

Case Report

Successful treatment of pyogenic liver abscesses by daptomycin

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Abstract: Pyogenic liver abscess is a condition with considerable mortality. The common etiology of liver abscesses after chemotherapy is fungi, especially candida albicans, and gram-positive bacteria. However, little is known about gram-positive bacterial infection as the cause of pyogenic liver abscess. In this study we reviewed our experiences with the use of daptomycin for the treatment of gram-positive bacteria caused pyogenic liver abscess in 5 patients with malignant hematological diseases. For these immunodeficiency patients, infectious pathogens are usually difficult to be identified. Gram-positive pathogens as a cause of pyogenic hepatic abscesses can be effectively and timely controlled by daptomycin.

Keywords: Pyogenic hepatic abscesses, daptomycin, leukemia, gram-positive pathogens

Introduction

Pyogenic liver abscess is a condition with considerable mortality. For patients with malignant hematological diseases, the uncommon causes of febrile after chemotherapy include hepatic abscess. For these patients who are immunocompromised, they have 3.6-fold increased risk for developing liver abscess [1]. Pyogenic liver abscesses are classified according to the etiology such as Clostridium species and gram-negative bacterial, amebic (*Entamoeba histolytica*), and fungal (mostly from *Candida albicans*) liver abscesses [2]. Although open surgical drainage is considered as an important treatment of choice, up to 60% of multiple liver abscesses are cured with intravenous antibiotics as the only treatment [3]. In addition, in patients with hematological diseases, it is difficult for abscess to be liquefied due to granulocytopenia and immunocompromise. Therefore, biopsy for diagnosis and drainage for treatment are difficult.

The common etiology of liver abscesses after chemotherapy is fungi, especially candida albicans, and gram-positive bacteria [4-6]. However, little is known about gram-positive bacterial infection as the cause of pyogenic liver

abscess. Daptomycin has remarkable activity against gram-positive pathogen [7]. In this study we reviewed our experiences with the use of daptomycin for the treatment of gram-positive bacteria caused pyogenic liver abscess in 5 patients.

Case 1

A 13-year-old girl was diagnosed as acute lymphoblastic leukemia, and was treated by chemotherapy with vincristine, idarubicin, cyclophosphamide and predison. After the chemotherapy, she had agranulocytosis with high fever and swelling of left facial soft tissue. After three days of tienam and vancomycin for anti-infection, she continued to have fever to more than 39.0°C daily. Chest CT scan was normal. Repeated blood culture results were negative. So Voriconazole injection was added for antifungal treatment. Her swelling of left facial soft tissue became normal and granulocytes counts recovered. However, she still had recurrent high fever. CT scan revealed that inferior lobe of left lung had a nodular lesion with diameter of 14 mm and well-circumscribed. Multiple nodular lesions were detected in the liver with diameter of 4-10 mm, and in the spleen with diameter of about 9 mm (**Figure 1A**). Nasal cavity CT showed

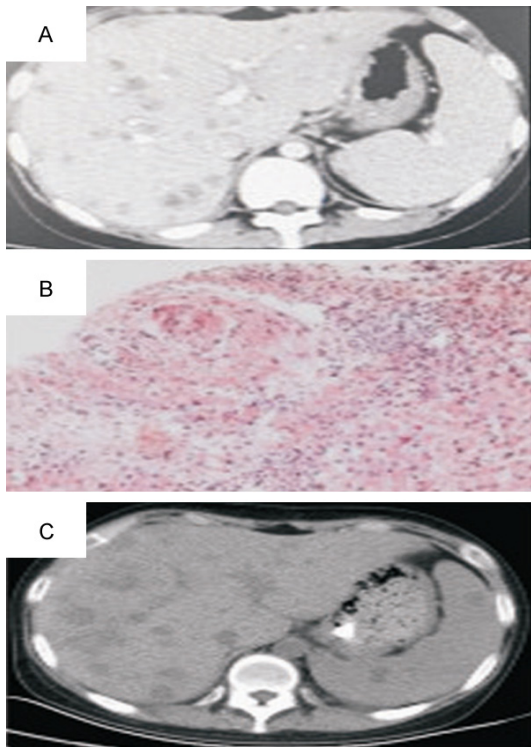


Figure 1. Presentation of Case 1. A. CT scan showed multiple nodular lesions in the liver with diameter of 4-10 mm, in enlargement spleen with diameter of about 9 mm. B. Liver needle biopsy showed that portal area was infiltrated by lymphocytes and monocytes and there was fibrocytes proliferation with hyaline change of collagenous fibrils. C. CT scan showed that liver nodular lesions became larger after anti-fungal treatment.

