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Case Report

Paradoxical response in a patient with non-small cell lung cancer who received nivolumab followed by anti-*Mycobacterium tuberculosis* agents

So Takata [a, *], Genju Koh [b], Yuki Han [c], Hiroko Yoshida [d], Takayuki Shiroyama [a], Hiromune Takada [a], Kentarou Masuhiro [a], Shingo Nasu [a], Satomu Morita [a], Ayako Tanaka [a], Syouji Hashimoto [d], Kiyoaki Uriu [e], Hidekazu Suzuki [a], Yoshitaka Tamura [c], Norio Okamoto [a], Takayuki Nagai [c], Tomonori Hirashima [a]

[a] *Department of Thoracic Oncology, Osaka Prefectural Hospital Organization Osaka Habikino Medical Center, 3-7-1, Habikino, Habikino City, Osaka, 583-8588, Japan*
[b] *Department of Medical Oncology, Yao Tokushukai General Hospital, 1-17, Wakakusa Town, Yao City, Osaka, 581-0011, Japan*
[c] *Department of Infectious Disease, Osaka Prefectural Hospital Organization Osaka Habikino Medical Center, 3-7-1, Habikino, Habikino City, Osaka, 583-8588, Japan*
[d] *Department of Clinical Laboratory, Osaka Prefectural Hospital Organization Osaka Habikino Medical Center, 3-7-1, Habikino, Habikino City, Osaka, 583-8588, Japan*
[e] *Department of Respiratory Medicine, Yao Tokushukai General Hospital, 1-17, Wakakusa Town, Yao City, Osaka, 581-0011, Japan*

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ABSTRACT

Anti-programmed cell death-1 (PD-1) agents enhance the antitumor immunoresponse. A number of reports have indicated that patients with malignancies who receive anti-PD-1 agents are at risk for tuberculosis (TB) infection. In this report, we present a patient with non-small cell lung cancer who developed pulmonary tuberculosis while receiving the anti-PD-1 agent nivolumab, and who subsequently demonstrated a paradoxical response (PR) 10 days after initiation of anti-MTB treatment. We suggest that anti-PD-1 agents not only induce the development of pulmonary TB, but also development of PR after anti-MTB treatment, through upregulation of the immune response. Furthermore, based on their radiological and immunological similarity, we speculate that the schema of development of PR closely resembles that of pseudoprogression in non-small cell lung cancer patients after anti-PD-1 treatment.

1. Introduction

Immunotherapy has led to drastic changes in the treatment of lung cancer [1–3]. Nivolumab is an anti-programmed cell death-1 (PD-1) antibody that works as an immune checkpoint inhibitor; it has demonstrated promising antitumor activity with a durable response, despite occasionally causing severe immune-related adverse events. Although immune-related adverse events such as interstitial pneumonitis, colitis, thyroid dysfunction, neuromuscular disease, type 1 diabetes mellitus, and adrenal insufficiency have been well-characterized [1,2], the influence of immune checkpoint inhibitors on infection remains unclear. To date, only limited data are available on the acute development of pulmonary tuberculosis (TB) during anti-PD-1 antibody immunotherapy [4–7]. Herein, we report a case of a patient who developed pulmonary TB during nivolumab treatment, and who subsequently showed a paradoxical response (PR) after initiation of anti-tuberculosis treatment. The patient provided informed consent for the publication of this report.

* Corresponding author. Department of Thoracic Oncology, Osaka Prefectural Hospital Organization Osaka Habikino Medical Center, 3-7-1, Habikino, Habikino city, Osaka, 583-8588, Japan.
E-mail address: sotakata@imed3.med.osaka-u.ac.jp (S. Takata).

