Atypical Splenic Abscesses Due to Clostridioides difficile

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Patient: Male, 90-year-old
Final Diagnosis: Clostridioides difficile splenic abscesses
Symptoms: Abdominal pain • fever • weight loss
Medication: —
Clinical Procedure: Antibiotics • splenectomy
Specialty: Infectious Diseases

Objective: Rare disease
Background: Splenic abscess is a rare infectious disease that occurs after bloodstream infection and trauma. It has become more common due to an increase in the number of immunocompromised patients. They typically present with round cystic lesions demonstrated by ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI). Clostridioides difficile (formerly Clostridium difficile) is a well-known cause of pseudomembranous colitis, but extraintestinal manifestations are very rare. To the best of our knowledge, only 9 cases of splenic abscess due to C. difficile have been reported in the literature.

Case Report: A 90-year-old man presented with weight loss, fever, and abdominal pain. Contrast-enhanced CT revealed splenomegaly with irregular hypodense nodules. Image-guided biopsy or drainage was not performed for a technical reason. MRI showed atypical nodules with mixed high and low signals on both T1- and T2-weighted images, which were inconclusive. A laparoscopic splenectomy was performed, which resulted in partial removal due to severe adhesion of the spleen to the surrounding tissues. Cultures of splenic pus yielded C. difficile, Enterococcus faecium, and Bacteroides fragilis. Pathological examination of the spleen showed widespread abscesses with hemorrhage and necrosis, leading to the diagnosis of splenic abscesses. Intravenous administration of vancomycin, clindamycin or metronidazole was ineffective. He died of fatal arrhythmia 5 months after the initial diagnosis of splenic abscess.

Conclusions: Splenic abscess can present with atypical imaging findings owing to chronic inflammation, bleeding, and necrosis. Although polymicrobial, this is the tenth reported case of splenic abscess caused by C. difficile.

Keywords: Abscess • Clostridioides difficile • Clostridium Infections • Magnetic Resonance Imaging • Splenic Diseases

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Background

Splenic abscess is a rare infectious disease, occurring in 0.05% to 0.7% of autopsy series [1-9]. The signs and symptoms include fever, abdominal pain in the left upper quadrant, leukocytosis, and splenomegaly [1-10]. The most frequent causative microorganisms are Staphylococcus, Streptococcus, Salmonella, Escherichia coli, and Klebsiella pneumoniae [1,3-7,9-11]. Monomicrobial abscesses are more common than polymicrobial abscesses [1,4-7,11]. Etiologies of splenic abscess include bloodstream infection from other infection foci (bacterial endocarditis, pneumonia, and gastrointestinal perforation), direct exacerbation from nearby locations, iatrogenic causes, trauma, and other causes (neoplasms, collagen disease, diabetes, intravenous drug abuse, embolic disorders, and immunodeficiency due to human immunodeficiency virus infection or cancer therapy) [1-8,10,11]. A recent report from North America identified a large proportion of cases with active malignancies or pancreatic disease as opposed to injection drug use, infectious endocarditis, or HIV, in contrast to prior reports [11]. The management of splenic abscesses consists of antimicrobial therapy with or without image-guided percutaneous drainage or splenectomy [1-8,10,11]. Singh et al reported a retrospective study on patients who were treated following a pre-defined management algorithm and showed the highest mortality in patients treated only with antimicrobial agents [10].

Typical splenic abscesses are readily diagnosed using ultrasonography (US) and computed tomography (CT) that demonstrate cystic lesions. They are round, hypoechoic lesions with an irregular wall on abdominal ultrasound and avascular on Doppler ultrasound [1,12]. On contrast-enhanced CT, they are hypodense lesions with occasional ring enhancement [1,12]. They are sometimes multicollotted with septations. Magnetic resonance imaging (MRI) is used when US and CT scan results are inconclusive, or when contrast enhancement is contraindicated [12]. Bacterial abscesses tend to be solitary and large, whereas fungal abscesses are often multiple and smaller [2,4,6,7,12].