soft tissue mass and biopsy analysis indicated aspergillosis. 1-3- β -D glucan and galactomannan test were both negative. She presented with right upper quadrant pain except for recurrent high fever. Then, voriconazole was switched to liposomal amphotericin plus caspofungin, and tienam was switched to cefoperazone sulbactam. One week later, ultrasound-guided liver needle biopsy was performed.

Pathological findings were shown in **Figure 1B**. CT scan showed that liver nodular lesions became larger after anti-fungal treatment (**Figure 1C**). Anti-fungal medications were switched to linezolid against gram positive bacterial. Three days later, febrile became better, and the temperature became normal 4 days later. Intravenous administration of linezolid with teicoplanin was continued, and then the patient was discharged with oral administration of linezolid. However, the patient got febrile again. Thus daptomycin was given for Gram-positive bacte-

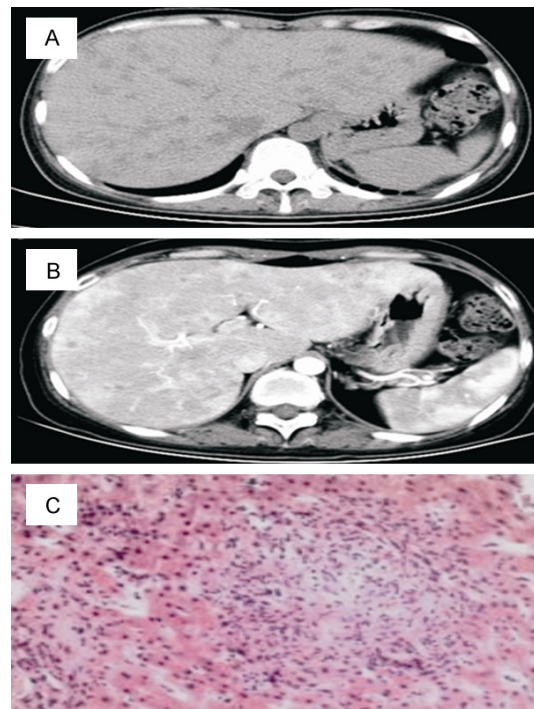


Figure 2. Presentation of Case 2. A. Multiple nodular lesions in the liver. B. Contrast-enhanced CT showed multiple nodular lesions, with not well-circum scribed and significantly enhanced circle in late arterial period. C. Histological examination showed the proliferation of chronic fibrous tissue and histiocyte with acute inflammation.

rial infection. Three days later, her temperature became normal. Sonography examination indicated that nodular lesions in the liver and spleen were still big. After treatment with daptomycin for two months, CT examination showed that the lesions became smaller. One and a half month after the cessation of the use of daptomycin, CT scan showed only one nodular lesion of 26×33 mm in left lateral external lobe of the liver.

Case 2

A 27-year-old woman with acute monocytic leukemia (AML-M5a) was admitted for the second chemotherapy, who had a history of spinal tuberculosis. The chemotherapy regimen was as follows: idarubicin intravenously administrated from day one to day three, and cytarabine intravenously administrated from day one to day seven. The patient got agranulocytosis with high fever. Blood culture showed Klebsiella pneumonia. After three days of tienam treatment, she still had fever. Teicoplanin was used for possible Gram-positive bacterial infection,

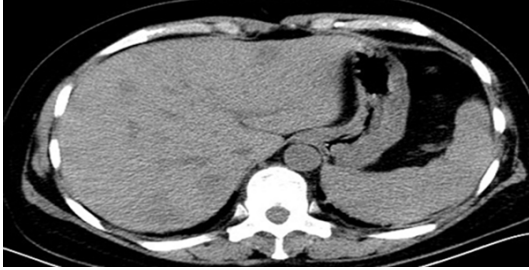


Figure 3. Presentation of Case 3. CT scan showed multiple hypodense nodular lesions in the liver and spleen.

