A flitting pneumonia in a patient with advanced melanoma

Introduction

This article presents the case of a 75-year-old man receiving immunotherapy for advanced melanoma who required urgent inpatient admission to the authors' emergency cancer treatment centre for a lobar pneumonia, having presented with pyrexia, respiratory distress and extensive right midzone consolidation on chest radiography. Despite initial treatment with intravenous co-amoxiclav and clarithromycin, then piperacillin-tazobactam, there were no signs of clinical improvement. A repeat chest radiograph on day 6 revealed a resolving right-sided consolidation but new left-sided interstitial changes – the pneumonia appeared to have flitted.

Computed tomography pulmonary angiography confirmed interstitial changes in both lungs consistent with an inflammatory pneumonitis rather than pneumonia, likely to have been caused by a drug reaction to immunotherapy, in this case, to the anti-programmed cell death-1 (PD1) antibody pembrolizumab. Antibiotic treatment for pneumonia was discontinued and oral prednisolone initiated on a 6-week weaning regimen, together with *Pneumocystis jirovecii* cover. Early corticosteroid therapy resulted in prompt clinical resolution.

Discussion

Pembrolizumab induces pneumonitis by blocking PD1 receptors on T cells that attenuate T cell function (Wu et al, 2017). This results in uninhibited T cell activity that can induce dramatic anticancer responses in patients with melanoma and other malignancies, but can also lead to toxicity within healthy tissues including the lung epithelium.

A meta-analysis (Wu et al, 2017) involving 6360 patients from 16 phase 2 and 3 clinical trials estimated the incidence of all-grade pneumonitis to be only 2.92% with antiPD1 antibodies (confidence interval 2.18–3.90%). In addition to its relatively

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CASE REPORT

A 75-year-old man with *BRAFV600E*-mutant metastatic melanoma required a switch in systemic anticancer treatment after his disease progressed on combination targeted therapy with the BRAF kinase inhibitor dabrafenib and MEK inhibitor trametinib. Involved sites included low-volume pulmonary disease, subcutaneous nodules and bone metastases at both L3 and sacrum. As second-line treatment, the first immunotherapy with the anti-programmed cell death-1 (PD1) antibody pembrolizumab was administered without any immediate complications, except for a disease-related admission as a result of pending cord compression at L3 from the metastatic bone disease, which required corticosteroid therapy.

Three weeks later, an acute presentation with pyrexia at 40°C, tachypnoea at 28 breaths per minute, hypoxia with oxygen saturations at 89% on air, tachycardia at 130 beats per minute and general malaise led to a further hospital admission at the emergency cancer treatment centre. Apart from a mild laryngitis, there were no localizing symptoms or signs of infection. White cell count was within the normal range and C-reactive protein level elevated at 240 mg/litre, from a baseline of circa 100 mg/litre. Admission chest radiography identified extensive right mid zone consolidation (*Figure 1*). Intravenous co-amoxiclav and clarithromycin were initiated according to trust guidelines for a lobar pneumonia.

By day 3 on systemic antimicrobials, dyspnoea was subjectively worsening, pyrexia ongoing and on chest auscultation bilateral mid and lower zone crepitations had developed. The admission blood culture did not demonstrate any growth and the C-reactive protein level failed to decline. Intravenous co-amoxiclav and clarithromycin were therefore discontinued and intravenous piperacillin-tazobactam commenced. Four days later on day 7, fevers and bilateral chest crepitations remained present despite the antibiotic switch. Repeat sputum, blood and urine cultures demonstrated no growth. Urinary antigens against *Legionella* and *Pneumococcus pneumoniae* were negative. The C-reactive protein level remained static. Repeat chest radiography revealed new bilateral perihilar ground-glass opacification with more extensive interstitial changes within the left lung than initially observed at the right mid zone. The pneumonia appeared to have flitted. In addition there was a small right-sided pleural effusion. Such radiographical features would be consistent with pulmonary oedema yet were incompatible with the clinical picture, which also seemed atypical for sepsis.

