Case Report

Pulmonary Sarcoidosis Activation following Neoadjuvant Pembrolizumab plus Chemotherapy Combination Therapy in a Patient with Non-Small Cell Lung Cancer: A Case Report

Ghina Fakhri a  Reem Akel a  Ziad Salem a  Ayman Tawil b  Arafat Tfayli a

Abstract

**Background:** Pembrolizumab is a humanized monoclonal antibody which serves to enhance the antitumor immune response by targeting programmed cell death 1 receptor. The use of pembrolizumab plus carboplatin/pemetrexed combination therapy results in improvement in overall survival and progression-free survival rates for non-small cell lung cancer (NSCLC) patients as compared to chemotherapy alone. However, numerous immune-mediated toxicities of pembrolizumab have been reported. **Case Presentation:** We report the case of a 74-year-old male patient diagnosed with stage IIIA programmed death-ligand 1-positive non-small cell lung adenocarcinoma treated with 4 cycles of carboplatin/pemetrexed plus pembrolizumab combination therapy followed by 2 cycles of pembrolizumab treatment. Follow-up PET-CT scanning showed a very good response at the level of the tumor but new-onset activity in bilateral hilar and mediastinal lymph nodes. Biopsy of these lymph nodes revealed a benign pathology with noncaseating granulomas consistent with immune-mediated sarcoidosis. **Conclusion:** The pathogenesis of immunotherapy-induced sarcoidosis is not yet known but has been reported in different cancers and using different checkpoint inhibitors.
To our knowledge, this case is the first in the literature displaying pulmonary sarcoidosis in a patient with NSCLC 4 months after having initiated chemotherapy plus pembrolizumab combination therapy.

**Introduction**

Lung cancer remains the leading cause of cancer mortality worldwide, with non-small cell lung cancer (NSCLC) being the most commonly diagnosed type. For all lung cancer patients, the 5-year survival rate lies at a dismal 15% [1]. Recently, there has been a shift in the treatment for NSCLC towards the use of immunotherapy, as several studies have demonstrated the ability of lung cancer to evade the immune system through cytokine alterations, cellular immune dysfunction, and antigen presentation defects [1, 2].

Immune checkpoints are molecules that serve to augment or inhibit the immune response. Programmed cell death 1 is a key immune checkpoint molecule that serves to counteract T-cell activation and proliferation, which makes blockage of this system a potential method for enhancing the antitumor immune response [3]. Pembrolizumab is a humanized monoclonal antibody targeting programmed cell death 1 receptor. A recent trial (KEYNOTE-021G) showed improvement in the overall response rate and in progression-free survival in patients randomized to pembrolizumab plus chemotherapy versus chemotherapy alone [4].

Immune-related adverse events (irAEs) associated with the use of immune checkpoint inhibitors include fatigue, pyrexia, chills, infusion reactions, dermatitis, colitis, and pneumonitis, as well as endocrine, liver, renal, and ocular toxicities [5]. We report a case of irAE – namely, sarcoidosis – in a patient with NSCLC treated with chemotherapy plus pembrolizumab combination therapy.

**Case Report**

This is the case of a 74-year-old male hypertensive patient, an ex-smoker (>50 pack-years) who in January 2017 presented with productive cough that progressed to include intermittent hemoptysis. At that time, he denied having chest pain, dyspnea, night sweats, or weight loss. An initial evaluation with a chest X-ray revealed a right upper lobe opacity. This was followed by a CT scan of the chest in March 2017, which showed a posterior right upper lobe lung mass (5.7 × 4.5 cm) invading the pleura, with right paratracheal lymph nodes. A CT-guided biopsy revealed moderately differentiated adenocarcinoma with extensive necrosis, positive TTF1, and programmed death ligand 1 +3/3 in 90% of the cells.

A PET-CT scan for initial staging showed an intensely FDG-avid, right apical necrotic lung mass extending to the pleural surface posteriorly and medially, and possibly to the retrotracheal space (6 × 6 cm; SUV\textit{max} = 18.6), with mildly FDG-avid subcentimeter right hilar and upper paratracheal lymph nodes (9 mm) with no evidence of distant metastatic disease (Fig. 1a, b).

As such, the patient’s tumor was staged as T2bN2M0 (stage IIIA, with limited mediastinal disease) and the patient was started on combination chemotherapy/immunotherapy with carboplatin/pemetrexed plus pembrolizumab (Keytruda) as of April 2017. He received 4 cycles of combination therapy, followed by 2 cycles of Keytruda.

