



Case Report

Acute myeloid leukemia with central nervous system extension and subdural seeding of vancomycin-resistant *Enterococcus faecium* after bilateral subdural hematomas treated with subdural daptomycin administration

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Received : 19 July 19
Accepted : 20 August 19
Published : 10 September 19

DOI
[10.25259/SNI_225_2019](https://doi.org/10.25259/SNI_225_2019)

Quick Response Code:



ABSTRACT

Background: We present a rare case of comorbid relapsed acute myeloid leukemia (AML) with the involvement of the central nervous system (CNS) and subdural seeding of vancomycin-resistant *Enterococcus faecium* (VRE). The safety profile, treatment approach with pharmacokinetic considerations, and evaluation of success for bilateral subdural administration of daptomycin after subdural hematoma (SDH) are assessed.

Case Description: A 45-year-old male with a history of AML who underwent chemotherapy (induction with 7 + 3) was admitted to oncology with relapsed AML confirmed by bone marrow biopsy, complicated by neutropenic fever and VRE bacteremia. After acute neurological changes with image confirmation of mixed-density bilateral SDHs secondary to thrombocytopenia, the patient was admitted to the neurosurgery unit and underwent bilateral burr hole craniotomies for subdural evacuation with the placement of the left and right subdural drains. Culture of the subdural specimen confirmed VRE seeding of the subdural space. The patient received the first dose of daptomycin into the bilateral subdural spaces 2 days after evacuation and was noted to have acute improvement on neurological examination, followed by a second administration to the left subdural space 5 days after evacuation with bilateral drains pulled thereafter.

Conclusion: In this patient, the complication of relapsed AML may have contributed to the rare extension of VRE into the CNS space. Screening for patients at risk of AML with CNS involvement and addressing coagulopathy and risk of infection may help mitigate morbidity. Bilateral administration of subdural daptomycin bolus into the subdural space was tolerated and possibly contributed to the patient's neurological improvement during an extended hospital course.

Keywords: Acute myeloid leukemia with central nervous system involvement, Acute myeloid leukemia, Daptomycin, Subdural administration, Subdural hematoma

INTRODUCTION

Incidence of central nervous system (CNS) involvement by acute myeloid leukemia (AML) in adult patients is reported to be 0.6%–2%^[1,2] and is generally more likely to occur in the setting of relapse than at initial diagnosis.^[1] CNS involvement portends poor outcomes with increased

morbidity and mortality.^[1,18] Alakel *et al.* demonstrated that adult AML patients with CNS involvement achieved remission 24% less often than those without CNS involvement and had significantly reduced overall survival.^[1] Furthermore, the immunocompromised state and propensity for coagulopathy associated with hematologic malignancies contribute to a heightened risk for infection and hemorrhagic complications.

Enterococcal meningitis comprises only 0.3%–4% of bacterial meningitis cases.^[17] Several treatment options exist with controversial prioritization of drugs including daptomycin, linezolid, and tigecycline.^[16] Daptomycin (Cubicin®) is a lipopeptide antibiotic with concentration-dependent bactericidal activity against a broad range of Gram-positive organisms and a tolerable safety profile.^[8] Its multifaceted mechanism of action to disrupt the cytoplasmic membrane and inhibit protein synthesis at all stages of the growth cycle has proven reliable in the treatment of deep-seated infections of multidrug-resistant *Staphylococcus*, *Streptococcus*, and *Enterococcus* pathogens.^[6] However, daptomycin registers a mean cerebrospinal fluid (CSF) penetration of 6% with poor CSF-to-serum ratio in the treatment of CNS infections through intravenous (IV) administration.^[15] Linezolid demonstrates excellent blood–brain barrier diffusion with a CSF-to-serum ratio near 1 but does not elicit bactericidal effect.

Given the rapid bactericidal efficacy of daptomycin against multidrug-resistant pathogens, efforts have been made to deliver the antibiotic through alternative methods to treat intracranial infections.^[6] Indeed, successful resolution of vancomycin-resistant *Enterococcus faecium* (VRE) ventriculitis with the administration of intraventricular daptomycin from an external ventricular drain has been documented.^[14] While intraventricular delivery has been tolerated, limited evidence,^[4,12,15] to date, exists regarding subdural administration of daptomycin to treat infectious seeding of the arachnoid space or parenchyma. Traditional management of subdural empyema involves burr hole with aspiration of pus in addition to subdural catheter placement for drainage and antibiotic administration.^[13] Advances in antibiotic blood–brain barrier and blood–spine barrier penetration have largely replaced direct subdural administration. Recent studies have demonstrated the necessity of higher doses of IV daptomycin to treat VRE.^[3]

