



Tumor complete response and pyogenic liver abscess secondary to concurrent microwave ablation plus atezolizumab and bevacizumab in liver cancer: a case report

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Background: Pyogenic liver abscess (PLA) could be fatal even after standard treatment with antibiotics and percutaneous drainage. Immune checkpoint inhibitors, bevacizumab or microwave ablation may cause PLA, respectively. This paper presents the first case of PLA secondary to the concomitant use of microwave ablation with atezolizumab and bevacizumab in the treatment of liver cancer.

Case Description: A 54-year-old Chinese man with Barcelona Clinic Liver Cancer (BCLC) C-stage liver cancer complained of fever and chills twenty-nine days after concurrent microwave ablation plus atezolizumab and bevacizumab. Post-hospitalization, a computed tomography revealed a rim-enhancing hypodensity within the right lobe of the liver, approximately 8.8 cm in diameter containing foci of gas. Laboratory examination revealed elevated white blood cell count, C-reactive protein and procalcitonin, and blood culture indicated the presence of *Escherichia coli* bacteremia. The patient was diagnosed with PLA complicated by septic shock, and due to recurrent fever, multiple courses of antibiotics (imipenem/cilastatin sodium, cefoperazone/sulbactam, meropenem, respectively) were administered in combination with five percutaneous drainages over the next 90 days. The patient's fever eventually resolved, and the patient was discharged. The patient was re-treated with two cycles of atezolizumab and bevacizumab initiated in March 2024. An imaging evaluation in May 2023 demonstrated tumor progression. Subsequently, the patient underwent one transarterial chemoembolization procedure and two cycles of atezolizumab and bevacizumab over the subsequent 2 months. Notably, the patient achieved a complete response at the July 2024 imaging evaluation.

Conclusions: In patients undergoing atezolizumab and bevacizumab, the potential risk of PLA versus the antitumor benefit of microwave ablation requires to be assessed. The use of multiple courses of antibiotics over a prolonged period did not appear to influence the effectiveness of atezolizumab and bevacizumab. Further studies are, however, needed to substantiate this finding.

Keywords: Pyogenic liver abscess (PLA); microwave ablation; atezolizumab; liver cancer; case report

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Introduction

Pyogenic liver abscess (PLA) is a type of liver abscess that usually results from bacterial invasion of the liver parenchyma (1). The most common risk factors for PLA include primary liver tumor and metastases, loco-regional liver procedures and liver cysts, and the typical symptoms of PLA are fever and abdominal pain (2,3). The treatment guidelines for PLAs remain unestablished, and the current common clinical treatment is antibiotics and invasive treatment procedures (3). Even after antibiotic therapy and invasive treatment procedures, PLA remains fatal, especially in patients with bacteremia, septic shock, multiple abscesses, or cancer (1). Atezolizumab plus bevacizumab is the standard first-line treatment for hepatocellular carcinoma (HCC) and has been reported to cause PLA (4,5). Microwave ablation is a common locoregional therapy for liver cancer with a reported incidence of liver abscess of 1.6% in a retrospective study (6). A high prevalence of multidrug-resistant bacteria has been observed in patients with PLA following locoregional treatments for liver cancer (2).

The presence of multidrug-resistant bacteria makes treating PLA more challenging. There is currently no safety data available for concurrent ablation in combination with atezolizumab and bevacizumab. Herein, we present the first case of PLA secondary to concurrent microwave ablation plus atezolizumab and bevacizumab for liver cancer to alert physicians to the risks of PLA. We present this article in accordance with the CARE reporting checklist (available at <https://jgo.amegroups.com/article/view/10.21037/jgo-24-467/rc>).

