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Case Report
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Effects and Side Effects of Nivolumab: From Pneumonitis to Complete Remission Complete Response of Metastatic NSCLC after Resolution of a Pneumonitis on Nivolumab Treatment

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Abstract

Non-Small Cell Lung Cancer (NSCLC) without driver mutations has limited the rapeutic options beyond first line chemo therapy. A 62-year-old patient was diagnosed with adenosquamous lung cancer, with initial oligometastatic stage IV disease and no driver mutations. After initial treatment with3 cycles of cisplatin-gemcitabine tumor progression with bone lesions was detected. On immunohistochemistry, the tumor showed a strong (over 50%) expression of PD-L1 on the membrane of tumor cells and treatment with nivolumab was given to the patient. Within two courses of nivolumab the clinical symptoms of acute dyspnea and cough occurred. The diagnosis of nivolumab related pneumonitis was found and the patient received treatment with high dose steroids and antibiotics. A PET-CT scan 12 weeks after the onset of the pneumonitis showed a complete remission of pneumonic infiltrates as well as further response of the bone lesions. Oncological decisions of further treatment included radiological and clinical follow-up without any further treatment with nivolumab. To date, 15months after the last treatment with nivolumab, the patient is still in complete remission. Nivolumab is the new standard of treatment in second line for NSCLC since the approval of FDA and EMA. This case shows not only how to manage an immune response related pneumonitis. In addition the case showed an exceptional response of this tumor to only two courses of nivolumab.

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Introduction

Lung cancer is the leading cause of death from cancer worldwide [1]. Non-Small Lung Cancer (NSCLC) without driver mutations had limited therapeutically options beyond first line chemotherapy. Based on the current ESMO guidelines Docetaxel is considered as second line therapy in NSCLC without oncogenic driver [2] with an unfavorable safety profile.

Case Report

A 62-year-old male patient was referred to our hospital with persistent cough and unintended weight loss of 10 kilograms within the previous 6 months. The patient was diagnosed with moderate differentiated adenosquamous lung carcinoma, with initial tumor stage cT3, cN2, cM1 (bone), UICC oligometastastic stage IV (Figure 1a). Further molecular testing presented no mutation in *EGFR* (epidermal growth factor receptor genotyping) and *K-RAS* (Kirsten rat sarcoma viral oncogene homolog) and neither ALK nor ROS1 rearrangements were detected. On immunohistochemistry, the tumor showed a strong expression (over 50%) of PD-L1 on the membrane of tumor cells (Figure 2). This case was presented at our interdisciplinary tumor board and a palliative chemotherapy was started with cis plat in and gemcitabine. After 2 cycles of chemotherapy the patient reported about hear loss and cisplatin was changed to carboplatin. Re-Staging after 3 courses of chemotherapy showed stable disease of the primary tumor but a progression of the bone lesion of the 1st sacral vertebra (Figure 1b). This case was re-discussed at our tumor board and due to the cavernous changes of the primary tumor, with increased risk of infections; a palliative sleeve resection of the right upper lobe with lymph node dissection was performed. At this time, the patient presented in good performance status and radiotherapy of the bone metastases was planned. Three weeks after radiotherapy a re-staging with PET-CT scans, showed progression of the disease in the

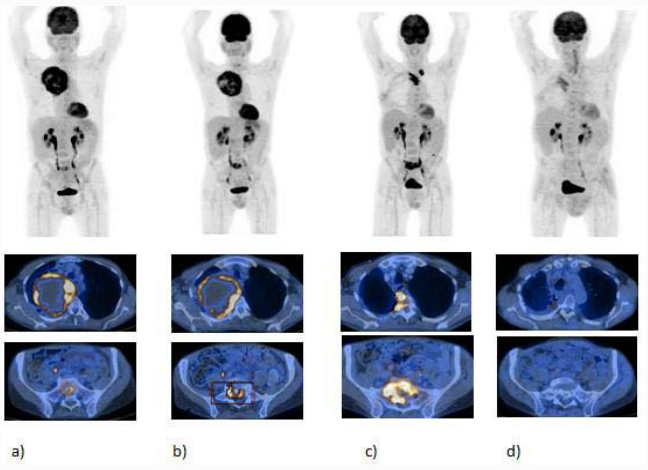

Figure 1: a) Initial staging of stage IV lung cancer with primary tumor in the right upper lung lobe and a singular bone metastasis in sacral bone; b) stable disease after 3 courses of chemotherapy; c) local recurrence and new lymphnode metastasis three weeks after radiotherapy of bone and sleeve resection of the lung, stage before start of nivolumab; d) 12 weeks after resolution of pneumonitis.

