CASE REPORT

# Complete Remission After Immunotherapy-Induced Abdominal Tuberculosis in a Patient With Advanced NSCLC Treated With Pembrolizumab: A Case Report

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Received 20 February 2022; revised 16 March 2022; accepted 26 March 2022
Available online - 31 March 2022

**ABSTRACT**

The use of immune checkpoint inhibitors (ICIs) has drastically transformed the therapeutic landscape in lung cancer. Special focus has been put on immune-related toxicity; however, infections can also seem during ICI treatment. Although rare, tuberculosis (TB) has been increasingly identified after ICIs, and it seems that the programmed cell death protein 1 and programmed death-ligand 1 pathway is directly involved in its pathophysiology. Here, we describe the case of a patient with advanced NSCLC who developed abdominal TB after 32 months of pembrolizumab and who remains in tumor remission 10 months after discontinuation of this drug. Routine screening for latent TB before ICI treatment is advised, with closer collaboration between infectious disease specialists and oncologists.



*Keywords:* Non–small cell lung cancer; Immune-checkpoint inhibitors; Tuberculosis; Case report

## Introduction

Immune checkpoint inhibitors (ICIs) alone or in combination with chemotherapy are an established standard-of-care in first- and second-line treatment of advanced NSCLC.[1]

The main safety concerns of ICI use are the so-called immune-related adverse events (irAEs) that most often

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Disclosure: *Dr. Abdayem reports conducting lectures for AstraZeneca; and receiving travel, accommodations, and expenses from Roche, Eli Lilly, and Pierre Fabre. Dr. Planchard reports having consulting, advisory role, or lectures for AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Daiichi Sankyo, Eli Lilly, Merck, Novartis, Pfizer, prIME Oncology, Peer CME, and Roche; receiving honoraria from AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Eli Lilly, Merck, Novartis, Pfizer, prIME Oncology, Peer CME, and Roche; having clinical trial research for AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Eli Lilly, Merck, Novartis, Pfizer, Roche, MedImmune, Sanofi-Aventis, Taiho Pharma, Novocure, and Daiichi Sankyo; and receiving travel, accommodations, expenses from AstraZeneca, Roche, Novartis, prIME Oncology, and Pfizer. The remaining authors declare no conflict of interest.*

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Cite this article as: Riudavets M, Wyplosz B, Ghigna MR, et al. Complete remission after immunotherapy-induced abdominal tuberculosis in a patient with advanced NSCLC treated with pembrolizumab: a case report. *JTO Clin Res Rep*. XXXX;X:XXXXXX.



