Clostridium difficile infection presenting as a leukemoid reaction: a case report and mini-review of the literature

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Abstract

Clostridium Difficile Infection (CDI) is a prevalent healthcare-associated infection primarily affecting the gastrointestinal tract. However, extraintestinal manifestations, such as abscess formation, are rare and pose significant diagnostic and therapeutic challenges. Furthermore, *Clostridium difficile*-associated Leukemoid Reactions (LR) are infrequent and often indicative of severe disease with poor prognostic implications. This report presents a rare case of an extraintestinal CDI manifesting as an abscess accompanied by a leukemoid reaction. A 50-year-old male presented with a fever and gait imbalance. Clinical examination revealed a febrile, hemodynamically unstable patient with an inflamed abscess in the right lumbar region. Laboratory investigations demonstrated marked leukocytosis and thrombocytosis. Despite initial empirical antimicrobial therapy with intravenous piperacillin-tazobactam and clindamycin, the patient exhibited persistent fever and progressive leukocytosis. Surgical drainage of the abscess was performed, and microbiological analysis identified *Clostridium difficile*. The antimicrobial regimen was modified to include intravenous metronidazole and vancomycin, resulting in clinical improvement and subsequent normalization of leukocyte counts. The patient made a complete recovery and was subsequently discharged. This case underscores the importance of considering atypical presentations of CDI, particularly in the absence of classical gastrointestinal symptoms. Early recognition, prompt surgical intervention, and targeted antimicrobial therapy are critical for favorable clinical outcomes. This report highlights the need for heightened clinical awareness regarding atypical presentations of CDI to ensure prompt diagnosis and optimal patient outcomes.

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Highlights

- *Clinicians should consider CDI even in the absence of classical gastrointestinal symptoms, particularly in patients presenting with abscesses, sepsis, or unexplained leukemoid reactions.*
- *Leukemoid reactions may serve as a surrogate marker of CDI severity and could aid in risk stratification.*
- *Early microbiological identification and source control through surgical drainage play a crucial role in the management of extraintestinal CDI.*
- *CDI spreads via contaminated hospital surfaces and equipment when infection control and cleaning protocols are poorly implemented.*
- *Future studies are needed to establish standardized treatment protocols for extraintestinal CDI, including the role of intravenous versus oral antibiotics.*

Introduction

Clostridium difficile infection (CDI) is the most common healthcare-associated infection, capable of causing outbreaks, posing significant treatment challenges, increasing healthcare costs, and contributing substantially to morbidity and mortality among hospitalized patients.[1] While intestinal CDI is well documented,

extraintestinal manifestations of CDI are relatively rare.[2] Reported cases of extraintestinal CDI have included the involvement of the small intestine, visceral abscess, reactive arthritis, septic arthritis, cellulitis, osteomyelitis, and empyema.[3-7] CDI can lead to diarrhea, sepsis, multi-organ failure, and may be fatal in severe cases.[8] However, unlike intestinal CDI, for which the Infectious Diseases Society of America (IDSA) has established treatment guidelines, no standardized protocols exist for the management of extraintestinal CDI.[9] This lack of definitive guidelines poses a clinical challenge in the diagnosis and treatment of such cases.

Case Report

A 50-year-old male presented with a two-day history of fever without chills or rigors, along with gait imbalance following a fall in the washroom one day prior. His medical history was unremarkable, except for a prior Cerebrovascular Accident (CVA) from which he had partially recovered. On examination, he was conscious, oriented, and febrile, with a temperature of 38.2°C. His vital signs included a pulse rate of 110 beats per minute, a respiratory rate of 22 breaths per minute, blood pressure of 80/60 mmHg, and an oxygen saturation of 94% on room air. On general examination, a 5×5 cm abscess was observed on his right lumbar region, which was warm but notably painless and nontender, as shown in Figure 1. A Non-Contrast Computed Tomography (NCCT) scan of the brain was performed to exclude the possibility of stroke due to the patient's gait imbalance; however, the results were unremarkable.