CASE REPORT

A 45-year-old male presented with relapsed AML with CNS involvement, complicated by neutropenic fever and sepsis with VRE bacteremia and subsequently developed bilateral subdural hematomas (SDHs) with seeding of VRE into the subdural spaces bilaterally. The patient was initially diagnosed with AML (*FLT3/NPM1* wild type, trisomy 7, 7q and 22q

deletions, and *TET2* and *UT2AF1* mutations) approximately 2 months before admission and was started on 7 + 3 therapy (cytarabine and daunorubicin). On outpatient oncology follow-up, he was found to have a right-sided facial droop secondary to Bell's palsy and admitted to the emergency department, where a head computed tomography (CT) was negative. The patient was subsequently admitted to an outside hospital for nausea and vomiting with a lactate dehydrogenase of 955 and white blood cell count of 78,000 with 35% blasts, for which he was initiated on allopurinol and hydroxyurea and transferred to our institution's hospital for further medical workup and bone marrow transplant evaluation.

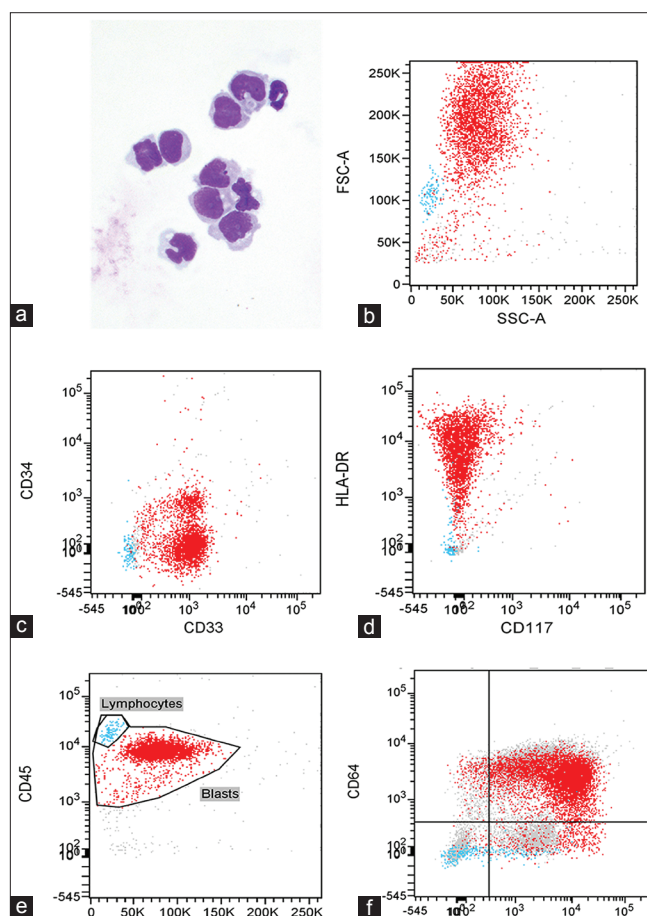


Figure 1: (a) Cerebrospinal fluid (CSF) cytology of Giemsa- and Papanicolaou-stained cytospin preparations showing monoblasts/promonocytes with round-to-folded nuclei, fine chromatin, and prominent nucleoli consistent for acute myeloid leukemia (AML) with monoblastic/monocytic morphology (Diff-Quik, ×600). (b-e) Flow cytometry of the CSF using FACSDiva software using CD45 versus side scatter gating showing a large myeloid blast population (91% of all cells). The blasts were CD45dim, CD33+, CD34-, CD117-, and HLA-DRbright, consistent with central nervous system involvement by the patient's AML with monocytic differentiation. (f) Flow cytometry of bone marrow showing expression of monocytic markers (CD64 and CD11c) in the blast population.

On admission to our institution's hospital, the patient was afebrile and hemodynamically stable. The patient was alert and oriented though unable to recall the details of previous hospital stays. He endorsed a 20 lbs weight loss over the past 3 months and intermittent 10/10 occipital throbbing headaches. The patient underwent a bone marrow biopsy, which showed relapsed AML, for which he completed high-dose cytarabine and mitoxantrone (HAM) reinduction. Due to new-onset Bell's palsy, CSF specimens were obtained; pathology and flow cytometry reports were consistent with AML with CNS involvement, Figure 1. During his hospital course, he developed neutropenic fever to 104 F with 4/4 blood cultures positive for multiple strains of VRE, all of which were susceptible to daptomycin with varying susceptibilities to linezolid. The patient had a negative transthoracic echocardiogram; potential sources of infection included peripherally inserted central catheter line, pulmonary (right lower lobe opacity at the time of infection), or urinary (culture showed rare VRE). The patient was initially treated with daptomycin 12 mg/kg IV every 24 h and linezolid 600 mg IV every 12 h. He was also initiated on voriconazole 4 mg/kg IV titrated to trough goal 2–4 mcg/mL and acyclovir 400 mg IV every 12 h for presumed fungal nodules and viral prophylaxis, respectively. Blood cultures sterilized after 3 days of therapy.