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2. Case report

We present the case of a 75-year-old Japanese man who was diagnosed with lung adenocarcinoma in 2015 in our hospital. Adenocarcinoma was diagnosed based on pathological examination of a bronchoscopic biopsy specimen. The primary lesion was located in the right upper lobe. The clinical stage was determined to be stage IV (T3N2M1b). The patient's carcinoembryonic antigen level was 2631 ng/ml when lung adenocarcinoma was diagnosed. Three continuous regimens of chemotherapy were administered: carboplatin and pemetrexed, carboplatin and nanoparticle albumin bounded paclitaxel, and S-1 combined with gemcitabine. In addition to chemotherapy, we prescribed 60 Gy in 30 fractions of palliative radiation therapy targeted to the primary lesion between the second- and third-line regimens. Following three cycles of the third-line regimen, we detected progression of the primary lesion and left adrenal metastatic lesion. Nivolumab was selected as fourth-line therapy. Following 6 courses of nivolumab, the patient's carcinoembryonic antigen level decreased from 4500 ng/ml to 35 ng/ml, and the size of the left adrenal lesion markedly decreased (Fig. 1). It was not possible to accurately evaluate the size of the primary lesion as it consisted of tumor, cavity, and atelectasis. We classified the outcome as a partial response, and there was no lung cancer relapse. The patient received nivolumab for three weeks as an outpatient. When he had received 15 cycles of nivolumab, he had an Eastern Cooperative Oncology Group (ECOG) performance status of 2. His white blood cell count was 9500/μL, with a lymphocyte count of 1187/μL, albumin level of 2.6 g/dL and hemoglobin level of 10.8 g/dL. He presented no respiratory symptoms.

However, three days after completing 15 cycles of nivolumab, the patient developed fever, cough, and purulent sputum. A new pulmonary opacity appeared in the right middle lobe and lower lobe (Fig. 2E,F). Ziehl-Neelsen staining of a sputum smear sample gave a positive result for mycobacteria, and the presence of *Mycobacterium tuberculosis* (MTB) was confirmed by polymerase chain reaction. We diagnosed the patient with pulmonary TB. MTB grew on sputum culture four weeks after the initial investigation, providing further confirmation of the diagnosis. Eight days after the last nivolumab dose (see Fig. 3), we ceased treatment. We then administered a course of anti-MTB medication using a four-drug combination of isoniazid, rifampicin, ethambutol, and pyrazinamide. The patient had hypoalbuminemia (albumin, 2.9 g/dL), anemia (hemoglobin, 10.4 g/dL) and lymphopenia (lymphocyte count, 510/μL) when we administered the anti-MTB medication.

Ten days after induction of anti-MTB treatment, the patient developed fever, with an axillary temperature above 38 °C. And the basal pulse rate was 98 beats per minute, while a pulse of 114 beats per minute reflected tachycardia. New opacities in the right middle and lower lung were also detected (Fig. 2H, I). There was no increase in lymphocyte count (lymphocyte count, 470/μL). We diagnosed the opacities as bacterial pneumonia and prescribed sulbactam/ampicillin. As the patient's fever did not improve, we ceased administration of rifampicin, pyrazinamide, and sulbactam/ampicillin, due to the possibility of drug-induced fever, and added moxifloxacin as an anti-MTB treatment. However, the fever was sustained, and the lung opacity increased in size. We measured KL-6 on X/10/17, the level of KL-6 was 411 U/mL. Then, on the basis of the clinical course mentioned above, we concluded that the fever and the opacities represented a PR. After starting prednisolone at a dose of 30 mg/day, the fever immediately improved. In the interval of MTB treatment interruption, drug susceptibility testing for MTB was performed, and the patient was revealed to be sensitive to all except levofloxacin. We restarted the four-drug combination treatment for two months, followed by treatment with a two-drug combination of isoniazid and rifampicin for seven months as planned long-term MTB treatment. Three months after initiation of anti-MTB treatment, the sputum culture of TB became negative for *Mycobacterium*. The pulmonary opacity in the right middle lobe and lower lobe disappeared (Fig. 2K and L). Because the patient had an ECOG performance status of 1 with good organ function, his cancer

