

Pneumonitis with Nonspecific Interstitial Pneumonia Pattern Caused by Nivolumab in a Patient with Metastatic Melanoma

Kenji Sawa¹, Tomoya Kawaguchi^{1,2*}, Shigeki Mitsuoka², Nao Kusutani³ and Kazuto Hirata¹

¹Department of Respiratory Medicine, Graduate School of Medicine, Osaka City University, Osaka, Japan

²Department of Clinical Oncology, Graduate School of Medicine, Osaka City University, Osaka, Japan

³Department of Dermatology, Graduate School of Medicine, Osaka City University, Osaka, Japan

*Corresponding author: Tomoya Kawaguchi, Department of Respiratory Medicine, Graduate School of Medicine, Osaka City University, 1-4-3 Asahimachi, Abeno-ku, Osaka 545-8585, Japan, Tel: +81-6-6645-3916; Fax: +81-6-6646-6160; E-mail: kawaguchi.tomoya@med.osaka-cu.ac.jp

Received date: March 10, 2016; Accepted date: March 21, 2016, 2016; Published date: March 27, 2016

Copyright: © 2016 Sawa K, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract

A 67-year-old man with metastatic melanoma was treated with nivolumab, which is an antibody against programmed cell death 1 (PD-1). After the 15th course of therapy, he developed drug-induced pneumonitis with a radiologic pattern that was consistent with nonspecific interstitial pneumonia (NSIP). The treatment with glucocorticoid was initiated and his symptoms and radiologic abnormalities rapidly resolved. Early initiation of glucocorticoid can be effective in the treatment of pneumonitis caused by nivolumab. Since increased use of immune checkpoint inhibitors is expected, radiologic and clinical information on pneumonitis caused by anti-PD-1 drugs is required. Here we report our case to provide the detailed radiologic finding of pneumonitis caused by nivolumab and the clinical outcome.

Keywords: Nivolumab; Metastatic melanoma; Pneumonitis; Interstitial pneumonia

Introduction

Antibodies against programmed cell death 1 (PD-1) that block inhibitory T-cell checkpoints comprise a new therapy for advanced cancers, including melanoma and non-small cell lung cancer (NSCLC) [1]. Nivolumab is a fully human IgG4 PD-1 immune checkpoint inhibitor antibody that disrupts PD-1-mediated signaling and restores antitumor immunity. Although recent studies have shown the effectiveness of PD-1 antibodies in melanoma and NSCLC [2,3], various immune-related adverse events (irAEs) have been reported. In the anti-PD-1 trials of Check Mate 017, 057, and 066, several irAEs have been reported. The overall frequency of all adverse events were 1.5-5%, and 1-2% patients developed pneumonitis (all grades) with 1% developing pneumonitis greater than or equal to grade 3 [4-6]. Post-marketing surveillance of nivolumab in Japan identified 42 cases (2.5%) of pneumonitis; 18 of these were greater than or equal to grade 3 [7]. All of 18 cases received glucocorticoid therapy, however one patient died. The detailed radiological findings have not been reported. Here, we report a case of pneumonitis with nonspecific interstitial pneumonia (NSIP) pattern associated with nivolumab in a patient with melanoma who was successfully treated with glucocorticoid. This report can improve our recognition of pneumonitis caused by nivolumab and provide information on appropriate treatment.

Case

A 67-year-old Japanese man with one pack-year smoking history was found to have a 15 mm nodule on his right plantar region. He was diagnosed with malignant melanoma by biopsy, and wide excision of the primary tumor and therapeutic lymph node dissection was completed; his final pathological stage was IIIC (T4bN3M0) [8]. In

addition, molecular testing for BRAF exon 15, was negative for the V600E mutation. Two months after surgery, he received combination adjuvant chemotherapy with intravenous dacarbazine, nimustine, and vincristine, and local injection of IFN-beta [9]. After the 5th cycle of treatment, a new nodule was found in his abdomen with diagnosis of metastatic malignant melanoma. He was then treated with nivolumab (2 mg/kg every 3 weeks).

After the 15th course of treatment, 11 months after the initial therapy, he visited a hospital because of high fever and cough. On examination, the temperature was 39.6 °C, oxygen saturation was 89% while the patient was breathing ambient air and the breath sounds were normal. Blood examination revealed white blood cells (WBC) 5500/ μ l with no elevation of eosinophils, C-reactive protein (CRP) 3.64 mg/dl, lactate dehydrogenase (LDH) 500 U/L, and sialylated carbohydrate antigen (KL-6) 537 U/ml. Previous WBC, CRP and LDH of this patient were within normal limit and baseline KL-6 was 112-181 U/ml. A chest computed tomography (CT) scan showed interstitial pneumonitis with ground-glass opacities and reticular opacities in the peripheral, bilateral lower lungs (Figure 1).