Thirty-one days after admission, the patient was intubated for inability to protect his airway after decompensation with increased emesis and somnolence. He was found to have acute bilateral mixed-density SDHs measuring 8 mm on the left and 5 mm on the right in the setting of profound thrombocytopenia (platelet count = 7 K/ μ L), Figure 2. He underwent emergent bilateral frontoparietal and right inferior temporal burr hole craniotomies for evacuation with subdural drain placement bilaterally. Intraoperative tissue sent for cultures was notable for the growth of VRE susceptible to linezolid and daptomycin, 7 days after sterilization of blood cultures. The patient's regimen was broadened to combination high-dose therapy of daptomycin 12 mg/kg IV every 24 h, linezolid 600 mg

IV every 8 h, imipenem/cilastatin 1000 mg IV every 8 h, voriconazole, and acyclovir prophylaxis. Due to the presence of subdural VRE and presumed unsuccessful treatment of recent VRE bacteremia, the inadequate blood–brain barrier penetration of IV daptomycin led to the decision that subdural administration of daptomycin would be required to adequately sterilize the subdural space. Daptomycin 5 mg in sodium chloride 0.9% 2 ml solution was aseptically compounded and administered into the subdural spaces bilaterally (total 10 mg) over 4 min followed by a 1–2 ml sodium chloride 0.9% flush. Following administration, the subdural drain was clamped for as long as tolerated. The right subdural drain was noted to have no additional output after POD #2. Subsequent head CT was confirmed stable on POD #3 with resolution of bilateral SDH. On POD #3, the patient was noted to have acute improvement: he was intermittently responding to commands, making his needs known, and moving all extremities spontaneously with equal strength. His pupils were equal, round at 3 mm, and reactive. The patient localized the right upper extremity and withdrew the left upper extremity and bilateral lower extremities.

Daptomycin 2.5 mg in sodium chloride 0.9% 2 ml solution with 1–2 ml saline flush was administered to the left subdural drain 72 h after the initial bolus dose (POD #5). Subdural daptomycin administration was limited to the left subdural drain in a setting of a nonfunctioning right subdural drain requiring removal. The patient remained on IV daptomycin, linezolid, and imipenem/cilastatin for broad-spectrum antibiotic coverage during this time and after subdural administration of daptomycin. The subdural drains were pulled after the second administration of daptomycin on POD #5 and the patient was transferred out of the ICU with planned bone marrow biopsy and reinduction-HAM chemotherapy.

The patient's hospital course was complicated by the observation of delta discharges over the left centroparietal and posterior regions consistent with ictal to interictal spectrum with the right upper limb and hand twitching indicating Epilepsia partialis continua on POD #11 through POD #19. The right-sided myoclonic jerk was noted to increase

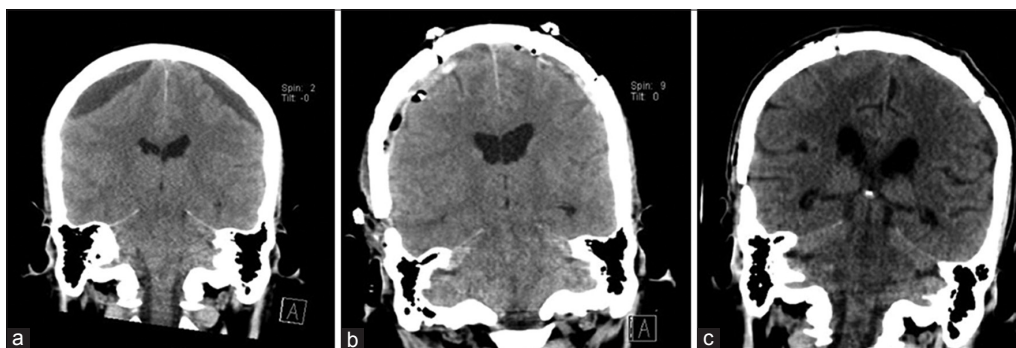


Figure 2: (a) Preoperative computed tomography (CT) head showing bilateral subdural hematomas, (b) postoperative CT head, with bilateral subdural drains intact, (c) 3-week postoperative CT head, after daptomycin administration and removal of subdural drains.

on deliberate movement of the right upper extremity, i.e., holding his arms outstretched in front of him and not noted at rest. Due to the acute onset, focal seizure secondary to cortical irritation from blood products or subdural daptomycin was suspected versus hemispasm secondary to Bell's palsy. Additional findings included generalized polymorphic theta slowing with prominent left temporal theta slowing. The patient was without clinical improvement after treatment with levetiracetam 1500 mg twice daily and phenytoin therapy. He was transitioned to levetiracetam 1500 mg twice daily and lacosamide 200 mg twice daily on hospital discharge.

