Seeing *C. diff* Differently: A Case of *Clostridioides difficile* Bacteremia in Metastatic Melanoma

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**Conflict of interest:** None declared

**Patient:** Male, 51-year-old  
**Final Diagnosis:** Atrial mass • *Clostridioides difficile* bacteremia • hemodynamic shock • metastatic melanoma  
**Symptoms:** Ascites • atrial flutter • edema • mass in abdomen • tachycardia  
**Medication:** —  
**Clinical Procedure:** Paracentesis • radiation therapy  
**Specialty:** Cardiology • Infectious Diseases • General and Internal Medicine • Oncology  

**Objective:** Rare disease  
**Background:** *Clostridioides difficile* infection (CDI) is a common community-acquired and nosocomial infection that usually presents as colitis. *C. difficile* bacteremia (CDB) is a rare blood infection, with only a few cases recorded in the literature. We seek to expound on the current literature by detailing the clinical course of a patient with metastatic melanoma who developed CDB.

**Case Report:** This case highlights the hospital course of a 51-year-old man admitted for a new onset of arrhythmia during the evaluation and management of a malignancy. The patient experienced hemodynamic collapse and rapid deterioration, which progressed to death. The etiology of death is thought to be septic shock due to CDB in the setting of multiple comorbidities.

**Conclusions:** The patient was predisposed to CDI because of the disruption of his intestinal milieu by the administration of a cephalosporin for the treatment of his suspected secondary bacterial peritonitis. His treatment with palliative radiation to his rectal mass placed him further at risk of CDI. We believe either of these could have contributed alone or synergistically to the development of his CDB.

**MeSH Keywords:** Arrhythmias, Cardiac • Bacteremia • *Clostridium difficile* • Melanoma  

**Full-text PDF:** https://www.amjcaserep.com/abstract/index/idArt/928169
Background

*Clostridioides difficile* is a spore-producing gram-positive anaerobic bacillus which frequently causes diarrhea associated with antibiotic use. It can generate toxins as well, specifically the enterotoxin toxin A and the cytotoxin toxin B, with toxin B being more virulent. The diarrhea is usually the result of normal intestinal flora disruption. It can be severe and cause complications such as toxic megacolon and pseudomembranous colitis [1]. Although *C. difficile* is a commonly encountered infection, extraintestinal manifestations such as invasion into the bloodstream are rarely observed. One study reported that of 18,601 instances of *C. difficile* infections (CDIs), there were only 2 cases (0.01%) of *C. difficile* bacteremia (CDB), and 1 of the 2 patients died [2]. Although cases are limited, mortality from our literature review appears to be about 40% to 50% [2–4]. We present a case of a middle-aged man with extensive lymphadenopathy and ascites who was hospitalized for new-onset atrial flutter and suspected hematologic malignancy. He was subsequently diagnosed with diffuse metastatic melanoma, and he quickly succumbed to complications of his treatment. One of 2 blood cultures grew *C. difficile* post-mortem. It is our objective to detail the circumstances leading up to this patient’s death, followed by a brief discussion about melanoma, a review of other cases of CDB, and concluding thoughts on why this patient may have acquired this rare disease.

Case Report

The patient was a 51-year-old man with a past medical history of hypertension, type 2 diabetes, and remote tobacco use who presented to his oncologist for evaluation of enlarging masses. A computed tomography (CT) of the chest, abdomen, and pelvis was obtained and showed numerous masses, including a left axillary mass, an abdominal mass, and a rectal mass. There was concern for lymphoma, and biopsies were performed. During a subsequent visit to his oncologist, the patient was tachycardic and was sent to the emergency department (ED) for further evaluation. He was diagnosed with new-onset atrial flutter with rapid ventricular response and was admitted to the hospital.

