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A Case of Durvalumab Induced Pneumonitis

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Abstract

Background: Historically patients with locally advanced stage III non-small cell lung cancer (NSCLC) were treated with double platinum-based chemotherapy with concurrent radiotherapy. Durvalumab is a selective, high-affinity, human IgG1 monoclonal antibody that blocks PD-L1 binding to PD-1 and CD80 receptors, allowing T cells to recognise and kill tumour cells. The recent PACIFIC trial demonstrated that consolidation durvalumab therapy significantly prolonged the progression-free and overall-survival in patients with unresectable, stage III NSCLC whose disease had responded after concurrent chemoradiotherapy. These results have led to the growing recognition of consolidation durvalumab therapy after chemoradiotherapy as the standard of care in this setting. However, this brings a new set of challenges including the recognition and management of immunotherapy-related toxicities including immunotherapy-related pneumonitis.

Case presentation: We present the case of a 55-year-old female who presented with worsening shortness of breath and dry cough after treatment with concurrent chemoradiotherapy (cCRT) and consolidation durvalumab therapy for stage IIIB non-resectable NSCLC. Serial imaging demonstrated the presence of new areas of multifocal consolidation in the right middle and upper lobes, with subsequent development of new ground glass opacities in the left upper lobe. Post-radiation pneumonitis was a less likely differential given that the radiological changes occurred outside the radiation field. Bronchoalveolar lavage excluded pulmonary infection and progression of malignancy. A subsequent diagnosis of immunotherapy-related pneumonitis was made. Her clinical symptoms and imaging improved with a tapering course of steroid therapy.

Conclusion: Immunotherapy-related pneumonitis is often considered a diagnosis of exclusion, with symptomatology that may overlap with other conditions such as post-radiation pneumonitis, pulmonary infection, and progression of malignancy. Timely recognition of the clinical and radiological features of this condition are important to facilitate early diagnosis and initiation of treatment.

Keywords: Durvalumab; Concurrent chemoradiotherapy

Introduction

Advanced NSCLC has historically been a diagnosis associated with poor outcomes, high symptom burden, and limited treatment options. The advent of immunotherapy durvalumab consolidation therapy in stage III unresectable NSCLC has been shown to significantly improve survival. However, this brings unique issues related to 'survivorship' after immunotherapy, such as immunotherapy-related adverse effects (irAEs). Immunotherapy-related pneumonitis is a clinically serious and potentially lethal adverse effect. The most common symptoms include dyspnoea, decreased exercise tolerance, and cough. Fever and chest pain may also occur. The differential of immunotherapy-related pneumonitis becomes particularly challenging in the setting of lung cancer as it may be clinically indistinguishable from other conditions such as post-radiation pneumonitis, pulmonary infection, tumour progression or pseudo-progression, or acute exacerbation of chronic obstructive pulmonary disease which may also occur after treatment. Computed tomography (CT) scans of the chest are critical in the diagnosis and management of pneumonitis. In this case report, we will discuss a case of a patient who developed pneumonitis secondary to durvalumab therapy.

Case Report

A 55-year-old female presented with a 3-month history of persistent dry cough and was subsequently diagnosed with unresectable stage IIIB (T4N2M0) NSCLC located in the right perihilar region with extension into the right upper and middle lobes. She underwent cCRT including a regimen of cisplatin and etoposide with 60 Gray (Gy) radiotherapy in 30 fractions. Two months after completion of chemoradiotherapy, an interval positron emission tomography (PET) CT scan demonstrated partial structural and metabolic regression of the tumour, with imaging findings also suggestive of post-radiation pneumonitis affecting the right lower lobe (Figure 1). The patient complained of an ongoing mild dry cough at this time. She was commenced on a course of oral prednisolone 25 mg daily tapered over 2 weeks. After some improvement in her cough, she was commenced on consolidation durvalumab therapy. After two 14-day cycles of durvalumab, she developed acute worsening shortness of breath and dry cough.

