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Nivolumab-induced organizing pneumonitis in a patient with lung sarcomatoid carcinoma

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ABSTRACT

Immune checkpoint inhibitors are known to induce 'immune pneumonitis' in 3–6% of patients treated for lung cancer. However, their dramatic efficacy in as much as 20% of patients led to recent registrations in squamous, and then non-squamous lung carcinoma, in second line setting after failure of first-line chemotherapy, while large phase 3 trials are on-going, to assess first-line immunotherapy, either alone or in combination with chemotherapy. Pulmonary Sarcomatoid carcinomas consist of a rare subset of highly aggressive and poorly differentiated non-small-cell lung carcinomas (NSCLC), with poor prognosis and chemo-resistance. Although exhibiting high expression of programmed death ligand-1 (PD-L1), their sensitivity to inhibitors of PD-1/PD-L1 axis is still unknown. Here we report a case of lung sarcomatoid carcinoma with Nivolumab dramatic and long-lasting efficacy, but occurrence of a very specific pattern of lung toxicity, the so-called 'organizing bronchiolitis syndrome'. As more and more NSCLC patients are promised to receive PD-1 inhibitors as part of their treatment, we feel that specific features of such Nivolumab-induced organizing pneumonitis should be known. Although corticosteroid sensitivity is high, recurrence is frequent because of premature steroid tapering, as for all other causes of organizing pneumonias, and probably because of the Nivolumab long tissue half-life.

1. Introduction

Antibodies targeting the programmed cell death-1 (PD-1) cell membrane antigen have emerged as a new therapy for advanced non-small cell lung cancer (NSCLC). Sarcomatoid lung carcinoma is a rare aggressive NSCLC subtype, with histological features of epithelial to mesenchymal transition (EMT), strong inflammatory stromal infiltration, and high levels of programmed death ligand-1 (PD-L1) [1]. However, specific data on immunotherapy efficacy are not available yet in this subset of lung cancers. A recent *meta*-analysis of 11 clinical trials demonstrated that immune checkpoint inhibitors lead to increased risk of all-grade pneumonitis (OR = 3.96; 95% CI:[2.02–7.79]; $p < 0.0001$) [2]. In the Checkmate 017 trial, the incidence of any-grade nivolumab-induced pneumonitis was 5% [3]. Various patterns of nivolumab-induced pneumonitis have been reported: acute or sub-acute diffuse glass-ground opacities, rarely evolving to acute respiratory distress syndrome, non systematized lung consolidations [4], or granulomatous sarcoid-like disease [5]. Organizing pneumonitis syndrome, has specific CT-scan and clinical features, frequently reported for drug-induced pulmonary toxicity, which deserve to be identified although frequently misdiagnosed, since corticosteroids are dramatically efficient, with complete resolution of lung abnormalities and respiratory symptoms, but with frequent recurrence [6,7].

2. Case-report

An active smoker, 70-year-old Caucasian male, was diagnosed with a mass in the right upper pulmonary lobe, mediastinal lymph nodes and bone metastases. Endobronchial ultrasound

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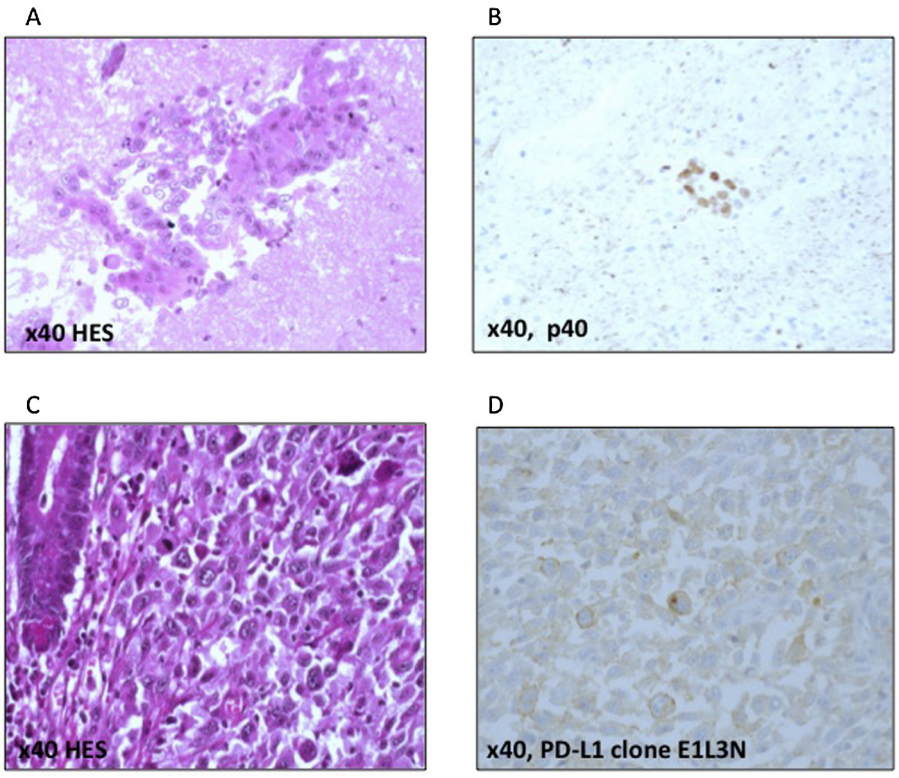