He was immediately started on IV diltiazem and therapeutic enoxaparin. The cardiologist performed a transesophageal echocardiogram on day 2 of his hospitalization, which revealed a 4.5×3.5 cm mass on the annulus of the tricuspid valve and a small clot in the left atrial appendage (Figure 1). The cardiologist recommended a cardiothoracic surgery evaluation for the atrial mass, and the cardiothoracic surgeon recommended medical management. Owing to the patient’s lack of heart rate control and borderline hypotension, the cardiology team added digoxin to his treatment regimen. In addition to cardiac concerns, the patient had anasarca with significant ascites, 4+ bilateral lower extremity edema, and evidence of hyperreflective hyponatremia. His sodium level was 127 on admission and remained low throughout his hospitalization. His fluid overloaded state persisted despite aggressive diuresis. A paracentesis was done on day 3 of his hospitalization and 4.1 L of ascitic fluid were removed under albumin cover. Fluid studies showed a white blood cell count of 17,000, with the polymorphonuclear cells approximating 8000 and a serum-ascites albumin gradient of 0.7. The lactic acid dehydrogenase level was 1600 units/L, protein 4.2 g/dL, and glucose 86 mg/dL. Although the patient did not clinically appear infected, he met the criteria for secondary bacterial peritonitis based on fluid studies and received 3 days of ceftriaxone while awaiting cytology and culture results. The culture had no growth and the cytology showed atypical melanocytes, confirming malignant ascites. Throughout his hospitalization, his heart rate remained poorly controlled despite maximal doses of IV diltiazem; the cardiologist increased the digoxin dose and added metoprolol. Four days after admission he converted to a normal sinus rhythm, but on day 5 he became tachycardic again.

The results of the patient’s biopsies were available early during his hospitalization and revealed metastatic melanoma rather than lymphoma, as was previously speculated. The patient denied any prior skin lesions. The medical oncology team tested for B-type Raf proto-oncogene (BRAF) status and started the patient on nivolumab inhouse with plans to start ipilimumab when he was an outpatient. The radiation oncology team began palliative radiotherapy to the rectal and intracardiac masses. Magnetic resonance imaging of the brain to evaluate for brain metastasis revealed 4 hemorrhagic metastatic lesions. The patient’s hemorrhagic lesions in the setting of an
atrial clot and recent prolonged episode of atrial flutter placed him at an increased risk for thrombotic stroke; therefore, he was changed from therapeutic to prophylactic enoxaparin and the neurosurgery team was consulted for additional anticoagulation recommendations. After obtaining a repeat head CT, which showed stability of the brain lesions, the neurosurgeon recommended using heparin for its ease of reversibility if anticoagulation was unavoidable. The patient was placed on a prophylactic dose of heparin. He converted to a normal sinus rhythm about a week after his admission, and his heart rate was maintained on oral metoprolol and diltiazem.

Meanwhile, the patient’s ascites worsened; therefore, he underwent a second paracentesis on day 9 of hospitalization and 3.5 L of fluid were removed. Early on day 10, he became hypotensive. He did have a leukocytosis, but this was ascribed to his metastatic disease, and the hypotension was attributed to hypovolemia from the recent paracentesis. He was given albumin and started on norepinephrine and stress-dose steroids for shock, and was transferred to the intensive care unit. Blood cultures were obtained. During the day, he weaned off vasopressors. That evening, a nurse documented multiple liquid stools and placed a rectal tube.

The following morning, day 11, the patient again required vasopressor support. He was started on vancomycin and cefepime and the steroids were continued. He had severe lactic acidosis, leukocytosis, rapidly worsening kidney injury, and metabolic encephalopathy. The oncologist attributed the patient’s condition to the large melanoma burden throughout his body. He rapidly deteriorated, and given his overall poor prognosis, his family elected to discontinue aggressive measures and focus on comfort. The patient died shortly thereafter. The blood culture results were available postmortem. One culture grew C. difficile and the other culture had no growth. Since the family did not request an autopsy, no further tissue samples were analyzed postmortem.

Discussion

There are numerous interesting points about this case. One is the diagnosis of metastatic melanoma in a patient who denied skin lesions. Melanoma is a cancer of melanocytes and therefore most commonly presents as cutaneous melanoma. It is often identified by biopsy of a suspicious nevus, which includes new meeting the popular ABCDE criteria (asymmetry, border irregularity, color variation, diameter greater than 6 mm, and evolution) [5]. However, regression of melanoma in a cutaneous lesion is possible; often the regression is partial, but it can be complete. Unfortunately, regressed cutaneous melanoma can still metastasize [6].

