Pneumonitis in Irradiated Lungs After Nivolumab: A Brief Communication and Review of the Literature

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Summary: Nivolumab is a feasible therapy option in patients with advanced non–small cell lung cancer (NSCLC) who progress on first-line treatment. However, there is limited information about an overlapping toxicity of PD-1 inhibitors when administered following thoracic radiotherapy (TRT). Three of 25 patients with advanced NSCLC were treated with palliative or curative intent. Nivolumab was initiated as second or third-line therapy after TRT for recurrent or progressive disease. All 3 patients developed grade 3 pneumonitis at some point during nivolumab therapy. Herein, we describe 3 cases of pneumonitis in patients with NSCLC started on nivolumab following TRT. Imaging analysis was strongly consistent with heterogenous lung parenchyma changes in the irradiated lung volume receiving a total dose of 15–20 Gy. Pulmonary toxicity was manageable; however, interruption of immunotherapy was necessary.

Key Words: immunotherapy, nivolumab, non–small cell lung cancer, radiation recall pneumonitis, thoracic radiotherapy

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Nivolumab is an effective, feasible treatment option in advanced non–small cell lung cancer (NSCLC). On the basis of CheckMate 017[1] and CheckMate 057,[2] nivolumab was approved as second-line standard, unrestricted for use independent of PD-L1 status.

Because of potential overlapping pulmonary toxicity, a combination of immunotherapy and thoracic radiotherapy (TRT) is an important point of clinical investigation. A meta-analysis on the risk of pneumonitis associated with immunotherapy reported a relatively low incidence of all-grade (2.9%) and high-grade (1.8%) pulmonary toxicity, respectively. The incidence of pneumonitis was higher in nonmelanoma patients.[3] However, a phase I dose-escalation cohort expansion trial (CA209-003) of nivolumab documented higher pneumonitis rates in 129 NSCLC patients with previous TRT. There were 7% and 1.3% of all-grade and grade 3–4 pneumonitis, respectively.[4,5] Herein, we describe 3 cases of severe pneumonitis in irradiated lungs of pretreated NSCLC patients on nivolumab.

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CASE 1

A 66-year-old female patient (exsmoker) with performance status (PS) Eastern Cooperative Oncology Group (ECOG) 1 was diagnosed with squamous NSCLC cT3cN2cM0 (UICC seventh edition). Radical surgery was performed after 4 cycles of neoadjuvant cisplatin/vinorelbine. Four weeks later, postoperative radiotherapy was delivered to a total dose of 50.0 Gy. The lung dose-volume histogram parameters were as follows: V20 (both lungs) 16% (519 mL), mean lung dose (MLD) 11.85 Gy (Fig. 1A2). On recurrence, the patient was started on nivolumab. Shortly after the first cycle, she developed grade 3 dyspnea. High-resolution chest computed tomography (CT) showed a patchy consolidation (Fig. 1A4). No pathologic findings were observed on bronchoscopy. Broncho-alveolar lavage (BAL) showed 60.6% macrophages, 9.3% lymphocytes, and 30% neutrophils. Microbiological analysis of BAL was negative. Corresponding changes in pulmonary function tests (PFTs) before and after the onset of pneumonitis are shown in Table 1. Immunotherapy was interrupted and the patient was started on corticosteroids tapered slowly over 5 weeks.

CASE 2

A 76-year-old male patient (nonsmoker) with PS ECOG 1 presented with oligometastatic NSCLC cT1cN2cM1b (UICC seventh edition) and received stereotactic radiosurgery for 2 brain lesions. Thereafter, 2 cycles of chemotherapy with cisplatin/pemetrexed followed. PET/CT showed partial remission (Fig. 1B1), concurrent chemoradiotherapy with cisplatin/pemetrexed to a total dose of 66.0 Gy was delivered. The lung dose-volume histogram parameters were as follows: V20 (both lungs) 22% (930 mL) and MLD 12.3 Gy, respectively (Fig. 1B2). Four months later, the patient presented with metastatic disease and was started on nivolumab. Shortly after the fourth application, he developed grade 3 dyspnea requiring immediate hospitalization, chest CT showed irregular ground-glass opacities with bilateral fibrotic changes (Fig. 1B4), BAL showed 9.6% macrophages, 5.6% lymphocytes, 84.6% neutrophils. Microbiological analysis of BAL was negative. The corresponding changes in PFTs before and after the onset of pneumonitis are illustrated in Table 1. Immunotherapy was interrupted and the patient was started on 50 mg prednisolone tapered off 5 mg every 4 days over 6 weeks.

