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Research Article

Pulmonary Mycobacterium Kansasii Disease Following Programmed Cell Death-1 Inhibitor Therapy in A Patient with Hepatocellular Carcinoma

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Abstract

Pulmonary non-tuberculous Mycobacterium (NTM) diseases following programmed death-1 (PD-1) and programmed death-ligand 1 (PD-L1) inhibitor immunotherapy have been infrequently reported and inadequately characterized. Herein, we report about a 28-year-old man with hepatocellular carcinoma (HCC) who presented with fever, hemoptysis, and apical cavity of the right lung, which gradually expanded following comprehensive treatments including six cycles of toripalimab, an anti-PD-1 antibody. Further workup yielded a diagnosis of pulmonary Mycobacterium kansasii disease with a positive acid-fast bacillus (AFB) smear and M. kansasii-NTM culture from bronchoalveolar lavage fluid. The patient finally died of progressive cancer, liver failure, and worsening pulmonary M. kansasii disease. Given the reported clinical observations showing that reactivation of Mycobacterium tuberculosis (MTB)/NTM infection was associated with PD-1/PD-L1 inhibitors and a high burden of MTB/NTM infection in China, We suspect that the pulmonary cavity lesions developed from the reactivation of a latent M. kansasii infection nodule induced by toripalimab. This nodule existed in the right upper lung at the time of the diagnosis of HCC. Physicians should pay more attention to the development of pulmonary NTM diseases in patients with cancer during immunotherapy regimens with immune checkpoint inhibitors. Additional clinical observations and further exploration of the underlying mechanisms are necessary for the optimal management of pulmonary NTM diseases. .

Key word: hepatocellular carcinoma (HCC); immune checkpoint inhibitors (ICIs); toripalimab; immunotherapy; non-tuberculous Mycobacterium (NTM); pulmonary Mycobacterium kansasii disease.

Introduction

Hepatocellular carcinoma (HCC), a malignant tumor with high morbidity and mortality in China, poses a severe threat to human health (1). Patients with early HCC can be clinically cured by surgical resection, liver transplantation, intervention, or ablation; however, most patients are already in an advanced stage when they seek medical treatment and have poor prognosis and short survival time using conventional treatments. Recently, immune checkpoint inhibitors (ICIs) have been shown to block co-inhibitory signaling pathways, restore T cell function, enhance immune killing activity, and significantly improve the survival of patients with cancer (2). Toripalimab, a selective, recombinant, humanized monoclonal antibody against programmed death protein 1 (PD-1), approved for use in several common malignant tumors, including nasopharyngeal cancer, malignant melanoma, urothelial carcinoma, and others in China, shows promising effects and prolongs overall survival (3). In addition, studies have shown that blocking PD-1 signaling can effectively control and eliminate pathogens in chronic infections (4). However, patients with active infections, such as tuberculosis (TB), in the clinical setting were excluded from clinical trials of ICIs for cancer. In recent years, an increasing number of clinical cases have shown that PD-1 inhibitor therapy in patients with cancer is unfavorable for controlling Mycobacterium tuberculosis (MTB) infection (2). It induces the reactivation of MTB infection and TB development, adversely affecting tumor control and patient survival [5, 6]. Few cases of pulmonary non-tuberculous Mycobacterium (NTM) disease induced by ICIs have been reported (7). Herein, we present a case of pulmonary M. kansasii disease with a positive acid-fast bacillus (AFB) smear and M. kansasii culture from bronchoalveolar lavage fluid (BALF) following immunotherapy with six cycles of toripalimab in a patient with HCC.

Case presentation

A 28-year-old man was diagnosed with HCC at Barcelona Clinic Liver Cancer (BCLC) stage C with a giant mass type, multiple intrahepatic metastases, and portal vein carcinoma thrombus in November 2019. His liver function was favorable, with Child–Pugh class A, and chest computed tomography (CT) images showed a small nodule in the upper right lung (Figure 1) and suspicious metastases in both lungs. He had a history of hepatitis B infection without antiviral therapy. He was a non-smoker and denied a history of alcohol consumption. He also had no history of TB or exposure to TB.