Although melanoma is typically considered a skin cancer, it does occasionally arise from melanocytes in the mucosa, eye, or central nervous system (CNS). Mucosal melanomas occur in only 1.4% of cases. They can be found anywhere there are melanocytes, including the oral and nasal cavity, paranasal sinuses, larynx, esophagus, rectum, anal canal, vagina, and cervix. The most common location for mucosal melanoma is the anorectal mucosa, which accounts for about 16.5% of mucosal melanomas [7]. For anorectal mucosal melanoma, patients with lymph node involvement have a 5-year survival of only 9.8%, compared to a 5-year survival of 26.7% for those without lymph node metastasis. Regardless, primary mucosal melanoma in any location portends a poor prognosis, in part because delayed diagnosis is common [7].

Primary uveal melanoma has a worldwide incidence of approximately 7000 cases per year. Uveal melanoma is the most common primary ocular cancer in the United States; although, retinoblastoma is more common worldwide. Uveal melanoma usually presents as loss of vision due to retinal detachment. Typically, by the time a patient seeks medical care for vision, metastasis has already occurred and prognosis is poor [8].

Primary CNS melanoma is a diagnosis of exclusion because CNS metastasis is common. Although primary CNS melanoma is rare and no formal diagnostic guidelines exist, some of its distinguishing features discussed in an article in the Journal of Clinical Neuroscience include a younger age, single CNS lesion, slower clinical progression, and no extracranial involvement. Contrarily, metastatic CNS melanoma is more common in older people and typically includes several brain lesions, a faster clinical progression, and extracranial involvement. Prognosis is better in primary than in metastatic CNS disease [9].

For the patient in this case, the primary melanotic lesion is unknown. Primary ocular and CNS melanoma are much less likely since he did not complain of visual symptoms, and there were already several CNS lesions and advanced metastasis at the time of diagnosis. It is likely the patient had either cutaneous melanoma, and the primary skin lesion was not observed or had regressed, or a primary mucosal melanoma. His rectal mass could have been primary or metastatic. Cutaneous melanoma is far more common, and it is also common for melanoma to metastasize to the gastrointestinal (GI) tract. A BRAF mutation is not frequently seen in mucosal melanoma but was present in this patient [7]. Per discussion with the oncology team at our facility, the final diagnosis of the primary melanotic lesion was not heavily pursued as it would not have significantly impacted the trajectory of his disease course.

The patient had diffuse metastases at the time of diagnosis, including presumed cardiac and brain metastases. Although no formal biopsies were obtained of the cardiac mass, it was...
likely metastatic melanoma because melanoma is one of the most common malignancies to metastasize to the heart [10]. It is probably this metastatic mass that caused the refractory atrial flutter with rapid ventricular response. He also had GI involvement, whether from metastasis or from a primary mucosal melanoma. It was for this reason the oncologist recommended targeted radiation therapy to the rectal mass.

The most notable oddity in this patient's case is the CDB, which is indeed a rare finding. According to a Finland study of records from the Helsinki University Central Hospital Laboratory Diagnostics over a 10-year period, extraintestinal manifestations of *C. difficile* were noted in only 31 of 18,601 (0.17%) cases of CDIs. Of those 31 cases, only 2 were bacteremia [3]. Another decade-long study in Taiwan found 12 patients with CDB in the National Cheng Kung University Hospital and the National Taiwan University Hospital, which have 1100 and 2800 beds, respectively [4]. A 2009 case study of a patient with Crohn's disease who had CDB was combined with a literature review searching for CDB from 1966 to 2008; the authors found 15 cases [2].

Exploring the individual characteristics of the patients who had CDB sheds light on the significance of the finding in this present case. Of the 2 patients in Finland, 1 had an episode of colitis 6 months prior to the diagnosis of *C. difficile* in an abdominal aneurysm. The other underwent palliative surgery for colon cancer and subsequently became bacteremic with multiple bacteria, including *C. difficile*. The former patient survived; the later died [3].

