Reactivation of TB during administration of durvalumab after chemoradiotherapy for non-small-cell lung cancer: a case report

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Background: Tuberculosis (TB) is considered to be an adverse effect of treatment with immune checkpoint inhibitors. **Methodology & results:** Our case was a 75-year-old woman diagnosed with unresectable stage III non-small-cell lung cancer. After radical chemoradiotherapy was completed, durvalumab was initiated as a consolidation therapy. However, since chest CT showed appearances of infiltration shadows scattered in the periphery of the lungs after five doses of immunotherapy, durvalumab was discontinued. 6 weeks later, the patient was aware of intermittent fever. Chest CT scan showed the appearance of a tree-in-bud pattern in the right lung. Acid-fast bacilli stain of sputum was positive and the PCR test was positive for *Mycobacterium tuberculosis*. **Conclusion:** Durvalumab as PD-L1 blockade may activate TB.

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Keywords: chemoradiotherapy • durvalumab • IGRA • immune checkpoint inhibitor • irAE • LTBI • NSCLC • PD-L1 blockade • pulmonary TB • TB

Background

Immune checkpoint inhibitors (ICIs) have become generalized anticancer agents in the treatment of all types of cancer. Non-small-cell lung cancer (NSCLC) is one of the most common cancers in the world. Many previous trials reported that ICIs provided clinical benefit in patients with NSCLC [1–5]. Therefore, ICIs are considered to be a useful treatment option for NSCLC.

Conversely, various immune-related adverse events have been reported following ICI treatment. Recently, several articles have reported that ICI may lead to the development of active TB [6–15]. However, the causal relationship between ICI and TB remains controversial. Here, we report a case of reactivation of TB following durvalumab treatment after chemoradiotherapy for unresectable stage III NSCLC.

Case presentation

The case reported here was a 75-year-old woman, a former smoker (45 packs per year) who quit smoking 10 years ago. The patient was referred to our hospital because of lower-limb paralysis, back pain and an abnormal chest shadow on chest x-ray in May 2019. A 67 mm tumor with cavity, calcification and direct invasion of the chest wall and thoracic spine was revealed in the right upper lobe by chest computed tomography (CT) (Figure 1A–C). In addition, CT showed calcification of the mediastinal lymph nodes and tracheal wall (Figure 1D). Although she did not remember the details, she had been treated for TB as a teenager. However, the result of initial T-SPOT.TB as an interferon-gamma release assay (IGRA) at the first visit our hospital was negative. Squamous cell carcinoma was detected by *trans*-bronchial lung biopsy performed for the diagnosis of the tumor, with no targeted gene mutations and over 50% of programmed death-ligand 1 (PD-L1) expression. She was diagnosed with NSCLC cT4N0M0 stage IIIA after brain MRI and bone scintigraphy revealed the absence of metastatic lesions in the brain and bones. She received radical chemoradiotherapy (weekly carboplatin [AUC2] plus paclitaxel [40 mg/m²] with concurrent thoracic radiotherapy at a daily dose of 2 Gy for a total dose of 66 Gy) for unresectable NSCLC. She experienced grade 3 lymphopenia, grade 2 leukopenia, neutropenia, anemia and hypoalbuminemia as adverse

Figure 1. CT images acquired at the diagnosis of stage III non-small-cell lung cancer in our case. (A) Primary non-small-cell lung cancer lesion at the right upper lobe of the lung with invasion of the chest wall and thoracic spine. (B & C) Primary non-small-cell lung cancer lesion at the right upper lobe of the lung presenting with cavity and calcifications. (D) Calcification of the mediastinal lymph nodes and tracheal wall.