Subsequently, the patient underwent five concurrent cycles of hepatic arterial perfusion chemotherapy (HAIC) with mFOLFOX regimen (Oxaliplatin 85 mg/m2 , over 2 hours, day1, Calcium Folinate 400 mg/m2, over 2 hours, day1, Fluorouracil 400 mg/m2, on day 1, Fluorouracil 2400 mg/m2, over 46 hours continuously, day1, repeated every three weeks) and PD-1 inhibitor toripalimab immunotherapy and lenvatinib-targeted therapy from December 2019 to May 2020 at other hospitals, followed by palliative stereotactic radiotherapy (DT PGTV 30.0 Gy/6Fx) in June 2020 (Figure 2A). However, all of these treatments were discontinued because of grade 3 abnormal liver function, and an enhanced CT scan demonstrated that the HCC mass remained stable but with a significant decrease in the level of AFP after seven months of therapy.

He was admitted to our hospital and received therapy for abnormal liver function on July 13, 2020, which returned to normal after two weeks of therapy. Unfortunately, new lesions were revealed with multiple inflammatory nodules and clusters in both

his upper lungs and a large cavity in his right pulmonary apex on chest CT examination on July 25 (Figure 2B) , although he had no significant cough, sputum, hemoptysis, or fever. He refused further examination and was required to resume toripalimab immunotherapy and lenvatinib-targeted therapy to control his tumor. On August 4, 2020, he received the sixth cycle of toripalimab along with oral lenvatinib daily.

He complained of fever, cough, and hemoptysis of approximately 10 mL of bloody sputum daily since August 30. Chest CT performed on September 13, 2020 (Figure 2C) showed increased lesions of inflammatory patchy shadow and an enlarged cavity size with a thick wall in the upper right lung. Bronchoscopy and bronchoalveolar lavage fluid (BALF) samples were collected for microbiological analysis. The acid-fast bacillus (AFB) smear was positive. however, GeneXpert MTB/RIF was negative. Mycobacterium culture was positive, and the gene test finally identified M. kansasii-NTM strains in the BALF, and the diagnosis of pulmonary M. kansasii disease was confirmed. toripalimab and lenvatinib immunotherapy were discontinued. Antibiotics regimen including isoniazid (INH), ethambutol (EB), azithromycin (AZM), and moxifloxacin (MXF) for M. kansasii was initiated on September 22, 2020. After one week of antibiotic treatment, his temperature returned to normal, bloody sputum ceased, and the symptoms of cough and sputum gradually improved. However, the patient required resumption of immunotherapy due to elevated AFP levels, and he received the seventh cycle of toripalimab immunotherapy and daily lenvatinib along with maintained antibiotics on September 30, 2020.

The patient had no cough, hemoptysis, or fever. Re-examination of the chest and abdominal CT showed that inflammatory lesions in both right upper lungs were gradually absorbed, and the cavity in the right upper lung was enlarged with a thinned cavity wall on October 23 (Figure 2D) compared to CT images on September 13 (Figure 2C). As his serum AFP level increased rapidly and HCC continued to progress, he received the eighth cycle of toripalimab immunotherapy and regorafenib, along with antibiotic treatment.

Unfortunately, his symptoms of fever, cough, and hemoptysis worsened again on November 2, 2020, despite intensified antibiotics. Chest CT re-examination showed increased inflammatory lesions in the right lung and significant expansion and thickening of the cavity lesion, indicating deterioration of pulmonary M. kansasii disease (Figure 2E). At the same time, his liver tumors progressed, and his liver function failed rapidly. As a result, he had to stop immunotherapy and TKIs therapy permanently, received palliative care, and finally died of liver cancer rupture and hemorrhage on January 21, 2021.

