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Case report

A rapidly progressive case of tuberculous pleurisy and pericarditis in a patient with non-small cell lung cancer that developed one month after receiving pembrolizumab monotherapy☆

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ABSTRACT

We report a rapidly progressive case of tuberculous pleurisy and pericarditis. A 59-year-old, male patient with non-small-cell lung cancer commenced pembrolizumab monotherapy one month before but soon thereafter had fevers and dyspnea. Radiography revealed increased right pleural effusion, novel left pleural effusion and cardiomegaly, which had been absent 10 days earlier when a reduction in the target lesion was confirmed. Computed tomography revealed the presence of pericardial fluid. Analysis of the pleural effusion didn't detect malignancy; however, the culture was positive for tuberculosis. It suggests that pembrolizumab may have induced severe inflammation leading to the rapid progression of the disease.

Introduction

Immune checkpoint inhibitors (ICIs), which have greatly advanced cancer treatment in recent years, may also induce tuberculosis [1]. Although ICIs have not previously been reported to be associated with an increased risk of infection [2], some studies have reported that tuberculosis can be triggered by a mechanism differing from that underlying exogenous reactivation [3]. Nonetheless, no unified explanation has been proposed [4]. Here, we report a rare, rapidly progressive case of tuberculous pleurisy and pericarditis that may have been induced by pembrolizumab. Differences in the symptoms of tuberculosis between patients receiving and not receiving ICI therapy are discussed together with a review of relevant, past studies.

Case presentation

A 59-year-old, male with Stage IVB, PD-L1 tumor proportion score (TPS) 95 %, and Kirsten rat sarcoma viral oncogene homologue (KRAS) G12C–mutated right non-small-cell lung cancer (NSCLC) diagnosed in October 2022 commenced pembrolizumab therapy 400 mg every six week as the first-line treatment in mid-November 2022. After the completion of one treatment cycle in early December 2022, the patient achieved a partial response of a reduction in the target lesion and a reduction in the volume of right pleural effusion. However, he presented to the emergency department with intermittent fever lasting a few days in mid-December. Radiographs revealed an increase in the right pleural effusion, a novel appearance of left pleural effusion and cardiomegaly, which were absent 10 days earlier. The patient was then referred to our department for examination and further treatment.

The patient had a history of smoking 12 packets of cigarettes per year but had ceased a few months prior to the current presentation. There was no significant medical history, including tuberculosis or allergies. There was also no family history of tuberculosis or a history of overseas travel.

Whole-body computed tomography (CT) performed after admission confirmed the partial response of the target lesion in the right S3 and metastases to the mediastinal lymph nodes. Radiography confirmed the increased bilateral pleural effusions, while CT also revealed a novel appearance of pericardial fluid. No other abnormalities were observed. The patient had C-reactive protein level of 8.78 mg/dL (reference range: 0.00–0.14) and an oxygen saturation of 92 % on 2 L/min via nasal cannula. Echocardiography didn't reveal the diastolic collapse of right

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atrium and ventricle, the collapse of left ventricle, or the paradoxical motion of interventricular septum. It also showed the entire circumference of pericardial fluid with an echo-free space of 14 mm. Tazobactam/piperacillin 18 g/day and prednisolone 60 mg/day (1 mg/day) were soon empirically administrated because infectious or immune-related adverse events (irAE) pleurisy and pericarditis were clinically suspected. A week after the admission, cytological analysis of the pleural effusion was found to be negative for malignancies and laboratory analysis revealed a mononuclear cell fraction of 65.3 % and an adenosine deaminase level of 64.5 U/L. After a couple of days more, a sample of the pleural effusion tested for tuberculosis with a polymerase chain reaction was positive, whereas sputum smears, which were performed three times, were negative for acid-fast bacilli. Based on these findings, tuberculous pleurisy was clinically diagnosed.

None of the findings suggests cardiac tamponade and the volume of pericardial fluid was insufficient to be sampled. However, tuberculous pericarditis was thought to be indicative considering the amount of pericardial effusion and the demand for oxygen were not significantly decreasing even after two weeks therapy with antibiotic and steroid. Then, both of them were stopped.

Pembrolizumab therapy was discontinued, and treatment with isoniazid 300 mg/day, rifampicin 600 mg/day, ethambutol 750 mg/day, and pyrazinamide 1500 mg/day was initiated. He was discharged at the end of January after his symptoms improved. On the day of discharge, drug-sensitive *Mycobacterium tuberculosis* was isolated from the sputum and pleural effusion cultures, leading to a diagnosis of pleurisy accompanied by pulmonary tuberculosis (Fig. 1).