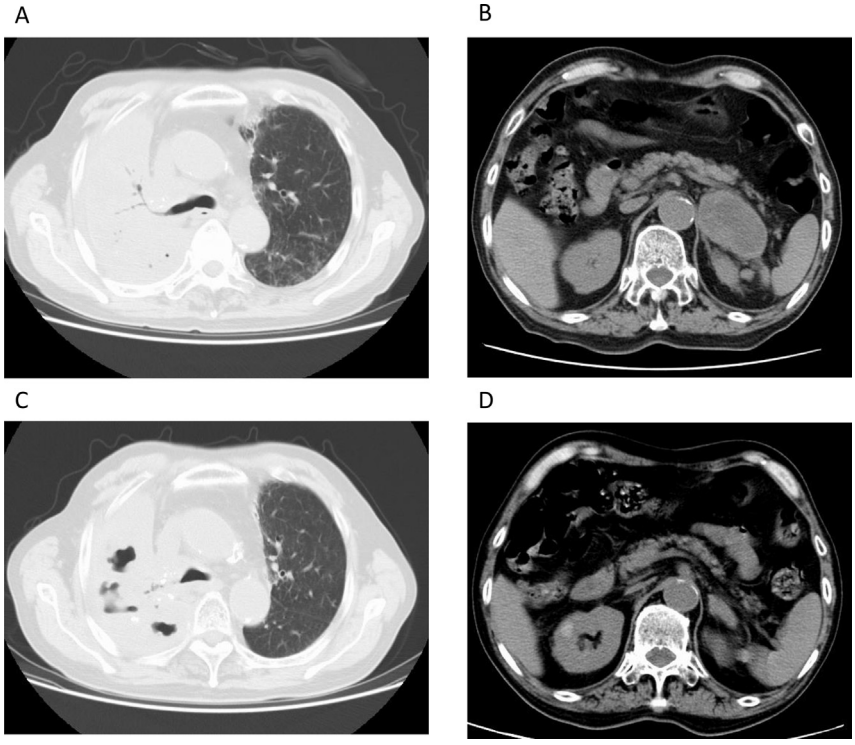

Fig. 1. Computed tomography images in primary and left adrenal metastasis lesion before induction of nivolumab (A and B) on X/2/17 and at the time of diagnosis of MTB infection (C and D) on X/9/1.

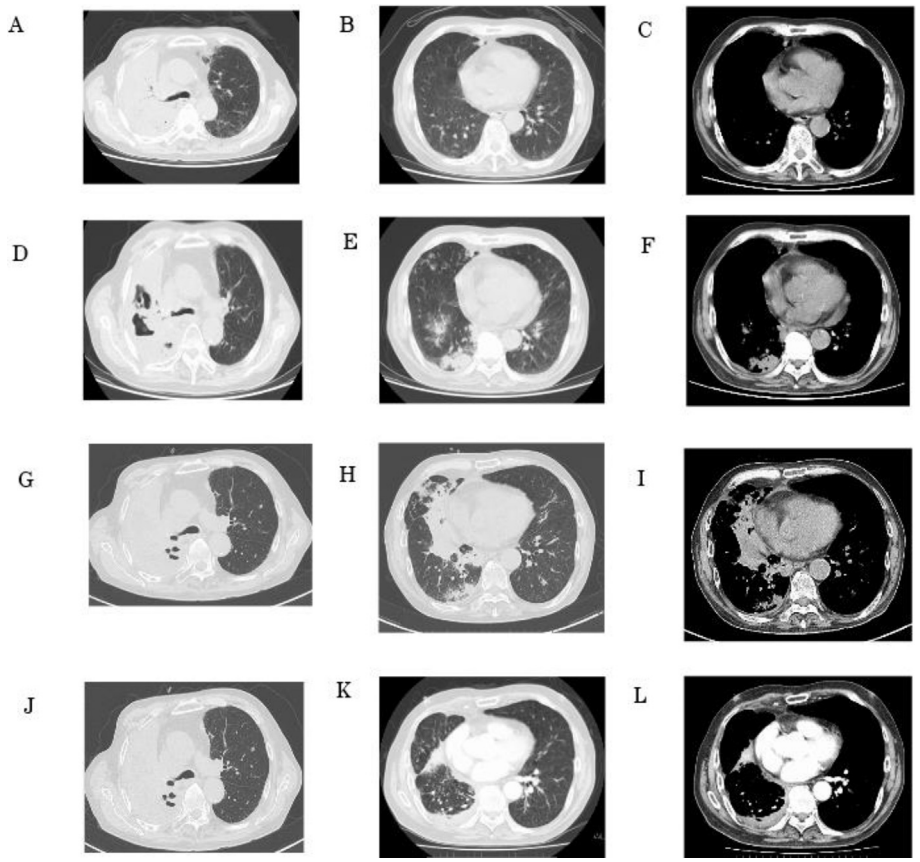

Fig. 2. Computed tomography images of the lung opacities, showing worse opacities at the time lung cancer was diagnosed (A, B, C) on X-2/5/13, after *Mycobacterium tuberculosis* infection (D, E, F) on X/9/1, and at the time of paradoxical response (PR) (G, H, I) on X/10/4. The opacities improved one year after PR onset (J, K, L) on X+1/11/20.