ISSN: 2666-3643
https://doi.org/10.1016/j.jtocrr.2022.100319

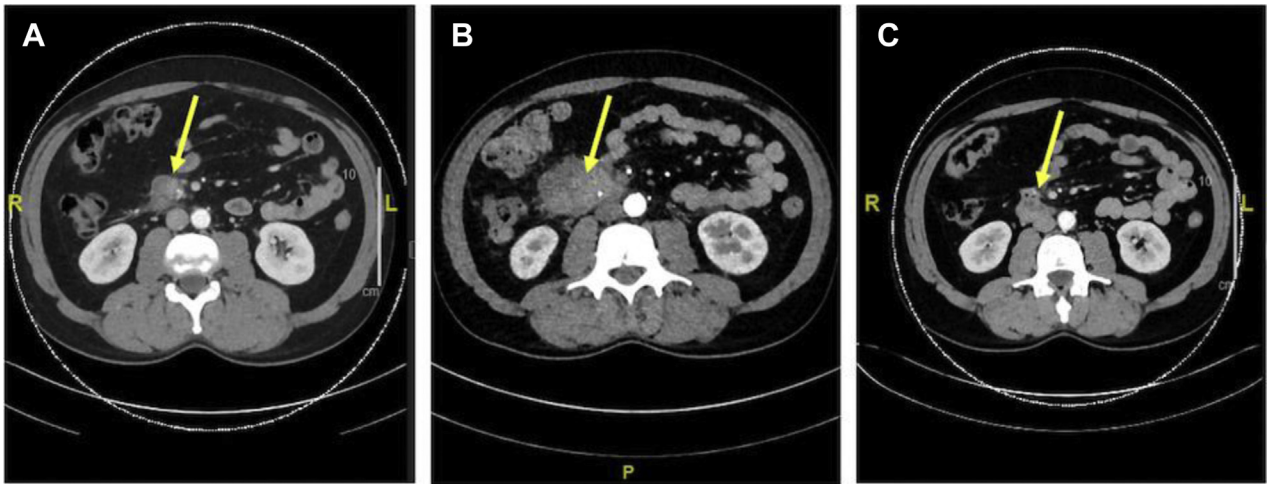


**Figure 1.** Comparison of abdominal CT scans between 2 months before (*A*, March 2021), at the initiation (*B*, May 2021), and after completing the anti-TB therapy (*C*, November 2021). CT, computed tomography; TB, tuberculosis.

affect the skin, gastrointestinal tract, and thyroid gland. In addition, infectious diseases, although rare, can occur.

Herein, we report a case of an ICI-induced abdominal tuberculosis (TB) in a patient with advanced NSCLC with brain, bone, and lymph node metastases who remains in complete response 10 months after ICI discontinuation after diagnosis of TB.

## Case Presentation

A 42-year-old former smoker man of North African Arab descent was diagnosed, in March 2018, with sarcomatoid carcinoma of the right upper lobe, AE1/AE3+, TTF1-, and programmed death-ligand 1 (PD-L1) 90%, cT4N0M1b (isolated metastasis in the iliac right bone) according to the eighth edition of the American Joint Commission on Cancer TNM staging system for NSCLC. Four cycles of cisplatin 80 mg/m$^2$ and vinorelbine 30 mg/m$^2$ were administered, concomitantly with thoracic radiotherapy (total of 66 grays [Gy] in 33 daily 2-Gy fractions) and stereotactic bone radiotherapy (30 Gy in three 10-Gy fractions every other day) until June 2018.

In July 2018, the patient presented with headache and gait instability. Computed tomography (CT) scan and magnetic resonance imaging detected bilateral adrenal (right mass of 36 mm and left medial lesion measuring 19 mm) and brain new metastases, with a unique right parietal lesion of 27 mm with marked edema. Pembrolizumab at the dosage of 200 mg every 21 days was initiated at the end of July after completion of stereotactic brain radiotherapy (30 Gy in three 10-Gy fractions every other day) and corticosteroid discontinuation. Complete response according to Response Evaluation Criteria in Solid Tumors version 1.1 criteria was obtained after 3 cycles and maintained during the successive radiologic controls.

In March 2021, imaging examinations revealed peritoneal involvement with fat infiltration, necrotic mesenteric, and retroperitoneal suspicious lymph nodes (Fig. 1*A*). Upper and lower gastrointestinal endoscopy was performed, with no remarkable findings. Given the stability of the disease in the thorax and the potential risks of a surgical biopsy, close surveillance was advised. Pembrolizumab was discontinued concomitantly in March 2021.

Nevertheless, in May 2021, control CT scan revealed progression of the previously described abdominal lesions (Fig. 1*B*). Positron emission tomography (PET)-CT scan revealed a right mesenteric hypermetabolic mass, abdominal lymph node involvement, and multiple hypermetabolic bone lesions (Fig. 2). Given the multisite and rapid evolution, a third-line treatment with weekly carboplatin area under the curve of 2 and paclitaxel 80 mg/m$^2$ was started after discussion in multidisciplinary tumor board.