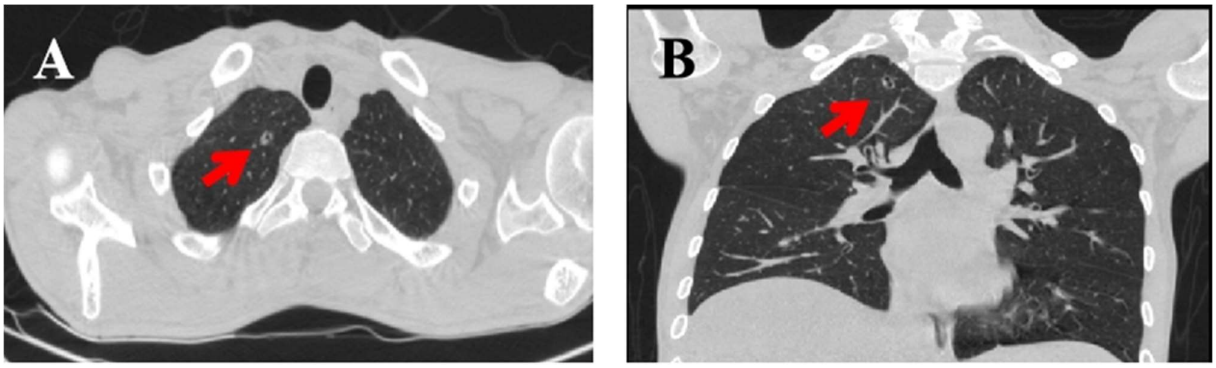

Figure 1. Chest CT of an existing small nodule in the right upper lung in the patient with HCC, which may be latent *M. kansasii* infection and finally developed pulmonary *M. kansasii* disease following

combined treatments, including PD-1 inhibitors. (A) Sagittal chest CT image. (B) Coronal chest CT image. Arrowheads show a small nodule in the right upper lung.

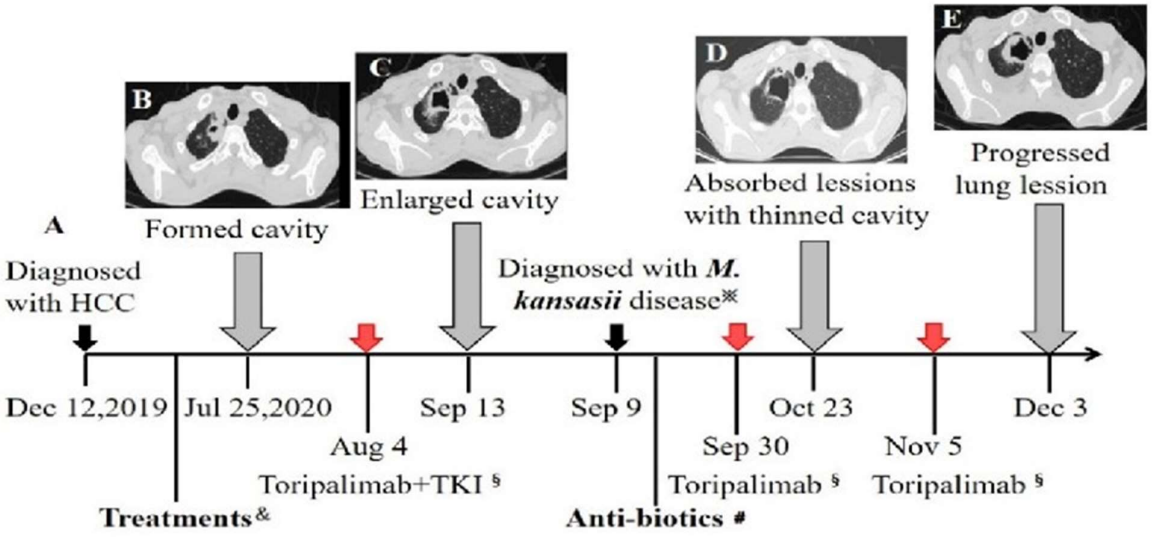

Figure 2. Development of pulmonary *M. kansasii* disease in a patient treated with PD-1 inhibitor Toripalimab for HCC.

(A) Timeline of therapies and disease status of a patient with HCC.

(B) Chest CT image with a formed cavity in the right upper lung of the patient with no cough, hemoptysis, and fever after seven months of combined treatments, including five cycles of PD-1 inhibitors on July 25, 2020.

