

Tuberculosis Following PD-1 Inhibitor in A Patient with Non-Small Cell Lung Cancer; A Case Report & Literature Review

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Abstract

Immune checkpoint inhibitors (ICIs) – anti-programmed death-1 (PD-1) and their ligands (PD-L1 and PD-L2) have become widely used in the treatment of several malignancies. Many immune-related adverse events have been linked to these agents. However, tuberculosis (TB) reactivation during their use is increasingly reported. Herein, we present a 58-year-old lady with advanced non-small cell lung cancer (NSCLC) ALK-negative, EGFR wild, and PD-L1 Immune histochemistry (IHC) strongly positive in 95% of tumor cells. The patient presented with high-grade fever and a history of productive cough for a 1-week duration. A few days later, she was diagnosed with pulmonary tuberculosis following the 6th cycle of Pembrolizumab, an anti-PD-1 monoclonal antibody. AFB smear and TB PCR from BAL were positive (rifampin resistance not detected), and she was accordingly started on Anti-TB medications. Immunotherapy was held. Of note, the patient had a history of sick contact with a patient with active TB infection ten years ago, but there was no documentation of latent TB or previous TB infection. Her HIV status is negative. Her sputum AFB smear continued to be positive after four weeks of anti-TB medications. Later, the patient was discharged after her sputum was cleared from AFB (negative x 2 sets). We assumed that our patient developed reactivation of pulmonary tuberculosis secondary to an immune checkpoint inhibitor (Pembrolizumab). She was not re-challenged with Pembrolizumab following TB diagnosis.

Keywords: checkpoint inhibitors; tuberculosis; non-small cell lung cancer (NSCLC); Anti-PD-1; toxicity management; immunotherapy; pembrolizumab

Background

Immune checkpoint inhibitors (ICIs) are a type of cancer immunotherapy that has provided a tremendous breakthrough in the field of oncology¹. They block specific proteins made by immune system cells, particularly T cells and some cancer cells, which in turn boost the immune system to kill cancer cells better². Currently approved checkpoint inhibitors target the molecules cytotoxic T-lymphocyte-associated protein 4 (CTLA4), Programmed death receptor -1 (PD-1), and Programmed death-ligand 1(PD-L1).

Recognition of cancer cells by the toxic T lymphocytes plays an essential role in the malignant cell killing. Cancer cells may escape this process by expressing programmed death-ligand 1 (PD-L1), which binds to the programmed death receptor-1 (PD-1) on T cells surface³. This interaction (PD-L1/PD-1) leads to inhibition of cytokines and T cells proliferation, and eventually, cancer cells will escape the killing process. So, blocking (PD-L1/PD-1) pathway by immunotherapy becomes imminent in cancer treatment⁴.

The role of ICIs has been studied in infectious diseases as well ⁵. Various human studies & animal models suggest that immune system activated by PD-1/PD-L1 blockade is effective in targeting certain viral, bacterial and fungal pathogens by limiting T cells dysfunction ⁵.

Nonetheless, in sharp contrast with other pathogens that cause chronic infection, accumulating reports demonstrate the occurrence of Mycobacterium Tuberculosis (MTB) infection during immunotherapy with ICIs even without prior immunosuppression ⁶.

Herein, we present a patient with advanced non-small cell lung cancer (NSCLC) who developed pulmonary tuberculosis following treatment with Pembrolizumab, an anti-PD-1 monoclonal antibody.

Case presentation:

A 58-year-old female patient, with 20 pack-year smoking history, and type 2 Diabetes Mellitus for two years. In 2015, an incidental right apical lung mass suggestive of Pancoast tumor was seen in chest CT (Figure 1 a & b) following abnormal chest X-ray. The patient refused further investigations at the time. In August 2018, she was admitted to Hamad General Hospital (HGH) with sepsis secondary to acute cholecystitis.

