**IMMUNOTHERAPY**

**Tuberculosis following PD-1 blockade for cancer immunotherapy**

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Because of the well-established therapeutic benefit of boosting antitumor responses through blockade of the T cell inhibitory receptor PD-1, it has been proposed that PD-1 blockade could also be useful in infectious disease settings, including *Mycobacterium tuberculosis* (MtB) infection. However, in preclinical models, MtB-infected PD-1\(^{-}\) mice mount exaggerated Th1 responses that drive lethal immunopathology. Multiple cases of tuberculosis during PD-1 blockade have been observed in patients with cancer, but in humans little is understood about MtB-specific immune responses during checkpoint blockade–associated tuberculosis. Here, we report two more cases. We describe a patient who succumbed to disseminated tuberculosis after PD-1 blockade for treatment of nasopharyngeal carcinoma, and we examine MtB-specific immune responses in a patient with Merkel cell carcinoma who developed checkpoint blockade–associated tuberculosis and was successfully treated for the infection. After anti–PD-1 administration, interferon-γ–producing MtB-specific CD4 T cells became more prevalent in the blood, and a tuberculoma developed a few months thereafter. MtB-specific Th17 cells, CD8 T cells, regulatory T cells, and antibody abundance did not change before the appearance of the granuloma. These results are consistent with the murine model data and suggest that boosting Th1 function with PD-1 blockade may increase the risk or severity of tuberculosis in humans.

**INTRODUCTION**

The therapeutic benefits of enhancing T cell function by blockade of coinhibitory receptor programmed cell death-1 (PD-1) and one of its ligands, programmed cell death ligand 1 (PD-L1), are now well established for multiple malignancies. Targeting the PD-1 pathway for treatment of chronic infectious diseases is also an area of active development (1). However, whereas PD-1 blockade unleashes beneficial tumor-specific T cell responses during cancer immunotherapy, increasing pathogen-specific T cell function through PD-1 blockade can either enhance control of infection or drive lethal immunopathology, depending on the timing of PD-1 blockade after infection and the particular microbe present (2). Given the long duration of standard treatment regimens for tuberculosis (TB) and the increasing prevalence of drug-resistant strains, host-directed therapies that prove particularly useful in TB (3, 4) are desirable. Human *Mycobacterium tuberculosis* (MtB)–specific CD4 T cells express PD-1 during active TB, and levels of PD-1 on MtB-specific T cells decrease after successful TB treatment (5, 6). Accordingly, PD-1 blockade has been suggested as a host-directed therapy for TB (7), but it is not clear whether PD-1 blockade would be beneficial or detrimental in human TB.

Preclinical data in mice suggest that boosting type 1 T helper cell (Th1) responses by targeting PD-1 may be detrimental during MtB infection. PD-1 knockout (PD-1\(^{-}\)) mice are hypersusceptible to MtB infection, developing large necrotic lesions with high bacterial loads and succumbing faster than even T cell–deficient mice (8–10). The inability of PD-1\(^{-}\) mice to control MtB infection is due to increased MtB-specific CD4 T cell responses, as early mortality in PD-1\(^{-}\) mice is prevented by CD4 T cell depletion (9). Moreover, it has been shown that overproduction of interferon-γ (IFN-γ) by CD4 T cells drives early mortality in MtB-infected PD-1\(^{-}\) mice (11). Thus, although IFN-γ–producing Th1 cells are required for host resistance to mycobacteria, their enhanced activity in the absence of PD-1 counterintuitively exacerbates TB in mice. The mechanisms of IFN-γ–driven disease exacerbation, however, are not yet defined.

Several cases of TB after checkpoint blockade have recently been reported (12–16), and the atezolizumab (anti–PD-L1) product label indicates cases of mycobacterial infections were also observed on trial. Therefore, there is a growing body of evidence suggesting that PD-1 might play a similar role in suppressing immunopathologic T cell responses in human TB. However, there is no information on MtB-specific immune responses in individuals developing checkpoint blockade–associated TB.