(C) Chest CT image with worsening thick-wall cavity in the right upper lung of the patient with significant symptoms of cough, hemoptysis, and fever after the resumption of one cycle of toripalimab and lenvatinib on December 13, 2020.

(D) Chest CT image with an absorbed thin-wall cavity in the right upper lung of the patient with symptoms after one week of specific antibiotics for *M. kansasii* on October 23, 2020.

(E) Chest CT image with worsening thick-wall cavity in the right upper lung of the patient presented deteriorative symptoms, liver function failure, and rapid tumor progression after the resumption of three cycles of PD-1 inhibitors on December 13, 2020.

&: Concurrent treatments, including five cycles of toripalimab, lenvatinib, HAIC-FOLFX chemotherapy, and following local radiotherapy.

※ Positive AFB, *M. kansasii*-NTM culture, gene of *M. kansasii*-NTM strains, and negative Xpert MTB/RIF assay for bronchoalveolar lavage fluid.

§ TKIs, including lenvatinib or regorafenib; toripalimab, PD-1 inhibitor.

Antibiotics, including isoniazid (INH), ethambutol (EB), azithromycin (AZM), and moxifloxacin (MXF), for *M. kansasii*-NTM.

Discussion and Conclusion

Many reports have shown that the development of infectious diseases such as TB during ICI immunotherapy in patients with cancer has become an emerging concern (2). Herein, we report a case of advanced HCC that developed pulmonary M. kansasii disease following multiple modality treatments, including six cycles of PD-1 inhibitor toripalimab, which showed a similar presentation with reactivation of MTB infection. It is worth noting that it may develop from pre-existing NTM-infected nodules in the right upper lung.

As is known to all, NTM are ubiquitous environmental bacteria including more than 190 species (a full list can be found at http://www.bacterio.net/mycobacterium.html) found in water and soil. Among them, approximately one-third of the strains are pathogenic to susceptible individuals, including M. kansasii, and cause pulmonary and extrapulmonary infections such as lymph nodes, joints, skin, soft tissue, and systemic disseminated diseases (8). Various host factors favor the growth of Mycobacteria and increase disease risk, including structural, immunological, and genetic differences (8).

Both patients with cancer on PD-1 blockade and PD-1 deficient mice (9) and rhesus macaques (10) are prone to autoimmunity and are sensitive to tuberculosis. Recently, a child with inherited PD-1 deficiency was diagnosed with severe abdominal TB and autoimmunity and finally died of pulmonary autoimmunity (11). Notably, one article described in detail three cases of patients with advanced non-small cell lung cancer developing pulmonary NTM diseases (one pulmonary M. avium complex disease and two pulmonary Mycobacterium intracellular diseases) following therapy with nivolumab (one patient) or atezolizumab (two patients) (7). Therefore, we suspected that the development of pulmonary M. kansasii disease in our case was closely related to the toripalimab PD-1 inhibitor immunotherapy. To our knowledge, there are no reports of lenvatinib-associated reactivation of latent MTB/NTM infections.

It is unclear whether pulmonary NTM disease develops from the reactivation of pre- existing infection or is a de novo infection. In the reported cases, no fibrocavitary or reticulonodular shadow was noted, which could indicate NTM infection at the initial lung cancer diagnosis (7). We suggest that the pulmonary M. kansasii disease cavity lesion in our case evolved from an existing NTM infection nodule present in the right upper lung at the time of HCC diagnosis and expanded gradually, and pulmonary M. kansasii disease developed after cycles of PD-1 inhibitor therapy. There are two main reasons for this. First, China has a high burden of MTB and NTM infections. Studies have consistently indicated that the geographic diversity of pulmonary NTM disease prevalence ranges from 3.2% in the northwest to 9.2% in the south across China (12). Second, NTM infection often presents as asymptomatic solitary pulmonary nodules, which are difficult to distinguish from MTB infection and others by chest CT and PET/CT and are commonly ignored (13). Therefore, our case highlights the potential risks of activating NTM infection in immunotherapy, especially with pulmonary NTM infectious nodules.