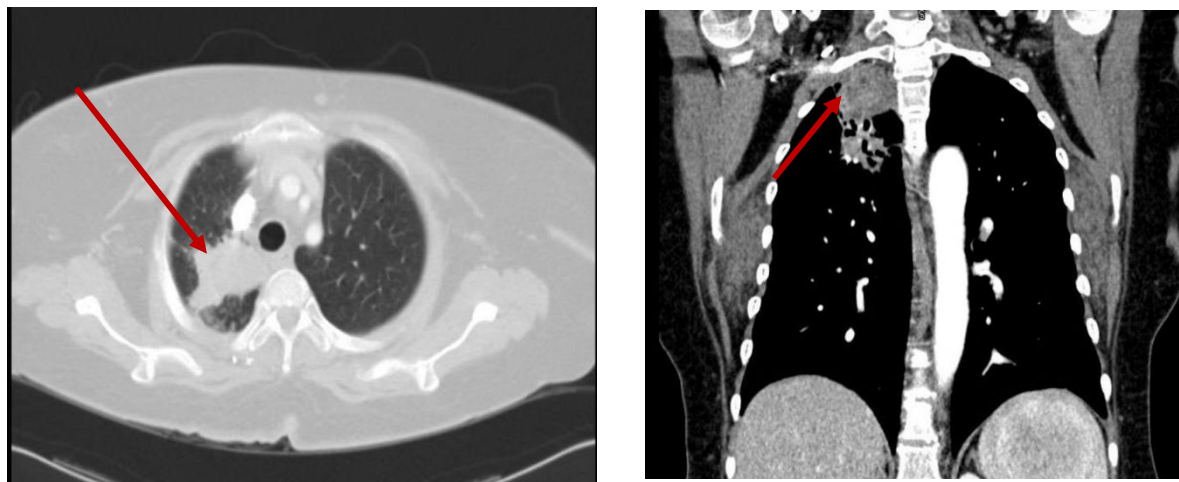


Figure 1 A & B: Chest CT showing a well-defined right apical mass lesion with pleural invasion and possible mediastinal extension, suggestive of Pancoast tumor (Red arrow).

Hospital course was complicated by left anterior cerebral artery (ACA) stroke. during the admission, further work up for lung mass done with biopsy from a left cervical lymph node, and diagnosis of metastatic pulmonary adenocarcinoma (stage IV) confirmed in Sep 2018 (Figure 2 A & B).

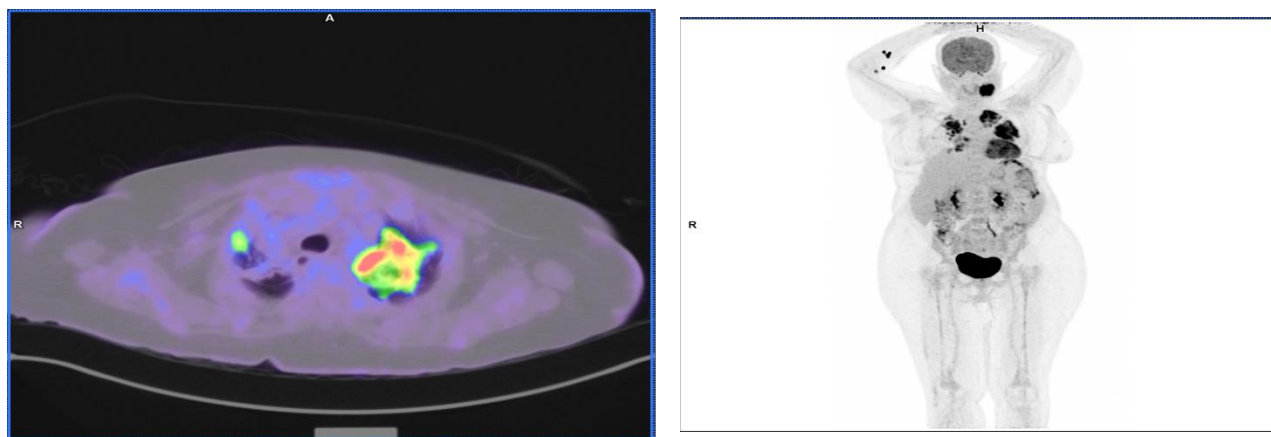


Figure 2 a & b: Left: fused FDG PET-CT image with lung window showing intense uptake in the apical mass, right: maximum intensity projection representation of whole body FDG distribution showing metastatic pulmonary adenocarcinoma (stage IV)

Immunohistochemistry (IHC) report was strongly positive for PD-L1 in 95% of the tumor cells (Figure 3A & B), negative ALK gene rearrangement, and no EGFR mutation was detected.

