Clostridioides difficile Pyogenic Liver Abscess With an Empyema

Suhas P. Dasari, BS; Mit A. Patel, BS; Vishmayaa Saravanan, BS; Sanjana Jha; Kayla L. O'Sullivan BS; Harpreet S. Gill, BS; Pramod Acharya, MD; Pinky Jha, MD

ABSTRACT

Introduction: Reports of extraintestinal manifestations of *Clostridioides difficile* (*C difficile*) infections are rare. The frequency of these infections comprises approximately 0.17% to 0.6% of all *C difficile* infections. While they are becoming more frequent worldwide, the precise trend is unclear.

Case Presentation: An 83-year-old female patient presented with pleuritic chest pain 2 to 3 months after a needle biopsy of her liver abscess confirmed *C difficile*. She was found to have extension of the liver abscess into the chest cavity, leading to empyema, and was treated with intravenous antimicrobials.

Discussion: This is the fifth known reported case of *C difficile* leading to a pyogenic liver abscess and the first case where the *C difficile* liver abscess was associated with an empyema. While long-term metronidazole is considered effective for managing extra intestinal *C difficile* infection, our patient was treated with vancomycin and meropenem.

Conclusion: To determine epidemiology and a proper treatment regimen for extraintestinal *C difficile* infection, a greater accumulation of cases is necessary.

INTRODUCTION

Clostridioides difficile (*C difficile*) is a gram-positive spore-forming anaerobic rod present in up to 5% of fecal specimens in healthy adults.[1] It has a well-known role as a causal pathogen in pseudomembranous colitis and antimicrobial-associated diarrhea but rarely causes extraintestinal infections. Thus, it had generally been thought to have little clinical extraintestinal significance, but when present, it demonstrates a high mortality rate.[1,2] Extraintestinal manifestations include peritonitis, intra-abdominal abscesses, bacteremia, brain abscesses, and bone and soft tissue infection.[3] These are thought to be driven by local spread into fluids and anatomically adjacent tissues.[3] To date, there have only been 4 reported cases of *C difficile*-induced pyogenic liver abscesses (PLA), which tend to be recurrent despite treatment.[2-5] The spore-forming ability of *C difficile* may contribute to this ability to form recurrent PLAs. Here we present the 5th case of *C difficile* PLA and the first reported case of a *C difficile* PLA causing an empyema.

• • •

Author Affiliations: Department of Internal Medicine, Medical College of Wisconsin (MCW), Milwaukee, Wis (Dasari, Patel, Saravanan, Jha S, O'Sullivan, Gill, Jha P); Department of Infectious Disease, MCW, Milwaukee, Wis (Acharya).

Corresponding Author: Suhas P. Dasari, email sdasari@mcw.edu; ORCID ID 0000-0001-7161-7305.

CASE PRESENTATION

An 83-year-old woman with a history of appendicitis, renal stones, and cholecystitis treated with a laparoscopic cholecystectomy within the past year presented to an outside hospital for a fever and right upper quadrant pain. She had unremarkable labs with benign white blood cell count, liver function tests, and C-reactive protein within normal limits. A computed tomographic (CT) scan of the abdomen revealed a 5.6 x 2.7 cm solid partially cystic liver lesion in the right hepatic lobe that was suspicious of a liver abscess (Figure 1). A needle biopsy and anaerobic culture of the liver abscess grew *C difficile*. The patient denied any previous history of *C difficile* colitis. Initially, she was supposed to be treated with 10 weeks of oral metronidazole as an outpatient, but she could not tolerate the medication due to nausea and weight loss, so she stopped at 7 weeks. Follow-up imaging showed expansion of the liver abscess.

By 2 to 3 months after stopping antimicrobial treatment, the patient presented with new onset pleuritic chest pain. Repeated imaging showed that the PLA had extended into the postero-

Figure 1. Axial Computed Tomography Without Contrast Taken at Outside Hospital Showing Solid Right-Sided Posterior Liver Mass (red arrow) Concerning for a Liver Abscess with a Concomitant Right-Sided Pleural Effusion