Some studies have suggested that development of TB is similar to the immune reconstitution inflammatory syndrome (14, 15). Some reports have suggested that ICI immunotherapy enhances CD4+T cell-mediated immunity and over-production of IFN-γ, which leads to excessive inflammatory reactions and tissue injuries in the MTB-infected environment and finally induces reactivation of TB (2, 5). PD-1 pathway facilitates host resistance to MTB by preventing the detrimental accumulation of NK cells, CD8+T cells, and CD4+T cells and over-production of IFN-γ (4, 16). CD8+T cells significantly increase cytotoxicity against IFN-γ-activated macrophages by blocking PD-1 signaling (17). CD4+T cells may facilitate MTB

infection in the absence of PD-1 pathways (4). Ultimately, the overall effect of ICIs on susceptibility to MTB infection or reactivation via PD-1 or PD-L1 antagonism is likely to depend on both host and specific mycobacterial factors (2). However, to date, the underlying mechanisms of reactivation of latent MTB infection and the development of TB remain unclear.

Consequently, we need to further discuss how to manage NTM infectious diseases. NTM is commonly resistant to various conventional anti-MTB drugs compared to MTB because of the strong hydrophobicity of the NTM cell wall and other factors, and different NTM species are sensitive to specific antibiotics (8). Therefore, the identification of strains and early diagnosis of pulmonary NTM diseases is the premise of effective prevention and control of NTM-associated lung diseases. Currently, there is a lack of effective strategies for managing NTM infection in patients with malignant tumors.

In summary, our case, together with cases from the literature, suggests that reactivation of NTM infection and development of pulmonary NTM diseases may be associated with immunotherapies and cause unfavorable outcomes for patients with cancer. Therefore, monitoring and early diagnosis of pulmonary NTM diseases and further investigation of their underlying mechanisms are warranted.

Pulmonary disease induced by the pathogenic microorganism NTM is difficult to differentiate from TB and may be seriously underestimated in patients with cancer, given the high burden of TB/NTM infection in China and widespread immunotherapies. Therefore, physicians should pay more attention to the development of pulmonary NTM diseases in patients with cancer during immunotherapy regimens with ICIs in areas with a high burden of NTM.

Abbreviation

MTB, Mycobacterium tuberculosis; LTBI, latent tuberculosis infection; TB, tuberculosis; NTM, non-tuberculous Mycobacterium; PTNMD, pulmonary non-tuberculous mycobacterial disease; MAC, Mycobacterium avium complex; CT, computed tomography; PD-1/PD-L1, programmed cell death 1/ programmed cell death-ligand 1; HCC, hepatocellular carcinoma; ICIs, immune checkpoint inhibitors; irAEs, immune-related adverse events; AFB, acid-fast bacillus; BALF, bronchoalveolar lavage fluid; MTB/RIF, Mycobacterium tuberculosis and rifampicin (RIF) resistance; HAIC, hepatic arterial perfusion chemotherapy; TACE, trans-catheter hemoembolization; AFP, alpha-fetoprotein.

Declarations

1) ***Consent to publication***

We declare that all authors agreed to publish the manuscript at this journal based on the signed Copyright Transfer Agreement and followed publication ethics.

2) ***Ethical approval and consent to participants***

This study (including images, personal and clinical details of the participant) was approved by the Clinical Research Ethics Committee of Shenzhen People's Hospital, China. Written consent was obtained from his relative (his father) for publication of the article.

3) ***Disclosure of conflict of interests***

We declare that no conflict of interest exists in this work.

4) ***Funding***

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5) Availability of data and material

We declare that the data supporting the results reported in the article are available in the published article and from the corresponding author upon reasonable request.

6) Authors' Contributions

JA, LP, XW, LX, FZ, PZ, and XH T contributed to the study conception and design. JA, LP, XW, LX, CQ, SL, and XH T managed and treated the patients involved in this study. JA, LP, and XW performed the analyses of the patient data. JA, XW, and ZF wrote the first draft of this manuscript. JA, XW, ZF, XT T and PZ wrote the manuscript. All authors reviewed and approved the final version of the manuscript.

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8) Authors' biography

None.

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