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CASE REPORT

A "Crazy Paving" Pattern on CT Scan in a Patient Treated with Pembrolizumab

Maurizio Marvisi[1,*], Sara Ramponi[1], Laura Balzarini[1] and Chiara Mancini[1]

[1]*Department of Internal Medicine, Istituto Figlie di San Camillo, Cremona, Italy*

ARTICLE HISTORY

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Abstract: ***Background*:** Programmed cell death protein 1 (PD-1) and its ligand, PD-L1, have shown great promise in clinical practice and have been incorporated into standard management of NSCLC. Pneumonitis is a serious autoimmune toxicity associated with the use of anti-PD-1/PD-L1 antibodies, resulting in significant morbidity and mortality.

***Methods*:** We described the case of a 73-year-old woman with no history of smoking developing exertional dyspnea four months after taking Pembrolizumab.

***Results*:** High resolution contrast CT scan (HRCT) presented a unilateral "crazy paving" pattern, and bronchoalveolar lavage (BAL) an important lymphocytosis (20% of total cell count). The patient reached clinical stability after the administration of systemic steroids (2mg\Kg\die) and was discharged with long term oxygen therapy.

***Discussion*:** Pulmonary toxicity is frequent when using PD-1 inhibitors, resulting in significant morbidity and mortality, often leading to the discontinuation of therapy. Clinical presentation is usually protean and HRCT pattern is nonspecific. This is the first case presenting a "crazy paving" pattern associated with BAL lymphocytosis.

***Conclusion*:** Oncologists, pulmonologists, radiologists and general practitioners have to consider PD-1 and PD-L1 inhibitor pneumonitis as a potentially disabling and fatal event.

Keywords: Pembrolizimab, PD-1 inhibitors, pulmonary toxicity, pneumonitis, NSCLC, ICIs, HRCT.

1. INTRODUCTION

Non-Small Cell Lung Cancer (NSCLC) is a common disease with a high mortality rate and poor response to cytotoxic therapy. In recent years, immunotherapeutic agents that target immune checkpoint pathways have shown great promise in clinical practice and have been incorporated into the standard managementof NSCLC [1]. These immunotherapies block the function of Immune Checkpoints (ICIs), thereby promoting T cell-mediated antitumor responses. Optimal T-cell activation requires two signals. The first signal involves the interaction between the T-Cell Receptor (TCR) and its cognate peptide-major histocompatibility complex molecule expressed on antigen presenting cells (APCs). The second co-stimulatory signal comprises CD28, which is constitutively expressed on T cells, binding to B7 ligands expressed on professional APCs. Cytotoxic T lymphocyte antigen 4 (CTLA-4) is an ICI that bears structural similarity to CD28, and it is upregulated on activated T cells and constitutively expressed on regulatory T cells. CTLA-4 competes with CD28 for binding to the B7 ligands, and it inhibits T cell–mediated immune responses. Other ICIs belonging to theCD28/B7 superfamily have been identified, and they include programmed cell death protein 1 (PD-1) and its ligand, PD-L1. Monoclonal antibodies targeting CTLA-4 (ipilimumab, tremelimumab), PD-1 (nivolumab, pembrolizumab), and PD-L1 (durvalumab, atezolizumab, avelumab) have been designed to block the function of these immune checkpoints, resulting in enhanced antitumoral responses. ICIs can cause a spectrum of toxicities mediated by their immunologic mechanism of action, including thyroiditis, colitis, myocarditis, inflammatory arthritis, hypophysitis and others [2, 3]. Pneumonitis is a serious autoimmune toxicity associated with the use of anti-PD-1/PD-L1 antibodies, resulting in significant morbidity and mortality rates, often resulting in the discontinuation of therapy [4]. In a recent meta- analysis of all published clinical trials of PD-1 and PD-L1 inhibitor therapy, the overall incidence of pneumonitis in the PD-1 inhibitor group was 3.6% and in the PD-L1 inhibitor group 1.3% [5].