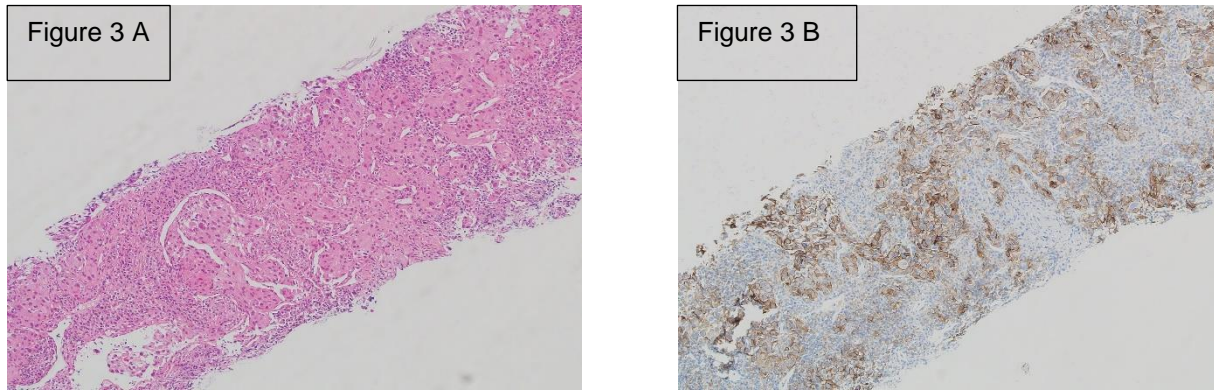


Figure 3 A: H&E lymph node is extensively infiltrated by nests and sheets of large malignant cells with large irregular-shaped nuclei, prominent nucleoli and abundant eosinophilic cytoplasm. Rare scattered anaplastic cells are also present.

Figure 3 B: immunohistochemistry showing PDL 1 is strongly positive in 95% of cells.

In March 2019, the patient started immunotherapy Pembrolizumab 200 mg every three weeks. PET CT on 14th July 2019 (following six cycles) showed mixed response with overall moderate progression. (Figure 4 A & B)

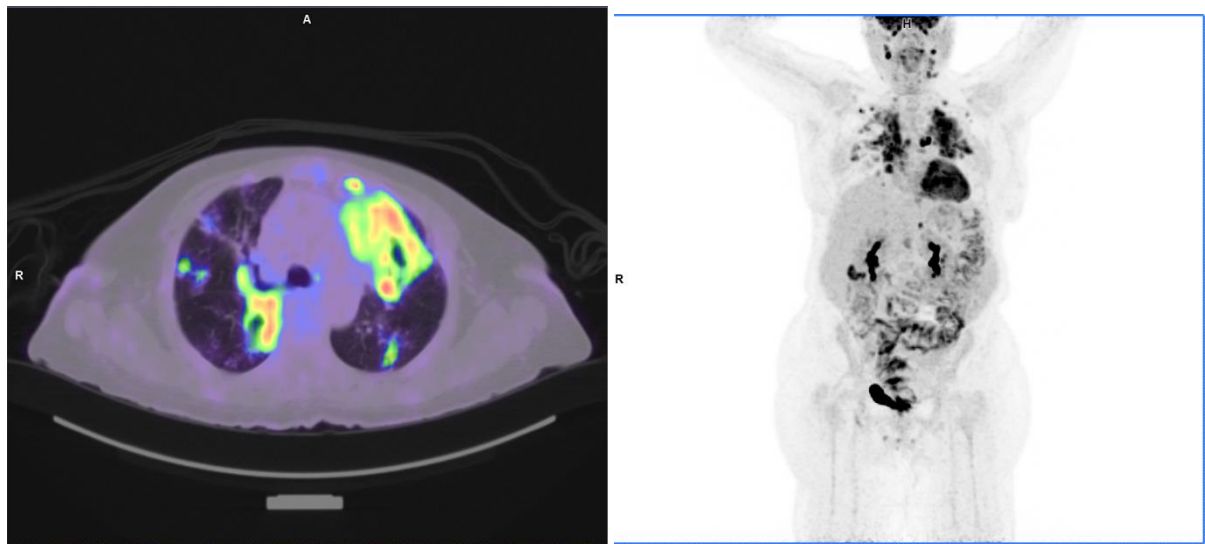


Figure 4 A & B PET CT (lung window) following 6 cycles of pembrolizumab showed mixed response with overall moderate progression