Here, we report two cases of TB in individuals receiving anti–PD-1 monoclonal antibodies as cancer treatment. In one patient with nasopharyngeal carcinoma (NPC), PD-1 blockade was followed by the rapid development of disseminated TB that was eventually fatal. In the second patient being treated with anti–PD-1 for Merkel cell carcinoma (MCC), pulmonary TB reactivation was much milder and was successfully treated with anti-TB therapy. Here, we characterize the peripheral adaptive immune response and the bacteria isolated from the pulmonary lesion after PD-1 blockade of the patient with MCC.
RESULTS
Lethal disseminated TB after PD-1 blockade in patient with NPC

A 59-year-old man with metastatic NPC enrolled in a clinical trial evaluating an anti–PD-1 therapy, nivolumab, at a dose of 3 mg/kg every 2 weeks in May 2016 (17) (Fig. 1A). Before study enrollment, no testing for latent TB infection was performed. The patient was HIV negative, but he had emigrated from Vietnam, a country highly endemic for TB, more than a decade before.

In June 2016, after three cycles of anti–PD-1 therapy, computed tomography (CT) scanning showed an interval development of ground glass and centrilobular nodular opacities throughout both lungs (Fig. 1C), which were not present from scanning 2 months prior (Fig. 1B). Other known sites of NPC remained stable or had decreased in size. The patient underwent transbronchial biopsy to obtain fragments of his lung’s right middle lobe at the site of the nodular infiltrate. Pathology revealed a single non-necrotizing epithelioid granuloma that stained positively for acid-fast bacilli (AFB) (Fig. 1, C and D). Sputum samples were positive for Mtb DNA by polymerase chain reaction (PCR) at this time, and AFB were found in the sputum and rectum samples. The patient was diagnosed with disseminated TB. The patient denied TB symptoms including shortness of breath, cough, fevers, chills, night sweats, or weight loss. He denied any history of TB or sick contacts and did not recall previous TB testing by purified protein derivative (PPD).

The patient stopped treatment with nivolumab in June 2016 after three cycles soon after the development of bilateral ground glass opacities was found. He underwent a bronchoscopy, bronchoalveolar lavage (BAL), and biopsy to evaluate the cause of the new opacities. Five days later, the patient presented to the hospital with lethargy, confusion, and hypoxemia, at which time the culture from his BAL specimen grew Mtb that was resistant to streptomycin but susceptible to other first-line drugs. The patient was initiated on an anti-TB medication regimen of rifampin (600 mg/day, intravenously), isoniazid (300 mg/day), ethambutol (1200 mg/day), pyrazinamide (1500 mg/day), and pyridoxine (25 mg/day) on 5 July 2016. The patient developed profound diarrhea. Cultures of stool grew Mtb. On 12 July 2016, air was found on routine chest x-ray, and the CT scan of his abdomen found moderate intraperitoneal air consistent with perforation of the proximal duodenum. Because of comorbidities and high operative risk, the surgery team recommended medical management including gastric tube decompression, proton pump inhibition, and bowel rest. Because the patient was on strict bowel rest, his oral anti-TB medication regimen was changed to parenteral treatment. This consisted of streptomycin (15 mg/kg per day, intramuscularly), rifampin (600 mg/day, intravenously), moxifloxacin (400 mg/day, intravenously), and linezolid (600 mg every 12 hours, intravenously). A goals-of-care discussion with the family resulted in a change in his resuscitative strategy to avoid intubation, chest compressions, and pressor medications. A sputum sample obtained on 22 July 2016 was positive for AFB. No other samples were obtained thereafter.

Despite ongoing antimycobacterial therapy, the patient’s condition progressively worsened. The patient had increased work of breathing requiring higher doses of supplemental oxygen, remained persistently febrile, and became hypotensive requiring normal saline boluses. The patient passed away in July 2016.