2. CLINICAL PRESENTATION

A 73-year-old woman with no history of smoking was admitted to the hospital in October 2018 for severe weakness and dyspnea on minimal exertion. The symptoms appeared a couple of months ago and worsened in the last two weeks.

*Address correspondence to this author at the Department of Internal Medicine, Istituto Figlie di San Camillo, Cremona, Italy; Tel: +390372421459; Fax: +390372421256 E-mail: mmarvis@alice.it

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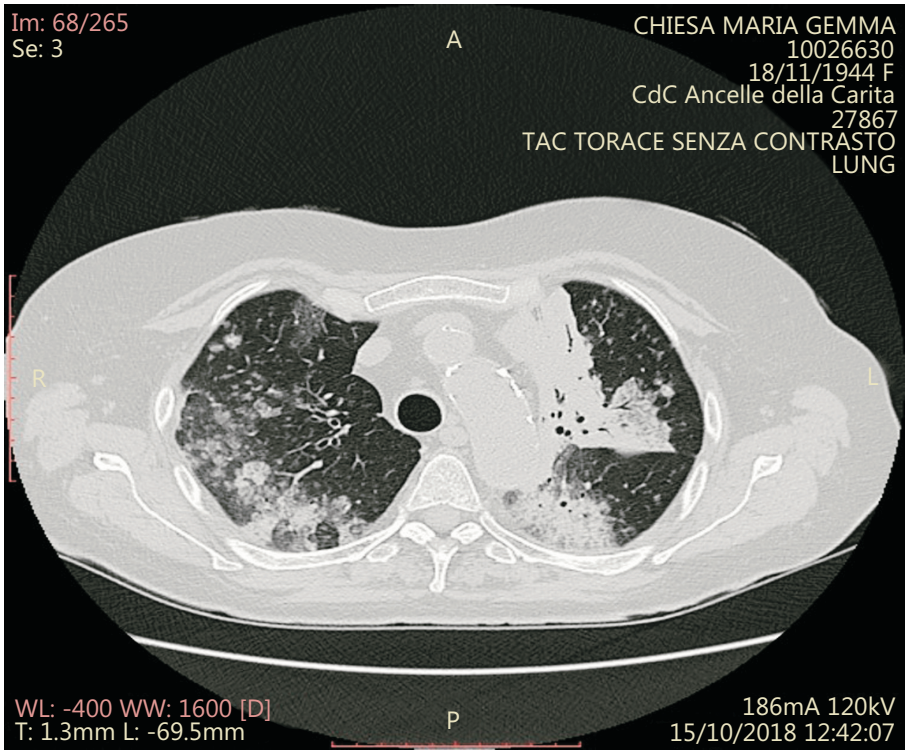

Fig. (1). HRCT, duffuse parenchimal opacities with air bronchogram at the upper lobes.