On 29th July 2019, she presented with a 1-week history of productive cough, high-grade fever, tachycardia, and low oxygen saturation (Temp: 39.2, HR: 130, SPO2: 91% on room air). Chest X-ray revealed a significant opacity in the left mid and lower lung zones. (Figure 5)



Figure 5: chest XR showing Large opacity noticed in the left mid and lower lung zones and Right upper zonal nodular and reticular shadowing

On 31st July 2019 CT Angiogram showed left sided large pulmonary consolidative mass lesion and areas of cavitation. (Figure 6)

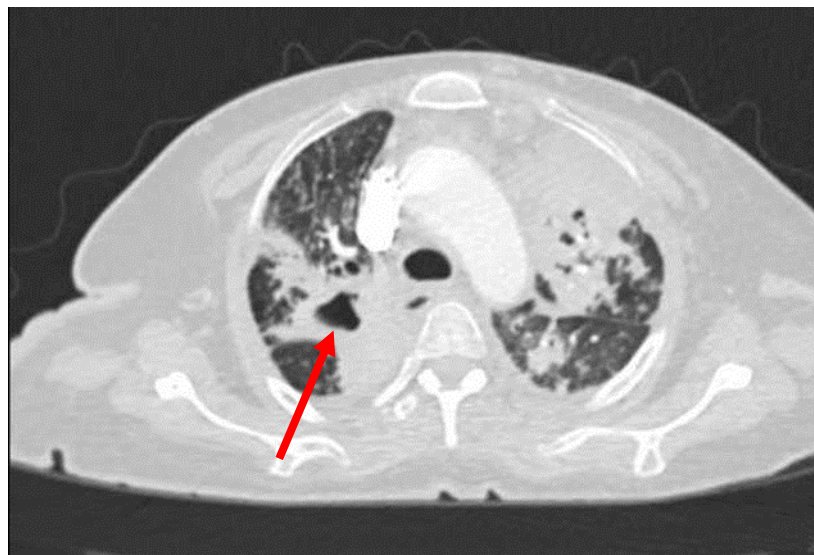


Figure 6: CT chest angiogram (lung window) showing consolidation with cavitory lesion in right upper lobe (red arrow)

She was treated with antibiotics as community-acquired pneumonia; however, she continued to spike fever. The initial microbiological workup was negative. Bronchoscopy and bronchoalveolar lavage (BAL) on 5th August 2019 showed positive AFB smear and TB PCR (rifampin resistance not detected). On 6th August 2019, she was started on anti TB medications (RIFA four. Further history revealed that she had sick contact with active TB patient ten years ago, but there was no documentation of latent TB or previous TB infection. Her HIV status was negative. Sputum AFB smear found positive and cleared six weeks following anti TB medications.

On 23rd August 2019, chest X-ray showed new bilateral reticular, and nodular pulmonary infiltrates (figure 7).

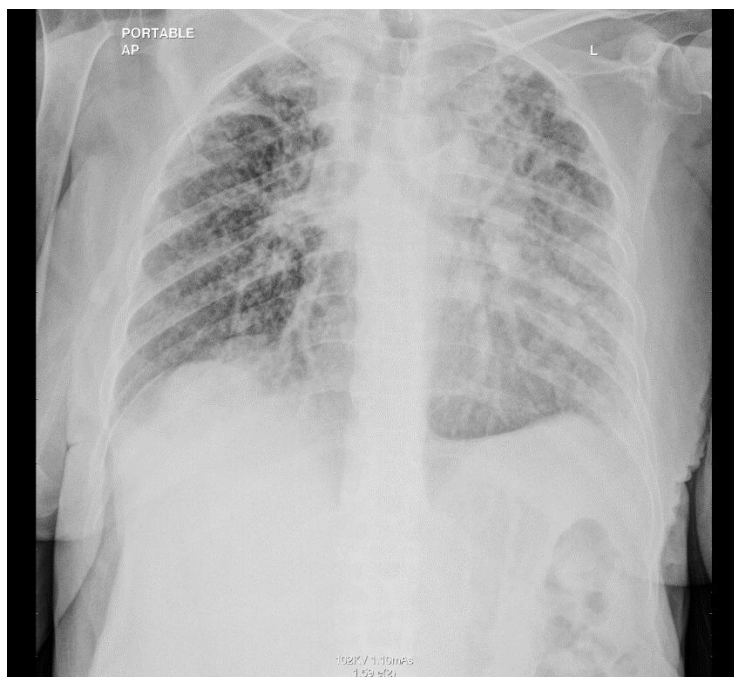


Figure 7: chest X-ray showed new bilateral reticular and nodular pulmonary infiltrates.