DISCUSSION

We report a unique presentation of CNS involvement by AML with monocytic differentiation, development of bilateral hematomas, and subdural VRE infection in the same patient. Traditional risk factors for CNS involvement of AML include elevated lactate dehydrogenase, hyperleukocytosis, CD56+ blast cells, and a prominent monocytic component.^[18,19] This patient was found to have all four risk factors including hyperleukocytosis of 78,000, elevated lactate dehydrogenase of 955, CD56+ AML at diagnosis, and AML with monocytic differentiation. A recent large study of adult AML patients with CNS involvement found that *FLT3* mutations were also associated with extramedullary extension of AML.^[1] In addition, 7q deletions have been associated with worse outcomes and CNS extension.^[7] Next-generation sequencing performed on our patient's bone marrow showed that his AML demonstrated trisomy 7 and 7q and 22q deletions but was *FLT3/NPM1* wild type.

Furthermore, evidence suggests that CNS involvement in AML increases the propensity for subdural hemorrhage and other intracranial bleeds.^[10] Our patient presented with thrombocytopenia and an immunocompromised state (ANC nadir 0 K/ μ L) with recovery during his hospital stay. The patient was likely predisposed to CNS involvement and bleeding given the characteristics of his AML and to multidrug-resistant infection given his immunocompromised state and multiple hospital admissions.

The previous reports have demonstrated an acceptable safety profile of subdural daptomycin for the treatment of VRE in the subdural space.^[9,11] We show a tolerated multistage bilateral and simultaneous administration of subdural daptomycin to treat subdural VRE infection. Due to its low CNS penetration, daptomycin was delivered subdurally at the subdural drain sites. Two doses were administered over 3 days, and then, the patient was continued on IV daptomycin, linezolid, and imipenem/cilastatin therapy with documented neurological improvement. This is a shorter time period than other previously reported studies that administered daptomycin for at least 7 days through intrathecal and intraventricular methods.^[5,11] However, the

risk of prolonged drain insertion after clinical improvement outweighed the benefit of continued subdural antibiotic administration. The present report represents the first case of subdural administration of daptomycin for the treatment of VRE seeding into the bilateral subdural spaces with the concurrent complication of AML with CNS involvement.

Analysis of peak and trough levels with follow-up culture of samples was attempted and would have improved our ability to evaluate the efficacy of daptomycin treatment for subdural seeding of VRE. In addition, daptomycin accumulation and discordance between the left and right spaces would assist in the evaluation of therapy and provide metrics for future administrations in the subdural microenvironments. Samples obtained from the subdural drain before and after subdural administrations may inform the degree to which IV antibiotics contributed to improvement or confounded subdural administrations. It may have been more appropriate to place an Ommaya reservoir for the consistent and reliable long-term administration and monitoring of subdural antibiotics. As Ommaya placement has been previously demonstrated to be successful for VRE ventriculitis,^[5] a similar utilization for subdurally seeded infections may also be recommended and would avoid clotting issues with subdural drains. It should be noted that *Epilepsia partialis continua* seizures could be due to inflammation secondary to infection, irritation from antibiotics, or autoimmune processes.^[16]

The complication of relapsed AML with monocytic differentiation may have contributed to the rare extension of VRE into the CNS space in our patient. Screening for patients at risk of AML with CNS involvement and addressing coagulopathy and risk of infection may help mitigate morbidity in future cases. Bilateral administration of subdural daptomycin was tolerated and possibly contributed to the patient's neurological improvement during his extended hospital course.

CONCLUSION

Subdural administration of daptomycin may be an appropriate treatment option for clinicians faced with managing this rare CNS infection in this complicated clinical setting.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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How to cite this article: Dietz N, Barra M, Zhang M, Zachariah M, Coumans JV. Acute myeloid leukemia with central nervous system extension and subdural seeding of vancomycin-resistant *Enterococcus faecium* after bilateral subdural hematomas treated with subdural daptomycin administration. *Surg Neurol Int* 2019;10:171.