CASE 3

A 56-year-old female patient (nonsmoker) with PS ECOG 1 was diagnosed with stage IV NSCLC with multiple brain metastases. She was initially treated with 5 cycles of cisplatin/pemetrexed and responded well, exhibiting partial remission. Three weeks later, she underwent palliative irradiation to the brain and thorax. V20 (both lungs) and MLD were 18% (380 mL) and 9.45 Gy, respectively (Fig. 1C2). Three months later, docetaxel/nintedanib was initiated due to progressive disease; however, the patient developed adrenal metastasis and was started on nivolumab. Restaging scans after 6 cycles revealed diffuse consolidations in both upper lobes (Fig. 1C4). The patient presented with grade 3 dyspnea also requiring immediate hospitalization. BAL revealed bronchial epithelial cells with macrophages and neutrophils. Microbiological analysis of BAL was negative. For changes in the PFTs see Table 1. Nivolumab was interrupted and treatment with 60 mg prednisolone was started, tapered off 5 mg every 4 days for 6 weeks.

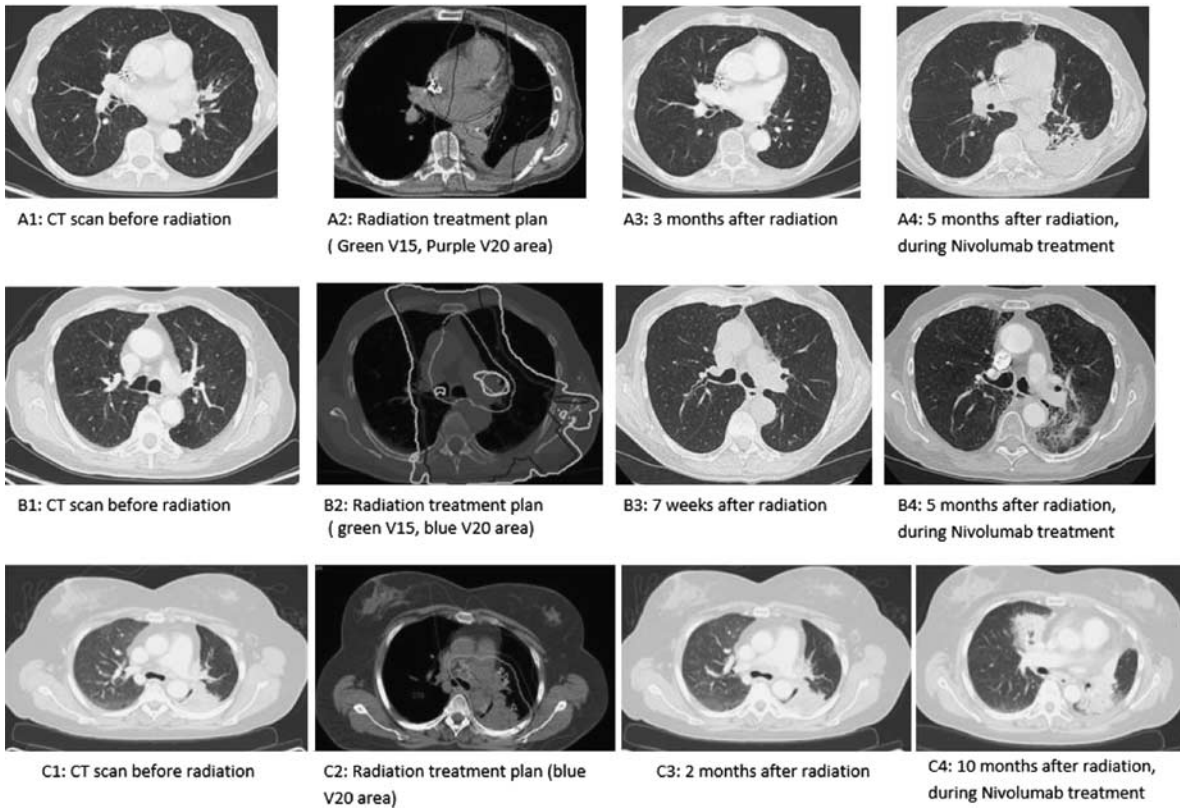

FIGURE 1. A–C, Diagnostic, radiotherapy and follow-up computed tomography (CT) imaging.