CT Chest on 26th August confirmed the progression of the disease, with innumerable bilateral lesions and new lesion in segment 6 of the liver (Figure 8).



Figure 8: CT Chest on 26th August confirmed progression of the malignant disease, with innumerable bilateral nodular lesions, and new hypodense lesion in segment 6 of the liver.

On 12th October 2019 patient started chemotherapy with carboplatin and pemetrexed as second line. PET CT on 22nd December 2019 (following four cycles) showed Good therapeutic response with near-complete remission of lung, liver, spleen, and lymph nodal involvements (Figure 9).

The patient remains on chemotherapy and anti TB medications for a proposed 9-month duration.

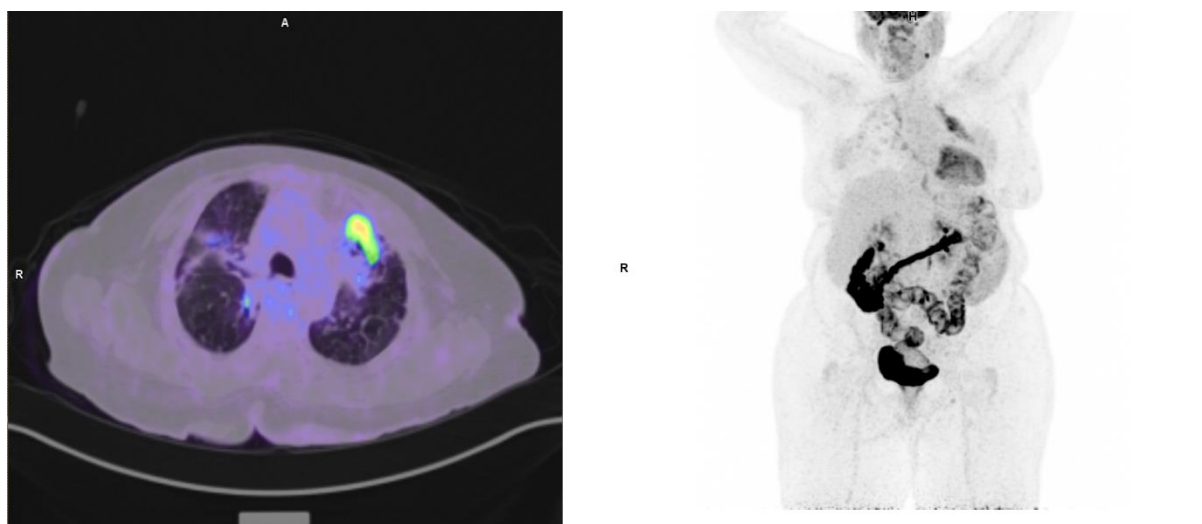


Figure 9 : PET CT following 4 cycles of pemetrexed and carboplatin chemotherapy showed near complete response.

Discussion:

TB reactivation is an established adverse effect in many cancers' biological agents, especially with TNF- α inhibitors^{7,8}. The incidence of TB reactivation in cancer patients is higher in hematological malignancies compared to solid tumors; among solid tumors, the highest incidence was showed in lung cancer followed by gastric cancer, breast cancer, liver cancer, and colon cancer respectively⁹.

With the expanding use of immune checkpoint inhibitors for the management of cancer, infectious complications of immune checkpoint inhibitors became an emerging adverse effect of these agents, including TB reactivation¹⁰.

The majority of patients infected with tuberculosis will develop a latency state where no signs of disease, up to ten percent of those patients may develop active tuberculosis infection¹¹. Containments of the infection is mediated by cytokines and the interaction between macrophages and T lymphocytes (CD4 and CD8)¹². Immunocompromised status is one of the most critical risk factors for reactivation including, HIV, organ transplanted patients, and patients receiving immunosuppressive therapy¹³.