On follow-up, PET-CT scanning showed a significant decrease in the size and FDG uptake of the right upper lobe mass, which appeared more necrotic (4.7 × 3.2 cm; SUV\textit{max} = 2.8),
with an interval increase in the size, number, and uptake of mediastinal and bilateral hilar lymph nodes ($\text{SUV}_{\text{max}} = 4.6$) and no evidence of distant metastatic disease (Fig. 1c, d). To rule out progression to stage IIIB, an endobronchial ultrasound-guided biopsy was performed, but it was inconclusive. The patient underwent surgical excision and sampling of the lymph nodes. Pathologic evaluation revealed 90% necrosis in the primary tumor; the lymph nodes were found to be negative for malignancy, but instead showed noncaseating granulomatous inflammation (Fig. 2).

**Discussion**

Sarcoidosis is a granulomatous disease of unknown etiology whose immunopathogenesis is not yet fully understood. The noncaseating granulomas develop as a result of the proposed interplay between three factors: (1) genetics determining HLA types, (2) exposure to one or more antigens, and (3) T-cell responses to that exposure mediated by interferon-γ and interleukin-2. Sarcoidosis may involve many organs, such as the lungs, skin, and kidneys, or the central nervous system, but the lungs and lymph nodes are the two most common sites [6].

The pathogenesis of immunotherapy-induced sarcoidosis is not yet known but has been reported in different cancers and using different checkpoint inhibitors. Several case reports have been published reporting the presence of sarcoidosis in patients diagnosed with melanoma after the use of nivolumab [6], ipilimumab [7, 8], pembrolizumab [8, 9], and ipilimumab plus nivolumab [10]. Other reports have also revealed that sarcoidosis is triggered after using checkpoint inhibitors in cancers such as Hodgkin lymphoma [11], renal cell carcinoma [12], and sarcoma [13]. One case report has described the triggering of cutaneous sarcoidosis in a patient diagnosed with lung adenocarcinoma after having been treated with pembrolizumab [14]. Cutaneous involvement of sarcoidosis was also reported in other case reports discussing patients with different types of cancers who were started on immune checkpoint inhibitors [8, 10, 11, 14, 15].

As such, reporting the presence of sarcoidosis in the setting of immunotherapy for the treatment of lung cancer is scarce, with only 2 reports so far [14, 15], both reporting sarcoidosis of the skin rather than pulmonary sarcoidosis. Our patient experienced pulmonary sarcoidosis after having been treated with both carboplatin/pemetrexed and pembrolizumab for NSCLC, which appeared only 4 months after initiating treatment. This is an important point to raise, since the relationship between sarcoidosis occurring after having initiated treatment with immunotherapy may be mistaken for having progression of the disease, and this warrants a tissue biopsy for confirmation.

**Conclusion**

Knowing that immunotherapy has a wider safety margin than chemotherapy, physicians continue to witness side effects emerging from using immune checkpoint inhibitors. Recently, more reports have described irAEs, especially sarcoidosis, even though its exact pathogenesis remains to be revealed. To our knowledge, this case is the first in the literature to show pulmonary sarcoidosis in a patient with NSCLC 4 months after having initiated chemotherapy plus pembrolizumab combination therapy. This stresses the importance of having a tissue biopsy to confirm the diagnosis of sarcoidosis and to exclude progression of disease.
Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

None of the authors have any conflict of interest to declare.

Author Contributions

All authors contributed equally to the literature search, data collection (including figures), and manuscript writing.

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Fig. 1. a Before treatment. 6 × 6 × 6 cm, intensely FDG-avid necrotic mass with SUV\(_{\text{max}}\) = 18.6. b Before treatment. Mildly FDG-avid lymph nodes in the paratracheal and hilar areas. c After treatment. Interval decrease in necrosis and complete resolution of FDG avidity with minimal residual peripheral uptake with SUV\(_{\text{max}}\) = 2.8. d After treatment. Interval increase in the size and uptake of the mediastinal right hilar lymph node and interval appearance of FDG-avid left hilar lymph nodes with SUV\(_{\text{max}}\) = 4.6.
Fig. 2. a H&E stain of a hilar lymph node showing numerous granulomas. Original magnification, ×40. b H&E stain showing noncaseating granulomas. Original magnification, ×400. c H&E stain showing granulomatous inflammation (G) on the left and adenocarcinoma (A) on the right. Original magnification, ×400. d H&E stain showing necrotic tumor (left), alveolar lung tissue (A), and granulomatous inflammation (G) interfacing with viable tumor (T). Original magnification, ×40.