondary to bowel perforation is the same (i.e., surgical debridement and broad-spectrum antibiotic coverage) as patients with FG or NSTIs attributable to other causes.

However, greater awareness of this atypical presentation in patients not typically considered at risk for FG may facilitate early diagnosis and treatment. In our case series, more than one third of patients with this syndrome died. Because it has not been well described previously, NSTIs attributable to bowel perforation that does not involve the perineum, genitalia, or anus primarily may be unrecognized, leading to delayed diagnosis, delayed surgical intervention, and poor outcome. Plain radiography, CT, and other imaging modalities can confirm the diagnosis, but occasionally, exploratory surgery may be justified on the basis of the clinical suspicion, even in the absence of CT confirmation. Urgent surgical

debridement is the treatment of choice, and repeated debridement usually is needed. An NSTI caused by bowel perforation typically is polymicrobial with gram-negative, gram-positive, and anaerobic bacteria as well as *Candida* spp. all commonly isolated. Therefore, when NSTI is suspected, empiric antibiotic therapy should be broad and directed toward enteric facultative and anaerobic flora.

Acknowledgments

This work was supported by the National Institutes of Health Grant No. 5T32 AI055413-14 to N.W.CJ.

All authors report no conflicts of interest to disclose.

Author Disclosure Statement

No competing financial interests exist.

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Address correspondence to:
Disha Kumar
Baylor College of Medicine
One Baylor Plaza
Houston, TX 77030

E-mail: disha.kumar@bcm.edu