The exact mechanism of TB reactivation following treatment with these agents remains not clearly understood. However, few preclinical studies in MTB infected PD-1-deficient mice & PD-1 blocked humans describe an increase in the IFN- α production by CD4 T cells which promote more bacterial replication and tissue destruction^{6,14,15}.

Furthermore, the role of (PD-L1/PD-1) pathway has been studied also to demonstrate its effect on *M. tuberculosis* infection; In mice model, PD-1 deficiency showed significant sensitivity to *M. tuberculosis* infection and high bacillary load after exposure to aerosol infection with *M. tuberculosis*. PD-1 deficient mice also showed dramatic survival reduction and lung tissue was found to be severely necrotic and inflamed in comparison to the control mice¹⁶. On the other hand, the data about (PD-L1/PD-1) pathway role in the cytolytic activity of T lymphocytes in the human being is more contradictory¹⁷. However, multiple reports highlighted the reactivation of pulmonary tuberculosis infection after the use of PD-1 inhibitors^{10,15,18-26}.

ICIs associated MTB infection was extensively searched by expediting all the reported cases through PubMed up to September 2019, with no language restriction applied. In general, 14 reported cases were identified retrieved from 11 articles^{10,15,18-26}, in addition to our case (Table 1). All the patients were either Caucasians or Asians, aged from 49 to 87 years and with male predominance.

With respect to their oncological diagnosis, 5 cases had metastatic non-small cell lung cancer (NSCLC), 5 cases had metastatic melanoma, 2 cases had metastatic head and neck squamous cell carcinoma (HNSCC), 1 case had Hodgkin lymphoma & 1 case had metastatic Merkel carcinoma.

For the ICIs, 8 cases were on Nivolumab, 5 cases were on Pembrolizumab, and only one case was on Atezolizumab. The time to diagnosis varied among patients and ranged between 4 & 36 weeks. In all patients, no latent TB testing (LTBT) before immunotherapy was done, and it was not clear whether TB infection is primary or secondary to latent TB reactivation. TB was microbiologically confirmed in all cases and followed by anti-TB drugs initiation. ICIs were maintained in three cases and discontinued or temporarily suspended in the remaining patients.

The time to diagnosis of TB in the current case occurred after six cycles of Pembrolizumab. TB was confirmed microbiologically by PCR and AFB. Our case gave a history of sick contact with a patient with active TB infection ten years ago, but there was no documentation of latent TB or previous TB infection.

To our knowledge, this is the first reported case from the Arab and the Middle East; it reinforces the previous observations of the association between ICIs administration and the development of MTB. Nevertheless, further studies in the clinical setting are necessary to establish the exact mechanism involved in this association. Oncologists' awareness & prompt recognition of this potential hazardous consequence are essential. Since there is no clear evidence whether LTBT prior PD-1/PD targeted immunotherapy is required, targeted LTBT before starting ICIs immunotherapy with TB chemoprophylaxis; yet to be explored, particularly in the regions where the MTB prevalence is high.

Ethics approval and consent to participate

The case report was approved the Medical Research Centre at Hamad Medical Corporation and the Hamad Institutional Review Board (IRB) under number MRC-04-20-095.

Consent for publication

This case report does not contain any personal identifier of the patient [such as name, photograph ... etc.]. It only includes radiological and pathological imaging, which does not contain any identifications. A written patient informed consent of patient information, images and publication was signed by the patient.

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Author Contributions

A.M.S & S.A.B contributed to the literature review and drafted the initial manuscript ;**M.S.E** critically revising the paper and helped in manuscript writing; **A.A.H & A.Y.M** contributed to data collection and helped in manuscript writing ; **Z.L.** helped in the radiology figures and helped in manuscript writing; **M.Z.S.** contributed to the pathology section of the case report ;**S.E** helped in manuscript writing; **K.I.R.** managed patient care and revise the final draft of the manuscript ; **N.E.O.** conceived and designed the idea, literature review, data collection, wrote the manuscript, overall organized the case report, supervised the project and proof-reading of the manuscript.

All authors gave final approval of the version to be published and agreed to be accountable for all aspects of the work.

Disclosure and radiology figures

The authors report no conflicts of interest in this work.

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Table 1 Summary of case reports documenting development of pulmonary TB in cancer patients treated with immune check point inhibitors.