Pulmonary TB after PD-1 blockade in patient with MCC

An 83-year-old man with metastatic MCC enrolled in a clinical trial evaluating an anti–PD-1 therapy, pembrolizumab, at a dose of 2 mg/kg in June 2015 (Fig. 2A) (18). Before study enrollment, no testing for latent TB infection was performed. The patient is an HIV-negative Caucasian from Florida, and there were no other co-morbidities associated with increased TB risk apart from his age. In December 2015, after 11 cycles of anti–PD-1 therapy, the CT scan showed a new right lower lobe pulmonary nodule measuring 1.1 by 1.6 cm (Fig. 2B). Other known sites of MCC remained stable or had decreased in size. The patient underwent video-assisted thoracic surgery to obtain a right wedge excision of the nodule in January 2016.
Pathology revealed necrotizing granuloma that stained positively for AFB (Fig. 2, C and D). No Mtb DNA in the nodule was detectable by PCR, and three tests for acid-fast organisms in sputum samples were also negative. The patient denied classic TB symptoms, any history of TB or sick contacts, and did not recall previous TB testing by PPD. He had not traveled outside the country in the past year, but did report a distant travel history to Europe, China, South America, and the Caribbean.

The patient continued on treatment per protocol and received his 12th cycle of pembrolizumab in January 2016. In February 2016, the culture from his lung specimen grew Mtb that was pan-susceptible to antibiotics. Although not performed before immunotherapy, after the detection of Mtb by culture, the patient was found to have a positive IFN-γ release assay (IGRA) test, which detects the presence of T cell responses to Mtb [unstimulated negative control (Nil), 0.1 IU/ml; mitogen-stimulated positive control–Nil, >10 IU/ml; Mtb antigen stimulation–Nil, 1.59 IU/ml]. The patient was initiated on an anti-TB medication regimen of rifampin (600 mg/day), isoniazid (300 mg/day), ethambutol (1200 mg/day), pyrazinamide (1500 mg/day), and pyridoxine (25 mg/day). Sputum collection from 9 February 2016 to 12 February 2016 was found to be negative for Mtb by AFB smear, PCR screening, and bacterial culture. The patient initially proved unable to tolerate anti-TB medications in the setting of pembrolizumab. The patient was hospitalized due to fever, confusion, and elevated liver enzymes, but no additional infectious etiology was found to explain his signs and symptoms. The patient was taken off pembrolizumab treatment in August 2016, with CT imaging showing a continued partial response.

After discontinuation of pembrolizumab, the patient tolerated an anti-TB regimen of isoniazid and rifabutin until he again developed elevated liver enzymes. Thus, he was changed to levetiracetam and rifabutin, which was well tolerated. Unfortunately, the patient developed a 6 cm by 7 cm duodenal metastatic mass, which on biopsy revealed an MCC. Given the patient’s progressive disease, pembrolizumab infusions were restarted in January 2017 with resultant marked reduction in the duodenal mass by April 2017. The patient completed 9 months of TB therapy on June 2017 without evidence of recurrence, and as of January 2018 has returned to his previous physical baseline of being able to perform a daily level of moderate physical activity (Fig. 2A).

**Increases in circulating Mtb-specific TH1 cells after PD-1 blockade preceding granuloma formation**

On the basis of the murine model data, we speculated that PD-1 blockade in the patient with MCC would lead to enhanced Mtb-specific TH1 responses (9, 11). Cryopreserved peripheral blood mononuclear cells (PBMCs) obtained immediately before treatment with pembrolizumab and at treatment cycles 5, 8, 11, and 14 were analyzed. PD-1 staining intensity decreased but was still detectable after administration of pembrolizumab (Fig. 3A). We measured mycobacteria-specific T cell responses by stimulating PBMCs with PPD and performing intracellular cytokine staining. Before treatment, there were no detectable IFN-γ or tumor necrosis factor (TNF)–producing PPD-specific CD4 T cells. However, approximately 3 months after the first dose of pembrolizumab, we detected a spike in PPD-specific TH1 cells, and antigen-specific TH1 cells were detected at all time points posttreatment (Fig. 3, B and C).