DISCUSSION

On the basis of several randomized trials, monotherapy with nivolumab is becoming an established standard in NSCLC patients who progress on/after first-line treatment.[1,2] Phase II and III trials investigating the feasibility of nivolumab concomitantly or as consolidation after chemoradiotherapy in stage III NSCLC are underway (NICOLAS-ETOP,[6] RTOG 3505).

Importantly, the potential overlapping of pulmonary toxicity of nivolumab and TRT is still unclear. The latest review on this issue cited only 2 case reports. Moreover, a recently published piece by Shibaki et al[7] described a similar phenomenon of radiation recall pneumonitis in 2 patients previously treated with TRT 2 years before immunotherapy. Because of paucity of data in this scenario, final conclusions cannot be drawn.[8] The majority of studies on combined immunoradiotherapy referred to patients with melanoma treated with intracranial stereotactic radiosurgery.[9,10] Lu and Liu[11] recently reported on 3 cases of pneumonitis in patients with melanoma, thymoma,

TABLE 1. PFTs Before and After Onset of Pneumonitis

PFT	Pretreatment PFT	1 mo After TRT	5 mo After TRT	
Case 1	VC max: 3.14 (120.2%) FEV1: 1.64 (78.1%) DLCO SB: 2.38 (33.3%) DLCO/VA: 0.56 (37%)	VC max: 3.28 (125.5%) FEV1: 1.77 (84.3%) DLCO SB: 2.91 (40.6%) DLCO/VA: 0.62 (41.3%)	VC max: 2.56 (98.8%) FEV1: 1.46 (70.7%) DLCO SB: 1.93 (27.1%) DLCO/VA: 0.53 (35.6%)	
	Pretreatment PFT	**2 mo after TRT**	**7 mo after TRT**	**8 mo after TRT**
Case 2	VC max: 4.73 (111.8%) FEV1: 2.80 (91%) DLCO SB: 5.06 (56.1%) DLCO/VA: 0.87 (70.8%)	VC max: 4.13 (97.7%) FEV1: 2.49 (81.1%) DLCO SB: 3.13 (34.7%) DLCO/VA: 0.56 (45%)	VC max: 3.31 (78.7%) FEV1: 2.57 (84.5%) DLCO SB: 1.85 (20.7%) DLCO/VA: 0.41 (33.2%)	VC max: 4.03 (95.9%) FEV1: 2.72 (89.2%) DLCO SB: 2.69 (30%) DLCO/VA: 0.48 (39.3%)
	Pretreatment PFT	**2 mo after TRT**	**11 mo after TRT**	**14 mo after TRT**
Case 3	VC max: 2.99 (92.57%) FEV1: 2.21 (83.1%) DLCO SB: 3.58 (43.08%) DLCO/VA: NA	VC max: 3.05 (94.43%) FEV1:2.27 (85.34%) DLCO SB: 3.64 (43.8%) DLCO/VA: NA	VC max: 2.24 (70%) FEV1: 1.72 (65.15%) DLCO SB: 2.88 (34.87%) DLCO/VA: NA	VC max: 2.31 (72.2%) FEV1: 1.70 (64.4%) DLCO SB: 2.67 (32.32%) DLCO/VA: NA

DLCO indicates diffusion capacity of the lungs for carbon monoxide; NA, not available; PFT, pulmonary function test; SB, single breath; TRT, thoracic radiotherapy; VA, alveolar volume; VC, vital capacity.