CT-guided retroperitoneal lymph node biopsy was ordered to complete the full workup and came back highly suggestive of nodal TB (granulomatous inflammatory reaction, with histocytes and multinucleated giant cell aggregates) (Fig. 3). Results of a Ziehl-Neelsen staining and reverse-transcriptase polymerase chain reaction were negative for mycobacteria. Nevertheless, given the strong suspicion of disseminated TB, a standardized regimen with isoniazid, rifampicin, pyrazinamide, and ethambutol was started in early June 2021. Chemotherapy was stopped after one cycle of treatment.

Night sweats and fever episodes that were retrospectively reported by the patient gradually resolved, and a PET-CT scan done in August 2021 revealed morphologic and metabolic regression of the abdominal

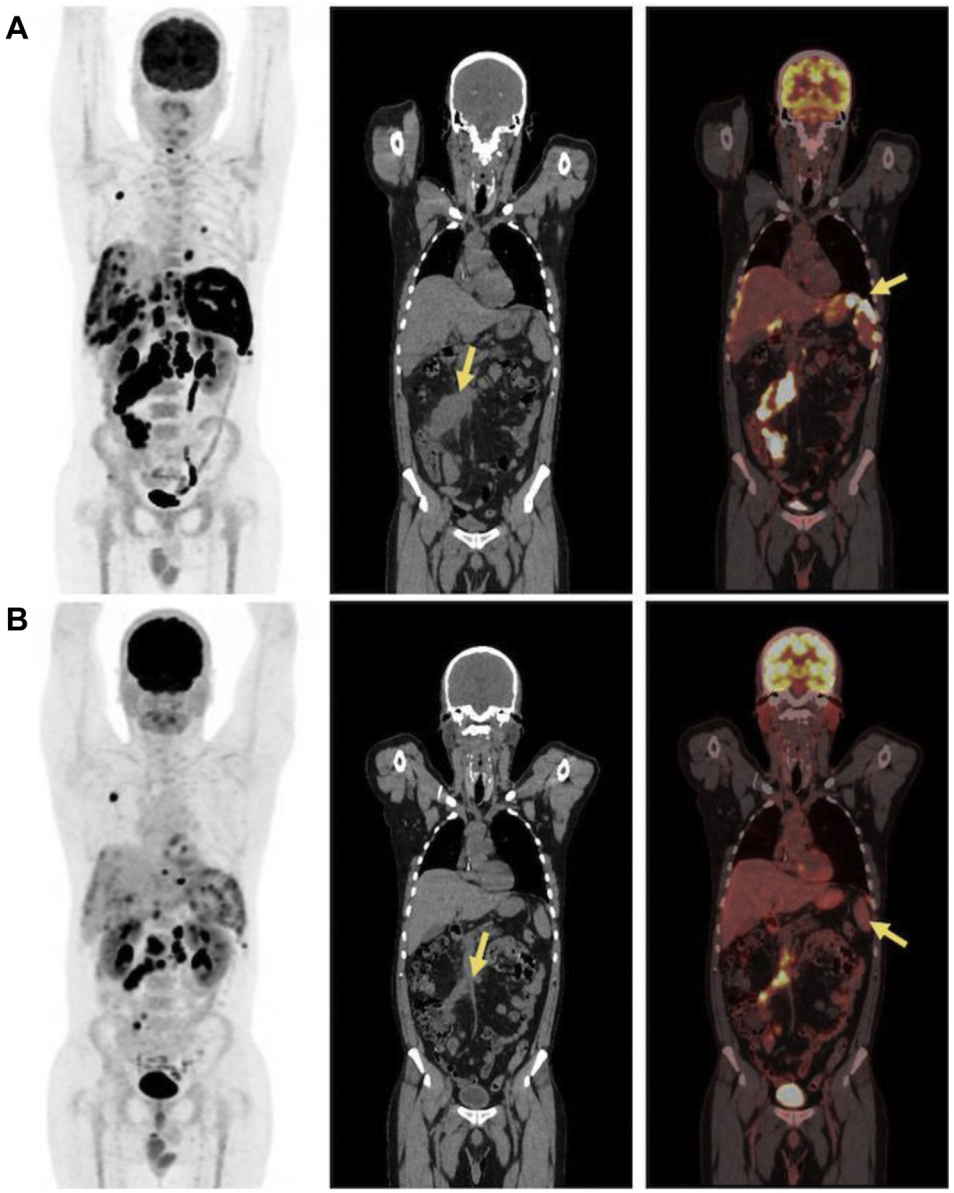


**Figure 2.** Comparison of abdominal findings between the PET-CT in May 2021 (*A*) and in August 2021 after 2 months of TB therapy, with reduction of the hypermetabolic right mesenteric mass and perigastric nodes, including thoracic and bone complete tumor remission (*B*). PET-CT, positron emission tomography-computed tomography; TB, tuberculosis.

abnormalities. Control imaging in November 2021, nearly 10 months after the last pembrolizumab cycle, revealed a persistent complete tumor response, both at thoracic and bone levels, including a decrease in the abdominal inflammatory findings after 6 months of anti-TB therapy (Fig. 1*C*).

