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LETTER TO THE EDITOR



# Development of pulmonary tuberculosis following treatment with anti-PD-1 for non-small cell lung cancer

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To the Editor,

Pharmaceutical blockade of immune checkpoint inhibitors has become a cornerstone in the treatment of several malignancies. Many patients experience immune-related adverse events [1]. However, treatment-related development or reactivation of infectious disease is rarely reported. Here, we present a patient with advanced non-small cell lung cancer (NSCLC), who developed tuberculosis (TB) following treatment with nivolumab, an anti-PD-1 monoclonal antibody.

In August 2015, a 56-year-old Caucasian male with 40 pack-years of smoking presented with weight loss, fever and cough. A fluoro-deoxy-glucose (FDG) positron emission tomography/computed tomography (PET/CT) demonstrated two infiltrates in the right upper lobe: a posterior, solid infiltrate and an anterior, diffuse infiltrate (Figure 1(A)). There was high FDG uptake in several mediastinal lymph nodes. Examination of nodal biopsies revealed metastasis from NSCLC, presumably of subtype adenocarcinoma (EGFR wild type, ALK negative) in station 10R and cells suspicious of malignancy in station 7. Final cTNM stage was T3N3M0. The patient was treated with concomitant chemoradiotherapy. In February 2016, CT showed progression of the anterior infiltrate, while there was regression of the posterior infiltrate and the mediastinal lymph nodes (Figure 1(B)). After six cycles of second-line pemetrexed, there was stable disease. In September 2016, PET/CT revealed progression of the anterior infiltrate. However, there were no signs of recurrence of the posterior infiltrate or nodal involvement (Figure 1(C)). A fine needle aspiration from the anterior infiltrate demonstrated cells suspicious of malignancy. Third-line treatment with nivolumab was initiated though testing for PD-L1 expression could not be conducted due to scarcity of cytological material. Initially, the patient responded. After 12 cycles, an apical infiltrate appeared in the right lung and there was progression of the previous infiltrate with cavitation (Figure 1(D)). PET/CT showed no signs of nodal or metastatic disease. The patient underwent a video-assisted thoracoscopic lobectomy. Histopathology showed necrotizing granulomatous inflammation of the lung and Ziehl–Neelsen staining revealed acid-fast bacteria within the areas of

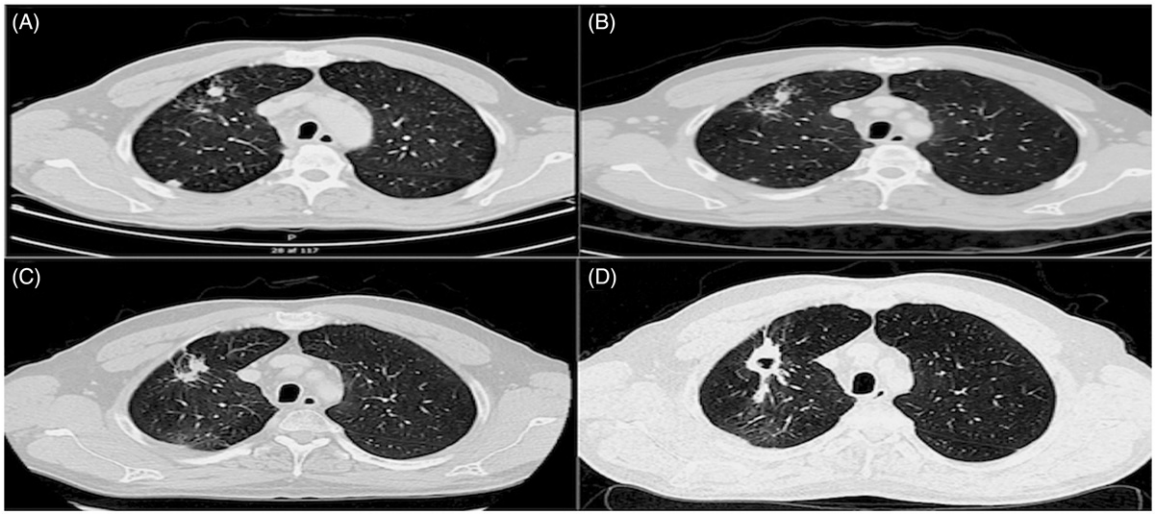


**Figure 1.** Axial contrast enhanced CT images of both primary infiltrates in the right upper lobe from different time points throughout the clinical course of the patient: before concomitant chemoradiation (A), two-months post-chemoradiation (B), before treatment with nivolumab (C), and after 12 cycles of nivolumab (D).

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necrosis. Polymerase chain reaction analysis was positive for *Mycobacterium tuberculosis* complex. There were no signs of malignancy. Antitubercular medication was initiated and nivolumab was discontinued. When asked, the patient stated that he had previously visited TB endemic areas.

## Discussion

To our knowledge, only two comparable cases have been published. One [2] describes an elderly Chinese patient with relapsed Hodgkin's lymphoma who developed symptomatic TB after five cycles of pembrolizumab. In the other case report [3], development of TB was detected in a Japanese patient with NSCLC following eight cycles of third-line nivolumab.

The mechanism of TB development following treatment with immunotherapeutic agents remains to be properly understood. Investigations in mice have demonstrated a possible protective effect of the PD1/PD-L1 interaction. One study [4] reported how PD-1 knockout (PD-1$^{-/-}$) mice had increased susceptibility when exposed to TB, perhaps because of defective lymphocyte proliferation. Another report [5] describes how PD-1 knockout mice rapidly succumbed to TB infection possibly due to increased CD4 T cell-mediated pathology. Thus, the PD1/PD-L1 interaction may contain a protective role under certain circumstances.

Development or reactivation of TB during treatment with immunotherapeutic agents remains a rare phenomenon, but ought to be kept in mind when treating patients with known latent infection or relevant previous exposure. The present case also emphasizes the importance of reevaluation and re-biopsy when progression is suspected.

## Disclosure statement

The authors declare no conflict of interest.

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LETTER TO THE EDITOR

# Interim FDG-PET/CT in Hodgkin lymphoma: what are we actually looking at?

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Recently, a study by Borchmann et al. [1] published in the Lancet Oncology included 440 patients with advanced-stage Hodgkin lymphoma who were positive (i.e., Deauville criteria score of 3-5) at interim $^{18}$F-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography (FDG-PET/CT) after two cycles of BEACOPP$_{escalated}$. These patients with positive interim FDG-PET/CT results were randomized to either six additional cycles of BEACOPP$_{escalated}$ ($N = 220$) or six additional cycles of rituximab-BEACOPP$_{escalated}$ ($N = 220$). Interestingly, interim FDG-PET/CT failed to identify a group of patients at high risk of treatment failure, with a high 3-year progression-free survival (PFS) of 91.4% (87.0–95.7%) for interim FDG-PET/CT positive patients who continued BEACOPP$_{escalated}$ and a 3-year PFS of 93.0% (89.4–96.6%) for those additionally treated with rituximab (risk difference 1.6%, log rank $p = .99$). Borchmann et al. [1] concluded interim FDG-PET/CT to be unable to identify patients at high-risk for treatment failure due to the very effective German Hodgkin Lymphoma Study group treatment (BEACOPP$_{escalated}$/rituximab-BEACOPP$_{escalated}$), which may overcome the adverse impact of the positive interim FDG-PET/CT result on patient outcome. In an accompanying editorial, Crump [2] speculated the relatively early timing of interim FDG-PET/CT with possible effects of G-CSF and prednisone, the use of a Deauville score of 3 as a

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