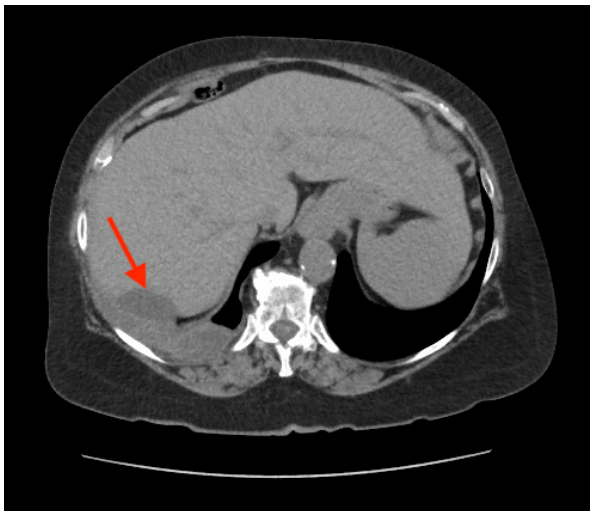


Figure 2. Axial Computed Tomography Without Contrast Taken Upon Admission Showing Enlarging Right-Sided Posterior Liver Mass Pleural Effusion (blue arrow)

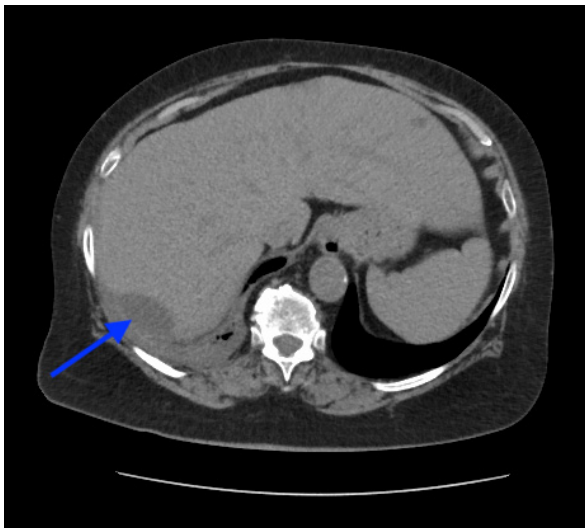
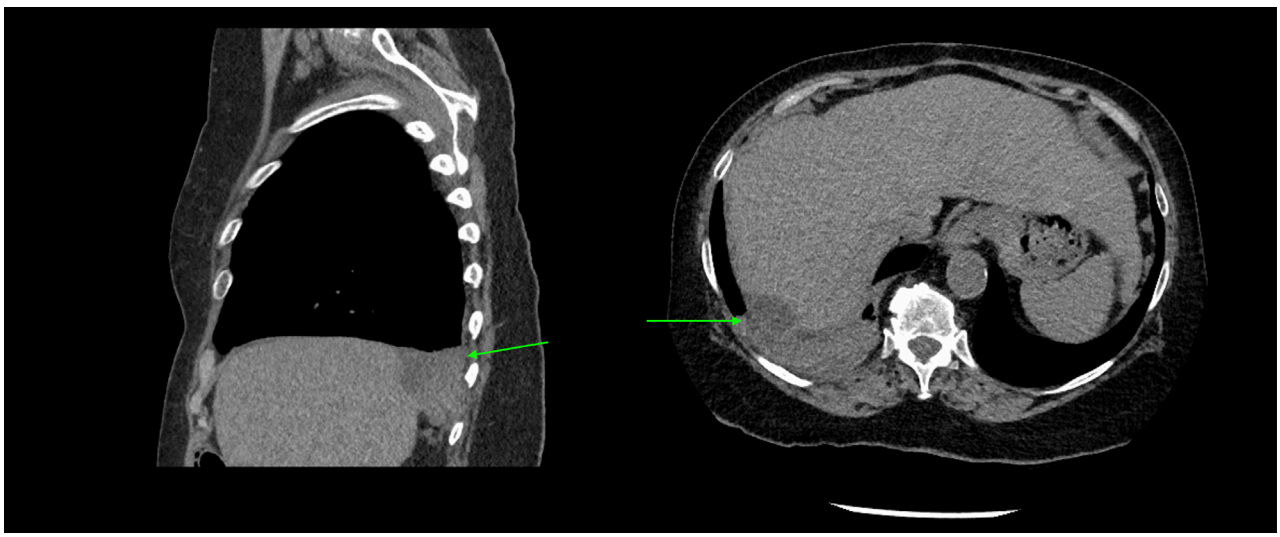