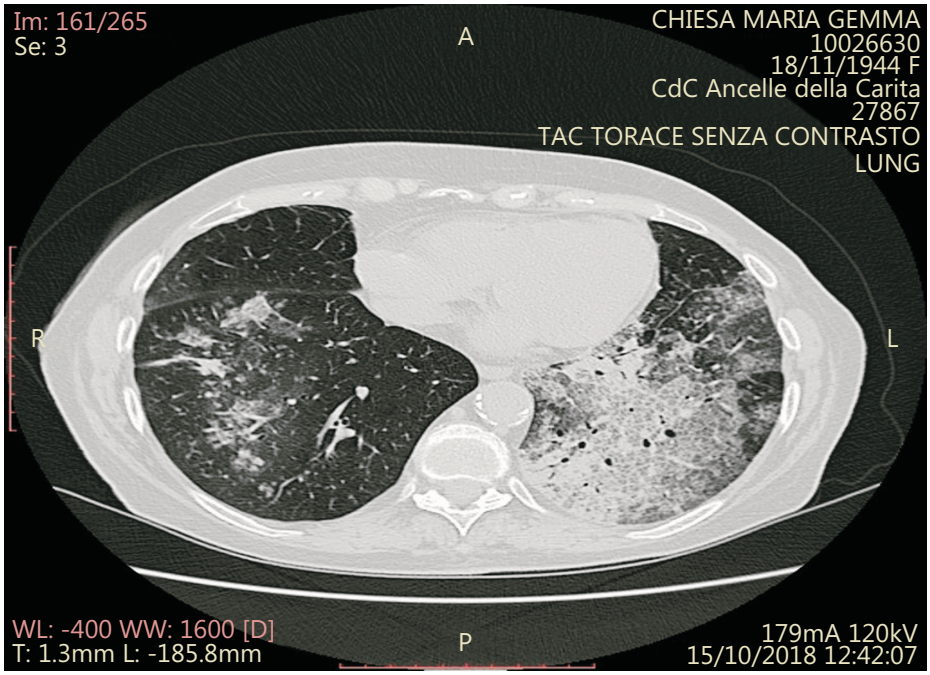

Fig. (2). HRCT, widespread thickening of the interlobular interstitium (crazy paving pattern) in the lower lobe.

She had received a diagnosis of NSCLC (adenocarcinoma: EGFR, ALK, ROS1, MET, KRAS, BRAF, WILD Type, PDL1 5%) 18 months before. She had no comorbidities and was not taking any drug. The CT- scan and PET-CT scan showed a lesion 7.5 cm in diameter on the superior segment of the upper left lobe and 3 metastatic nodules in the right lung with an enlargement of the hilar lymph nodes (T4N2M1) She began neoadjuvant chemotherapy (June 2017) with Carbo/pemetrexed (pemetrexed 500 mg/m² and carboplatin AUC 5 mg/mL per min) for 4 cycles and then continued with pemetrexed. The thoracic surgeon re-evaluated the patient but ruled out the possibility of radical surgical treatment. In April 2018 a CT scan showed an increased size in the principal lesions and the appearance of a new lesion in the right lung. At the end of April, she started a second line therapy with Pembrolizumab at a dose of 2\mg\Kg die every 3 weeks. Four months later she began to experience dyspnea during exertion. Chest X-ray, spirometry

(curve\volume curve), echocardiography and exercise test were normal. The patient first came to our attention at the beginning of October; on that occasion we performed a blood gas analysis at rest (pH 7.38, PaO2 66 mmHg, PaCO2 38 mmHg) and a global spirometry including carbon monoxide diffusing capacity (DLco)showing a significant reduction (60% of that predicted). Physical examination highlighted the presence of fine crackles at the end of inspiration in the left lower lobe. The blood exams showed a normal value of ESR (7 mm) and CRP (0.5mg\L), and a minimal increase in LDH (800 U\l). High resolution contrast tomography highlighted the presence of diffuse parenchymal opacity with "air bronchogram" resembling organizing pneumonia (OP) at the upper lung lobes and widespread thickening of the interlobular interstitium , the so-called "crazy paving" pattern, in the left lower lobe (Figs. **1** and **2**). In a few days her clinical condition worsened. Arterial blood gas value at rest was: PaO2 44 mmHg, PaCO3 32 mmHg, pH 7.50, HCO3- 16 mEq\L. Bronchoscopy with bronchoalveolar lavage (BAL) was negative for infections (viral, fungal, bacterial and Pneumocystis jirovecii). The BAL pattern showed a mild lymphocytosis (20% of total cell count) with a normal CD4\CD8 ratio. A diagnosis of checkpoint inhibitor pneumonitis was made considering the close relationship between starting pembrolizumab and symptoms appearing, the CT scan pattern, and the BAL data: mild lymphocytosis with normal T Helper\suppressor ratio and the negative results for infection. Pembrolizumab was stopped and steroid therapy (2 mg\Kg die) was started. The patient gained clinical stability after a week and was discharged with long term oxygen therapy (4\l\min at rest and 5\l\min walking).

