CASE REPORT

Pneumonitis: a serious adverse effect of PD-L1 inhibitors including pembrolizumab

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Accepted 22 April 2018

SUMMARY

A 70-year-old man presented with breathlessness, cough and fever while receiving pembrolizumab for melanoma. A CT pulmonary angiogram demonstrated small bilateral upper lobe segmental pulmonary emboli with patchy ground-glass opacities and basal peribular consolidation, in keeping with organising pneumonia. He was treated for community-acquired pneumonia and pulmonary emboli but rapidly deteriorated, with increasing hypoxia and dyspnoea. He was admitted to the intensive care unit for support with continuous positive airway pressure and high flow nasal oxygen. His clinical condition improved once he received high-dose intravenous methylprednisolone to treat pneumonitis. His treatment was continued with a weaning course of high-dose oral steroids, and he was discharged with a requirement for high doses of oral steroids and continued to deteriorate. He was referred to palliative care for symptom management and died a month following hospital discharge, as a result of pneumonitis due to pembrolizumab.

BACKGROUND

Pembrolizumab is a humanised monoclonal antibody, which acts by blocking the interaction with a ligand on tumour cells in the programmed cell death protein-1 (PD-L1) immune-checkpoint receptor pathway. It is licensed for use in the treatment of advanced malignant melanoma that is unresectable or metastatic, and current National Institute for Health and Care Excellence (NICE) guidelines recommend its use in patients who have not previously been treated with ipilimumab.¹ Pembrolizumab was first evaluated in the large phase I KEYNOTE-001 study.² In a pooled analysis of the 411 patients with advanced melanoma enrolled in KEYNOTE-001, the response rate was 34% after a median follow-up duration of 18 months.³ Furthermore, the response was maintained in 81% of those patients, and the median overall survival was 25.9 months.³ Pembrolizumab significantly prolongs progression-free and overall survival with fewer high-grade toxic events in patients with advanced melanoma in comparison to the previous standard of care, ipilimumab.⁴

Pembrolizumab is associated with toxic effects (mainly immune-related events) of grade 3 or 4 severity in 14% of patients.⁴ Immune-related adverse events are generally manageable; therefore, its tolerability profile is felt to be acceptable.⁵

In January 2017, NICE published guidance on the use of pembrolizumab for PD-L1 non-small cell lung cancer (NSCLC) after chemotherapy.⁶ Pembrolizumab was subsequently licensed for use in untreated PD-L1-positive metastatic NSCLC. KEYNOTE-024 was an open-label, phase III, randomised controlled trial which compared pembrolizumab with standard care and demonstrated that progression-free survival was higher in the pembrolizumab group.⁷ Furthermore, the overall survival was significantly longer in patients treated with pembrolizumab than in those receiving standard treatment.⁷ Overall, both the intention-to-treat results and the crossover-adjusted results suggested a statistically significant survival benefit for pembrolizumab compared with standard care. In its review, NICE concluded that pembrolizumab has an important extension-to-life benefit for people with untreated metastatic PD-L1-positive NSCLC compared with standard care.⁷

Furthermore, a recent phase II trial demonstrated that pembrolizumab has antitumour activity and acceptable tolerability in cisplatin-ineligible patients with urothelial cancer, suggesting this may become a new therapy option for patients who are cisplatin-ineligible or not suitable candidates for chemotherapy.⁸ As such, the number of patients receiving PD-L1 inhibitors is likely to increase in the future.

Pneumonitis is listed as an uncommon adverse effect of PD-L1 inhibitors, occurring in up to 5% of patients.⁹ A recent literature review of 2460 patients receiving a PD-L1 inhibitor for NSCLC found that 2% developed pneumonitis.¹⁰ As such, the clinical and radiological features are not well described. In addition, the overall clinical course and prognosis from PD-L1 inhibitor pneumonitis is not well documented, with only one small case series listing three patients who developed pneumonitis following pembrolizumab treatment for malignant melanoma.^{11 12} In this case series, one patient died, one recovered and one remains on follow-up.

Here we present a case of pneumonitis caused by pembrolizumab, which had been prescribed for the treatment of metastatic melanoma. Despite a clinical response to high-dose steroids, the patient deteriorated on a weaning regimen of oral corticosteroids and subsequently died.

CASE PRESENTATION

A 70-year-old man initially presented to oncology department for investigation and management of metastatic melanoma. He was noted to have right nodal disease, which was kept under surveillance.

To cite: Rickard F, Hyams C, Low AT. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2018-224485

However, 8 months after his initial diagnosis, the patient underwent a positron emission tomography (PET)/CT which detected supraclavicular and infraclavicular nodal spread. He was therefore started on pembrolizumab in November 2016 and completed the first cycle with no complications. He received a dose of 237.5 mg pembrolizumab. Cycle 2 started in December 2016 but was stopped prematurely due to development of both autoimmune hepatitis and a skin hypersensitivity reaction, which were treated with a weaning regime of oral prednisolone. Other medical history included atrial flutter, type 2 diabetes mellitus, hypothyroidism and non-Hodgkin's lymphoma. His regular medication included bisoprolol, metformin and levothyroxine.