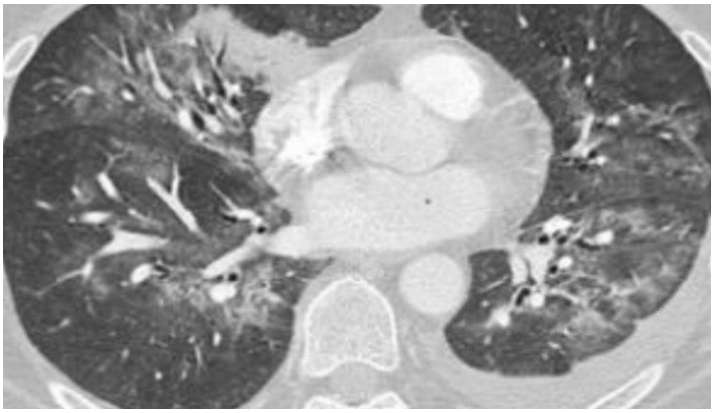

Figure 1: *CT scan demonstrated multifocal consolidation.*

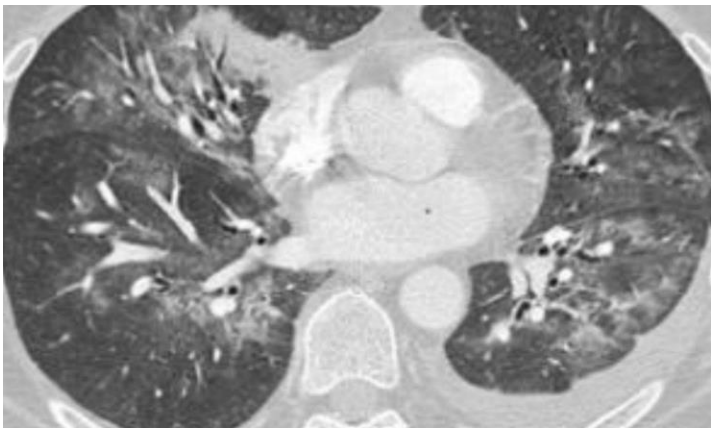

Figure 2: *Serial CT scans showing multifocal consolidation.*

Investigations included a CT pulmonary angiogram (CTPA) which was negative for pulmonary embolism, however there was a marked increase in consolidative changes in the right upper lobe (Figure 2). Durvalumab therapy was ceased, and the patient was commenced on oral prednisolone 25 mg daily. Oral prednisolone was tapered over the next 12 weeks with improvement in symptoms. However, serial CT scans during this time demonstrated new areas of multifocal consolidation in the right middle and upper lobes (Figure 3), with subsequent development of new ground glass opacities in the left upper lobe (Figure 3).

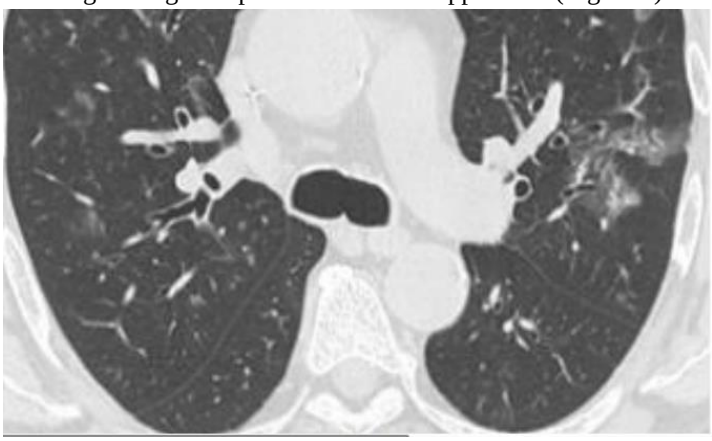

Figure 3: *Marked improvement in bilateral hilar consolidation.*

Two weeks after completing the course of prednisolone, the patient began to develop rapidly progressive breathlessness and dry cough resulting in hospitalisation. Repeat CTPA revealed the development of bilateral hilar consolidation.

Differential diagnoses

The development of these pulmonary changes were concerning for pulmonary infection (e.g., viral, bacterial, Pneumocystis jirovecii pneumonia (PJP) infection), immunotherapy-related pneumonitis, post-radiation pneumonitis or progression of malignancy. The presence of bilateral progressive radiological changes outside the radiation field made post-radiation pneumonitis less likely. PJP remained a possibility given the prolonged course of steroid immunosuppression. Diagnostic bronchoscopy with bronchoalveolar lavage did not reveal the evidence of malignancy or infection, specifically, lavage was negative for PJP. Therefore, the diagnosis of immunotherapy-related pneumonitis was made after careful exclusion of other differentials.

The patient was recommenced on a moderate dose of prednisolone to be tapered slowly. Her shortness of breath and cough slowly improved over the next 3 months, and a repeat CT chest showed marked improvement in the bilateral pulmonary changes.

Outcome and follow up

The patient's case and radiology were discussed at the Statewide Interstitial Lung disease multi-disciplinary meeting (ILD-MDM). The consensus diagnosis was that of durvalumab-induced

pneumonitis, however, a further PET-CT was recommended to exclude progressive malignancy.