Case presentation

In August 2023, a 54-year-old Chinese man complained of fever and chills twenty-nine days after receiving microwave ablation for his liver cancer. He had a ten-year history of hepatitis B virus infection and was diagnosed with Barcelona Clinic Liver Cancer (BCLC) C-stage liver cancer on October 22, 2022. He had no medical history or family history of diabetes or liver abscesses. He received conventional transcatheter arterial chemoembolization (TACE) combined with hepatic arterial infusion chemotherapy with oxaliplatin 100 mg and raltitrexed 4 mg twice on October 27, 2022, and December 2, 2022, respectively. From November 7, 2022, he received treatment of atezolizumab 1,200 mg plus bevacizumab 400 mg, every 3 weeks for 11 cycles (*Figure 1*), and the tumor achieved a complete response assessed by enhanced magnetic resonance imaging. Due to the considerable size of the tumor (16.5 cm) and the necessity to prevent the recurrence of the tumor, a microwave ablation procedure was performed on August 1, 2023, with no intestinal tract in the vicinity of the anatomical structures at the ablation site. The two last cycles of atezolizumab plus bevacizumab were on July 26, 2023, and August 29, 2023, respectively. He had intermittent fever with a maximum temperature of 39.2 °C, occasional abdominal distension, pain in the liver area, and no nausea or vomiting. Physical examination revealed abdominal tenderness without pressure or rebound pain, and liver pain and fatigue were less severe than before. Laboratory tests revealed a white blood cell (WBC) count of $17.8 \times 10^9/L$ (normal range, $3.5 \times 10^9 - 9.5 \times 10^9/L$), C-reactive protein (CRP) of 151.9 mg/L (normal range, 0.1–8.2 mg/L), procalcitonin (PCT) of 2.335 µg/L (normal range, 0–0.5 mg/L), and platelets of $24 \times 10^9/L$ (normal range, $125 \times 10^9 - 350 \times 10^9/L$), albumin 35.6 g/L, hemoglobin 140.2 g/L, blood glucose 5.05 mmol/L, body mass index 20 kg/m². The patient's dietary status and nutrition were

Highlight box

Key findings

- Concurrent microwave ablation plus atezolizumab and bevacizumab in the treatment of liver cancer could induce a pyogenic liver abscess (PLA), which would negatively impact progression-free survival after antibiotic treatment.

What is known and what is new?

- PLA is a rare disease caused by bacterial invasion of healthy liver parenchyma. The etiology of PLA includes factors such as radiofrequency ablation, malignant biliary obstruction, and chemoembolization. Antibiotics and percutaneous drainage are the mainstay of treatment for PLA. Patients with cancer or septic shock have a higher mortality rate. A systematic review and meta-analysis revealed that antibiotic use could negatively impact clinical outcomes in liver cancer patients treated with immune checkpoint inhibitors.
- We present the first case of PLA secondary to concurrent microwave ablation plus atezolizumab and bevacizumab for liver cancer to alert physicians to the risks of PLA.

What is the implication, and what should change now?

- The causality between PLA and the combination of atezolizumab and bevacizumab and microwave ablation, the mechanism by which atezolizumab and bevacizumab cause PLA, and the potential correlation between PLA and transcatheter arterial chemoembolization-induced localized necrosis remain unclear at this time. More etiologic research will be needed to answer these questions.