had previously demonstrated a positive response to nivolumab, and his strong desire to try taking nivolumab again, we restarted nivolumab treatment after obtaining approval from the Cancer Board; treatment commenced four months after induction of anti-MTB treatment. One year after induction, anti-MTB treatment was stopped. As of January 31, 2018, we have performed 46 cycles of nivolumab treatment. The lung cancer has displayed partial response without relapse of MTB infection.

3. Discussion

To the best of our knowledge, this is the first case report in which a patient developed pulmonary TB while receiving an anti-PD-1 agent and experienced PR after treatment with anti-MTB agents.

Previous reports have shown that there is a risk of developing pulmonary TB in cancer patients who receive anti-PD-1 treatment and concurrent administration of anti-PD-1 and anti-MTB agents is an appropriate treatment option in some cases [3–7].

This case report also shows that it is important to monitor for PR in patients receiving immune checkpoint inhibitors followed by anti-MTB agents.

In this case, PR developed 10 days after initiation of MTB treatment. A previous study defined PR as worsening of clinical or radiological findings following initiation of appropriate anti-MTB therapy without evidence of disease relapse or the presence of another diagnosis [8]. And previous report suggested that the duration between the time of anti-Tb treatment initiation and the time of PR onset ranged from 1 week to 27 months [9]. This case met the criteria defined above. Cheng et al. reported that risk factors for PR include anemia, hypoalbuminemia, lymphopenia, and lymphocyte count increase, all of which except the latter were present in this case. We think that it was not only nivolumab that caused hypoalbuminemia, anemia, and lymphopenia, but also the chronic inflammation from lung cancer and the MTB infection. Their study also indicated that the incidence of PR is only 2.4% lower than that of extra pulmonary TB [10]. However, in light of previous studies [3–6] and the present case, it is possible that the incidence of PR in patients receiving anti-PD-1 agent followed by anti-MTB agents is higher than that in the study by Cheng et al. [10].

Previous reports have also suggested that anti-MTB treatment induces PR by cell-mediated immune reconstitution [11]. Hassan et al. [12] reported that anti-MTB treatment induced a reduction in the gene expression of PD-1, PD-L1 and PD-L2 in T-cells and natural killer cells. This may suggest that a PR after anti-MTB treatment develops through suppression of the PD1-PD-L1 pathway. Furthermore, we suggest the possibility that anti-PD-1 agents not only induce the development of pulmonary TB but also PR after anti-MTB treatment through upregulation of the immune response. In this case, lymphocyte counts did not increase during the tuberculosis-related PR, unlike in typical PR. Our hypothesis is as follows. When a patient develops typical PR, lymphocyte counts increase owing to the recovery of immunological or nutritional status, thereby upregulating the immunological reaction to MTB. On the other hand, as in this case, the upregulation of immunological reaction may have been caused mainly by nivolumab, without an associated increase in lymphocyte count. We hypothesized that the right upper lobe cavitation consisted of space where necrotic tissue was produced, because of the efficacy of nivolumab. and was then evacuated. We cannot deny the possibility that the