Figure 3. Sagittal (left) and Axial (right) Computed Tomography Without Contrast Showing Direct Spread of Right-Sided Pyogenic Liver Abscesses Into Lung Parenchyma and Formation of an Empyema (green arrows)



medial right hemidiaphragm with a 3.8 x 2.3 cm fluid collection, pleural effusion, and an empyema (Figure 2). She was admitted, managed nonoperatively, and treated with intravenous (IV) vancomycin and meropenem for 6 weeks. A subsequent biopsy was not pursued due to her advanced age and the belief that further invasive interventions would not significantly alter clinical decision-making unless she failed a complete course of broad-spectrum antimicrobials. Meropenem was added on with vancomycin due to its coverage of species such as pseudomonas, actinomyces, and klebsiella, which could have potentially infiltrated the PLA. After completing antimicrobial therapy, a repeat CT scan of the liver and chest showed improvement in the right pleural effusion with stabilization of the consolidative mass extending from the liver, across the right hemidiaphragm, and into the lung (Figure 3). Her hospital stay was 7 days, and she is being followed clinically without antimicrobials. If there is a recurrence of symptoms, repeat imaging and potential surgical intervention would then be considered.

Table. Summary of *Clostridioides Difficile* Pyogenic Liver Abscess (PLA) Cases

Case	Demographic Features	Source of PLA Inoculation	Diagnostic Modality	PLA Size Upon Diagnosis	Treatment	Outcomes
Sakurai[1] et al	75-year-old female	Potentially due to drainage catheter used to work up non-infectious liver cyst	Rap1-ANA-II	Not stated	Treated initially with percutaneous drainage and IV imipenem/cilastatin sodium. Switched to IV vancomycin on HD 4 for 4 weeks, failed to improve. Successfully treated with metronidazole but recurred 11 months later. Then treated with percutaneous drainage and 3 weeks of imipenem followed by metronidazole for 4 months.	Patient fully recovered and has remained disease free
Ulger[3] et al	80-year-old female	Potentially due to history of angioplasty 3 years prior	Drained pus grew *C difficile* on anaerobic cultures; identified using Rapid ID 32A	Several lesions on ultrasound and CT, largest measuring 6.4 x 3.4 cm	Treated with piperacillin-tazobactam, patient underwent cholecystectomy and drainage of liver abscesses. On postop day 3, when *C difficile* was identified, patient was switched to IV ceftriaxone and metronidazole. Antimicrobials stopped on day 14 and patient acutely worsened. Failed to improve on IV imipenem and metronidazole.	Patient died on HD 18
Roy[4] et al	63-year-old male	*C difficile* colitis leading to sigmoid colon perforation	Anaerobic cultures grew *C difficile*	Not stated	Treated with IV meropenem, percutaneous drains, and exploratory laparotomy that revealed perforation and required partial colectomy. After laparotomy and colectomy, IV vancomycin, metronidazole, and micafungin were added. Final coverage was IV micafungin and oral metronidazole for 8 weeks.	Patient fully recovered
Morioka[5] et al	74-year-old male	Transarterial chemo-embolization	Blood cultures *revealed C difficile*; identified with mass spectrometry	Not stated	Initially treated with IV ceftriaxone and meropenem. Meropenem eventually transitioned to ampicillin/sulbactam. When *C difficile* was identified, ampicillin/sulbactam replaced with IV vancomycin and oral metronidazole. These were stopped within 2 weeks due to toxicity. Patient had recurrent symptoms, 7 days oral metronidazole followed by 7 days oral vancomycin were administered. Patient reoccurred within a month; treated with IV ceftriaxone and oral vancomycin. Patient failed to improve; treatment switched to oral metronidazole for 6 weeks.	Patient's symptoms have not recurred after final treatment
Current case	83-year-old female	Laparoscopic cholecystectomy within past year	Anaerobic culture of liver abscess needle biopsy grew *C difficile*	5.6 x 2.7 cm solid partially cystic liver lesion in right hepatic lobe	Initially treated with 7 weeks of metronidazole (out of a 10-week course). Final treatment was IV vancomycin and meropenem for 6 weeks.	Stabilized clinically with improved symptoms and reduction in mass size on imaging

Abbreviations: IV, intravenous; *C difficile, Clostridioides difficile;* HD, hospital day; CT, computed tomography; postop, postoperative.