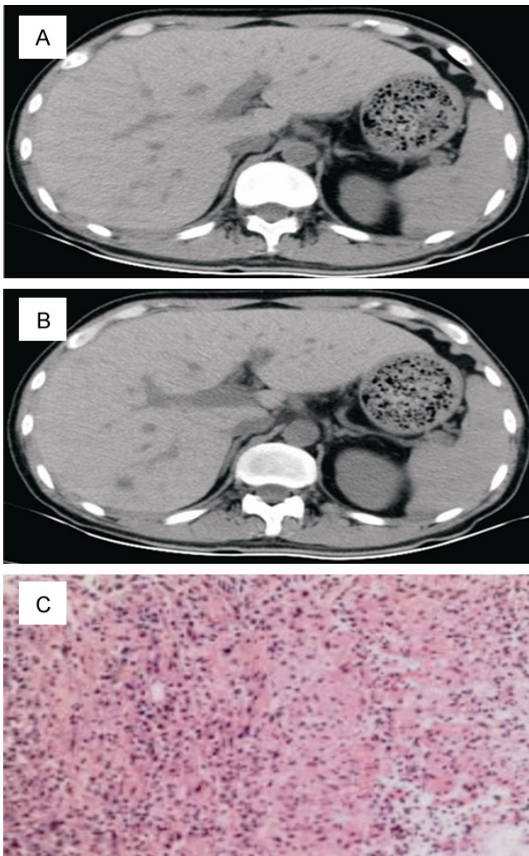


Figure 4. Presentation of Case 4. A, B. CT scan demonstrated hypodense lesions in the liver and spleen. C. Ultrasound-guided fine needle aspiration biopsy showed inflammation changes of the liver tissues, which were likely granulomatous inflammation.

but the fever did not disappear. Chest CT scan showed that right upper lung had a nodular lesion. Then itraconazole was given for possible fungal infection. Meanwhile, granulocyte colony-stimulating factor and transfusion were given for hematopoietic recovery. After granulocytes recovered, the patient still had high fever. CT scan showed that nodular lesion in the lung became smaller, but multiple nodular lesions

were found in the liver (**Figure 2A**). Repeated blood cultures were negative. Itraconazole was switched to Cancidas. Five days later, amphotericin B was added in combination with Cancidas for anti-fungal treatment. However, the fever did not disappear. Given her past history of spinal tuberculosis, anti-tuberculosis was given with intravenous administration of rifampicin and oral administration of isoniazid and pyrazinamide. Contrast-enhanced CT showed multiple nodular lesions (**Figure 2B**).

A needle biopsy of the nodules was performed with ultrasonography. Stains for microorganisms, including Gram and Ziel-Neelsen, were negative. No fungal hyphae on the tissue smear. Histological examination revealed the proliferation of chronic fibrous tissue and histiocyte with acute inflammation (**Figure 2C**). After the administration of 24 days of Cancidas, total dose of 3 g amphotericin B, and 10 days of anti-tuberculosis, the fever still remained. Thus we considered Gram-positive bacterial infection and used daptomycin. Her temperature gradually went down to normal after two weeks of daptomycin treatment.

Case 3

A 13-year-old woman was diagnosed as AML-M4. In the past two phases of chemotherapy, she had agranulocytosis and high fever after each therapy. Her leucocytes recovered and she was admitted for the third chemotherapy. However, she was febrile and CT scan revealed multiple hypodense nodular lesions in the liver and spleen (**Figure 3**). She was treated with Tazocin, tienam and linezolid sequentially, but the temperature could not go down. CT scan with contrast demonstrated the lesions in the liver and spleen, which were suspected as leukemia cells infiltration. PET/CT demonstrated multiple markedly metabolized nodules in the liver and spleen, which were also reported as leukemia cells infiltration.

Ultrasound-guided fine needle aspiration biopsy showed no pathological findings and negative microorganisms. Bone marrow aspiration indicated complete remission. Thus we suspected the nodular lesions in the liver and spleen as infection. Voriconazole and tigecycline were intravenously administered. Thereafter, febrile became better, but the temperature still fluctuated around 38°C. Reexamination of bone marrow aspiration showed complete remission. Ultrasound-guided fine needle aspiration biop-