TABLE 2. Summary of Current Evidence of Overlapping Pulmonary Toxicity

References	Patient No.	Study Design	Tumor Type	Stage	TRT	Immunotherapy	Concurrent vs. Sequential	Pneumonitis Rate
Lu and Liu[11]	3	Case report	Pulmonary metastasis	IV	Yes	Pembrolizumab and Nivolumab	Sequential	All patients after 4 cycles
Miyoshi et al[15]	1	Case report	NSCLC	IIIB	Yes	Nivolumab	Sequential	Patient developed Pneumonitis after 3 cycles
Khunger et al[13]	5038	Meta-analysis	NSCLC	—	Yes	PD-1 and PD-L1 inhibitors	Sequential	The incidence of any grade pneumonitis was significantly higher with PD-1 inhibitors than with PD-L1 inhibitors (3.6%, 95% CI, 2.4%–4.9% vs. 1.3%, 95% CI 0.8%–1.9%) Grade 5 pneumonitis in 7, 3 of these patients treated with radiation
CA 209-003[4,5]	129	Phase I	NSLCC	—	Yes	Nivolumab	Sequential	7% for all-grade pneumonitis 1.3% for grade 3–4 pneumonitis
Shibaki et al[7]	2	Case report	NSCLC	—	Yes	Nivolumab	Sequential	Both patients
Durm et al (2017)[12]	83/93 evaluable	Phase II	NSCLC	III	Yes	Pembrolizumab	Sequential	20.5% any grade pneumonitis 3.6% grade 3–5 pneumonitis

CI indicates confidence interval; NSCLC, non–small cell lung cancer; TRT, thoracic radiotherapy.

and jejunal adenocarcinoma treated with PD-1 inhibitors and radiotherapy.

Previous results, including a meta-analysis detected a very low incidence of immune-related pneumonitis in patients treated with PD-1 inhibitors.[1–3] In contrast, a phase I dose-escalation cohort expansion trial (CA209-003) of nivolumab including 129 NSCLC patients pretreated with TRT revealed a 7% incidence of all grade pneumonitis.[4,5] In addition, a recent phase II study presented at ASCO 2016 showed an incidence of 20.5% for all grade and 3.6% for grade 3–5 pneumonitis in patients treated with consolidation pembrolizumab initiated 1–2 months following concurrent chemoradiotherapy.[12]

Furthermore, in a recent meta-analysis, grade 5 pneumonitis was described in seven patients treated with PD-1 inhibitors. Three of these patients were treated with thoracic radiotherapy before PD-1 inhibitors.[13] On the basis of this data, a higher risk for immune-related pulmonary toxicity in this patient cohort can be supposed.

Herein, we presented a case study with grade 3 pneumonitis in the irradiated lungs of pretreated NSCLC patients undergoing immunotherapy. In all cases, extensive imaging and bronchoscopy were performed on onset of respiratory symptoms. Nivolumab was interrupted and all patients were started on corticosteroids for the following 5 to 6 weeks with relatively rash alleviation of symptoms. Median time from the end of TRT to manifestation of pneumonitis was 167 days indicating an importance of careful follow-up for early signs and symptoms of pneumonitis throughout successive treatment with immune-checkpoint inhibitors. Extensive imaging analysis was strongly consistent with broadly based parenchyma changes in the irradiated lung volume receiving 15–20 Gy. A relatively low MLD and the timing of the onset of pneumonitis in all 3 cases, makes a case against sole radiation-induced lung injury (RILI).[14] However, a synergistic effect of TRT on immune-related pneumonitis or counterpart nivolumab effect on the induction of RILI could not be excluded.

Clinical and fundamental research of pneumonitis and RILI is urgently required. Despite the ever-increasing continuous application of immunotherapy prior and following TRT in patients with advanced lung cancer, there has not been much progress in the investigation of immunological aspects of immunotherapy-induced and radiation-induced lung injury. Our case study underscores the importance of this problem. Table 2 displays a summary of the current evidence on the incidence of pneumonitis in various reports and studies.

In conclusion, in our current study all 3 patients achieved a durable response; however, this was at the cost of severe pulmonary toxicity, which was manageable in all cases. A detailed analysis of the described overlapping toxicity in pretreated NSCLC patients will be performed within the scope of a planned single-center prospective trial.

CONFLICTS OF INTEREST/ FINANCIAL DISCLOSURES

None reported. All authors have declared that there are no financial conflicts of interest with regard to this work.

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