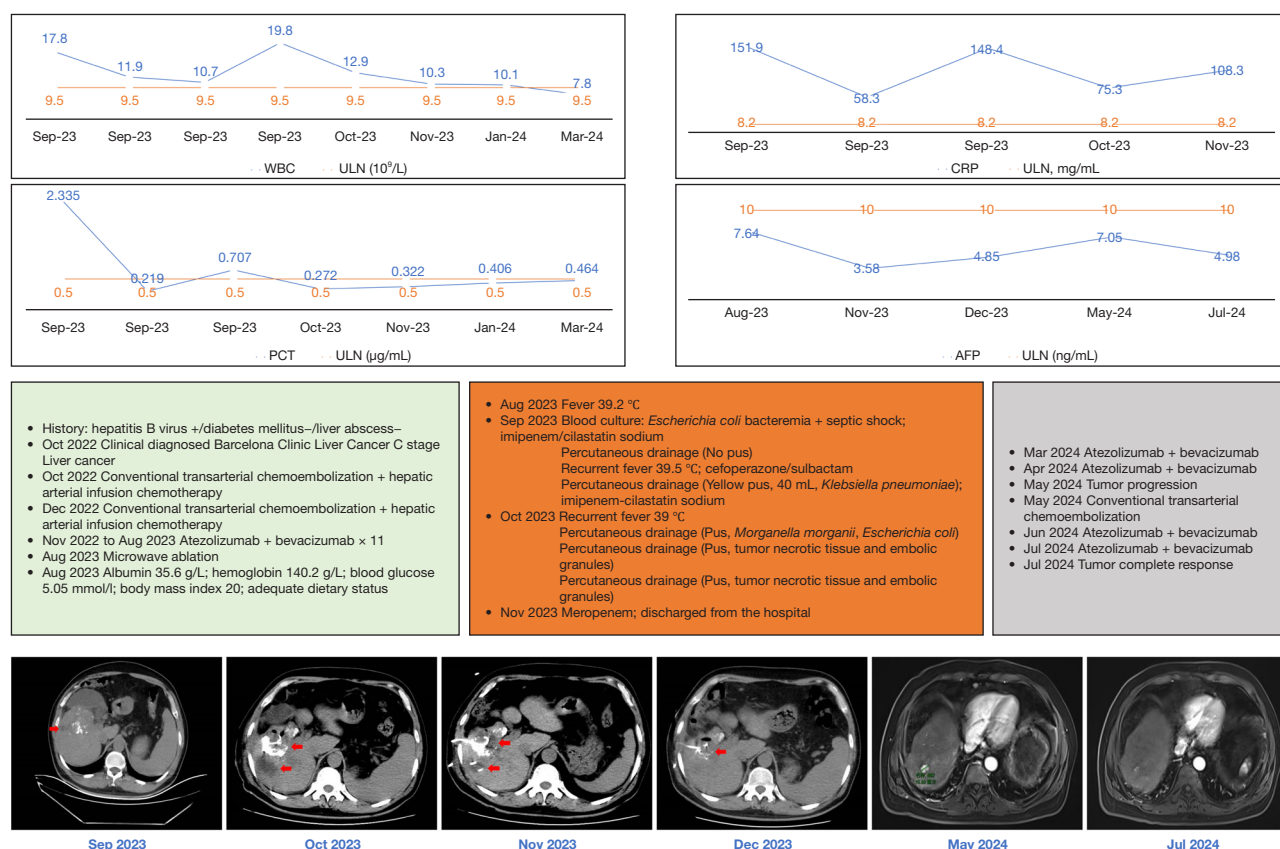


Figure 1 Timeline of laboratory findings, treatments, and imaging. The red arrows points to the lesion. WBC, white blood cell count; ULN, upper limited of normal; CRP, C-reactive protein; PCT, procalcitonin; AFP, alpha-fetoprotein.

normal. Blood culture results indicated the presence of *Escherichia coli*, and the patient was subsequently diagnosed with PLA with *Escherichia coli* bacteremia and septic shock. Based on the results for drug sensitivity, the patient was given imipenem/cilastatin sodium 1 g (once every 8 hours) combined with plasma transfusion, magnesium isoglycyrrhizinate injection (200 mg/day); polyene phosphatidylcholine injection (1,395 mg/day), and other symptomatic treatments. On September 9, 2023, abdominal computed tomography suggested multiple patches of evolving hypodensities around the previously ablated lesion, as compared with CT abdomen from September 1, 2023. Percutaneous drainage did not show pus, and WBC, CRP, and PCT continued to decrease without fever. On September 19, 2023, he had a sudden onset of right upper quadrant pain accompanied by fever with a maximum temperature of 39.5 °C. Laboratory examination revealed a WBC count of $19.8 \times 10^9/L$, CRP of 148.4 mg/L, and PCT of 0.707 $\mu g/L$. He was given cefoperazone/sulbactam 3 g

(once every 12 hours) as empiric prophylaxis.