Table 1. Results of patient's blood count in clinical courses.					
	At the start of chemoradiation therapy	After 6 weeks from the start of chemoradiation therapy	After 9 weeks from the start of chemoradiation therapy (at the start of durvalumab)	After 25 weeks from the start of chemoradiation therapy (at the durvalumab discontinuation)	After 33 weeks from the start of chemoradiation therapy (at the diagnosis of TB)
WBC (10 ³ /μl)	12240	2330	5640	5340	8190
Neu (10 ³ /μl)	5090	1620	4460	3900	6880
Lym (10 ³ /μl)	2130	440	540	830	730
Ht (%)	32.1	24.7	28.4	31.1	26.1
Hb (g/dl)	10.3	8.0	9.2	9.7	8.1
Plt (10 ³ /μl)	30.5	18.4	37.1	15.3	46.5
Ht: Hematocrit; Lym: Lymphocyte; Neu: Neutrophil; Plt: Platelet; WBC: White blood cell.					

events of chemoradiotherapy. Table 1 shows her blood count including lymphocyte count of clinical courses. Her clinical symptoms, such as lower-limb paralysis and back pain, improved significantly and chest CT showed tumor shrinkage after chemoradiotherapy (Figure 2A–D). Biweekly durvalumab treatment was started 2 weeks after the end of the radiation therapy. Bone marrow suppression including anemia and lymphopenia gradually recovered during durvalumab administration. (Table 1) At the time of fifth course of this therapy, chest CT revealed a reduction of the primary lesion, but showed the appearance of small infiltration shadows scattered in the periphery of both lungs (Figure 2E & F). She had no subjective symptoms. Durvalumab was discontinued and CT was performed again 1 month later, because of the possibility of the development of interstitial lung disease as an immune-related adverse events. This chest CT showed the presence of enlarged infiltration shadows in both lungs, including the areas around the primary lesion (Figure 2G & H). We recommended bronchoscopy for the diagnosis of this condition, but the patient rejected this diagnostic modality because of its invasiveness and requested follow-up. However, 2 weeks later she was referred to our hospital because she was aware of an intermittent fever of 38–39°C and night sweats. Chest CT showed enlargement of the cavity of the primary lesion, with infiltrate shadows surrounding the primary lesion. In addition, a tree-in-bud pattern was apparent in the right middle and inferior lobes (Figure 2I & J). T-SPOT.TB and Ziehl–Neelsen staining of a sputum smear sample were positive at this time point. Finally, sputum samples were positive for *Mycobacterium tuberculosis* (Mtb) DNA, as assessed using PCR. She was diagnosed with reactivation of TB and was transferred to our hospital, where isolation control was conducted. Currently, she continues anti-TB medication and her pulmonary TB is controlled by medication. Her lung cancer is controlled without recurrence despite of anticancer treatment discontinuation.

Discussion

Several previous reports have described a risk of developing TB during programmed death 1 (PD-1) blockade treatment [6–15]. However, to the best our knowledge, this manuscript was the first report of TB reactivation during durvalumab therapy after radical chemoradiotherapy for stage III NSCLC.

Figure 2. CT images acquired during the clinical course of our case. (A & B) CT images acquired at the diagnosis of non-small-cell lung cancer. (C & D) The primary lesion exhibited shrinkage after chemoradiotherapy. (E & F) CT images acquired after five courses of durvalumab therapy. Although the primary lesion showed further reduction, the appearance of new infiltration shadows scattered in the periphery of both lungs was noted. Therefore, durvalumab was discontinued. (G & H) CT images acquired 1 month after durvalumab was discontinued. Chest CT showed enlarged infiltration shadows in both lungs, including the areas around the primary lesion. (I & J) CT images acquired at the diagnosis of active pulmonary TB. Infiltration shadows surrounding the primary lesion and a tree-in-bud pattern in the right inferior lobe were observed.

Durvalumab is an ICI that was developed as a human IgG1 monoclonal antibody that inhibits the binding of PD-L1 to PD-1 and CD80. The international PACIFIC Phase III trial, which compared durvalumab with placebo after chemoradiotherapy using platinum doublet for stage III unresectable NSCLC, showed that the progression-free survival and overall survival were longer with durvalumab versus placebo treatment [16,17]. Therefore, durvalumab consolidation therapy after radical chemoradiotherapy is currently considered as a standard therapy for unresectable stage III NSCLC.