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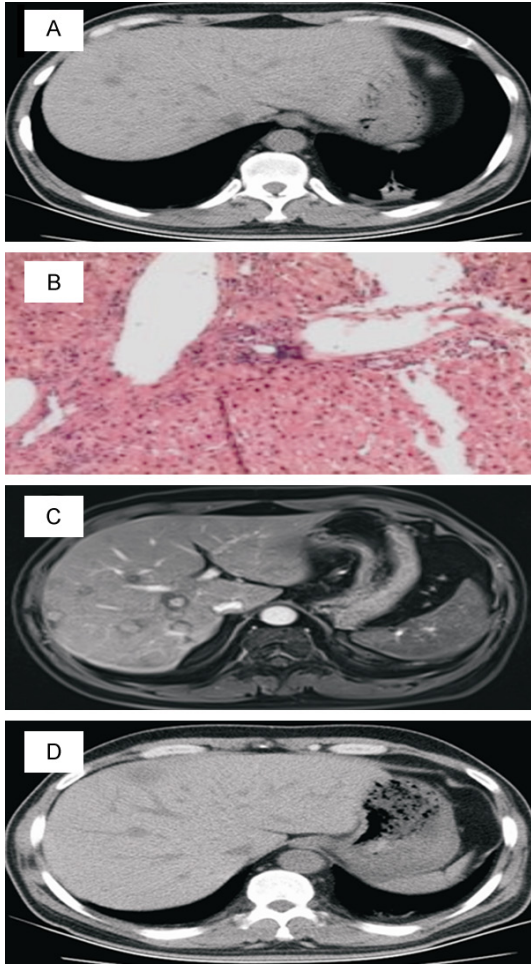


Figure 5. Presentation of Case 5. A. CT scan showed multiple nodular lesions in the liver. B. Ultrasound-guided fine needle aspiration biopsy showed no evident inflammation and fibrosis. C. Contrast-enhanced CT showed that after the discontinuation of daptomycin for twenty days, hypo-density nodular lesions in the liver got bigger and more than before, with the diameter of about 18 mm and well-circumscribed. D. About two months after the discontinuation of daptomycin, only two nodular lesions were left in the liver.

sy showed proliferative fibrosis with the infiltration of inflammation cells. Staining for microorganisms was negative. No fungal hyphae on the tissue smear. Nothing was cultured.

Ten days after the use of voriconazole and tigecycline, CT scan with contrast demonstrated that the lesions in the liver and spleen became smaller. However, the temperature gradually elevated with the use of voriconazole and tigecycline. Then tigecycline was switched to daptomycin. Three days later, her temperature gradually decreased to normal. Daptomycin was given for about a total of 50 days. Subsequently,

patient received multiple rounds of chemotherapy. Eight months after the discontinuation of daptomycin, CT scan showed that the liver still had some hypodense nodular lesions but markedly improved.

Case 4

A 38-year-old man with acute monocytic leukemia (AML-M5) had Gram-positive bacterial sepsis after chemotherapy, which was cured by daptomycin. After another round of chemotherapy, he got agranulocytosis. He was treated by tienam and voriconazole for recurrent high fever. Blood culture showed streptococcus hemolyticus. CT scan demonstrated hypodense lesions in the liver and spleen (**Figure 4A, 4B**). Ultrasound-guided fine needle aspiration biopsy showed inflammation changes in the liver, which were likely granulomatous inflammation (**Figure 4C**). Thus we suspected Gram-positive bacterial infection in the liver and spleen. He received daptomycin treatment for 19 days, and his temperature became normal. He received daptomycin treatment for another week. After that, linezolid was given during the patient was admitted for chemotherapy. Half a year later, CT scan showed that there was no nodular lesion in the liver and spleen.

Case 5

A 40-year-old man with acute monocytic leukemia (AML-M5a) was admitted for the third round of chemotherapy. He had IA regimen chemotherapy (idarubicin and cytarabine were intravenously administrated) and got partial remission (PR). Then he received the second IA regimen and got complete remission (CR). After the third IA regimen chemotherapy, he got agranulocytosis and febrile. He received tienam, vancomycin and voriconazole injection for anti-infection, but febrile did not get better. During that period, he had intestinal hemorrhage. CT and MRI scan revealed multiple nodular lesions in the lung and liver (**Figure 5A**). He received liposomal amphotericin B and voriconazole for anti-fungal treatment. But febrile did not get better. Ultrasound-guided fine needle aspiration biopsy was performed and no infection or malignant evidence was found (**Figure 5B**). Then anti-fungal treatment was switched to anti-Gram-positive bacterial therapy with daptomycin. Subsequently, his temperature gradually got normal. Contrast-enhanced MRI showed that after the discontinuation of daptomycin for