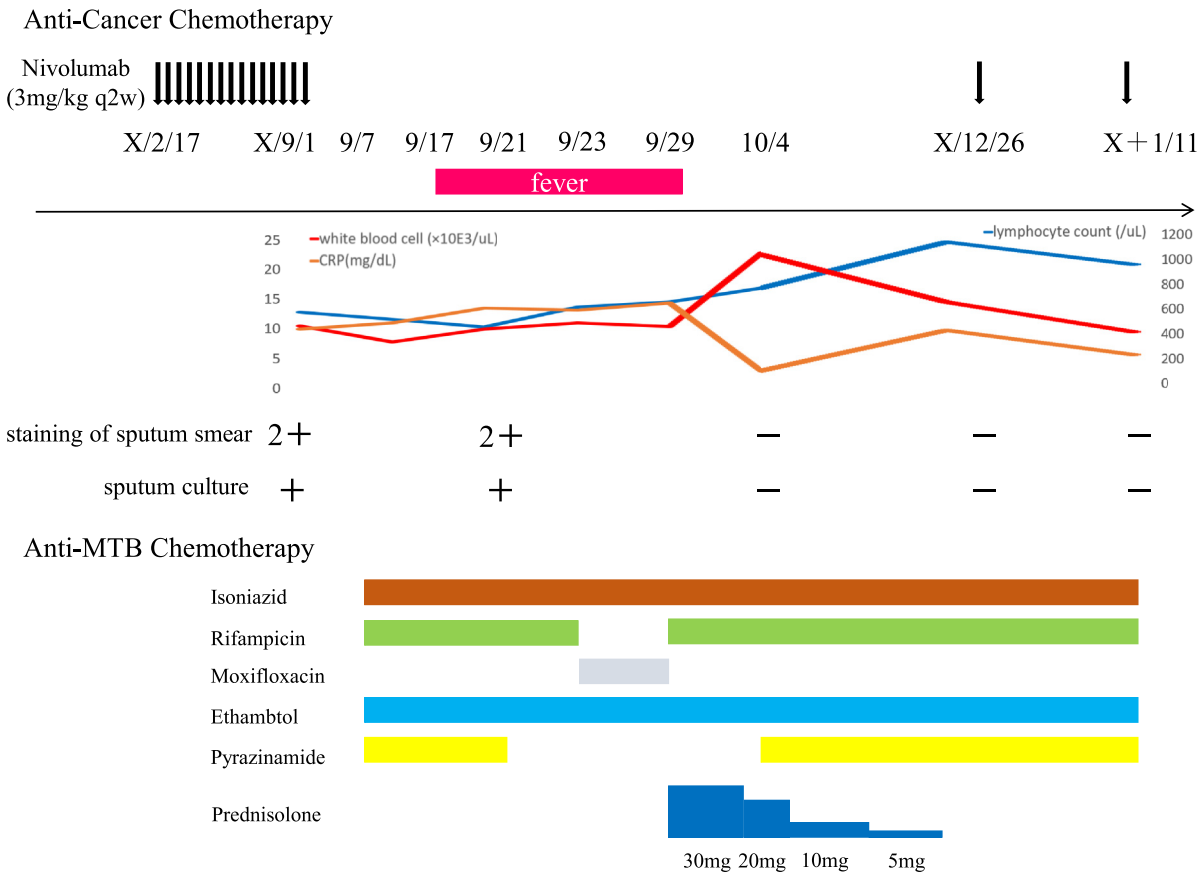

Fig. 3. Clinical course from the time of nivolumab induction to completion of MTB treatment and prednisolone dose in this patient. MTB: *Mycobacterium tuberculosis*; PR: paradoxical response.

right upper lobe cavitation was due to cancer-related PD or pulmonary tuberculosis. However, The CEA level did not increase after re-starting nivolumab, and the size of left adrenal lesion did not increase either. Further, the patient's condition has been better than it was before the use of nivolumab. And the new opacities in right middle lobe and lower lobe appeared just when pulmonary TB presented, and the right upper lobe cavitation did not change from its appearance three month before. Therefore, we hypothesize that the opacity of pulmonary TB was in the right middle and lower lobes.

We did not find a new shadow suggesting a tuberculosis-related PR-like response after re-starting nivolumab. However, the original shadow, which we presume was from a PR, remained longer than in previous reports of PR. We hypothesize that re-starting nivolumab caused the prolongation of the rest of the shadow.