## Discussion

The ICIs are antibodies that target either the programmed cell death protein-1 and PD-L1 or cytotoxic T-lymphocyte—associated protein 4 receptors to activate antitumor immunity in numerous tumor types, including lung cancer. In opposite to chemotherapy-induced immunosuppression, ICIs promote immune activation, thus decreasing the likelihood of infectious complications compared with standard cytotoxic cancer therapies.

*Mycobacterium tuberculosis* represents a pathogen of significant clinical and epidemiologic importance in patients with cancer worldwide. Although TB reactivation remains a rare phenomenon in low-incidence areas, there has been a small but growing number of reported cases in patients with cancer treated with ICIs.[2]

Possible mechanisms behind the development of TB in ICI-treated patients with cancer include direct disruption of cellular immune response against TB by

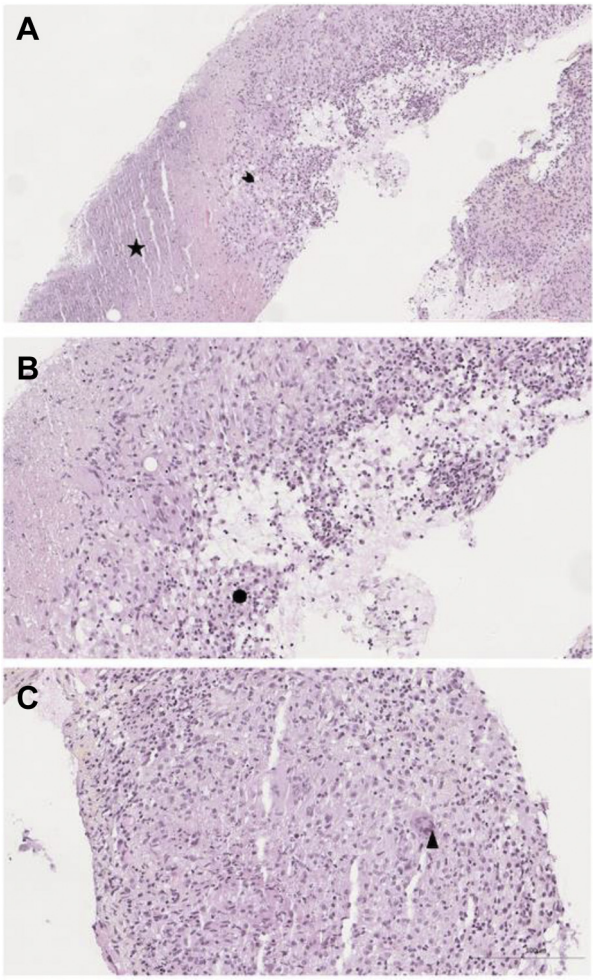


**Figure 3.** Anatomopathologic results from the retroperitoneal scan-guided biopsy. (*A*) The histologic analysis of the lymph node needle biopsy specimen was marked by a dense inflammatory and polymorphic inflammatory infiltrate incorporating necrotic fields (star) and granulomatous reaction (arrow). (*B*) Reactive small lymphocytes were visible at the edge of granulomas (round). (*C*) Some giant multinucleated cells were identified within the histiocytic reaction (triangle).