Figure 1: The day of admission: ground-glass opacities and reticular opacities in the peripheral, bilateral lower lungs.

He was admitted and received intravenous antibiotics. His sputum and blood culture showed no bacteria and serum β D-glucan level was not elevated. To exclude pulmonary edema, echocardiography was performed by a cardiologist and there was no sign of heart failure. Instead of the treatment, he developed shortness of breath (Modified British Medical Research Council grade 2) on the next day of admission and high fever of more than 39 °C persisted, and these symptoms were getting worse over a couple of days.

In addition, oxygen saturation was decreased with oxygen supply at 4 L/min on the 2nd day. Based on CT scan and clinical course, we diagnosed drug-induced pneumonitis. Bronchoscopy was not performed. We started glucocorticoid therapy with 1 mg/kg prednisolone on the 3rd day of admission.

After starting this treatment, his fever, respiratory symptoms and hypoxemia immediately remitted and the interstitial shadows on the chest X-ray disappeared. A follow-up CT on days 28 showed resolving radiologic findings (Figure 2). Finally, we diagnosed this as drug-induced pneumonitis with NSIP pattern caused by nivolumab. The prednisolone was gradually tapered over 2-month period and the patient was in good condition on days 76.

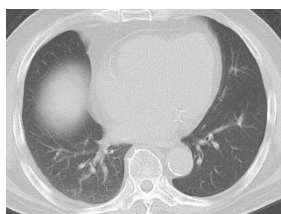


Figure 2: Days 28-the radiologic findings resolved after glucocorticoid therapy.

Discussion

No specific tests have been established for the diagnosis of drug-induced pneumonitis other than re-challenge with the suspected drug.

No./Ref	Age/Sex	Drug/Cycle	CT at clinical diagnosis of pneumonitis	Classification	Treatment	Outcome
1/[11]	38/ Female	Nivolumab (3 mg/kg)/6 cycles	Diffuse GGO and diffuse reticular opacities Consolidations Traction bronchiectasis Centrilobular nodularity Decreased lung volume	AIP/ARDS	IV antibiotics, steroids, infliximab Requiring ICU admission	Died
2/[11]	58/Male	Nivolumab (1 mg/kg)/4 cycles	Peripheral and lower lung GGO, reticular opacities and consolidations	NSIP	Oral steroid No admission needed	Alive
3/[12]	70/ Female	Nivolumab (2 mg/kg)/4 cycles	Multiple GGO surrounded by consolidations of air bronchograms in lower lung field	OP	Oral steroid (0.5 mg/kg)	Alive
4/[13]	70/ Female	Nivolumab (2 mg/kg)/3 cycles	GGO with airspace consolidations scattered with a peculiar distribution	OP	IV antibiotics Admission needed Steroid was not administrated	Alive
Current case	67/Male	Nivolumab (2 mg/kg)/15 cycles	Peripheral lower and bilateral lung GGO, reticular opacities and consolidations	NSIP	IV antibiotics, IV→oral steroid (1 mg/ kg) Admission needed	Alive

GGO: Ground-glass Opacity; AIP: Acute Interstitial Pneumonia; ARDS: Acute Respiratory Distress Syndrome; NSIP: Nonspecific Interstitial Pneumonia; OP: Organizing Pneumonia.

Table 1: Patient characteristics in malignant melanoma and the radiological findings of pneumonitis caused by nivolumab.

However, in practice, the diagnosis is usually based on the combination of clinical and radiologic findings, and the exclusion of other causes of pneumonitis such as infections, pulmonary edema, or pulmonary malignancy [10]. We did not perform bronchoscopy, and we could not exclude other diseases completely. However, his clinical symptoms and radiologic pattern were compatible with drug-induced pneumonitis, and glucocorticoid therapy led to a rapid and good response; therefore, the diagnosis of drug-induced pneumonitis caused by nivolumab is reasonable.

Drug-induced pneumonitis has been recognized as a life-threatening adverse event among patients treated with antineoplastic agents including anti PD-1 drugs. There have been few detailed reports on pneumonitis caused by anti PD-1 drugs, and we have little published data about its radiological features and patterns.