Fig. 1. Histology. (A and B) EBUS Cytology features, (A) ×40 magnification; Hematoxylin-Eosin- Saffron (HES) staining of EBUS cytology sampling showing nests of tumor large cells, (B) ×40 magnification; p40 immunostaining showing some nest of tumor cells expressing p40 protein, suggesting squamous differentiation, (C and D) Surgical resection of the small intestine metastasis (C) ×40 magnification, HES staining of the small intestine metastasis showing large poorly differentiated cells, with giant and spindle cells, and rare epithelioid features, (D) ×40 magnification; PD-L1 immunostaining using clone E1L3N (Cell Signalling™ catalog No. 13684S; 1:1600 dilution) and showing diffuse membranous stainig of tumor cells at moderate intensity.

(EBUS)-mediated *trans*-bronchial cytology sampling showed nests of tumor cells with features of NSCLC with squamous differentiation (Fig. 1A and B). Molecular tests for EGFR, K-Ras, B-Raf, HER2 mutations and ALK rearrangement were negative. For first-line therapy, from October 2014, he received cisplatin, gemcitabine, and necitumumab anti-EFGR monoclonal antibody, as a part of a Phase II trial. He exhibited partial response, supporting necitumumab maintenance monotherapy until May 2014. He then received docetaxel as second-line at thoracic progression. In December 2014, he presented with intestinal occlusion, revealing small intestine and spleen metastases from a sarcomatoid carcinoma (Fig. 1C and D), while right upper lobe lung tumor was stable. On comparing the initial cytology sample with the intestinal tumor histology features, both exhibited the same sarcomatoid differentiation, with the exiguity of the EBUS sampling explaining the initial misdiagnosis. 80% of the small intestine metastasis tumor cells expressed moderately membranous PD-L1 antigen as shown by immunohistochemistry (Fig. 1D), using the rabbit monoclonal antibody E1L3N from Cell signaling™. Sequencing for Exon 14 skipping mutations was negative using primer sets for sequencing MET exon 14 and flanking introns.

Nivolumab was initiated on March 13, 2015 (3 mg/kg every 2 weeks) according to the French expanded access program (ATU). The patient performance status improved from 1 to 0 within 15 days of Nivolumab treatment, at which point the patient was able to resume work. Partial response was obtained at 6 weeks of treatment (April 22, 2015; CT scan), while Nivolumab-induced Grade 2 hyperthyroidism was diagnosed.

After 3 months under nivolumab (June 17, 2015, CT-scan), left upper lobe consolidations with air bronchogram were observed. The patient was apyrexial, and the clinical examination was normal. Serum procalcitonin was not increased. Pulmonary function test results are provided in Fig. 2A. The bronchoalveolar lavage (BAL) fluid sampled from the lingula was sterile, yet showed hyper-cellularity, with 1,170,000 cells/mm^3 (32.5% lymphocytes [30.5% CD4, 67% CD8], 65% macrophages, 2% neutrophils, and 0.5% eosinophils). No other long-term or recent treatment was reported.

As all other diagnoses had been excluded, nivolumab was considered the putative cause of the pulmonary abnormalities. Since the patient was asymptomatic and his pneumonitis mild, nivolumab was continued, the last infusion administered on June 18. On July 2, he developed Class II NYHA dyspnea on exertion. His pneumonitis was found to be bilateral with ground glass opacities in the lower right lobe and more significant condensation of the lingula. Oral prednisone was initiated at 1 mg/Kg/day. The patient's symptoms and radiographical abnormalities resolved rapidly. The prednisone was gradually tapered off over a 3-month period. On September 23, lung CT scan confirmed on-going partial response with almost complete disappearance of pneumonitis features. Prednisone was discontinued, though the patient suffered relapse of pneumonitis symptoms 2 months later, with dyspnea, bilateral end-inspiratory crackles on thorax auscultation, mild hypoxemia (PO_2: 68 mmHg), pulmonary test alteration (Fig. 2B), and lymphocytic alveolitis on BAL (270,000 cells/mm^3 [51% lymphocytes – predominantly CD8+ – 38% macrophages, 9% neutrophils, 2% eosinophils, and 1% mastocytes]). The BAL fluid remained sterile. Other pneumonitis etiologies were eliminated by extensive investigation (habitus, recent treatments) and complete autoantibody serum measurement.

We categorized this respiratory disease as an organizing pneumonitis-like syndrome, according to the radiological features of bilateral non-systematized alveolar consolidations, ground-glass