Abdominal computed tomography showed that the lesion encircled the right anterior branch of the portal vein, with iodine oil deposition of similar extent, decreased enhancing component, and increased gas compared to the previous abdominal computed tomography, and the gas adjacent to the liver capsule was faint. The lesion was surrounded by multiple patches of slightly hypodense shadows of a similar extent compared to the previous one. On September 25, 2023, ultrasound-guided percutaneous drainage of the liver lesion was performed, and 40 mL of yellow pus was drained with a bacterial culture suggestive of *Klebsiella pneumoniae*. According to the drug sensitivity results, the antibiotic was changed to imipenem-cilastatin sodium 2 g (once every 8 hours), and the WBC, CRP, and PCT continued to decrease. On September 7, 2023, he experienced a fever again with a body temperature of 39 °C. He also reported occasional abdominal distension, pain in the liver area, and noticeable fatigue symptoms. Repeated percutaneous

drainage was performed. The bacterial culture results of the drained fluid revealed the presence of *Moraxella catarrhalis* and *Escherichia coli*. On October 23, 2023, and October 30, 2023, ultrasound-guided percutaneous drainage was performed, and pus containing necrotic tissue with embolized particles from the TACE was obtained during drainage. On November 6, 2023, the patient's blood culture was positive again, and he started intravenous infusion of Meropenem based on the result of drug susceptibility testing. As of November 17, 2023, the blood culture was negative, and the WBC count was $10.3 \times 10^9/L$, CRP 108.3 mg/L, and PCT 0.322 $\mu g/L$. The patient did not present with a recurrent fever and was discharged from the hospital. The patient was re-treated with two cycles of atezolizumab and bevacizumab initiated in March 2024. An imaging evaluation in May 2023 demonstrated tumor progression. Subsequently, the patient underwent one TACE and two cycles of atezolizumab and bevacizumab over the subsequent 2 months. Notably, the patient achieved a complete response at the July 2024 imaging evaluation.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

International Multidisciplinary Team (iMDT) discussion

Discussion among physicians from Jilin Cancer Hospital

To our knowledge, this is the first reported case of PLA secondary to concurrent microwave ablation plus atezolizumab and bevacizumab in the treatment of liver cancer. PLA is a rare infectious disease that invades the liver parenchyma with an incidence of 5.6 per 100,000 in mainland China, and the most common bacterial causes of PLA are *Klebsiella*, *Escherichia coli*, *Enterobacter* species, *Proteus* species, and *Pseudomonas* species (7,8). Biliary infections, intra-abdominal infections, radiofrequency ablation, or chemoembolization may cause PLA, and risk factors include diabetes mellitus, previous liver surgery, and liver malignancy (1,9). One case of bevacizumab-related fistula/abscess (non-gastrointestinal) and one case of PLA were reported in the IMbrave150 study. Still, no liver

abscess was reported in the IMbrave050 study of adjuvant therapy in patients with resected or ablated hepatocellular carcinoma (4,5,10). The occurrence of PLA was also not reported in the two observational studies that underwent ablation following atezolizumab and bevacizumab (11,12). In the current case, the patient did not have a history of diabetes mellitus or liver abscess. However, since the clinical diagnosis of liver cancer was based on imaging and alpha-fetoprotein, it was not certain that the patient had a comorbid biliary malignancy. To assess the correlation between PLA and antitumor drugs, we used the World Health Organization-Uppsala Monitoring Centre (WHO-UMC) causality assessment system (13). Based on the assessment criteria, we judged the causality between PLA and atezolizumab + bevacizumab to be "possible" because PLA had a reasonable temporal relationship with drug intake, could be attributed to microwave ablation, and did not respond to drug withdrawal. We also evaluated the correlation between PLA and TACE. Since the longest known interval between TACE and PLA is 2 months, we judged the causality between PLA and TACE to be "unlikely", but we do not yet know whether the chronic damage caused by TACE was also a causative factor for PLA (14).