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Table 1. Clinical parameters of 5 cases

	case 1	case 2	case 3	case 4	case 5
CRP (mg/L)	23.4	38.4	68.5	106	116
PCT	0.255	0.23	0.341	0.092	0.585
AKP (U/L)	132	223	355	16	254
γ-GT (U/L)	115	231	160	26	720
Total duration of daptomycin use (days)	60	60	50	40	30
Time to normal temperature (days)	3	14	3	20	10
Time to the recovery of the liver (months)	3.5	2.5	9	7.5	3

CRP, C-reactive protein, normal range: 0-8 mg/L; PCT, procalcitonin, normal range: 0-0.5 ng/ml; AKP, alkaline phosphatase, normal range: 45-125 U/L; γ-GT, γ-glutamyl-transferase, normal range: 10-60 U/L.

twenty days, hypo-density nodular lesions in the liver were more and bigger than before, with the diameter of about 18 mm and well-circumscribed (**Figure 5C**). The total duration of daptomycin therapy was about one month. Then he received linezolid therapy during chemotherapy. About two months after the discontinuation of daptomycin, only two nodular lesions were found in the liver (**Figure 5D**).

Discussion

In this study, five patients with acute leukemia underwent chemotherapy and received many sorts of intravenous antibiotics for a long period. For such patients, pyogenic liver abscess is the uncommon infection involved sites. Unfortunately, multiple hepatic nodular lesions were usually misdiagnosed as leukemia infiltration. Due to host immunodeficiency after chemotherapy, infection can be the most possible cause.

We consider that it is hard to make an early diagnosis of multiple hepatic nodular lesions. Even with ultrasound-guided percutaneous needle aspiration, pathogenic bacteria are difficult to be identified. For the 5 cases in this study, broad-spectrum antibiotics had been administered before daptomycin was given, especially case 2 who had recurrent fever for over half a year. Only in case 4, due to streptococcus hemolyticus in blood culture, Gram-positive infection was first considered for target therapy. In contrast, the other four cases were treated for Gram-negative bacterial or fungal infection, even with vancomycin, linezolid or tigecycline. Linezolid or tigecycline were effective at first, but the efficacy did not last long. Da-

ptomycin, vancomycin and linezolid were active against Gram-positive pathogens, such as *S. aureus*. Daptomycin was four- to eight-fold more potent than vancomycin and linezolid. Therefore, daptomycin may control Gram-positive bacterial infection more efficiently.

For leukemia patients, it is important to control the current febrile hepatic infection, and it is essential to find new highly active antibacterial agents

such as daptomycin. Daptomycin can quickly kill gram-positive pathogens and has unique mechanisms of action [8]. Of the five cases, only case 2 had delayed chemotherapy for 21 months and relapsed, thus daptomycin used in the present study improved the prognosis of patients with pyogenic hepatic abscesses. In addition, continuous use of daptomycin for up to two months is safe (**Table 1**). No elevated creatinephosphokinase (CPK) and other side effects were observed. Of the five cases, 4 cases had elevated alkaline phosphatase (AKP) and γ-glutamyl-transferase (γ-GT) (**Table 1**), which suggested that biliary system might be involved in the pathogenesis of liver abscesses.

Among the 5 cases, 4 cases received ultrasound-guided fine needle aspiration biopsy. Pathological analysis showed chronic inflammation, such as the proliferation of chronic fibrous tissue or granulomatous inflammation. In mouse model, infection with streptococcus pneumonia induced the progression of established lung fibrosis [9]. Taylor *et al.* demonstrated granulomatous disease in 27 of 34 patients with inflammatory mastitis and concomitant *Corynebacterium* infection, which is a Gram-positive bacillus [10]. Thus, acute infection in the liver, an important immune organ, can cause chronic inflammation-like reaction, which may be due to autoimmune and hypersensitivity processes [11].

In summary, we summarized the use of daptomycin for the treatment of pyogenic multiple hepatic abscesses in hematological patients. For immunodeficiency patients, infectious pathogens are usually difficult to be identified.

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Gram-positive pathogens as a cause of pyogenic hepatic abscesses can be effectively and timely controlled by daptomycin.

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Disclosure of conflict of interest

None.

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