PD-1 blockade (nivolumab and pembrolizumab) is considered a risk for the development of active TB. However, this relationship remains controversial. According to preclinical data, PD-1 knockout mice are hypersensitive to Mtb infection, develop large necrotic lesions with a high bacterial load, and exhibit earlier death compared with T-cell deficient mice [18]. Other research has shown that PD-1 knockout mice develop uncontrolled TB because of increased Mtb-specific CD4 T cell (especially TH1 cells) and IFN- γ response [19,20]. These results suggest that PD-1 blockade promotes the reactivation of TB by eliciting an excessive immune response against mycobacterium. In addition, increased T regulatory cells and decreased TB-antigen-specific T cells were observed in PD-1 knockout mice [21]. These findings indicate that the appropriate immune response is inhibited by PD-L1 blockade. Moreover, our case suggests that the same mechanism causes the activation of TB during treatment with durvalumab, which represents a PD-L1 blockade.

Interestingly, our case had a history of TB treatment and the imaging results showed several calcified lesions (the primary lesion, the mediastinal lymph nodes and the tracheal wall), which is characteristic of old pulmonary TB, despite the initial negative IGRA. IGRA detection of the immune response to specific Mtb antigens has good sensitivity and specificity for diagnosing latent tuberculosis infection (LTBI) [22]. In particular, the sensitivity and specificity of T-SPOT.TB for diagnosing LTBI are high [22]. In contrast, previous research reported an IGRA reversion rate of 5.2–22% [23]. Therefore, we considered our case to have LTBI with reactivated TB infection caused by durvalumab. In addition, it is suggested that LTBI represents a risk of reactivation of TB during immunotherapy.

This work had several limitations. Our case received chemotherapy before durvalumab administration, which may have affected TB activation. In particular, our case experienced grade 3 lymphopenia during chemoradiotherapy. There is no denying that the immunosuppressive state may have affected the reactivation of TB. However, we consider that the effects of chemotherapy were small, because 4 months passed since the start of durvalumab until the diagnosis of TB and the course of chest CT imaging. As Table 1 showed, anemia and lymphopenia caused by chemoradiotherapy was recovered during durvalumab administration, though not completely. In contrast, in relation to the hypothesis of the reactivation of TB during immunotherapy mentioned above, the immunosuppressive state that was caused by grade 3 lymphopenia reactivated the latent TB, with PD-L1 blockade worsening this reactivated TB state by eliciting an excessive immune response against TB. Further case accumulation and analysis are needed to confirm the hypothesis formulated for our single case.

Conclusion

In conclusion, we experienced a case of reactivation of TB following durvalumab treatment after chemoradiotherapy for stage III NSCLC. PD-L1 blockade may have the potential to reactivate latent TB infection.

Summary points

- Several case reports have demonstrated that immune checkpoint inhibitors have a potential risk of reactivation of latent tuberculosis infection (LTBI).
- A 75-year-old woman was diagnosed with unresectable stage III NSCLC in 2019. She had a medical history of pulmonary tuberculosis (TB) at an early age. After radical chemoradiotherapy (weekly carboplatin [AUC2] plus paclitaxel [40 mg/m²] with concurrent thoracic radiotherapy at a daily dose of 2 Gy and total dose of 66 Gy) was completed, durvalumab (at a dose of 10mg/kg/body intravenous drip every 2 weeks) administration was initiated as a consolidation therapy.
- In 2019, after five doses of immunotherapy, computed tomography (CT) scanning of the chest showed small infiltration shadows scattered in the periphery of both lungs were observed, despite the shrinkage of the primary lesion.
- Since we considered the development of interstitial lung disease as an immune-related adverse events of durvalumab, durvalumab was discontinued.
- 1 month after durvalumab discontinuation, enlarged infiltration shadows were apparent on chest CT in both lungs, including the areas surrounding the primary lesion, despite the absence of subjective symptoms.
- 2 weeks later, she became aware of intermittent fever and night sweats. Chest CT showed the appearance of a tree-in-bud pattern in the right middle and inferior lobes and of enlargement of the infiltrate shadows surrounding the primary lesion.
- Acid-fast bacilli stain of sputum was positive and the PCR test was positive for *Mycobacterium tuberculosis*.
- Currently, she continues anti-TB medication, whereas anti-lung cancer treatment is still withheld.
- Durvalumab consolidation treatment after radical chemoradiotherapy for stage III NSCLC has the potential risk of reactivation of LTBI.

Financial & competing interests disclosure

H Sakai and H Mizutani received honoraria from AstraZeneca. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Ethical conduct of research

We obtained informed consent from the patient for the publication of this case report and associated images. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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