Although only a single immunotherapy cycle with pembrolizumab had been administered, an immune-related pneumonitis was considered. Corticosteroid therapy for pending cord compression at L3 had been discontinued 2 days before admission. Hence, cessation of steroid therapy might have allowed a previously suppressed pneumonitis to flare. Urgent computed tomography pulmonary angiography confirmed ground-glass changes within both lungs, with a resolved right middle lobe consolidation and new interstitial changes present within the left upper lobe, consistent with an inflammatory pneumonitis that was flitting (*Figure 2*). Intravenous piperacillin-tazobactam was discontinued and oral prednisolone started on a 6-week weaning regimen with co-trimoxazole cover for *Pneumocystis jirovecii*. A dramatic symptomatic improvement allowed prompt discharge home.

Three weeks after admission, the C-reactive protein level had returned to baseline and a chest radiograph demonstrated almost complete resolution of the interstitial changes except for persistent airspace shadowing within the right mid zone. Pembrolizumab was permanently discontinued given the respiratory toxicity encountered.

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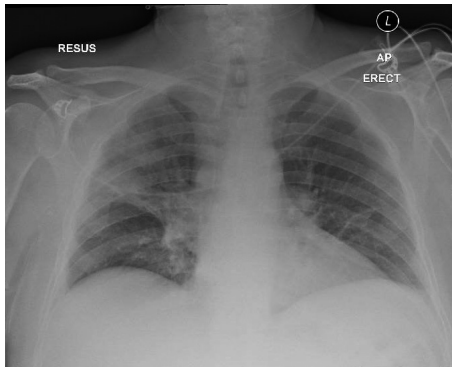

Figure 1. Admission chest radiography showing extensive right mid zone consolidation.

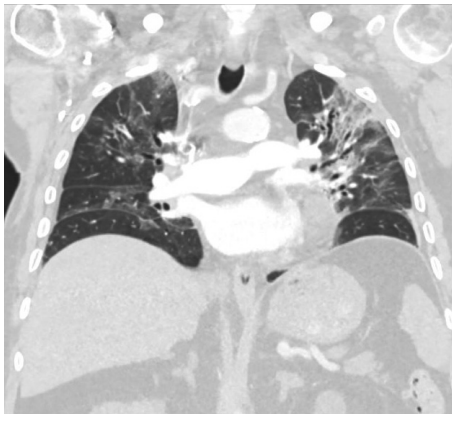

Figure 2. Computed tomography pulmonary angiography showing new interstitial changes within the left upper lobe.

rare frequency, a short time to market has resulted in limited documentation of the clinical and radiological features that characterize immune-related pneumonitis (Rickard et al, 2018). Pneumonitis tends to develop between 7.4 and 24.3 months after commencing antiPD1 treatment and specific risk factors are known to increase its likelihood. For example, the incidence is lower in patients with melanoma as opposed to patients with non-small cell lung cancer, renal cell carcinoma or those with an underlying chronic respiratory condition.

By such measures, this patient was deemed to be at low risk of developing pneumonitis, having metastatic melanoma, becoming unwell early within a month of receiving his first pembrolizumab dose and lacking any underlying lung pathology except for the pulmonary metastatic disease. Despite this, chest radiography and computed tomography pulmonary angiography both demonstrated radiological changes typical for an antiPD1-induced pneumonitis with bilateral (and flitting) consolidation, as well as ground-glass opacities (Rickard et al, 2018). The radiological appearances are very similar to an interstitial pneumonia (Leroy et al, 2017), frequently leading to the same process of unsuccessful antibiotic escalation before initiating definitive treatment with corticosteroids (Rickard et al, 2018). BJHM

LEARNING POINTS

- Pneumonitis should be considered in all patients receiving programmed cell death-1 inhibitors who present with respiratory symptoms or fail to respond to antibiotics for a presumed pneumonia.
- Interstitial changes on chest imaging should raise the suspicion of pneumonitis in patients receiving immunotherapy.
- Early treatment with corticosteroids in immunotherapy-related toxicity such as pneumonitis can result in prompt clinical resolution.
- All patients on immunotherapy who present as an emergency with a toxic complication should be managed with input from specialist teams who are familiar with treatment algorithms.
- Immune-related adverse events frequently lead to interruptions in further immunotherapy administration and can lead to permanent treatment discontinuation if severe.

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Wu J, Hong D, Xiangnau Z, Lu X, Miao J. PD-1 inhibitors increase the incidence and risk of pneumonitis in cancer patients in a dose-independent manner: a meta-analysis. Sci Rep. 2017 Mar 8;7:44173. https://doi.org/10.10381/srep44173

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