3. DISCUSSION

An expanding body of evidence supports the efficacy of ICIs in a variety of tumor types. In NSCLC, anti PD-1 /PD-L1 ICIs have been studied in the first line, maintenance and second-line setting [1, 3]. The incidence of pneumonitis has been evaluated in large clinical trials and in meta-analyses. Khunger *et al.* showed an overall incidence of all-grade pneumonitis in the PD-1 inhibitor group of 3.6% and in the PD-L1 inhibitor group of 1.3%. The use of PD-1 and PD-L1 inhibitors in the first line setting was associated with a significantly higher incidence of all-grade pneumonitis compared with previously treated patients [4, 5]. Khunger *et al.* hypothesized that the lower incidence of pneumonitis in PD-L1 inhibitors could be due to the sparing of PD-1/programmed death-ligand 2 (PD-L2) interaction with PD-L1 inhibitors, which might be an important player in mediating immune tolerance in the lungs [5]. There were seven deaths attributed to pneumonitis, all in patients who had been treated with PD-1 inhibitors. Across all the trials, no clear relationship between the occurrence of pneumonitis and treatment duration or dose level was noted. Six out of these seven patients were former smokers, and three were treated with radiation therapy prior to PD-1/PD-L1 inhibitor therapy. In patients with underlying pulmonary pathologies, such as COPD, interstitial lung diseases, and lung cancer often resulting from smoking exposure, early diagnosis of pneumonitis is challenging, and failure to recognize the symptoms and signs of pneumonitis could lead to poor outcomes [1, 5]. The time to onset of symptoms from drug administration can be quite variable. Naidoo and coworkers reported a median time to onset of symptoms of 2.8 months. [6] Suresh *et al* suggest that more severe grades of pneumonitis tend to occur within 100 to 200 days of therapy initiation. [1] Chest CT scan (HRCT) is the imaging modality of choice for diagnosis. Nishino at al reviewed imaging from 20 cases and reported an Organizing Pneumonia (OP) pattern in 65% of cases, followed by nonspecific interstitial pneumonia (NSIP) in 15% of cases. [7] The role of bronchoscopy is currently unknown. The vast majority of patients undergo bronchoscopy to rule out infections. However, studies examining the utility of BAL are sparse. [1] Recently, Leroy *et al.* published a report of 3 cases of patients with metastatic melanoma and lung metastasis. They developed pulmonary toxicities with an NSIP- OP pattern on TC scan and BAL data showed a mild lymphocytosis (ranging from 22-35%). The management strategy is based on corticosteroid therapy. Current guidelines recommend a dose of 1 mg\kg\die of prednisone, and 2-4 mg\Kg\die for higher grade pneumonitis. Patients who remain without clinical improvement after 72 hours of therapy are considered steroid refractory. In these cases infliximab, IV Immunoglobulin, and tocilizumab may play a key role [8-10]. Our case has some peculiarities. The first clinical manifestation appeared 4 months after the start of therapy and worsened progressively in a couple of months. The only clinical manifestation was dyspnea on minimal exertion accompanied by oxygen desaturation. High-resolution contrast tomography described a unilateral "crazy paving" pattern that is the hallmark of this case. Interesting was BAL data showing considerable lymphocytosis with a normal CD4\CD8 ratio. Systemic steroids were useful in gaining clinical and radiological stability.

CONCLUSION

To conclude, pneumonitis induced by ICIs, and in particular PD-1 inhibitors, is frequent in everyday clinical practice. Given the nonspecific pattern on presentation, vigilant attention to respiratory symptoms is required for early detection of pulmonary involvement. Pulmonologists, oncologists, radiologists and general practitioners have to consider this important and potentially fatal adverse event. Unilateral "crazy paving" on HRCT and lymphocytosis in BAL may be useful tools.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

STANDARD FOR REPORTING

The CARE guidelines and methodologies were followed in this study.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

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