Clostridioides difficile, formerly Clostridium difficile, is a spore-forming, toxin-producing, gram-positive anaerobic bacillus. It is a well-known cause of antibiotic-associated diarrhea and subsequent pseudomembranous colitis. However, it rarely causes extraintestinal manifestations [13-15]. In 10-year retrospective single-center studies, Mattila et al and Gupta et al reported that only 0.17% and 0.6% of the C. difficile infection cases were extraintestinal, respectively [13,14]. To the best of our knowledge, only 9 cases of splenic abscesses due to C. difficile have been reported in PubMed and Google Scholar databases (Table 1) [11,16-23].

We report the case of a patient diagnosed with splenic abscesses with atypical imaging findings. Although polymicrobial, this is the tenth case of splenic abscess caused by C. difficile.

Case Report

A 90-year-old man was admitted to the hospital with left-sided abdominal pain, weight loss (-6 kg in a month, body weight 43 kg, body mass index 17.7), and low-grade fever (37.2°C). He did not have diarrhea. He had a history of gastric ulcer, myocardial infarction, bronchial asthma, benign prostate hypertrophy, hypertension, and dyslipidemia, but not colitis, diabetes mellitus, chronic liver disease, or recent dental treatment. He was taking famotidine. Past oral antibiotic use was unknown. He denied health hazards, such as smoking tobacco or drinking alcohol. He had no recent travel history.

Blood tests showed a white blood cell count (WBC) of 10 590/µL (normal range 3500 to 9000), hemoglobin level of 12.4 g/dL (14.0 to 18.0), platelet count of 253 000/µL (120 000 to 360 000), and elevated C-reactive protein (CRP) of 7.5 mg/dL (0.0 to 4.0). Left shift was not observed in the WBC differential: neutrophils 72.7% (37.0 to 72.0), lymphocytes 19.5% (19.0 to 49.0), monocytes 6.3% (2.0 to 11.0), eosinophils 1.2% (0.0 to 5.0), and basophils 0.3% (0.0 to 3.0).

Contrast-enhanced CT showed splenomegaly with more than 80 irregular hypodense areas (maximum size 2 cm) but no ring enhancement (Figure 1A). Trace fluid accumulation was observed around the spleen. CT performed 3 years previously showed a normal-sized spleen. Abdominal US showed splenomegaly and multiple irregularly demarcated masses with mixed echogenicity and poor blood flow (Figure 1B, 1C). Since these imaging findings were inconclusive, an MRI was performed. It showed atypical splenic nodules with mixed high and low signals on both T1- and T2-weighted images (Figure 2). Nodules that showed high signal on T2-weighted images had high signal on diffusion-weighted images and low signal on apparent diffusion coefficient images, suggesting inflammation or malignancy.

The differential diagnoses of splenic nodules in this patient included abscesses due to infectious endocarditis, malignant lymphoma, plasmacytoma, sarcoidosis, and metastatic tumors. Bacterial cultures of the urine and blood were negative. Echocardiography did not reveal a valvular vegetation. The elevated soluble interleukin-2 receptor level was 696 U/mL (122 to 496). Serum immunoglobulin levels were: elevated IgA was 1050 mg/dL (110 to 410); elevated IgE was 862 IU/mL (<250); and IgG and IgM were normal. Serum protein fractionation and serum protein immunoelectrophoresis revealed bimodal M-proteins, IgG-lambda, and IgA-lambda. A bone marrow aspiration/biopsy revealed no signs of malignancy. Levels of angiotensin-converting enzyme, carcinoembryonic antigen, carbohydrate antigen 19-9, and prostate-specific antigen were normal. Upper endoscopy revealed chronic gastritis and gastric ulcer scar. Lower endoscopy revealed 7 polyps, which were...
removed and submitted to pathological examination: 5 in the ascending and transverse colon were benign adenomas and 2 in the transverse colon were adenocarcinomas with negative margins. These results are insufficient for the diagnosis of splenic nodules. Image-guided biopsy or drainage was not possible because of the fluid accumulation around the spleen, which can inhibit hemostasis after the procedure.