Risk factors for failure of antibiotic therapy include malignancy, septic shock, and hyperbilirubinemia, among others, and antibiotics alone are only 61% effective for PLAs >5 cm in diameter (1). Patients with gas-forming pyogenic liver abscess (GFPLA) have significantly higher rates of sepsis and pleural effusion, as well as longer hospital stays compared to non-GFPLA patients (15). The maximal diameter of the abscess is an independent factor for prolonged hospital stay (16). The patient had no signs of PLA on follow-up computed tomography (CT) 5 days after the ablation procedure, and developed fever 1 month after the procedure, which was initially considered as a possibility of PLA in combination with laboratory tests. However, considering that the treatment of PLA by puncture placement and drainage may cause the patient to carry a drainage tube for a long time, which seriously affects the quality of life, the initial treatment strategy for PLA was to apply anti-infective drugs. The patient's initial CT scan revealed a gas-forming PLA with a maximum diameter of 8.8 cm. Subsequent CT scans showed a diameter of over 10 cm. Subsequently, a puncture and drainage of the liver abscess was performed and the pus and embolic agent were drained. This, along with septic shock, may have contributed to the patient's prolonged use of antibiotics

which may have negatively impacted the patient's progression-free survival (17).

There is one primary limitation associated with this case report. Since the patient refused to receive a biopsy during the PLA treatment, we could not know the pathological diagnosis of the tumor, the type of tissue damage resulting from PLA, the relationship between PLA and antitumor therapy, and the potential mechanism resulting in PLA.

Several issues on the treatment of this patient were further discussed as follows

Q1. The question remains as to whether the development of liver abscesses can be attributed to the application of atezolizumab. Is the pathogenic mechanism an alteration of the patient's immune microenvironment?

Expert opinion 1: Ho Jong Chun

I have the following thoughts on this question: The authors determined the possibility of immunotherapy drugs affecting the occurrence of PLA only using the WHO-UMC causality assessment system. This was judged solely based on the temporal relationship between the administration of immunotherapy drugs and the occurrence of PLA. I think the authors should describe in detail the immunological relationship in addition to the temporal relationship. In general, immunotherapy drugs are accompanied by changes in the patient's immune environment, which can cause normal bacteria to transform into pathogens that cause serious infections. In addition, the role of antibiotics in this regard can only be limited in a state where normal immune function is reduced.

Expert opinion 2: Driss Raissi

The development of liver abscesses, specifically PLAs, in the context of concurrent microwave ablation plus atezolizumab and bevacizumab, may indeed be attributed to the disruption of the patient's immune microenvironment which is already known to be affected by natural killer (NK) cells. According to the manuscript, the case presented illustrates a scenario where a liver abscess developed after such a combination therapy in a liver cancer patient.

The manuscript suggests that while PLA is a rare and severe infection of the liver parenchyma typically caused by bacterial invasion, the concurrent use of atezolizumab and bevacizumab with microwave ablation might have influenced the patient's immune microenvironment, making it more susceptible to infection.

Moreover, the adverse effects of immune checkpoint

inhibitors like atezolizumab on the immune system can include immune-related adverse events, which might disrupt normal immune surveillance that usually keeps infectious processes under check. The disruption of this process can lead to an increased risk of severe infections, including liver abscesses. The manuscript highlights that antibiotic therapy negatively impacts clinical outcomes in liver cancer patients treated with immune checkpoint inhibitors, suggesting that the immune modulation by atezolizumab could contribute to such complications.

Q2. For primary large liver cancer (lesion diameter >10 cm), should the treatment strategy pursue the possibility of complete cure, but TACE combined with ablation combined with atezolizumab and bevacizumab, which increases the chance of complications, and how should it be balanced clinically?

Expert opinion 1: Ho Jong Chun

The role of immunotherapy in large HCC larger than 10 cm is limited, but the role of TACE and ablation is also limited, so combination therapy is often pursued. Since the occurrence of infectious complications like this case presentation is frequently fatal, conservative treatment that focuses on safety rather than curative treatment should be prioritized. Even if the number of treatment sessions increases and the treatment period becomes longer, a step-by-step approach is necessary. Rather than changing the immune environment by administering immunotherapy drugs first, it is believed that a solution to this problem is to use immunotherapy drugs after maximizing tumor reduction through local treatments, such as TACE, radioembolization, or ablation. Of course, infectious complications may occur with only local treatments, but in these cases, since the immune environment is preserved, prophylactic antibiotics may play a sufficient role.