Laboratory investigations at the time of admission revealed a hemoglobin level of 10.5 g/dL, a total leukocyte count of 69,000/mm³, and a platelet count of 640,000/mm³. Liver function tests and coagulation parameters were within normal limits. Renal function was impaired, as evidenced by a serum creatinine level of 2.4 mg/dL and a urea level of 120 mg/dL. Additionally, hyponatremia was present, with a serum sodium level of 128 mEq/L. Peripheral blood smear revealed a markedly elevated total leukocyte count with a left shift extending up to the promyelocyte stage and the presence of toxic granulations. No blasts were observed, and BCR-ABL testing for Chronic Myeloid Leukemia (CML) was negative. A comprehensive infectious disease workup, including Computed Tomography (CT) imaging of the abdomen and chest, did not reveal any significant abnormalities. Additionally, a two-dimensional echocardiographic assessment was also normal. Blood and urine cultures yielded no growth. Notably, inflammatory markers, including serum procalcitonin and C-Reactive Protein (CRP), were elevated. The patient initially received a bolus of intravenous fluids and was started on vasopressor support, along with broad-spectrum intravenous antibiotics, including piperacillin-tazobactam and clindamycin, in conjunction with other supportive measures. While the patient's shock was resolved with the instituted treatment, he remained febrile, and his leukocyte count continued to rise, reaching 85,000/mm³ despite ongoing therapy.

The next day, the abscess was surgically drained. Although the patient became afebrile after the procedure, his leukocyte count continued to increase. Culture analysis of the drained abscess revealed the presence of *Clostridium difficile*. In response, antimicrobial therapy was escalated to include intravenous metronidazole and vancomycin while piperacillin-tazobactam was continued. After a two-week course of antibiotics, the patient showed gradual clinical improvement and achieved hemodynamic stability. Leukocyte counts normalized, and the acute kidney injury resolved. He was successfully discharged from our institution. At the two-week follow-up, his laboratory parameters remained within normal limits, he was hemodynamically stable, and he reported no new complaints.

This case is of particular interest due to the rarity of *Clostridium difficile*-associated abscess leading to a leukemoid reaction. The successful management included a combination of surgical drainage and targeted antibiotic therapy, resulting in clinical resolution. This case highlights the importance of considering atypical infectious sources in patients presenting with persistent leukocytosis despite broad-spectrum antibiotics.

Discussion

Clostridium difficile is primarily recognized for its role in antibiotic-associated diarrhea and pseudomembranous colitis; however, its potential to cause extraintestinal infections remains uncommon. The incidence and severity of CDI have increased in recent years. The occurrence of a leukemoid reaction in conjunction with CDI is uncommon and signifies a serious condition with a poor prognosis.[10] One of the rarest presentations is *C. difficile*-associated leukemoid reaction, which refers to an extreme elevation in White Blood Cell (WBC) count, often exceeding 50,000 cells/mm³, in response to infection. Leukemoid reactions have been widely reported in severe infections, malignancies, and stress responses. Leukocytosis in CDI is thought to be driven by severe systemic inflammation, cytokine release, and toxin production. Studies suggest that extreme WBC elevations may correlate with disease severity, potentially serving as a prognostic marker for adverse outcomes, including septic shock, multi-organ dysfunction, and mortality.[11,12]

The most significant risk factor for developing CDI is the use of broad-spectrum antibiotics such as penicillins, cephalosporins, fluoroquinolones, and clindamycin which disrupt the normal gut microbiota, leading to dysbiosis and allowing *C. difficile* to proliferate and cause infection.[13,14] Other risk factors include proton pump inhibitor use, advanced age, immunosuppression, underlying comorbidities, previous CDI, renal or hepatic failure, recent hospitalization, and prolonged hospital stays.[15,16]