To further examine the immune alterations associated with the development of TB after PD-1 blockade in this case, we measured other T cell populations. In certain settings, interleukin-17A (IL-17A) has been shown to be pathogenic in Mtb-infected mice (19), but PPD-specific TH17 cells, which are defined by their production of IL-17A, were not detected in this patient at any time point (Fig. 3D). CD8 T cells are the principal antitumor effector cells boosted by PD-1 blockade during cancer immunotherapy (20). In contrast, mycobacteria-specific CD8 T cells were not detected after PD-1 blockade (Fig. 3E). Foxp3+ regulatory T cells express PD-1 and have been implicated in the regulation of Mtb-specific immune responses (21), so we asked whether TB after PD-1 blockade was associated with expansion of this immunosuppressive cell type. We found that pembrolizumab treatment was not associated with changes in the frequency of Foxp3+ CD4 T cells in the peripheral blood of this individual (Fig. 3F). Effector T cells can sometimes transiently up-regulate Foxp3 after stimulation, so these data also indicate that PD-1 blockade was also not associated with a significant up-regulation of Foxp3 by effector T cells. In summary, TB in this patient was not
associated with an increase in T<sub>H</sub>17 cells, CD8 T cells, or Foxp3<sup>+</sup> CD4 T cells.

Although we were unable to detect PPD-specific cytotoxic CD8 T cell responses in this individual, we asked whether the Mtb-specific CD4 T cells displayed the ability to degranulate by measuring the appearance of CD107 on the cell surface after stimulation. We found that PPD-specific TH<sub>1</sub> cells present at cycle 8 just before the development of the pulmonary lesion displayed the ability to degranulate based on the appearance of CD107a on the cell surface after antigen stimulation (Fig. 3G). Although we were not able to directly measure killing, these data indicate that the Mtb-specific CD4 T cells that expanded after PD-1 blockade were potentially cytotoxic.

PD-1 was not detected on Mtb-specific CD4 T cells from peripheral blood (Fig. 3H), which reflects either interference of PD-1 staining by pembrolizumab or, alternatively, the anatomical site sampled, as PD-1 expression is greatly increased on peripheral blood in mice and non-human primates (<sup>9</sup>, <sup>22</sup>, <sup>23</sup>). Ki67, a marker of proliferating cells, was only found in ~1% of the PPD-specific CD4 T cells at cycle 5 (Fig. 3H), suggesting that the first time point available for analysis may have been already past the peak CD4 T cell proliferative response.

Recently, there has been renewed interest in the role of antibodies in TB (<sup>24</sup>), so we next tested whether PD-1 blockade affected Mtb-specific antibody responses. Serum concentrations of Mtb-specific immunoglobulin G (IgG) changed minimally or not at all in the interval between pretreatment and appearance of pulmonary tuberculosis (Fig. 4). However, after anti-TB chemotherapy was initiated, antibody responses to Rv3804 (Ag85A), Rv1886 (Ag85B), and Rv3841 (BrfA) rose sharply. Therefore, although antibody responses against some Mtb proteins did increase after pembrolizumab treatment, they did so months after the TB-related adverse event, so it is unlikely that they played a role in the development of TB.