The abdominal pain spontaneously disappeared immediately after admission. Ceftriaxone was administered for possible bacterial infection, but he had persistent low-grade fever, and his CRP level did not decrease. The patient’s general condition improved after replacing ceftriaxone with meropenem, which could additionally cover resistant gram-negative bacteria and anaerobes. The patient refused to undergo laparoscopic splenectomy. He was administered a pneumococcal vaccine for future splenectomy. He was discharged without a prescription for oral antimicrobials.

Ten days later, the patient was readmitted to the hospital with a fever (38.2°C) and recurrent left-sided abdominal pain. The WBC count was 16 290/µL, and the CRP was 17.3 mg/dL. CT showed exacerbation of splenomegaly (craniocaudal length 11 cm) and ascites. Bacterial cultures of the urine and blood were

Table 1. Characteristics of Clostridioides difficile splenic abscesses in the literature. * PubMed database was searched using key words, “splenic” AND “abscess” AND “Clostridium” AND “difficile”. Only 6 cases of splenic abscesses due to C. difficile were found [16-21]. A Google Scholar search for items written in English dated between 1983 (when the first case of C. difficile splenic abscess was reported [16]) to May 2022 with all the words “splenic abscess Clostridium difficile”, with the exact phrase “splenic abscess”, with at least one of the words “single-center” or “multi-center” or “case report”, without the words “textbook book chapter program meeting conference” led to 76 matches. Duplicates were removed. The selected items were manually reviewed and narrowed down to 3 reports [11,22,23].

| Age | Sex | Preceding Cd infection | Abscess culture | Blood culture | Stool culture Cd toxin test | CT findings of the spleen |
|-----|-----|------------------------|----------------|--------------|----------------------------|--------------------------|
| 68  | M   | Cd bacteremia          | Cd             | Cd           | NA                        | No abscess (CT was taken more than 11 days before death) |
| 62  | M   | Bacteremia (Cd, C. fallax, C. perfringens, C. ramosum, E. coli) 5 months previously | Cd, Pseudomonas paucimobilis | Cd | NA | An area of decreased attenuation |
| 58  | M   | None                   | Cd             | NA           | NA                        | Air within the spleen parenchyma and subcapsular space |
| 82  | M   | Cd colitis             | Cd, Coagulase-negative staphylococci | E. coli | Cd toxin (+) | A large hypodense area |
| 51  | M   | Cd bacteremia (Diarrhea was observed but stool specimen was not tested for Cd) | Cd | Cd | NA | Splenomegaly and a wedge-shaped low-density area on contrast-enhanced CT |
| 65  | F   | Cd bacteremia          | Cd             | Cd           | NA                        | NA |
| 79  | M   | Chronic Cd infection after hemicolectomy Cd colitis | Cd | (−) | Cd toxin (+) | Subcapsular perisplenic fluid collection |
| 54  | M   | None                   | Cd             | (−)          | NA                        | Subcapsular abscess |
| 32  | M   | NA                     | NA             | NA           | NA                        | NA |
| 90  | M   | None                   | Cd B. fragilis E. faecium | (−) | Cd toxin (−) | Splenomegaly Multiple low-density areas on contrast-enhanced CT Fluid accumulation around the spleen |

Cd – Clostridioides difficile; CT – computed tomography; NA – not available.
Table 1 continued. Characteristics of *Clostridioides difficile* splenic abscesses in the literature. * PubMed database was searched using key words, “splenic” AND “abscess” AND “Clostridium” AND “difficile”. Only 6 cases of splenic abscesses due to *C. difficile* were found [16-21]. A Google Scholar search for items written in English dated between 1983 (when the first case of *C. difficile* splenic abscess was reported [16]) to May 2022 with all the words “splenic abscess *Clostridium difficile*, with the exact phrase “splenic abscess”, with at least one of the words “single-center” or “multi-center” or “case report”, without the words “textbook book chapter program meeting conference” led to 76 matches. Duplicates were removed. The selected items were manually reviewed and narrowed down to 3 reports [11,22,23].