In the study in Taiwan, of the 12 patients with documented CDB, 6 were polymicrobial, 4 had diarrhea, 5 had an underlying GI disease, and 5 recently received antibiotics. Regarding antibiotics treatment, 10 of 12 isolates were available, all of which were sensitive to vancomycin and metronidazole. The 4 patients who did not receive vancomycin or metronidazole died. The other 8 were treated with either vancomycin or metronidazole, and only 1 of them died. Total mortality was 42%. The authors of this study also conducted a literature review of PubMed articles published in English between 1962 and 2009. They found 20 cases of CDB, of which 75% had GI disease; 10 of 19 patients died, with the outcome of the twentieth patient unknown [4]. The literature review in the Crohn's disease case study showed 40% mortality [2].

As to the rarity of CDB, it may truly be a rare growth in the blood. However, it may also be underdiagnosed. CBD is extremely difficult to culture because of its anaerobic properties [11].

Another consideration is the clinical relevance of CDB; although, limited data make this difficult to determine. However, a 2006 article entitled “The possible significance of *Clostridium* spp. in blood cultures” examined 80 cases of *Clostridium* bacteremia and compared them to cases of *Bacillus* bacteremia. Although none of the specific *Clostridium* species were *C. difficile*, the conclusion was that *Clostridium* bacteremia is clinically important more often than not [12]. Given this information and the high mortality in the few documented cases that exist, it is prudent to treat *C. difficile* bacteremia as clinically significant unless further evidence arises to the contrary.

The patient in the present case did not complain of diarrhea throughout most of his hospitalization; it was not until the day before his death that nursing staff noted significant diarrhea. Given the lack of symptoms initially, he may have been an asymptomatic carrier who developed symptoms as he became more ill. Alternatively, he may have acquired a nosocomial CDI owing to the duration of his hospitalization and the interventions provided that placed him at higher risk. It is thought that *C. difficile* develops in part because of the disturbance of the normal gut microbiome, specifically from antibiotics [1]. Cancer patients have multiple risk factors as well, including prolonged and/or recurrent hospitalizations, immunosuppression, and therapies that can alter the microbiome [13]. There is also a paucity of data showing the effects of radiation therapy on the predisposition to CDI [14].

During his hospitalization, this patient received ceftriaxone, one of the more common antibiotics that predispose patients to CDIs [1]. He was hospitalized for over a week, was on immunotherapy, and received radiation treatments to the rectum, increasing his risk of contracting *C. difficile* [13,14]. Regarding how he developed bacteremia from *C. difficile*, it is possible that the radiotherapy facilitated translocation of the bacteria into the bloodstream. Several of the aforementioned cases of CDB involved either GI disease or GI manipulation. Alternatively, there may be an as-yet undocumented association between melanoma of the GI tract and *C. difficile*. Given the propensity of *C. difficile* to cause GI illness, it is most probable that translocation from the intestines to the bloodstream occurred in our patient. However, because little is known about CDB, the possibility that bacteremia developed by some other means cannot be excluded.

**Conclusions**

The patient in this case had severe disease and multiorgan involvement from metastatic melanoma. Even without the hemodynamic shock at the end of his life, he had a poor prognosis. Only 1 of his blood cultures grew *C. difficile* and, although he developed watery diarrhea the day prior to his death, no stool samples were sent for analysis. It is therefore uncertain whether he had *C. difficile* diarrhea. However, as seen in the studies mentioned above, CDB can exist in the absence of
diarrhea. The patient’s recent antibiotic use with ceftriaxone and the GI melanoma, immunotherapy, and radiation treatments to the rectum likely placed him at a higher risk of developing *Clostridium difficile* infection. He was treated empirically with vancomycin and cefepime, and, although data are extremely limited, it appears vancomycin is an appropriate treatment for CDB. However, patients with CDB have a high mortality risk, and given this patient’s multiple comorbidities, it is not surprising that he did not recover.

**Institution where work was done**

Miami Valley Hospital, Dayton, OH, U.S.A.

**Conflict of interest**

None.

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