In January 2017, 41 days following cessation of the second cycle of pembrolizumab, he presented to the Acute Oncology Unit with a 2-week history of worsening cough with occasional white sputum and breathlessness. There was no haemoptysis. He was febrile (temperature 37.8 C) and noted to have a heart rate of 120 beats per minute and respiratory rate of 20. His pulse oximetry was 92% on room air. Clinical examination revealed bibasal crepitations to the mid-zones.

INVESTIGATIONS

Initial blood tests demonstrated a normal white cell count of $8.3 \times 10^9/L$, neutrophil count $6.4 \times 10^9/L$ and haemoglobin 118 g/L. The C reactive protein was raised at 55 mg/L. Both liver and renal function tests were normal on blood investigations. An arterial blood gas on room air showed a pH of 7.46, pCO_2 4.3, pO_2 8.1 and HCO_3 24.5 consistent with type 1 respiratory failure. Blood cultures were taken, but no organisms grew on culture. Sputum culture did not grow any organisms. Urinary antigens against legionella and pneumococcal pneumonia were negative. A throat swab was negative for respiratory viruses on PCR testing. An autoimmune screen was negative.

A chest radiograph revealed bilateral infiltrates in the right and left lower zones (figure 1A). A CT pulmonary angiogram (CTPA) scan revealed small bilateral upper lobe segmental pulmonary emboli and patchy, predominantly subpleural, ground glass opacities with basal peribulbar consolidation (figure 1B). A lung biopsy was not performed, as the patient was too unwell to undergo this procedure.

TREATMENT

The patient was commenced on intravenous co-amoxiclav, and after his CTPA, he was started on therapeutic dose enoxaparin (1.5 mg/kg). However, the patient continued to deteriorate over the next 24 hours, and subsequently required 10 L/min oxygen to maintain his saturations. A repeated chest radiograph was obtained, which showed similar bilateral infiltrates in the bases and midzones. However, a repeat arterial blood gas demonstrated a worsening type 1 respiratory failure, with pH 7.45, pCO_2 4.8, pO_2 14.3, HCO_3 25.8 and Sats 97%. The patient was increasingly tachypnoeic with a respiratory rate of 25.

His co-amoxiclav was discontinued, and instead the patient received intravenous piperacillin and tazobactam (Tazocin). He was also started on oseltamivir and high-dose co-trimoxazole (trimethoprim and sulfamethoxazole). He was also started on 1 mg/kg of prednisolone as treatment for a pneumonitis. However, over the next 16 hours, the patient continued to deteriorate. He required increasing levels of oxygen support and subsequently he desaturated to 90% on 15 L oxygen. His respiratory rate continued to rise despite the increasing oxygen, and the patient was subsequently transferred to the intensive care unit.

OUTCOME AND FOLLOW-UP

After transfer to the intensive care unit, the patient was commenced on alternating continuous positive airway pressure (CPAP) therapy and high flow oxygen via nasal cannula. He also received intravenous fluconazole. Further investigations for infection including atypical serology and beta glucan were negative. The patient's inflammatory markers, including his white cell count, remained static.

After 24 hours further treatment, it was felt that this patient did not have a likely infective cause for his deterioration. As such he was diagnosed as having a pneumonitis secondary to PD-L1 inhibitor treatment. The patient was therefore commenced on intravenous methylprednisolone at a dose of 1 g daily and oral prednisolone was discontinued. He initially deteriorated in the subsequent 24 hours; however, he then began to improve clinically over the following week. He was weaned off CPAP and began to wean off high flow nasal oxygen. The intravenous methylprednisolone was decreased in dose to 2 mg/kg.

Figure 1 (A) Admission chest radiograph, reported as showing patchy haziness seen in both lower zones in keeping with consolidation. (B) Admission CT pulmonary angiogram showing appearances within the lungs of patchy, predominantly subpleural, ground glass opacities and basal peribulbar consolidation which is in keeping with an organising pneumonia.

Figure 2 Chest radiograph on discharge from hospital, showing improved but ongoing haziness in the lower zones.

Following a total of 9 days on the intensive care unit, the patient was stepped down to a respiratory high care unit. Over the course of the following 3 weeks, his oxygen requirement was slowly weaned, but he continued to require 1 L/min oxygen via nasal cannula. During his admission to the respiratory ward, he received daily physiotherapy input. The methylprednisolone was switched to prednisolone 1 mg/kg, with a plan to wean by 10 mg every 2 weeks. Thirty-four days after his admission to the hospital, the patient was discharged home with radiological and symptomatic improvement (figure 2).

However when he was reviewed in outpatient clinic 6 days after discharge, the patient had become increasingly symptomatic and had been unable to wean his prednisolone below a dose of 70 mg/day. He had ongoing shortness of breath and a persistent oxygen requirement. The patient was referred to the community palliative care team for symptom management input, and unfortunately died 1 month later from his respiratory condition.