concurrent medications (e.g., cytotoxic chemotherapy or steroids), cancer-induced immunosuppression, or a direct effect of ICIs per se. In fact, the programmed cell death protein-1 and PD-L1 pathway is involved in the pathophysiology of TB through inhibition of CD4+ and CD8+ T-cell effector functions, thus limiting an excessive immune response. Hence, patients receiving ICIs could develop an immune reconstitution-like reaction to subclinical TB, similar to that developed in the context of human immunodeficiency virus infection during the recovery of the CD4+ T-cell population.[3] Furthermore, recent data suggest that ICIs can result in TB reactivation by dysregulation of tumor necrosis factor-$\alpha$, interleukin-18, and interferon-$\gamma$ in granulomas and increase in both bacterial load and inflammatory changes.[3]

Our patient was Moroccan and traveled back and forth to his home country between immunotherapy injections. The frequent traveling and the atypical abdominal presentation, which was probably preceded by a silent respiratory primary infection, are in favor of a disseminated reactivation rather than a primary TB.

In our case, there were no obvious immunocompromising risk factors other than the 32-month exposition period to pembrolizumab in addition to the primary tumor disease, which was in complete response when the opportunistic infection appeared in March 2021. Of note, results from prepembrolizumab viral serologies were negative; however, tuberculin test was not performed because there is no clear consensus on routine TB screening before ICI therapy. Importantly, Koch's bacilli are rarely detected in nodal TB forms, hence the negative microbiology findings in our case.

Therefore, with all the previous data, we could assume that our patient developed an abdominal disseminated TB reactivation induced or favored by pembrolizumab, even after 31 months of treatment, because immunotherapy was the only intercurrent potential risk factor that we have identified. The question remains open, and long-term side effects are poorly studied and not reported in studies requiring follow-up of long-term responders.

A positive association between the development of irAEs and ICI outcomes has been largely described. A recently published meta-analysis including 34 studies and a total of 8115 patients with advanced NSCLC reveals a correlation between the development of irAEs and both survival times and objective response rates.[4] Both primary and secondary (reactivation) TB reflect an exaggerated immune response in the host and might also predict a favorable tumor response to ICIs, although further studies are needed to confirm such association.

In line with this case, a previous case of abdominal TB in a young patient with metastatic nasopharyngeal carcinoma has been reported. The patient was treated with anti-TB medication and later rechallenged with pembrolizumab without further TB relapse or tumor progression.[5]

## Conclusions

In conclusion, as far as we are aware, we report here the first case of anti-PD-L1–induced abdominal TB reactivation in a patient with complete tumor response after 32 months of pembrolizumab for metastatic sarcomatoid carcinoma of the lung who remains in remission 10 months after discontinuation of immunotherapy.

Of note, this is an atypical late TB presentation, with regard to the cancer diagnosis and immunosuppressive treatment initiation.

This clinical case highlights the importance of investigating any new or unexpected lesions before modifying cancer therapy. Moreover, accurate TB screening methods, especially in patients coming from endemic zones, and proper management of opportunistic infections during treatment with immunotherapy should be well defined in patients with cancer.

## CRediT Authorship Contribution Statement

**Mariona Riudavets**: Conceptualization, Data curation, Writing - original draft.

**Pamela Abdayem, Benjamin Wyplosz, Maria Rosa Ghigna, Angela Botticella, Pauline Pradere, Ines Kasraoui, Charles Roux, Cecile Le Pechoux, and Camilo Garcia:** Validation, Writing - review & editing.

**David Planchard:** Project administration, Conceptualization, Data curation, Supervision, Validation, Writing - review & editing.

## Acknowledgments

The patient involved in this case report gave her informed consent authorizing use and disclosure of her health information.

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