As shown in the Table 1, to the best of our knowledge, there have been five reports with detailed radiological findings of patients with melanoma that developed nivolumab-induced pneumonitis [11-13]. One was acute interstitial pneumonia/acute respiratory distress syndrome (ARDS/AIP) pattern and two cases, including the current case, were NSIP pattern; the other two cases were organizing pneumonia (OP). In three cases, glucocorticoid therapy was effective.

In this case, the chest CT scan showed ground-glass opacities and reticular opacities in the peripheral, bilateral lower lungs, and these radiologic findings were consistent with an NSIP pattern, which is relevant to case 2 in the Table 1. This patient also responded well to glucocorticoid therapy.

Systemic corticosteroids to treat irAE do not appear to have an impact on the tumor response, and the management of adverse events should be the first priority if the patient's symptoms are aggressive and severe [13].

Our experience indicates that early initiation of glucocorticoids can be effective to treat drug-induced pneumonitis caused by anti PD-1 antibodies.

Increased use of immune checkpoint inhibitors is expected in several types of cancer. As shown in Table 1, one patient had died of drug-induced pneumonitis. Recent meta-analysis showed that the use of immune checkpoint inhibitors was associated with an increased risk of all-grade pneumonitis compared with chemotherapy or placebo controls [14]. We have to use these drugs carefully and prompt diagnosis and management of drug-induced pneumonitis are required. And we have to collect more information on cases of pneumonitis and study intensively its pattern of disease and effective treatments.

References

1. Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, et al. (2012) Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *The New England Journal of Medicine* 366: 2443-2454.
2. Topalian SL, Sznol M, McDermott DF (2014) Survival, durable tumor remission, and long-term safety in patients with advanced melanoma receiving nivolumab. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology* 32: 1020-1030.
3. Rizvi NA, Mazieres J, Planchard D, Stinchcombe ET, Dy GK, et al. (2015) Activity and safety of nivolumab, an anti-PD-1 immune checkpoint inhibitor, for patients with advanced, refractory squamous non-small-cell lung cancer (CheckMate 063): a phase 2, single-arm trial. *The Lancet Oncology* 16: 257-265.
4. Brahmer J, Reckamp KL, Baas P, Crino L, Eberhardt EEW, et al. (2015) Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. *The New England Journal of Medicine* 373: 123-135.
5. Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, et al. (2015) Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. *The New England Journal of Medicine* 373: 1627-1639.
6. Robert C, Long GV, Brady B, Dutriaux C, Maio M, et al. (2015) Nivolumab in previously untreated melanoma without BRAF mutation. *The New England Journal of Medicine* 372: 320-330.
7. Nakamae A, Deie M, Adachi N, Nakasa T, Nishimori M, et al. (2012) Effects of knee immobilization on morphological changes in the semitendinosus muscle-tendon complex after hamstring harvesting for anterior cruciate ligament reconstruction: evaluation using three-dimensional computed tomography. *Journal of Orthopaedic Science: Official Journal of the Japanese Orthopaedic Association* 17: 39-45.
8. Balch CM, Gershenwald JE, Soong SJ, Thompson JF, Atkins MB, et al. (2009) Final version of 2009 AJCC melanoma staging and classification. *J Clin Oncol* 27: 6199-6206.
9. Umeda T, Aoki K, Yokoyama A, Ohara H, Hayashi O, et al. (1998) Changes in immunological parameters after combination adjuvant therapy with intravenous DTIC, ACNU, and VCR, and local injection of IFN-beta (DAV + IFN-beta therapy) into malignant melanoma. *The Journal of Dermatology* 25: 569-572.
10. Camus P, Fanton A, Bonniaud P, Camus C, Foucher P (2004) Interstitial lung disease induced by drugs and radiation. *Respiration; International Review of Thoracic Diseases* 71: 301-326.
11. Nishino M, Sholl LM, Hodi FS, Hatabu H, Ramaiya NH (2015) Anti-PD-1-Related Pneumonitis during Cancer Immunotherapy. *The New England Journal of Medicine* 373: 288-290.
12. Nakashima K, Naito T, Omori S, Takahashi T (2015) Organizing Pneumonia Induced by Nivolumab in a Patient with Metastatic Melanoma. *Journal of Thoracic Oncology: Official Publication of the International Association for the Study of Lung Cancer*.
13. Sano T, Uhara H, Mikoshiba Y, Koyabashi A, Uchiyama R, et al. (2016) Nivolumab-induced organizing pneumonia in a melanoma patient. *Japanese Journal of Clinical Oncology*.
14. Abdel-Rahman O, Fouad M (2016) Risk of pneumonitis in cancer patients treated with immune checkpoint inhibitors: a meta-analysis. *Therapeutic Advances in Respiratory Disease*.