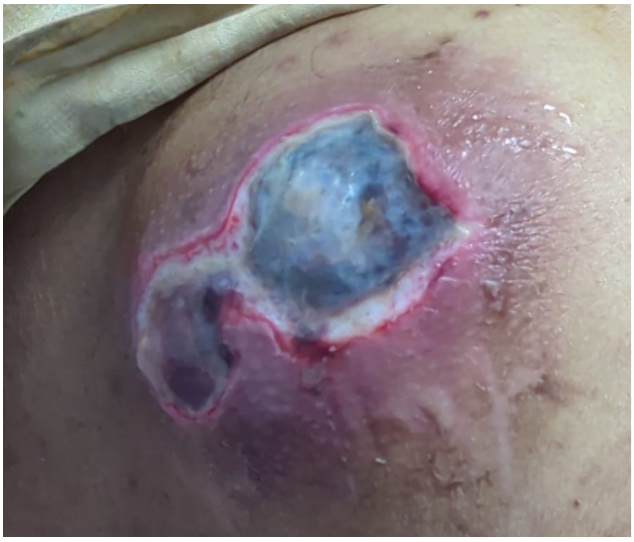

Figure 1. Abscess in the right lumbar region.

Although *C. difficile* is predominantly linked to gastrointestinal pathology, extra-intestinal manifestations, including abscess formation due to CDI, are exceedingly rare, with only a few cases documented in the literature.[17] The mechanism behind extraintestinal dissemination remains unclear but may involve hematogenous spread, direct inoculation, or translocation from the gastrointestinal tract. In this case, the lack of gastrointestinal symptoms (such as diarrhea or colitis) initially obscured the diagnosis, emphasizing the importance of considering CDI in patients with soft tissue infections and systemic inflammatory responses. The identification of C. difficile in the abscess culture was unexpected, reinforcing the need for broad-spectrum microbiological testing in cases of persistent sepsis with unusual presentations.

Reports in the literature describe cases of *C. difficile* bacteremia without associated diarrhea, highlighting its ability to disseminate systemically.[18] Furthermore, a documented case of *C. difficile* spinal epidural abscess illustrates its capacity to infect soft tissues, albeit infrequently.[19] The study by Albrich and Rimland found that among 162 CDI patients, 22% had thrombocytosis, and 60% had leukocytosis. *C. difficile* toxin A was more common in thrombocytosis with leukocytosis, suggesting these markers may help diagnose infections.[20]

Unlike intestinal CDI, for which treatment guidelines are well established, there are no standardized protocols for extraintestinal CDI. Current guidelines for treating intestinal CDI recommend oral vancomycin or fidaxomicin for first episodes, recurrences, and severe cases. Metronidazole is now reserved for mild infections and should only be considered when vancomycin or fidaxomicin, are unavailable, as it is no longer recommended as first-line therapy. However, the role of oral versus intravenous antibiotics in extraintestinal infections remains uncertain.

While CDI is traditionally linked to healthcare settings, recent reports highlight a rising incidence in the community even among individuals without prior healthcare exposure or antibiotic use, as seen in our case.[21-22]

In our case, initial empiric therapy with piperacillin-tazobactam and clindamycin was insufficient, as evidenced by progressive leukocytosis and persistent fever. The turning point in management was the identification of C. difficile in the abscess culture, prompting a switch to intravenous metronidazole and vancomycin, which led to clinical resolution. This case underscores the importance of early surgical intervention for abscess drainage, as source control is essential in managing deep-seated infections. Additionally, risk factors for extraintestinal CDI should be carefully evaluated. Although our patient had no prior history of hospitalization or antibiotic use, further research is warranted to clarify host susceptibility, bacterial virulence mechanisms, and optimal treatment approaches for extraintestinal CDI.

This case highlights the importance of considering atypical infectious sources in patients with leukocytosis and fever. Clinicians should remain vigilant in recognizing unusual infectious presentations of *C. difficile*, especially in patients lacking classical gastrointestinal manifestations.

CDI is commonly transmitted through contaminated surfaces in hospitals. Inadequately cleaned surfaces and medical equipment can serve as reservoirs for its spores, facilitating transmission to patients when infection prevention and control measures, including effective cleaning protocols, are not properly implemented.[23]

Conclusions

Clinicians should consider CDI even in the absence of classical gastrointestinal symptoms, particularly in patients presenting with abscesses, sepsis, or unexplained leukemoid reactions**.** Leukemoid reactions may serve as a surrogate marker of CDI severity and could aid in risk stratification**.**

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