| Age | Sex | Abscess No. & size | Antibiotics for abscess treatment | Surgical treatment | Outcome | Reference |
|-----|-----|--------------------|-----------------------------------|--------------------|---------|-----------|
| 68  | M   | Solitary 6×5 cm    | Postoperatively; iv penicillin G for 6 days | None                | Died on day 28 after initial presentation (diagnosed by autopsy) | Saginur 1983 [16] |
| 62  | M   | Solitary 4 cm 100 mL | Preoperatively; Piperacillin, netilmicin Postoperatively; Cefoxitin, metronidazole | Splenectomy         | Resolved | Studemeister 1987 [17] |
| 58  | M   | Solitary 12×10×5 cm | Perioperatively; I.v cefazidime, i.v vancomycin, i.v metronidazole Postoperatively; i.v penicillin G | Splenectomy Resection of ischemic small intestine | Resolved | Stiegblauer 1995 [18] |
| 82  | M   | Solitary 16×13 cm  | Postoperatively; I.v vancomycin for 4 weeks | US-guided drainage | Died 2 months later from respiratory failure of unknown cause | Kumar 1997 [19] |
| 51  | M   | Solitary 7 cm      | Preoperatively; Im procaine penicillin for 2 weeks, I.v penicillin and metronidazole Postoperatively; I.v vancomycin | US-guided trans-diaphragmatic drainage | Resolved 8 weeks postoperatively | Shedda 2000 [20] |
| 65  | F   | Solitary 9×11 cm   | Postoperatively; I.v metronidazole | Splenectomy         | Resolved | Bedimo 2003 [21] |
| 79  | M   | Solitary 11×4 cm   | Postoperatively; Oral vancomycin, I.v metronidazole, Daptomycin, Vancomycin, Cefepime | US-guided drainage | Died on day 16 from respiratory failure and withdrawal of life sustaining measures | Ball 2014 [22] |
| 54  | M   | Solitary 17.6×15.7×11 cm 900 mL | Preoperatively; I.v vancomycin and Piperacillin/Tazobactam Postoperatively; I.v metronidazole | CT-guided drainage | Residual abscess 4.4×1.8 cm 6 months postoperatively Lost to follow-up | Agha 2019 [23] |
| 32  | M   | Solitary 4 cm      | NA                                 | Percutaneous drainage | Resolved | Radcliffe 2022 [11] |
| 90  | M   | More than 80 abscesses Maximum 2 cm | Preoperatively; I.v Ceftriaxone, Meropenem Postoperatively; I.v Vancomycin, Clindamycin, Daptomycin, Teicoplanin, Fosfomycin, Metronidazole, Oral Linezolid, Clindamycin | Laparoscopic Splenectomy (subtotal) | Died 5 month after diagnosis of fatal arrhythmia | This case |

*Cd – Clostridioides difficile; CT – computed tomography; im – intramuscular injection; iv – intravenous injection; NA – not available; US – ultrasound.*
**Figure 1. Images of the splenic abscesses.** (A) Coronal section of contrast-enhanced computed tomography. The spleen was enlarged. Splenic abscesses appeared as multiple lesions with irregular margins and low resorption (arrows). Trace fluid accumulation was present (not shown). (B) Ultrasonography. The splenic abscesses showed irregular margins and mixed echogenicity inside (arrows). (C) Doppler ultrasound. The splenic abscesses were avascular.
negative. Meropenem relieved the fever and decreased CRP from 19.5 mg/dL to 11.7 mg/dL, but the abdominal pain persisted. A laparoscopic splenectomy was performed. The spleen was highly adherent to the diaphragm, greater omentum, and the posterior abdominal wall. During dissection, a large amount of white pus was drained from the spleen. The diagnosis of splenic abscesses was made based on pathology (Figure 3). Due to the massive accumulation of neutrophils, hemorrhage, and necrosis, very little of the normal structure of the spleen remained. Since there was a possibility of residual abscesses, follow-up CT was performed 9 days after surgery. It revealed a residual spleen, suggesting that the splenectomy was subtotal. CRP decreased from 11.7 mg/dL to 3.9 mg/dL without postoperative antibiotics. *C. difficile*, *Enterococcus faecium*, and *Bacteroides fragilis* were detected in the pus culture (Table 2). Intravenous vancomycin and clindamycin were administered based on the sensitivity test results. The patient’s general condition improved, but his CRP level increased again. Vancomycin and clindamycin were replaced with oral linezolid and clindamycin, respectively. His stool was negative for *C. difficile* antigens and toxins, and he was discharged.

