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

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TUBERCULOSIS CASE REPORT

TITLE: Complete remission after immunotherapy-induced abdominal tuberculosis in a patient with advanced non-small cell lung cancer treated with pembrolizumab: a case report.

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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 appear during ICIs treatment.

Although rare, tuberculosis (TB) has been increasingly identified following ICIs and it seems that the PD-1/PD-L1 pathway is directly involved in its pathophysiology.

Here, we describe the case of a patient with advanced non-small cell lung cancer (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 ICIs treatment is advised, with closer collaboration between infectious disease specialists and oncologists.

KEYWORDS (2-5)

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 non-small cell lung cancer (NSCLC).[1]

The main safety concerns of ICIs use are the so-called immune-related adverse events (irAEs) that most commonly affect the skin, gastrointestinal (GI) tract and thyroid gland. In addition, infectious diseases, although rare, can occur.

Herein, we report a case of an ICIs-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 ICIs discontinuation following 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 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 80mg/m2 and vinorelbine 30mg/m2 were administered, concomitantly with thoracic (total of 66 grays [Gy] in 33 daily 2-Gy fractions) and stereotaxic 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 36mm and left medial lesion measuring 19mm) and brain new metastases, with a unique right parietal lesion of 27mm with significant edema. Pembrolizumab at the dose 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 corticosteroids discontinuation. Complete response according to RECIST 1.1 criteria was obtained after 3 cycles and maintained during the successive radiologic controls.

In March 2021, imaging exams revealed peritoneal involvement with fat infiltration, necrotic mesenteric and retroperitoneal suspicious lymph nodes (Figure 1A). Upper and lower GI 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.

However, in May 2021, control CT scan showed progression of the previously described abdominal lesions (Figure 1B). Positron Emission Computed (PET)-CT scan showed a right mesenteric hypermetabolic mass, abdominal lymph node involvement and multiple hypermetabolic bone lesions (Figure 2). Given the multi-site and rapid evolution, a third line treatment with weekly carboplatin AUC 2 and paclitaxel 80mg/m2 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 tuberculosis (granulomatous inflammatory reaction, with histocytes and multinucleated giant cell aggregates) (Figure 3). A Ziehl-Neelsen staining and real-time protein chain reaction (RT-PCR) were negative for mycobacteria. However, 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 showed morphologic and metabolic regression of the abdominal abnormalities. Control imaging in November 2021, nearly 10 months after the last pembrolizumab cycle, showed a persistent complete tumor response, both at thoracic and bone levels, as well as a decrease in the abdominal inflammatory findings after 6 months of anti-TB therapy (Figure 1C).

DISCUSSION

Immune-checkpoint inhibitors are antibodies that target either the PD-1/PD-L1 or cytotoxic T-lymphocyte associated protein-4 (CTLA-4) receptors in order 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 to standard cytotoxic cancer therapies.

Mycobacterium tuberculosis represents a pathogen of significant clinical and epidemiologic importance in cancer patients 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 ICIs-treated cancer patients include direct disruption of cellular immune response against TB by concurrent medications (e.g., cytotoxic chemotherapy or steroids), cancer-induced immunosuppression, or a direct effect of ICIs *per se*. In fact, the PD-1/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 (HIV) infection during the recovery of the CD4+ T-cell population.[3] Furthermore, recent data suggest that ICIs can result in TB reactivation via dysregulation of TNF-α, IL-18 and IFN-γ in granulomas and increase in both bacterial load and inflammatory changes.[3]

Our patient was Moroccan and travelled back and forth to his home country between immunotherapy injections. The frequent traveling as well as 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 pre-pembrolizumab viral serologies were negative; however, tuberculin test was not performed since there is no clear consensus on routine TB screening prior to ICI therapy. Importantly, Koch 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 favoured by pembrolizumab, although after 31 months of treatment, since 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 ICIs outcomes has been largely described.

A recently published meta-analysis including 34 studies and a total of 8115 patients with advanced NSCLC, shows 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 re-challenged with pembrolizumab without further TB relapse or tumor progression.[5]

CONCLUSION

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 regards 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, as well as proper management of opportunistic infections during treatment with immunotherapy should be well defined in patients with cancer.

FIGURES

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).

Figure 2. Comparison of abdominal findings between the TEP-TC in May 2021 (A) and in August 2021 after 2-months of TB therapy, with reduction of the hypermetabolic right mesenteric mass and peri-gastric nodes, as well as thoracic and bone complete tumor remission (B).

Figure 3. Anatomopathological results from the retroperitoneal scan-guided biopsy

A, the histological analysis of the lymph node needle biopsy 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).

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

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DECLARATIONS

Conflicts of interest

MR: no conflicts of interest.

BW: no conflicts of interest.

MRG: no conflicts of interest.

AB: no conflicts of interest.

PA: Lectures: AstraZeneca; travel, accommodations, expenses: Roche, Eli Lilly, Pierre Fabre.

PP: no conflicts of interest.

IK: no conflicts of interest.

CR: no conflicts of interest.

CLP: no conflicts of interest.

CG: no conflicts of interest.

DP: Consulting, advisory role or lectures: AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Daiichi Sankyo, Eli Lilly, Merck, Novartis, Pfizer, prIME Oncology, Peer CME, Roche.

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Authors contribution

MR: Conceptualisation, Data curation, Writing - original draft. PA, BW, MRG, AB, PP, IK, CR, CLP and CG: Validation, Writing - review and editing. DP: Project administration, Conceptualization, Data curation, Supervision, Validation, Writing - review and editing.