DISCUSSION

PD-L1 inhibitors, such as pembrolizumab, are now used in the treatment of a number of malignancies, including malignant melanoma and NSCLC, as well as head and neck squamous cell carcinoma (after platinum based chemotherapy) and refractory non-Hodgkin's lymphoma. It is expected that their use will continue to expand in the future.

Pneumonitis is a known side effect of PD-L1 inhibitors. However, there is a lack of reported cases in the literature, and as such there is no clear consensus for the presentation or management of this life-threatening adverse effect. The mechanism of PD-L1 inhibitor-related pneumonitis remains undetermined, however it is hypothesised that the deregulation of immune effectors and T cells in the pulmonary interstitium results in a subsequent inflammatory response. Patients with PD-L1 inhibitor pneumonitis have a predominance of lymphocytes in bronchoalveolar lavage and infiltration of lymphocytes on a lung biopsy.¹³ Furthermore, patients who had pneumonitis after taking ipilimumab have a higher proportion of activated T cells

in bronchoalveolar lavage fluid compared with normal control.¹⁴ An alternative hypothesis is that PD-L1 inhibitors increase the interaction between repulsive guidance protein b and PD-L2 by reducing the interactions between PD-1 and PD-L2. This may result in the clonal expansion of lung-resident T cells and a subsequent decrease in immune-tolerance signalling pathways.¹⁵

In terms of incidence, several meta-analyses have shown that the incidence of all-grade pneumonitis during anti-PD-L1 immunotherapy is approximately 3% for all-grade and 1.5% for high-grade pneumonitis.⁶ Incidence appears to vary with different tumour types; pembrolizumab-induced pneumonitis is less frequent in patients with melanoma than in patients with NSCLC, with an incidence of under 1% and approximately 5%, respectively.^{16–18}

There are little available data with regard to factors that precipitate pneumonitis in patients treated with anti-PD-L1 inhibitors. However, the reaction appears to be dose-independent. Data have revealed that the incidence of pneumonitis is higher in patients with a background of asthma or chronic obstructive pulmonary disease (COPD) than in those without it (5.4% and 3.1%, respectively), as well as in patients who had previously undergone thoracic radiotherapy (6% vs 2.6%).¹⁷ Clinical presentation of the pneumonitis includes cough, dyspnoea and tachypnoea, with or without hypoxia.¹⁸ Radiological appearance on imaging resembles interstitial pneumonia, in particular on high-resolution CT scanning.¹⁹

Several pieces of literature^{20 21} have outlined proposed treatment of PD-L1-related pneumonitis, which is based on clinical experience and case reports, as well as pre-existing management advice. For grade 1 disease (radiographic changes only), delay in treatment alone is advised, with repeat imaging every 3 weeks. For grade 2 (patient symptomatic with cough and dyspnoea), management should include delay of treatment, admission to hospital, administration of intravenous methylprednisolone 0.5–1.0 mg/kg/day and subsequent tapering of steroids over 1 month. Repeat imaging is advised in days to weeks. For grade 3–4 disease (characterised by hypoxia and life-threatening respiratory compromise), the patient should be admitted to hospital with consideration of Intensive Therapy Unit (ITU) admission, and administration of intravenous methylprednisolone 2–4 mg/kg/day. Additional immunosuppression should be considered at 48 hours if there is inadequate improvement. Steroids should be tapered over 6 weeks.

This patient had melanoma, therefore his risk of pneumonitis should have been less than if he had a diagnosis of NSCLC. He did not have underlying asthma or COPD and had not undergone previous thoracic radiotherapy. His case was therefore considered relatively low risk of developing pneumonitis. His

Learning points

- ▶ PD-L1 inhibitors can cause pneumonitis in patients, which can present with a similar clinical picture to an infective process.
- ▶ It can be difficult to distinguish on radiological imaging alone whether these patients have an infective process or if there is a pneumonitis.
- ▶ PD-L1 pneumonitis should always be in the differential diagnosis of patients presenting with respiratory distress and hypoxic respiratory failure on this type of immunotherapy.
- ▶ Treatment with high-dose corticosteroids can be effective in the treatment of PD-L1 inhibitor-induced pneumonitis.
- ▶ PD-L1 pneumonitis is a condition which can result in death.

presentation was consistent with previous literature reports, and there were no atypical features. He was treated with intravenous methylprednisolone as advised but did not receive additional immunosuppression.

From this case we have learnt that immune-mediated reactions, including pneumonitis, are potential adverse effects of PDL-1 inhibitors and should be considered as a diagnosis when those patients taking these checkpoint inhibitors become unwell. As this case unfortunately demonstrates, it can be a fatal adverse effect. It is therefore very important to keep this disease in the forefront of our minds so that treatment can be initiated as soon as possible to reduce morbidity and mortality.

Contributors FR and CH prepared the manuscript and figures, and performed a literature review. ATL oversaw the manuscript and edited the paper and figures.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent Next of kin consent obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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