The clinical course was uneventful. A decrease both in pleural effusion and in pericardial fluid was also confirmed radiologically over several weeks and months, and bimonthly sputum cultures consistently returned negative results. That finding also suggests the tubercular etiology in pericarditis is more likely than that of bacterial and irAE.

Discussion

Previous studies examining the role of ICIs, specifically anti-programmed death protein 1 (PD-1)/ programmed cell death ligand 1 (PD-L1) inhibitors, in tuberculosis have failed to identify the precise pathomechanism underlying this phenomenon. Normally, PD-1/PD-L1 assists in maintaining homeostasis after the formation of granuloma lesions in tuberculosis. One hypothesis maintains that ICIs can dysregulate the immune response and induce hyper-inflammation against tuberculosis similar that seen in immune reconstitution inflammatory syndrome (IRIS) in patients with human immunodeficiency virus (HIV) infection, which can then lead to an endogenous reactivation [3]. Other previous report suggests PD-1/PD-L1 blockade affects the host-pathogen interaction even in the absence of immunosuppression, which favors their proliferation over host control because of the dysregulated immune response. Sustained antigen exposure from persistently tuberculosis-infected cells can cause an overexuberant immune response toxic to the host. It also suggests immune checkpoints may regulate homeostasis in LTBI by tolerogenic signaling while signaling disruption with PD-1/PD-L1 blockade can promote hyper-inflammation, infection reactivation [5]. The mortality rate associated with such cases is reportedly 28.57 %, which is higher than that associated with patients without ICI therapy [6], supporting the hypothesis.

In the present patient, the T-SPOT.TB test was not performed when NSCLC was diagnosed because no risk factors for tuberculosis had been identified and a culture of bronchoalveolar lavage fluid was negative for acid-fast bacilli. Furthermore, CT revealed no evidence of past tuberculosis, such as calcification, or active tuberculosis. Although it was unclear whether a latent tuberculosis infection (LTBI) was present, the patient was highly unlikely to have had active tuberculosis before pembrolizumab therapy was initiated.

These findings indicate three possible patterns in the development of tuberculosis in this patient: primary tuberculosis, exogenous reinfection, or endogenous reactivation. First, primary tuberculosis is usually