**No evidence of recent local transmission of the Mtb strain isolated from the patient with MCC**

The Mtb strain isolated from the lung nodule of the patient with MCC was identified as Euro-American lineage 4 [spoligotype (777776777760601) and mycobacterial interspersed repetitive units–variable number tandem repeat (MIRU-VNTR) pattern (22422153323)], which causes the majority of TB in North America and Europe but relatively few cases in other regions of the world (<sup>25</sup>). There were only 12 other cases of TB in the United States due to infection with this specific bacterial genotype between December 2013
and December 2016. In this patient’s home state of Florida, there were only three other cases between 2007 and 2016. The most recent previous case was ~11 months before the development of the tuberculoma in the patient reported here, and all were in counties several hundred miles away. Moreover, in the same time period, there were no reported cases of TB due to this genotype of bacteria in the state of Georgia, where the patient was treated with pembrolizumab for MCC. Therefore, the case of TB in this individual was neither temporally nor geographically associated with a cluster of transmission. Together, the patient’s risk factors, such as age, travel history, and lack of contact with TB patients, along with the lack of evidence for local transmission of this bacterial genotype collectively suggest that TB in this patient was likely due to a preexisting latent Mtb infection.

DISCUSSION

In this study, we provide two case reports of checkpoint blockade–associated TB. One individual developed disseminated fatal disease after PD-1 blockade, whereas the other presented with a single pulmonary lesion and was successfully treated for TB. We were able to characterize the adaptive immune response in the patient who survived. In this individual, PD-1 blockade was followed by expansion of circulating Mtb-specific T<sub>H1</sub> cells, but not Mtb-specific T<sub>H1</sub> cells, CD8 T cells, or increased antibody responses. The increase in T<sub>H1</sub> cells was followed by the development of a necrotic tuberculoma in the lung that contained AFB. These results are consistent with data from the murine model of Mtb infection that predict a potential exacerbation of TB upon PD-1 blockade.

In mice, PD-1 deficiency boosts Mtb-specific T<sub>H1</sub> cell expansion and effector functions, but rather than leading to enhanced bacterial control, the increased production of IFN-γ by CD4 T cells drives large necrotic lesions and leads to accelerated death of the host (9, 11). No long-term PD-1 antibody blockade studies have been performed in Mtb-infected animals; however, short-term blockade of the PD-1 pathway (i.e., ~2 weeks) with monoclonal antibodies in Mtb-infected mice results in neither a therapeutic nor a detrimental outcome (26, 27). Therefore, it is not yet clear if exacerbation of TB in the setting of the PD-1<sup>−/−</sup> mouse model may be an accurate predictor of detrimental outcome after long-term blockade with monoclonal antibodies. The cases reported here suggest that the PD-1<sup>−/−</sup> mouse data may be generalizable. Nevertheless, these results suggest that PD-1 blockade in Mtb-infected humans can lead to Mtb-specific T<sub>H1</sub> cell–mediated pathology. These results have implications for the development of host-directed therapies for TB and the clinical management of individuals receiving checkpoint inhibitors for cancer.

There are several limitations to our study. The age of the patient with MCC was in itself a predisposing factor for TB, as it is thought that the decline in immunity with age may allow for the reactivation of latent Mtb infection. However, the Mtb-specific T<sub>H1</sub> response was boosted after PD-1 blockade, suggesting that it is unlikely that this was TB reactivation due to declining immunity associated with immunosenescence. We should also point out that the use of PPD as a stimulation antigen may have limited our ability to detect Mtb-specific CD8 T cells, as whole protein antigens may preferentially stimulate CD4 T cells. However, in mice, it has been shown that CD8 T cells have very little contribution to the pathology observed in Mtb-infected PD-1<sup>−/−</sup> mice (9). Last, validation of these results with kinetic analysis of Mtb-specific T cell responses in additional cases of checkpoint blockade–associated TB and analysis of T cell responses from the airways or lungs from these individuals will be required to support the hypothesis that boosting T cell responses through PD-1 blockade exacerbated TB.