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FIGURES

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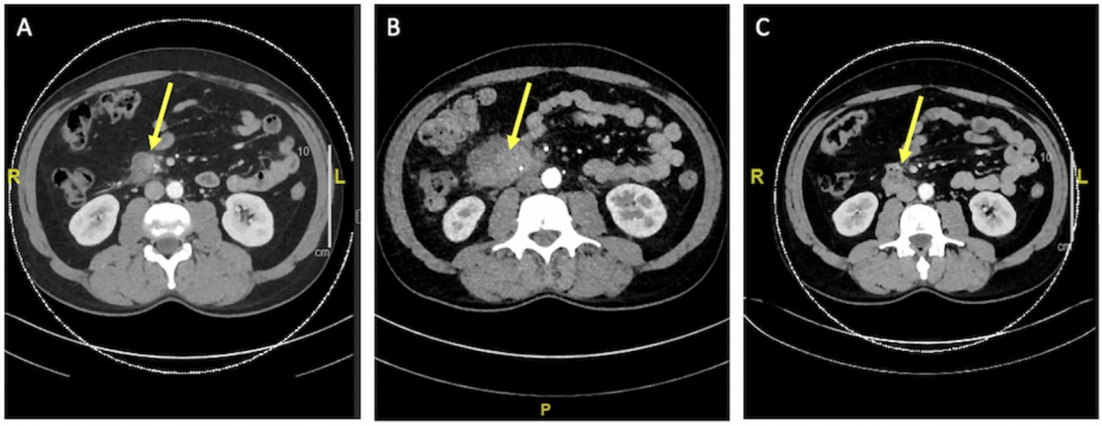

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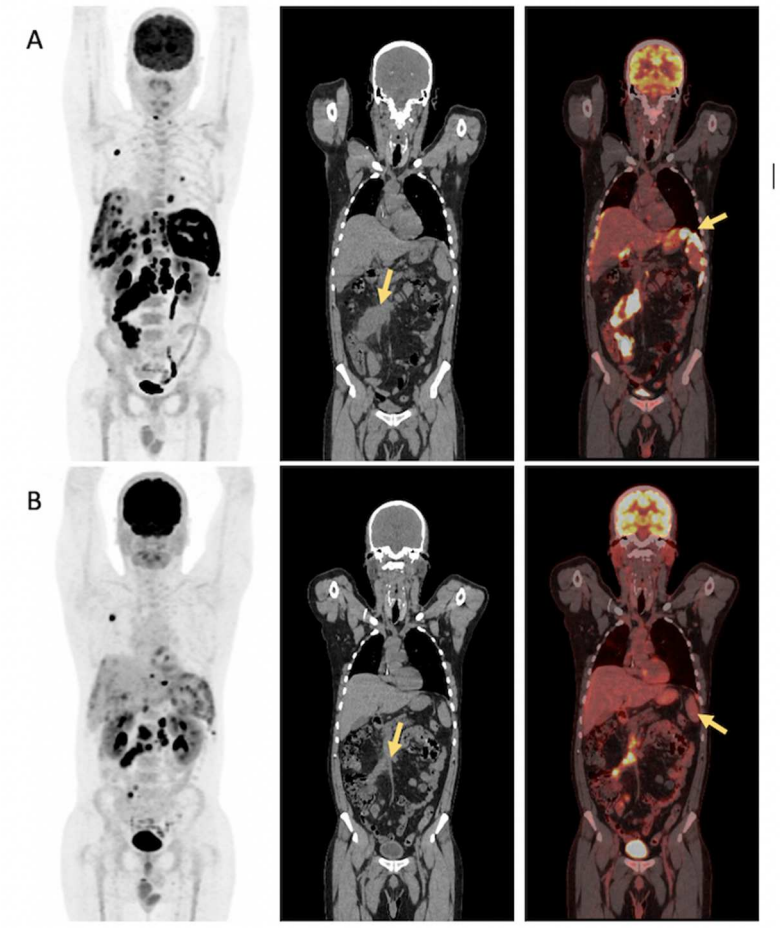

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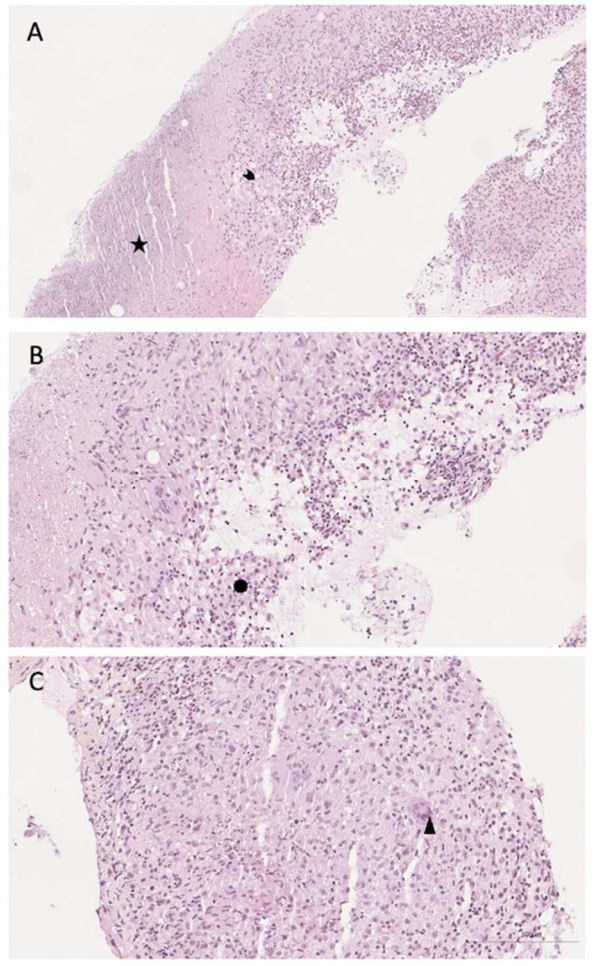

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