Ref. number	Age/sex	Ethnic origin	Diagnosis	Time to TB diagnosis (after how many cycles of ICPIs)	How Diagnosed	Treatment	Outcome of TB	ICPI resumed
Ref ¹⁰	50 / M	Caucasian	Metastatic melanoma	4 cycles of Pembrolizumab	Histology and tuberculin skin test conversion	4-drug regimen, maintenance of the ICPI	Complete regression of pleural effusion	Yes
	64 / M	Caucasian	Metastatic NSCLC	2 cycles of Nivolumab	Histology, positive bone culture and PCR	4-drug regimen, discontinuation of the ICPI	Rapid death after a second operation for spinal cord compression	No
Ref ¹⁵	59 / M	Asian	metastatic NPC	3 cycles of Nivolumab	Histopathology, Positive sputum culture, PCR	discontinuation of the ICPI, 4 drug therapy then IV Anti-TB due to patient condition	Expired 1 month after diagnosis with TB reactivation	No
	83/ M	Caucasian	metastatic MCC	12 cycles of Pembrolizumab	AFB negative but culture positive, positive IFN- γ release assay	discontinuation of the ICPI, 4 drug therapy, then ICP restarted due to evidence of progression	The patient completed 9 months of TB therapy without evidence of recurrence	Yes
Ref ¹⁸	76/F	Caucasian	Advanced Melanoma	8 cycles of Nivolumab+/-Ipilimumab	BAL culture , PCR	Discontinuation of the ICPI, 3 drug therapy	Patient expired with acute respiratory failure 3 days after initiation of Anti-TB	No
	85/M	Caucasian	Metastatic melanoma	9 cycles of Atezolizumab	Sputum Culture	Maintainace of the ICPI, 4 drug therapy	Complete remission of P. TB	Yes
Ref ¹⁹	87 / M	Asian	HL	5 cycles of Nivolumab	Positive sputum culture	3-drug regimen, discontinuation of the ICPI	Complete remission of P. TB	No
Ref ²⁰	72 / M	Asian	Metastatic NSCLC	8 cycles of Nivolumab	Positive BAL culture and PCR Positive IGRA conversion	TB therapy (no details given)	Not specified	No details
Ref ²¹	59 / M	Asian	Metastatic NSCLC	3 cycles of Nivolumab	Histology, and positive pericardial fluid culture	Treatment for TB (no details given), maintenance of the ICPI	Complete regression of pericarditis	Yes
Ref ²²	65 / F	Asian	Advanced melanoma	10 cycles of Pembrolizumab	Liquid culture and positive BAL	4-drug regimen and pause of ICPI	Complete remission of P. TB	Yes
Ref ²³	56 / M	Caucasian	Metastatic NSCLC	12 cycles of Nivolumab	Histopathology, Positive sputum culture, PCR	Treatment for TB (no details given), discontinuation of the ICPI	Not specified	No

Ref. number	Age/sex	Ethnic origin	Diagnosis	Time to TB diagnosis (after how many cycles of ICPIs)	How Diagnosed	Treatment	Outcome of TB	ICPI resumed
Ref ²⁴	49/ M	Asian	Stage 4 SCC of hard palate	6 cycles of Nivolumab	Positive sputum culture, AFB stain, PCR	Treatment for TB (no details given), discontinuation of the ICPI	The patient expired five months after the diagnosis of TB because of bacterial pneumonia with acute respiratory failure.	No
Ref ²⁵	75 / M	Asian	Metastatic NSCLC	15 cycles of Nivolumab	AFB stain, Positive sputum culture, PCR	hold of the ICPI, 4 drug therapy,	paradoxical response (PR) 10 days after initiation of anti-MTB treatment, culture and AFB negative post 3 months of TB treatment	Yes
Ref ²⁶	56 /F	Caucasian	Metastatic NSCLC	Not defined	AFB stain, positive culture	Discontinuation of the ICPI, 4 drug therapy	Not specified	No
Current case	58/F	Caucasian	Metastatic NSCLC	6 cycles of Pembrolizumab	AFB smear and TB PCR from BAL	Discontinuation of the ICPI, 4 drug therapy	Currently patient is still receiving her Anti-TB medication along with the new line chemotherapy, clinically stable	No