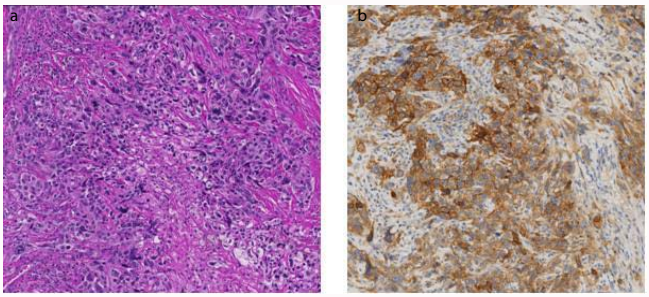

Figure 2: Histology of tumor tissue. a) Hematoxylin-eosin staining of tumor; b) PD-L1 staining of tumor.

supraclavicular lymph nodes and local recurrence (Figure 1c). Second line treatment with nivolumab with 3mg/kg every 14 days was initiated. The patient received two courses of treatment and then presented to the emergency unit with dyspnea and cough. The patient's ECOG performance status was 3, his saturation of Peripheral Oxygen (PiO2) was 67% without fever and with normal blood pressure values and heart rate. The laboratory findings showed an increase in the LDH with 680 U/l and CRP with 157 mg/l. A CT scan of the thorax showed ground glass opacities in both lungs (Figure 3). Lymph nodes were documented enlarged and anivolumab-induced pneumonitis was suspected as well as tumor progression was considered in differential diagnosis. The patient was treated with high dose steroids methyl prednisolone (MPDN) 250mg iv (single dose) as well as intravenous broad-spectrum antibiotics (piperacillin/tazobactam) for 6 days and switched to oral antibiotics (amoxicillin/clavulanate) for additional 3 days as well as trimethoprim-sulfamethoxazol for a total duration of 15 days. After 3 days from initial treatment, the patients' conditions improved dramatically with normalization of PiO2. Corticosteroids were then administered orally and tapered continuously for a total of three weeks (treatment schedule: PDN 200mg for 2days, 100mg for 2days, 50mg for 2days, 25mg for 2days, 20mg for 2days, 10mg for 2days, 5mg for 2days). A PET-CT scan 12 weeks after the onset of the pneumonitis showed a complete remission of pneumonic infiltrates and a metabolic subtotal response and morphological very good partial response of the lymph nodes metastases and local

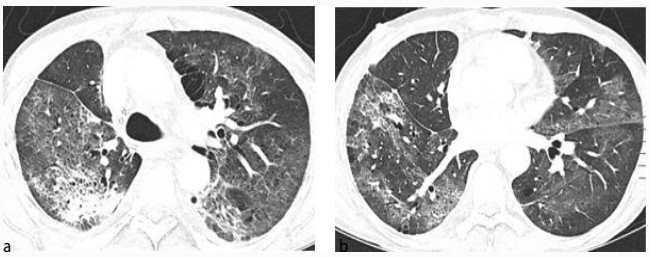

Figure 3: Imaging presentation of PD-1 related pneumonitis within 6 weeks under treatment with Nivolumab. Typical ground glass opacities with consolidation are seen. In the lower picture also a pericardial effusiuon was documented.

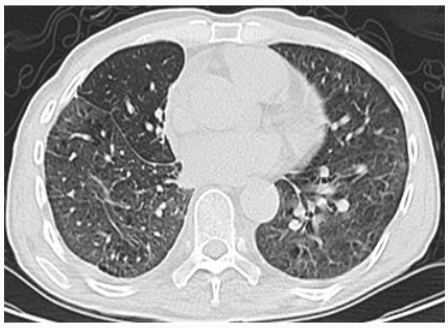

Figure 4: Response after treatment with corticosteroids. This CT scan of the lung was made after 8 weeks after diagnosis of PD-1 related pneumonitis. Patient was treated with corticosteroids and dosages were tapered and stopped. At this scan resolution of pneumonitis could be detected.

recurrence (Figure 1d) as well as further response of the bone lesions. Oncological decisions of further treatment included radiological and clinical follow-up without any further treatment with nivolumab. To date, 15 months after the last treatment with nivolumab and under surveillance after recovery of the immune therapy induced pneumonitis, the patient is still in complete remission.

Discussion

Nivolumab is the new standard of treatment in second line for NSCLC since the approval of FDA and EMA based on the data from the double-blinded phase III study Checkmate 057 comparing nivolumab versus docetaxel [3]. Overall survival, overall response rates as well as median duration of response were favorable in the nivolumab arm. Moreover, grade 3 to 4 treatment-related adverse events were less frequent in the nivolumab compared to the docetaxel group. Although nivolumab is a drug with a very good tolerability and good to moderate drug safety profile, the knowledge as well as the handling of the side effects are the major challenges with this new class of compounds. Beside known adverse events like fatigue and diarrhea, severe toxicities with immunologic related events may also occur. Here we describe a case of nivolumab-induced pneumonitis, which is known to occur in about 1% of the patients as immune related adverse event (irAE) [4]. Typically these irAEs occur between week 6-8 under treatment with PD-1 medication and may present in different clinical severity [5]. Imaging findings of our patient show typical ground glass opacities and some compact formations, as previously described [6]. Also pneumonia or tumor progression should be ruled out in these cases. However, in our patient neither a bronchoscopy nor a biopsy could be performed due to his critical clinical conditions. As previously reported, immune-related pneumonitis should receive corticosteroids intravenously on

an early phase and then taper of dosage should follow clinical and radiographic improvement [6]. Here we describe our treatment scheme and, as we couldn't exclude pneumonia, antibiotics were added to the corticosteroids. This case shows not only how to manage an immune response related pneumonitis, but also emphasize the exceptional response of this tumor to only two courses of nivolumab.

Conflict of Interest Statement

All authors disclose any actual or potential conflict of interest including any financial, personal or other relationship with other people or organizations that could inappropriately influence this work.

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