DISCUSSION

To the best of our knowledge, we report the first case of a monomicrobial *C difficile* PLA extending into the pleural cavity to form an empyema and the fifth overall reported case of a *C difficile* PLA. All 5 reported cases are summarized in the Table. The frequency of extraintestinal *C difficile* infection (CDI) is thought to be 0.17% to 0.6% of all CDIs, with proton pump inhibitors and antimicrobial exposure being the highest risk factors.[5] To try to quantify the occurrence of extraintestinal CDI, in 2020 Urban et al performed a retrospective observational study in a Hungarian university hospital over 10 years and found an incidence of 0.003/1000 patients of extraintestinal *C difficile* reported at their facility.[2]

In 2001, Sakurai et al reported the first case of a recurrent PLA in a 75-year-old woman without any prior history of diarrhea or antimicrobial use.[1] The drained liver abscess grew a pure culture of *C difficile* that was polymerase chain reaction (PCR) negative for toxins A and B. The patient was treated with percutaneous drainage interventions and a multitude of antimicrobials—including a failed trial with vancomycin—and seemed to respond best to long-term metronidazole therapy. In 2016, Ulger et al reported a case with multiple liver abscesses caused by toxigenic *C difficile* isolated from drained pus in an 80-year-old woman without any diarrhea or antimicrobial use before diagnosis.[3] This patient was treated with multiple antimicrobials, including metronidazole, but succumbed to her illness. In 2017, Roy et al reported a unique case of hospital-acquired *C difficile* (toxin B) infection in a 63-year-old man treated with antimicro-

bials for necrotizing pancreatitis, who later developed *C difficile* colitis.[4] He eventually developed *C difficile*-cultured abscesses in the pancreas and liver spread via sigmoid colon perforation. The liver abscess drainage grew *C difficile* and *Candida glabrata* and was the only polymicrobial PLA of these cases. That year, Morioka et al reported the first case of recurrent bacteremia and PLA as a complication of transarterial chemoembolization (TACE) caused by *C difficile* strains positive for toxin A, toxin B, and binary toxin.[5] Our patient was unlike the prior cases as she did not respond to metronidazole therapy and subsequently developed an empyema that only stabilized with IV vancomycin and meropenem. Additionally, unlike the prior cases reported, our patient had normal laboratory findings.

The pathophysiology of extraintestinal *C difficile*—especially for PLA—is not fully understood, partially due to its rare incidence. It is possible that the spore formation of *C difficile* contributes to its pathogenesis, as these spores can persist in various environments for an extended time period and even in stool samples after therapeutic intervention.[1] Sakurai et al proposed a mechanism of action where there is direct inoculation via skin damage, either from trauma or percutaneous interventions.[1] This was seen in all reported cases as some form of intervention through the skin and was present in each patient history. In Sakurai et al's case, they believed that a catheter was responsible for spreading the spores into the portal circulation.[1] In the case presented by Ulger et al, there was a history of angioplasty 3 years prior, which the authors proposed to be a potential route of colonization.[3] Roy et al reported a unique cause of *C difficile* PLA as their proposed mechanism of action was secondary to sigmoid colon perforation from antimicrobial-induced *C difficile* colitis.[4] Morioka et al reported a case that occurred subsequent to TACE intervention.[5] In our case, we believe the patient was inoculated with *C difficile* via her recent cholecystectomy, which led to the formation of her initial PLA within the same year. We suspect that when the outside hospital performed a needle biopsy of the PLA, an iatrogenic portal of entry was generated, allowing the pathogen to enter the pleural cavity to form an empyema and contributing to our unique presentation.

Urban et al noted that most cases of extraintestinal *C difficile* infections are preceded by gastrointestinal disease either by *C difficile* colitis or surgical/anatomical disruption of the colon.[2] PLAs themselves are a rare but deadly entity, as untreated cases are uniformly fatal and there is 30% mortality in treated cases.[2] PLA is reported to occur in 8 to 20 cases per 100,000 hospital admissions, with the right lobe most commonly involved due to its size and increased blood supply.[3] Interestingly, these tended to be polymicrobial, while the *C difficile* liver abscesses tended to be monomicrobial. The typical pathogenic mechanism of *C difficile* in the intestines is through the production of exotoxins A, B, and binary toxin; toxin-producing strains of *C difficile* are the cause of antimicrobial-associated diarrhea in 15% to 25% of reported cases.[2] Other than the case reported by Sakurai et al,[1] all other cases were toxin producing. Testing for toxins was not done in our case. Ulger et al proposed that the toxin-positive isolate promoted local tissue destruction leading to the fatal damage and multiorgan failure seen in this case.[3]

Currently, there is no standard guideline for the diagnosis of monomicrobial *C difficile* PLAs. In our review of the literature, we noted that CT images revealed focal hypodense lesions in the liver of all reported cases. Ultrasonography was also used to localize the abscesses in 2 cases before acquiring CT images.[1,3] Prior patients tended to present with a fever and localized pain, as well as lab markers including high levels of C-reactive protein and liver function tests.[1,3] Our patient did not follow this pattern as she had laboratory values within normal limits; however, she did have characteristic CT imaging findings that helped with diagnosis. In all cases—except the report by Morioka et al[5]—the final identification of *C difficile* was made by biopsy and culture of the PLA.