He was hospitalized 2 more times because of persistent inflammation, appetite loss, and hypokalemia. Intravenous clindamycin, daptomycin, teicoplanin, fosfomycin, and metronidazole were administered, but were ineffective. Biopsy or drainage of the remaining spleen was not performed, because the intervening lung would have been punctured, resulting in pyothorax. The patient died of fatal arrhythmia 5 months after the initial diagnosis of splenic abscesses. Autopsy showed abscesses in and around the spleen and inflammation directly spreading from the spleen to the diaphragm,

Figure 2. Magnetic resonance imaging. (A) T1-weighted image. (B) T2-weighted image. (C) Diffusion-weighted image. (D) Apparent diffusion coefficient image. Splenic nodules (arrows) had mixed high and low signals on both T1- and T2-weighted images. Nodules that showed high signal on T2-weighted images had high signal on diffusion-weighted images and low signal on ADC images, suggesting inflammation or malignancy.
Figure 3. Histopathology of splenic abscesses. Hematoxylin and eosin. Original magnification ×20. Inset, original magnification ×200. A – abscesses as shown by accumulation of neutrophils; H – hemorrhage; N – necrosis; S – normal splenic tissue.

Discussion

Splenic abscesses typically have an internal liquid-like pattern, showing low signals on T1-weighted images and high signals on T2-weighted images on MRI [12]. In the present case, the abscesses were highly variable, showing mixed high and low signals on both T1- and T2-weighted images. The imaging findings corresponded to mixed components of abscesses, including liquidous or solidified pus, hemorrhage (acute, subacute, and chronic), necrosis, and inflammation, which were confirmed by pathology.

Only 9 cases of splenic abscesses due to C. difficile have been reported in the literature (Table 1) [11,16-23]. There was a strong male predominance, and the average age was 64.1 years (range 32-90 years). All but our patient had a typical large solitary cystic lesion without loculation.

Seven of the 10 cases (70%) of C. difficile splenic abscesses were monomicrobial (Table 1). This is compatible with the fact that splenic abscesses are more often monomicrobial than polymicrobial [1,4-7,11]. In contrast, 60-91% of cases of other types of extraintestinal C. difficile infection (ECDI) were polymicrobial [13-15,24]. Chung et al reported that the most frequently identified co-isolates in ECDI were Enterococcus (spp. faecalis, faecium, avium) and E. coli [24]. Regarding the splenic abscesses in our case, E. faecium and B. fragilis were co-isolates. B. fragilis is an anaerobic bacterium and a rare cause of splenic abscesses, detected in only 5 out of 220 patients in 6 reports [3-7,9]. Co-infection of C. difficile with B. fragilis and that of C. difficile with E. faecium were observed in 9 and 7 cases out of 53 cases of ECDI, respectively [13,15]. One patient was co-infected with C. difficile, B, fragilis, E. faecium, and other bacteria [15].

Underlying diseases and predisposing factors of ECDI [13-15,24] as well as C. difficile splenic abscesses [11,16-23] include gastrointestinal disruption (malignancy, perforation, surgery, enterocolitis, and bleeding), hospitalization, multiple antibiotic exposure, prior C. difficile infection, and severe comorbidities.
Table 2. Antimicrobial susceptibility of bacteria detected in cultures of pus collected during surgery.