Mtb infection is the leading cause of death due to a single infectious agent despite the availability of chemotherapy (28). There is great need for the development of improved therapies for both drug-resistant and susceptible Mtb infection (4). The success of PD-1 blockade in cancer immunotherapy has led to persistent interest in treating human TB with PD-1 blockade to boost Mtb-specific T cell function, despite murine model data demonstrating extreme susceptibility of Mtb-infected PD-1<sup>−/−</sup> animals. These data support exercising caution when treating TB with proinflammatory strategies in general, but PD-1 blockade in particular. It is worth noting that animal data suggest that not all mycobacterial infections may be exacerbated by PD-1 deficiency, as Bacillus Calmette-Guérin (BCG) is more readily cleared in PD-1<sup>−/−</sup> mice (29). Moreover, not all checkpoint-targeting therapies are likely to result in exacerbated Mtb infection, as TIM-3<sup>−/−</sup> mice control virulent Mtb infection better than wild-type animals (30).

As PD-1 blockade becomes more globally deployed in TB endemic regions, it is possible that TB-related adverse events in cancer immunotherapy may increase. Unlike immunosuppressive biologic therapies used for the treatment of autoimmune disease, very few investigational protocols incorporating anti–PD-1 or anti–PD-L1 therapy require TB prescreening. These cases highlight that treatment with anti–PD-1 in a patient with latent or active TB may have
deleterious outcomes, as suggested by murine model experiments. Our study suggests that TB screening before checkpoint therapy may be warranted.

**MATERIALS AND METHODS**

**Study design**

In recently reported studies of PD-1 blockade for the treatment of NPC (17) (ClinicalTrials.gov ID: NCT02339558) and MCC (18) (ClinicalTrials.gov ID: NCT02267603), two participants developed TB as an infection-associated adverse event. The objectives of this study were (i) to evaluate disease progression in both patients after anti–PD-1 treatments and (ii) to identify changes to the Mtbc-specific immune responses that were associated with the development of TB in the survived patient. No data were excluded from this study. Written informed consent was obtained from the patient before conducting the study. The protocol was approved by an institutional review board at each participating center. Primary data are reported in table S1.

**Flow cytometry and antibody assay**

For intracellular cytokine staining, cryopreserved PBMCs were incubated for 1 hour at room temperature. Plates were washed and followed by the addition of 1 N H₂SO₄. Optical densities (ODs) were read at 450 and 570 nm. Antibody levels were calculated by OD 450nm – OD 570nm subtracted from control wells of antigen and HRP alone.

**Bacteriological analysis**

Sputum samples underwent decontamination with N-acetyl-L-cysteine–sodium hydroxide, and AFB stains were performed using modified Kinyoun preparation. After decontamination, the specimens were plated onto Middlebrook 7H11 agar and Lowenstein-Jensen slant culture and inoculated on BD BACTEC MGIT tubes (BD Biosciences), which were incubated in the BD BACTEC MGIT automated mycobacterial detection system. After positivity on the instrument, the AccuProbe Culture Identification test (Hologic) identified the isolate as Mtbc. Drug susceptibility assays were performed by the Georgia Public Health Laboratory for the patient with MCC or ARUP Laboratories for the patient with NPC.

**Genotyping of Mtbc isolate**

The Mtbc isolate of the patient with MCC was submitted for spoligotype and MIRU-VNTR pattern genotypic analysis as has been required per U.S. Centers for Disease Control and Prevention protocols since 2004 (32). The genotypic pattern was compared with the patterns of all other Mtbc specimens collected in the United States using the TB Genotyping Information Management System database (33).

**REFERENCES AND NOTES**


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Competing interests: D.L.B. has received royalties from patents held relating to PD-1 blockade. All the other authors declare that they have no competing interests. Data and materials availability: All data associated with this study are present in the paper or Supplementary Materials.

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Preaching caution with PD-1 blockade for TB

Scientists are interested in leveraging PD-1 blockade for diseases other than cancer, such as tuberculosis (TB). Barber et al. studied two patients with cancer who developed active TB during PD-1 blockade. Analysis of longitudinal samples available from one of the patients revealed the presence of TB-specific Th1 cells before presentation of TB. These results are in line with previous work in mouse TB models, which showed that PD-1 deficiency exacerbated disease. This report indicates that PD-1 blockade for treating tuberculosis in humans may instead worsen the disease.