Discussion

Approximately one-third of patients with NSCLC have stage III locally advanced disease at diagnosis [1,2]. Historically, the standard of care for patients with good performance status and unresectable stage III NSCLC was concurrent platinum-based doublet chemotherapy and radiotherapy followed by observation alone [3]. However, survival among patients who received chemoradiotherapy remained poor, with a phase III clinical trial demonstrating that a combination of concurrent cisplatin, etoposide, and chest radiotherapy resulted in a benefit in median overall survival (OS) of 15 months, with 3- and 5-year survival of 17% and 15% respectively [3,4]. More recently, the use of immune checkpoint inhibitors has altered the landscape of anti-cancer treatment in patients with stage III lung cancer diagnoses.

The phase III PACIFIC trial represents a landmark advancement in the treatment of unresectable, stage III NSCLC patients whose disease had responded or stabilised after cCRT [3]. One year maintenance durvalumab therapy significantly improved progression-free survival (PFS) (HR 0.52; 95% CI 0.42-0.65, p< 0.0001; median 16.8 versus 5.6 months) and overall survival (OS) (HR 0.68, 95% CI 0.53-0.87, p= 0.00251) versus placebo. These results have led to the growing recognition of the 'PACIFIC regimen' (durvalumab after cCRT) as the standard of care in this setting [5]. An updated exploratory analyses 5 years post randomisation demonstrated ongoing PFS and OS benefits of durvalumab compared to placebo. The estimated 5-year PFS and OS rates were 33.1% and 42.9% for durvalumab and 19.0% and 33.4% for placebo respectively. Survival benefit favoured durvalumab versus placebo across all PDL-1 subgroups; the only exception was OS in the post-hoc subgroup with PD-L1 tumour cell (TC) expression <1% (HR 1.15, 95% CI 0.75-1.74) although PFS still favoured durvalumab in this subgroup (HR 0.80, 95% CI 0.53-1.20) [6]. Further research is still required to determine the optimal duration of durvalumab treatment following cCRT.

Consolidation durvalumab has demonstrated improved PFS and OS compared to placebo however it has not come without its associated immune-related toxicities. The most common adverse effect of any grade in those receiving anti-PDL1 treatment are fatigue, gastrointestinal (bloody diarrhoea, abdominal pain, hepatitis, and jaundice), endocrine (altered thyroid function and hypocalcaemia), peripheral neuropathy, and dermatological irAEs [3]. Respiratory adverse events, such as pneumonitis, are the most common cause of immune-related deaths and have been reported to occur 7 to 24 months after commencing treatment [3,7]. Patients with suspected pneumonitis may present with non-specific respiratory symptoms of shortness of breath, cough, fever, or chest pain [7].

Pneumonitis is of particular interest in stage III NSCLC, as these patients are also at high risk of developing radiation pneumonitis due to the temporal proximity of chemotherapy, radiation treatment, and consolidation with durvalumab. Real world studies have suggested differences in the frequencies of pneumonitis among patients who received durvalumab consolidation therapy after chemoradiotherapy. These heterogeneities were thought to be related to the differences in volume of lung parenchyma that received 20 Gy (V20) and mean lung dose (MLD). Many previous reports have shown a correlation between V20/MLD and the incidence/severity of pneumonitis [8]. The National Comprehensive Cancer Network (NCCN) guidelines recommend that V20 should not exceed 35-40% and that the MLD should not exceed 20 Gy [9]. There was a trend towards more rapid onset of pneumonitis in patients receiving radiotherapy (RT) and immune checkpoint inhibitor (ICI) (median time of onset 1.2 months, range 0.1-34.3) compared with patients who received RT (median onset 3.1 months, range 0.4-12.0) or ICI alone (median onset 2.7 months, range 0.1-17.4, p=0.12) [10].

Differentiating between radiation pneumonitis and immune-related pneumonitis can be challenging clinically due to timing of onset and overlapping symptoms, and thus the comparison of morphology on CT imaging is increasingly important. Both RT- and ICI-pneumonitis can often manifest as ground-glass opacities (GGOs) and consolidations on CT, and both frequently assume a pattern of cryptogenic organising pneumonia (COP) or acute interstitial pneumonia/acute respiratory distress syndrome (AIP/ARDS) but differ in their spatial distribution [3,10-12]. There are no universally accepted criteria to define the components of pneumonitis caused mainly by RT and that caused mainly by ICI. Furthermore, both RT and ICI may act synergistically to promote inflammation of the lung parenchyma [10]. The distinction between RT vs. ICI pneumonitis is clinically relevant as treatment algorithms for RT versus ICI pneumonitis differ in that ICI-pneumonitis requires higher doses of steroids and occasionally immunosuppressive agents and may necessitate prolonged or indefinite discontinuation of ICI [10]. Radiation pneumonitis classically displays unilateral involvement, smaller areas confined to the radiation field, and sharp borders, whereas immune-related pneumonitis tends to be bilateral with a larger area involved and is less likely to display sharp borders [3]. Among patients who receive both RT and ICIs, some changes were confined to the ipsilateral lung with sharp borders resembling RT-pneumonitis, while others resembled the bilateral distribution of typical ICI pneumonitis [3,10,12].