There are very few guidelines or prior examples as to how *C difficile* should be treated within the context of liver abscesses. Urban et al reported that generally there was no resistance to metronidazole or vancomycin, with 20.5% of cases being resistant to clindamycin and 9.7% being resistant to rifampin.[2] Among previous mentioned cases, vancomycin and metronidazole have been used as first-line options. Thus, in the context of liver abscess, these cases demonstrate that after abscess drainage, IV then oral metronidazole proves effective as a first-line treatment. This is corroborated by the first detailed case of liver abscess caused by *C difficile* in Scandinavia, in which drainage following 4 weeks of metronidazole proved to be more effective than vancomycin.[1] The authors went on to postulate that metronidazole may be more effective than vancomycin in the treatment of PLA. One reason for metronidazole's success may be due to its high penetration to the liver, but certain reports claim that clinically significant isolates of *C difficile* actually may be less susceptible to metronidazole due to growing resistance.[5,6] For this reason, it is important to identify the toxins and antimicrobial sensitivity of the specific *C difficile* organism, drain the abscess, and treat with a metronidazole-based regimen if appropriate. Interestingly, our patient did not respond to metronidazole initially and actually worsened to develop pleuritic and lung parenchymal involvement. She stabilized only after being given 6 weeks of IV vancomycin and meropenem.

CONCLUSIONS

Here we report the fifth known case of *C difficile* PLA and the first known case where it directly led to a chest empyema. While lab markers like liver function tests were a diagnostic clue in previously reported cases, they were unremarkable in our case. There was a history of percutaneous intervention allowing for *C dif-*

ficile spores to seed the liver in 4 out of the 5 cases of *C difficile* PLA in the literature, including ours. These spores contribute to the pathogenesis of this rare condition, as they can form recurrent PLAs that are refractory to antimicrobial therapy. While prolonged metronidazole has been effective in eradicating infection in the past, this was not the case for our patient and may point towards growing antimicrobial resistance.

Funding/Support: None declared.

Financial Disclosures: None disclosed.

REFERENCES

1. Sakurai T, Hajiro K, Takakuwa H, Nishi A, Aihara M, Chiba T. Liver abscess caused by *Clostridium difficile*. *Scand J Infect Dis*. 2001;33(1):69-70. doi:10.1080/003655401750064112

2. Urbán E, Terhes G, Gajdács M. Extraintestinal *Clostridioides difficile* infections: epidemiology in a university hospital in Hungary and review of the literature. *Antibiotics (Basel).* 2020;9(1):16. doi:10.3390/antibiotics9010016

3. Ulger Toprak N, Balkose G, Durak D, et al. *Clostridium difficile*: a rare cause of pyogenic liver abscess. *Anaerobe*. 2016;42:108-110. doi:10.1016/j.anaerobe.2016.09.007

4. Roy M, Dahal K, Roy AK. Invading beyond bounds: extraintestinal *Clostridium difficile* infection leading to pancreatic and liver abscesses. *BMJ Case Rep.* 2017;2017:bcr2017220240. doi:10.1136/bcr-2017-220240

5. Morioka H, Iguchi M, Kuzuya T, Mikamo H, Yagi T. Recurrent bacteremia and liver abscess caused by *Clostridium difficile*: a case report. *Medicine (Baltimore).* 2017;96(35):e7969. doi:10.1097/MD.0000000000007969

6. Banawas SS. *Clostridium difficile* infections: a global overview of drug sensitivity and resistance mechanisms. *Biomed Res Int.* 2018;2018:8414257. doi:10.1155/2018/8414257

advancing the art & science of medicine in the midwest

WMJ

WMJ (ISSN 1098-1861) is published through a collaboration between The Medical College of Wisconsin and The University of Wisconsin School of Medicine and Public Health. The mission of *WMJ* is to provide an opportunity to publish original research, case reports, review articles, and essays about current medical and public health issues.

Visit www.wmjonline.org to learn more.