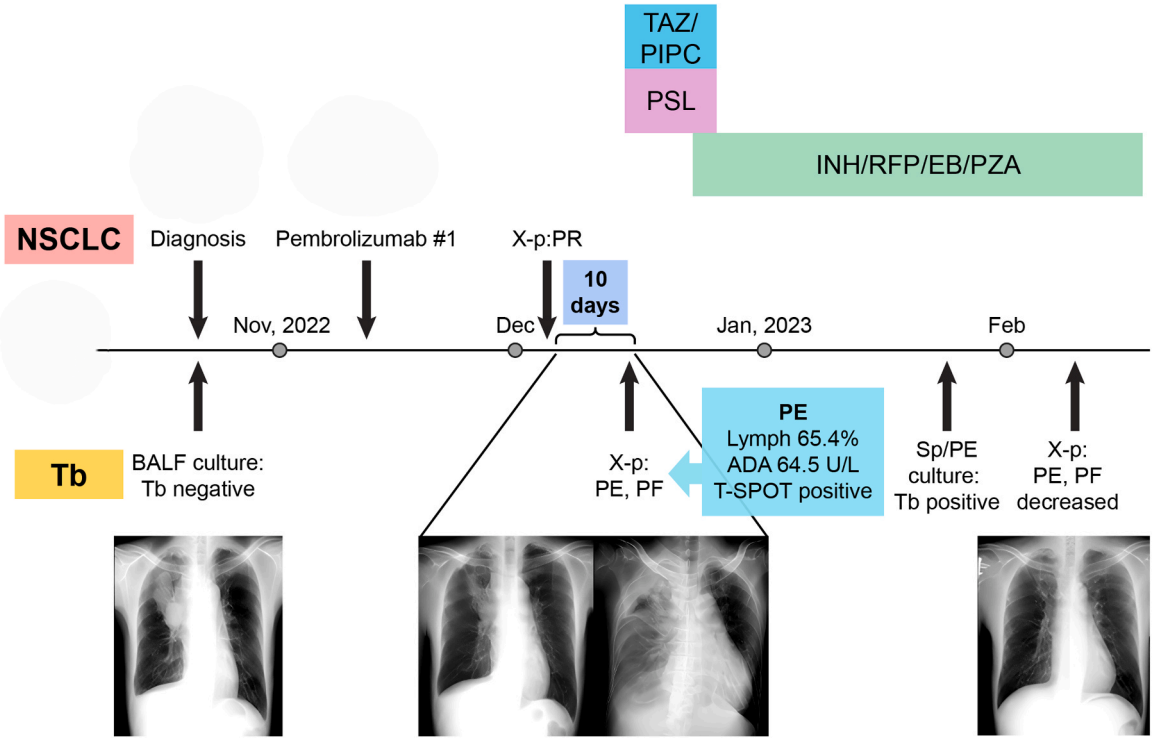

Fig. 1. The clinical course of treatment; both NSCLC and tuberculosis. NSCLC: Non-Small Cell Lung Cancer, Tb: tuberculosis, BALF: Bronchoalveolar Lavage Fluid, X-p: X-ray photograph, PR: partial response, PE: pleural effusion, PF: pericardial fluid, lymph: lymphocyte, ADA: adenosine deaminase, TAZ/PIPC: tazobactam-piperacillin, PSL: prednisolone, INH: isoniazid, RFP: rifampicin, EB: ethambutol, PZA: pyrazinamide, Sp: sputum.

thought to occur in infants within two years of their first exposure because their nascent cellular immunity is incapable of containing the pathogen in granulomatous lesions. However, the medical history of the patient rendered this possibility highly unlikely [7]; moreover, the infection prevention measures against severe acute respiratory syndrome coronavirus 2 during the years 2020–2022 had reduced the risk of tuberculosis, further reducing the likelihood of the patient contracting a *M.tuberculosis* infection during this period. However, had the disease developed in this manner, the development within such a short span of ten days would be in accordance with the reports of rapidly progressive disease described in some previous case reports of primary tuberculosis [8]. Second, exogenous reinfection is sometimes evident in severely immunocompromised patients chiefly those with an HIV infection, and in people living in a high-prevalence country with a history of exposure to a large amount of the pathogen, suggesting that this pattern of onset was also unlikely in the present patient for the same reason as above [9]. A test for HIV in this patient was negative. Endogenous reactivation was thus the most probable pattern, considering also that the expected infection prevalence in the age group of the patient is estimated to be 11.1 % by the previous study [10]. If the interpretation of the hypothesis as stated is correct, pembrolizumab therapy may have caused an immune response and reactivation of *M. tuberculosis* leading to the rapid progression of the disease. A previous report described a 59-year-old male patient with tuberculous pericarditis accompanied by pericardial tamponade that had developed after receiving nivolumab monotherapy for NSCLC [11]. It also developed within a relatively short period of from two to four weeks. There are two similarities between the previous and present cases, such as the patient background and ICI monotherapy. The previously referenced report also concluded that nivolumab therapy induced a hypersensitivity response similar to that observed in the present case [11].

Although some previous reports have implicated ICIs in the onset of the disease, other potential causes, such as cytotoxic agents just before ICI treatment, immunosuppressors, and advanced age, cannot be completely ruled out. The significance and novelty of the present report lies in the fact that the patient had no these risk factors for tuberculosis and that no cases are confirmed so far which noticeably developed the disease within several days although there are some cases from within a few weeks to months in the previous studies [3,11]. When we encountered a patient with fever and progressive pleurisy developed over three weeks and with the partial response of lung cancer, it may not be so difficult for us to state tuberculosis as a differential diagnosis. However, it is usually hard for us to do so if the disease develops within about a week because it is normally a chronic infection [12].

Thus, the appearance of symptoms that are atypical of the clinical course of a malignancy in patients receiving ICI therapy should prompt clinicians to perform appropriate tests and consider tuberculosis in the differential diagnosis even though the patients present with a 10-day history of fever. Also, it is important for pulmonary teams to work together with cardiology/cardio-oncology teams as needed considering that it is sometimes hard to comprehend the etiology of cardiac events like the present case and that cardiac complications in ICI therapy often become an emergency. And then finally, the T-SPOT.TB test before and during ICI therapy should be performed to assess the risk of developing active tuberculosis as it is a point for reflection of the present case. They also help us to be alert to tuberculosis development during ICI therapy [13].

CRediT authorship contribution statement

Kazuhito Misawa: Writing – review & editing. **Kageaki Watanabe:** Writing – review & editing. **Yukio Hosomi:** Writing – review & editing. **Noriyo Yanagawa:** Writing – original draft, Supervision. **Saori Ikeda:** Writing – original draft, Conceptualization.

Consent

Written consent was obtained from the family of the patient.

Ethical approval statement

This study was conducted in accordance with the principles of the Declaration of Helsinki. Written consent was obtained from the family of the patient.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: The authors have reported to ID Cases the following: KW and YH has received lecture fees and research funding from AstraZeneca K.K. (Osaka, Japan). The remaining authors (SI, KM and NY) declare no conflicts of interest. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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