In addition to immune-induced pneumonitis is considered a diagnosis of exclusion, and workup to rule out other aetiologies, including pulmonary infection and cancer progression should take place [11]. There is an increased incidence of severe pneumonitis, both radiation- and immune-related in patients with poorer

performance status, worse lung function, prior respiratory disease, and smoking history [3,13]. Pulmonary function testing is not routinely performed prior to commencement of ICI treatment, however, is often used as part of the diagnosis of pneumonitis, which commonly demonstrates a restrictive pattern and significantly decreased gas transfer [3]. In selected cases, a diagnostic bronchoscopy with bronchoalveolar lavage (BAL), with or without a transbronchial biopsy could be considered; however, their role in diagnosis has not been clearly defined in current clinical practice guidelines. In cases of clinical and radiologic doubt, bronchoscopy with BAL could help to rule out infections and malignancy as competing diagnoses, especially in suspected grade 2-4 pneumonitis [11-13]. Recently, the identification of biomarkers in BAL which could indicate the occurrence of ICI-related pneumonitis is under research. Elevated levels of interleukin (IL)-17A and IL-35 have been found to be associated with the development and severity of ICI-related pneumonitis [12,14]. A multidisciplinary approach involving medical oncologists, infectious disease and respiratory physicians is recommended.

Guidelines on the management of irAEs have been published from the European Society for Medical Oncology (ESMO), the American Society for Clinical Oncology/National Comprehensive Cancer Network (ASCO/NCCN), and the Society for Immunotherapy of Cancer (SITC). In grade I pneumonitis, the clinician should consider withholding ICI, monitor the patient clinically every 2-3 days and offer a repeat CT chest in 3 weeks; upon radiographic resolution, the ICI could be resumed, and no further imaging is needed. Upon clinical or radiographic deterioration, the patient should be treated as grade II. In grade II pneumonitis, ICI should be withheld and treatment with corticosteroids should be initiated (prednisone 1 mg/kg orally), and empirical antibiotics should be considered. If symptoms improve after 48-72 hours, corticosteroids should be tapered for 6 weeks; upon clinical deterioration, the patient should be treated as grade 3-4. In grade 3-4 pneumonitis, treatment with ICI should be permanently discontinued and treatment should consist of corticosteroids ([methyl] prednisolone 2-4 mg/kg/day or equivalent) and empirical antibiotics should be administered. Upon clinical improvement after 48-72 hours, the corticosteroids could be reduced to 1 mg/kg and then tapered over 8 weeks. Upon clinical deterioration after 48-72 hours, additional immunosuppressive strategies should be implemented (e.g. addition of infliximab, mycophenolate mofetil, or cyclophosphamide), weighing the benefit/risk ratio for the patient [13].

Rechallenge with checkpoint inhibitors following immune-related adverse events is highly controversial. In the PACIFIC study, durvalumab rechallenge was an option for patients who developed ≤ grade 2 pneumonitis after initiation of durvalumab, which resolved to grade 1, and who achieved reduction in prednisone or an equivalent to a dose of ≤ 10 mg/day [8,11]. In a retrospective study of 302 patients who received durvalumab post chemoradiotherapy for NSCLC, pneumonitis of any grade was observed in 83% of patients and severe pneumonitis was observed in 34% of patients. In more than 80% of the patients who were rechallenged with durvalumab based on the rechallenge criteria of the PACIFIC study, severe relapse did not occur. The PACIFIC trial rechallenge criteria have also been endorsed in the European Society for Medical Oncology (ESMO) guidelines [8,12].

Conclusion

Immune checkpoint inhibitors have revolutionised the treatment of locally advanced stage III NSCLC. However, this brings a unique set of toxicities to treatment including immunotherapy-related pneumonitis. There are ongoing gaps in the ability to distinguish immunotherapy related pneumonitis from other causes, such as post-radiation pneumonitis, pulmonary infection and cancer progression. Therefore, the clinical presentation often presents as a diagnostic dilemma for clinicians. Ideally, immune-related adverse effects are managed most effectively when detected early via a multidisciplinary approach involving medical oncologists, radiation oncologists, and respiratory physicians. Leading into the future where immunotherapy becomes more integrated into standard of care in cancer treatment, further research is required to explore a reliable and early diagnosis of immunotherapy-related pneumonitis.

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