Expert opinion 2: Driss Raissi

Clinical balance strategy: to balance the potential for a complete cure with the risk of complications, the following clinical strategies can be considered:

- ❖ Risk assessment: thoroughly evaluate the patient's risk factors for complications, including liver function, immune status, and previous treatments.
- ❖ Staggered treatment approach: instead of concurrent therapy, consider a staggered approach where TACE and ablation are performed first, followed by systemic therapy after a period of recovery.
- ❖ Close monitoring: implement rigorous monitoring protocols for early detection of complications such as

infections. Regular imaging and laboratory tests can help detect adverse events promptly.

- ❖ Prophylactic measures: use prophylactic antibiotics judiciously in high-risk patients to prevent infections, though the potential negative impact on immune therapy outcomes should be considered.

Q3. After the occurrence of the liver abscess, the abscess lesions of the patient gradually shrank after abscess puncture and catheter drainage, but there were still repeated infections and the tube could not be extubated. In addition to the application of antibiotics, how should we adjust the follow-up treatment strategy?

Expert opinion 1: Ho Jong Chun

Infectious complications such as PLA that occur after local treatment can be treated with intensive and proper antibiotics administration and percutaneous drainage in a normal immune environment. Surgical resection is the only treatment if there is no improvement with these treatments. However, there are cases where resection is not possible for various reasons, and in these cases, it is difficult to expect a viable follow-up treatment strategy.

Expert opinion 2: Driss Raissi

The follow-up treatment strategy for recurrent liver abscess should involve a combination of continuous antibiotic therapy, regular imaging, repeat drainage procedures, close follow-up with drainage catheter upsizes as needed, managing underlying conditions, long-term follow-up, and optimizing immune function. Each step should be tailored to the patient's specific clinical scenario to achieve the best possible outcome:

- ❖ Continuous antibiotic therapy: continue with the appropriate antibiotics based on the latest culture and sensitivity results. In this case, the patient was treated with imipenem-cilastatin and meropenem, which were effective against the cultured bacteria.
- ❖ Repeat drainage procedures: if the abscess persists or recurs, repeat percutaneous drainage may be necessary. Biliary and bowel fistulas should be excluded with sinograms, as these can be the cause behind recurring liver abscesses.
- ❖ Long-term follow-up: establish a follow-up plan with blood work and cross-sectional imaging to ensure the abscess does not recur and to monitor the patient's overall health and response to cancer treatment.
- ❖ Optimize immune function: given that immune checkpoint inhibitors like atezolizumab can affect the immune system, monitoring the patient's immune

status and adjusting the cancer treatment regimen might be necessary to balance the benefits and risks of immunotherapy and prevent further infection.

Further discussion based on MDT expert opinions

In most cases, PLA was secondary to bacterial infections in patients who have experienced immunocompromise following glucocorticoid treatment for immune checkpoint inhibitor-associated cholangitis (18-20). Furthermore, T-lymphocytes have a key role in the formation of liver abscesses and may be further facilitated by immune checkpoint inhibitors that deregulate T cell suppression (21,22).

The occurrence of multi-drug resistant infection was found to be significantly associated with loco-regional procedures for liver cancer (2). This finding serves to highlight the additional challenges faced in the management of PLA. Accordingly, the authors agree with the MDT experts' recommendation to refrain from employing loco-regional treatments in concurrence with atezolizumab + bevacizumab.

Conclusions

Patients with liver cancer already have a high risk of PLA with localized therapy, while further antibiotic therapy negatively impacts the clinical outcome in liver cancer patients treated with immune checkpoint inhibitors. In the era of immune checkpoint inhibitor therapy, clinicians should use the modality of concurrent microwave ablation plus atezolizumab and bevacizumab with caution.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent for publication of this case report and accompanying images was obtained from the patient. A copy of the written consent is available for review by the editorial office of this journal.

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