|                      | **E. faecium** |                      | **C. difficile** |                      | **B. fragilis** |
|----------------------|----------------|----------------------|------------------|---------------------|-----------------|
|                      | MIC            | Susceptibility       | MIC              | Susceptibility      | MIC            |
| Ampicillin           | 8             | R                    | 1                | I                   | >1             |
| Amoxicillin-sulbactam| 16            | R                    | 0.5              | S                   | >1             |
| Piperacillin-tazobactam | 8         | R                    | <4               | S                   | >16            |
| Vancomycin           | 1             | S                    | Piperacillin-tazobactam | <16    | S             |
| Teicoplanin          | 0.5           | S                    | Teicoplanin      | >16                |                |
| Daptomycin           | 0.5           | S                    | Daptomycin       | >16                |                |
| Minocycline          | 8             | I                    | Minocycline      | 2                   | S              |
| Levofoxacin          | 4             | R                    | Meropenem        | 2                   | S              |
| Fosfomycin           | 32            | S                    | Fosfomycin       | 1                   | S              |
| Linezolid            | 1             | S                    | Linezolid        | 4                   | S              |

MIC – minimal inhibitory concentration (µg/mL); S – susceptible; I – intermediate; R – resistant. Susceptibility was determined based on Interpretive Categories defined in the Clinical and Laboratory Standards Institute (CLSI) M100-ED32: 2022 Performance Standards for Antimicrobial Susceptibility Testing, 32nd Edition (https://clsi.org/standards/products/free-resources/access-our-free-resources/).

(immunosuppression, diabetes, liver cirrhosis, and alcohol use disorder). Preceding or concomitant *C. difficile* enterocolitis is observed in only 10% of patients with ECDI [24]. In patients with *C. difficile* splenic abscesses, 6 out of 10 cases had preceding *C. difficile* infections (2 colitis (20%) and 4 bacteremia [40%]) (Table 1).

The limited knowledge about the prognosis of *C. difficile* splenic abscesses from few available case reports is relatively favorable, which could be affected by comorbidities and the success rate of drainage or surgery (Table 1). The antibiotics used to treat *C. difficile* splenic abscesses were intravenous vancomycin, metronidazole, and penicillin, although antimicrobial susceptibilities of *C. difficile* were not available except for our case (Tables 1, 2). The systematic review and meta-analysis on *C. difficile* infection among hospitalized diarrheal patients showed that the resistance to metronidazole and vancomycin was low compared to other drugs, including clindamycin [25]. A single-center retrospective study on ECDI demonstrated that all isolates (100%) were susceptible to metronidazole and piperacillin-tazobactam, while 63% and 9% of isolates were susceptible to ertapenem and clindamycin, respectively [14]. In our case, multiple antibiotics, including vancomycin, clindamycin, and metronidazole, were susceptible in vitro but ineffective in vivo, partly because source control was not achieved due to incomplete splenectomy.

It is perplexing how intestinal bacteria caused splenic abscesses in this case. Blood and stool cultures were negative. He had no recorded episodes of preceding *C. difficile* infection (bacteremia or colitis), surgery, or trauma. Nevertheless, severe adhesion of the spleen to the surrounding tissue revealed by surgery and autopsy implied that the inflammation process was chronic. Since he had colon cancer, the simplest explanation is that the damaged mucosal barrier was the entry site of intestinal bacteria. It is unlikely that the colon cancer perforated and the bacteria spread directly to form splenic abscesses, since there was no adhesion between the colon and spleen [26]. Of note, *B. fragilis* and certain *Streptococcus*, *Fusobacterium*, and *Peptostreptococcus* species are enriched in the colorectal cancer microbiota [27]. Enterotoxigenic *B. fragilis* exerts oncogenic effects by activating proinflammatory responses [28]. Moreover, the risk of colorectal cancer development was significantly increased in patients with bacteremia due to bacteria enriched in colorectal cancer microbiota [29]. Thus, we hypothesize that the patient might have had bacteremia due to *B. fragilis*, *C. difficile*, and *E. faecalis*, which might have induced both splenic abscesses and colon cancer.

**Conclusions**

Splenic abscesses caused by *C. difficile* are extremely rare. According our database search, this is the tenth case of *C. difficile* splenic abscesses. Unlike previous reports, our case did not have a preceding *C. difficile* infection, and the abscesses were multiple and polymicrobial. The inflammation was chronic and destructive, resulting in atypical MRI findings.
Department and Institution Where Work Was Done

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