Recently, Kato et al. [13] reported that a non-small cell lung carcinoma (NSCLC) patient who was administered nivolumab showed a kind of pseudoprogression in the form of ground-glass opacity surrounding the primary lesion in the lung. They prescribed prednisolone, after which the ground-glass opacity diminished, and the primary lesion shrank [13]. We cannot completely rule out the possibility that the new opacity of our patient resulted from pseudoprogression. However, the new shadow in the right-middle and lower lobes appeared just when the patient developed fever, cough, and purulent sputum, and was diagnosed with pulmonary TB. Moreover, the worsening opacities, which appeared to be MTB lesions after four-drug (isoniazid, rifampicin, ethambutol, and pyrazinamide) treatment, appeared in each lobe of the right lung but not in the region surrounding the primary lesion. Subsequently, we hypothesized that the new opacity resulted from PR. The computed tomography image at the time of PR onset in our case closely resembled that of pseudoprogression in the NSCLC patient in the report by Kato et al. [13]. We speculate that the schema of PR development may be similar to that of pseudoprogression in NSCLC patients after immune checkpoint inhibitor treatment, considering their radiological and immunological similarity.

The relationship between immune checkpoint inhibitor treatment and MTB infection remains unclear [14]. It is a possibility that blockade of the PD-1 and PD-L1 pathway is a risk factor for MTB infection or PR. However, further study will be necessary for conclusive proof of whether immune checkpoint inhibitors can result in worsening of chronic infection.

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This study had no funding source.

Authorship

All authors meet the ICMJE authorship criteria.

Conflict of interest statement

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References

[1] Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. N Engl J Med 2015;373(17):1627–39.
[2] Brahmer J, Reckamp KL, Baas P, Crino L, Eberhardt WE, Poddubskaya E, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. N Engl J Med 2015;373(2):123–35.
[3] Reck M, Rodriguez-Abreu D, Robinson AG, Hui R, Csoszi T, Fulop A, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. N Engl J Med 2016;375(19):1823–33.
[4] Fujita K, Terashima T, Mio T. Anti-PD1 antibody treatment and the development of acute pulmonary tuberculosis. J Thorac Oncol 2016;11(12):2238–40.
[5] Lee JJ, Chan A, Tang T. Tuberculosis reactivation in a patient receiving anti-programmed death-1 (PD-1) inhibitor for relapsed Hodgkin's lymphoma. Acta Oncol 2016;55(4):519–20.
[6] Chu YC, Fang KC, Chen HC, Yeh YC, Tseng CE, Chou TY, et al. Pericardial tamponade caused by a hypersensitivity response to tuberculosis reactivation after anti-PD-1 treatment in a patient with advanced pulmonary adenocarcinoma. J Thorac Oncol 2017;12(8):e111–4.
[7] Picchi H, Mateus C, Chouaid C, Besse B, Marabelle A, Michot JM, et al. Infectious complications associated with the use of immune checkpoint inhibitors in oncology: reactivation of tuberculosis after anti PD-1 treatment. Clin Microbiol Infect 2018 Mar;24(3):216–8.
[8] Cheng VC, Ho PL, Lee RA, Chan KS, Chan KK, Woo PC, et al. Clinical spectrum of paradoxical deterioration during antituberculosis therapy in non-HIV-infected patients. Eur J Clin Microbiol Infect Dis 2002;21(11):803–9.
[9] Church LWP, Chopra A, Judson MA. Paradoxical reactions and the immune reconstitution inflammatory syndrome. Microbiol Spectr 2017;5(2).
[10] Cheng SL, Wang HC, Yang PC. Paradoxical response during anti-tuberculosis treatment in HIV-negative patients with pulmonary tuberculosis. Int J Tuberc Lung Dis 2007;11(12):1290–5.
[11] Bell LC, Breen R, Miller RF, Noursadeghi M, Lipman M. Paradoxical reactions and immune reconstitution inflammatory syndrome in tuberculosis. Int J Infect Dis 2015;32:39–45.
[12] Hassan SS, Akram M, King EC, Dockrell HM, Cliff JM. PD-1, PD-L1 and PD-L2 gene expression on t-cells and natural killer cells declines in conjunction with a reduction in PD-1 protein during the intensive phase of tuberculosis treatment. PLoS One 2015;10(9). e0137646.
[13] Kato R, Hayashi H, Tanizaki J, Tanaka K, Takeda M, Nakagawa K. Peritumoural ground-glass opacity associated with tumour pseudoprogression in a patient with non-small cell lung cancer treated with nivolumab. ESMO Open 2017;2(1). e000145.
[14] Wykes MN, Lewin SR. Immune checkpoint blockade in infectious diseases. Nat Rev Immunol 2018;18(2):91–104.