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PD-L1 induction in tumor tissue after hypofractionated thoracic radiotherapy for non-small cell lung cancer

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ABSTRACT

We report on a 67-year old male with advanced stage lung adenocarcinoma (initially PD-L1 negative, EGFR and ALK negative) diagnosed in 2014. The patient received 4 lines of palliative chemotherapy from 2014 to 2017, however the disease progressed. In 2015, he also received palliative hypofractionated radiotherapy to a mediastinal mass, which was causing discomfort and pain. Since there was some data, that radiotherapy could induce PD-L1 expression, a new biopsy was taken in 2017 from the irradiated mediastinal mass. Subsequent pathologic report revealed that PD-L1 status was turned to be highly positive, with tumor proportion score of 100%. Similar high expression of PD-L1 was detected in a new metastasis in the duodenum, which was excised due to a duodenal perforation in 2017. From October 2017 to October 2019, the patient had 2-years of treatment (32 courses) with pembrolizumab and has had a positive effect (partial response) on all the lesions and following stabilization of the disease. Currently, this patient is under follow up and he is in a good condition without any complaints. Last CT-scan in March 2020 showed persisting partial response.

1. Introduction

Despite the development of diagnostic methods, most of non-small cell lung cancer (nsclc) cases are still diagnosed in advanced stages with distant metastases [1].

For metastatic stage IV nsclc, drug therapies are mainly used [2,3]. The choice of medical treatment is based on factors such as histology, molecular pathology, age, performance status, comorbidities and the patient's preferences. Possible drugs include tyrosine kinase inhibitors for EGFR (Epidermal Growth Factor Receptor) mutation positive tumors, specific inhibitors for ALK (Anaplastic Lymphoma Kinase) rearranged nsclc, immunotherapy with immune checkpoint inhibitor Pembrolizumab for PD-L1 (Programmed Death Ligand-1) strongly positive tumors (PD-L1 tumor proportion score, TPS $\geq$50%) or immunotherapy and chemotherapy combinations.

Next to these systemic nsclc treatments, patients with metastatic lung cancer can be treated with thoracic radiotherapy to relieve tumor related symptoms (hemoptysis, bronchial obstruction, cough, shortness of breath, and chest pain) and to improve health related quality of life [4]. More recently, the addition of local radiotherapy has also been shown to improve treatment efficacy and patient survival compared to chemotherapy alone [5].

We present here a case, where radiotherapy not only resulted in a long-lasting treatment response but also could have induced PD-L1 expression in initially PD-L1 negative tumor enabling thereby subsequent effective immunotherapy with pembrolizumab despite of previously received 4 lines of systemic chemotherapy regimens.

2. Case report

A consent was obtained from the patient to present his case. This case describes a 67- year old Caucasian male with no previous illnesses, ECOG 0-1, who was diagnosed with advanced stage IV adenocarcinoma of the lung in July 2014. At the time of diagnosis, the patient had a peripheral tumor in the upper lobe of the right lung with metastasis to the lymph nodes in the upper right mediastinum, right axilla and neck. The patient complained about a mass on the neck and was referred to a general surgeon by his general physician. An enlarged supraclavicular lymph node was

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excised and the initial diagnosis of lung adenocarcinoma was obtained. The tumor was EGFR, ALK negative and PD-L1 negative (tumor proportion score, TPS 0%; Fig. 1A).

Treatment timeline of this patient is depicted in Fig. 2. The patient was initially treated with palliative cisplatin and gemcitabine combination chemotherapy for 4 courses. Cisplatin was changed to carboplatin from the second course. Since the patient had a positive effect in primary tumor and all the metastases, we proceeded with maintenance therapy with pemetrexed. After 9 courses, the computed tomography (CT) scan in June 2015 showed negative dynamics and new axillary metastases. Due to progression, patient received 3rd line chemotherapy with docetaxel for 6 courses. In December 2015, the right upper mediastinal lymph node mass had enlarged and caused discomfort and chest pain for the patient. To relieve the symptoms, he received hypofractionated radiotherapy to the upper mediastinal mass 45 Gy total in 15 fractions (radiotherapy plan is shown in Fig. 3). In the beginning of 2016, after the palliative radiotherapy, we continued with chemotherapy again with carboplatin plus gemcitabine, since during this 1st line regimen the disease did not progress. The patient received 6 courses of palliative chemotherapy and a CT scan in September 2016 showed a stable disease. He continued with follow-up. CT scan in February 2017 showed again a progression and enlargement of the right upper mediastinal mass. Since it had been 9 months since the last chemotherapy, we continued with the carboplatin plus gemcitabine regimen again for 6 courses. CT scan in August 2017 showed a further progression. Previously irradiated right upper mediastinal mass was enlarged even more and infiltrated the right *v. subclavia; v.brachiochephalica; v. azygos and v. cava superior*. In September 2017 we decided to re-biopsy the irradiated mass in the right upper mediastinum (CT-guided transthoracic biopsy) due to the knowledge that radiotherapy could induce PD-L1 expression. Pathologic report confirmed that patient had metastatic adenocarcinoma of the lung, however, the expression of PD-L1 turned out to be highly positive (TPS 100%; Fig. 1B). Afterwards, the patient submitted an application to Estonian cancer treatment foundation "The Gift of Life" to get a reimbursement for immunotherapy with pembrolizumab since it was not reimbursed by national healthcare system at that time. Meanwhile, an emergency operation was performed on 30th of September 2017 because of duodenal perforation. The perforation was due to a mass in the duodenum. A piece of the duodenum with the attached mass was excised and the histology confirmed metastasis of lung adenocarcinoma, also PD-L1 highly positive (TPS 100%; Fig. 1C). In October 2017, the patient was in good condition, ECOG 1 and highly interested in proceeding the treatment. Since the charity fund "The Gift of Life" agreed to cover the cost of immunotherapy, the treatment with pembrolizumab was started. CT scan in December 2017 showed a positive effect (partial response) since the right upper mediastinal mass was decreased in size. We continued with pembrolizumab, which the patient tolerated very well without any immune-related adverse events. In October 2019 the patient has had 2-years of treatment (32 courses) with pembrolizumab and has had a positive effect (partial response) on all the lesions and following stabilization of the disease. After stopping immunotherapy, the patient was in a good condition, ECOG 0, returned to work and had no complaints. Currently, this patient is under follow up and the last CT-scan in March 2020 showed persisting partial response.

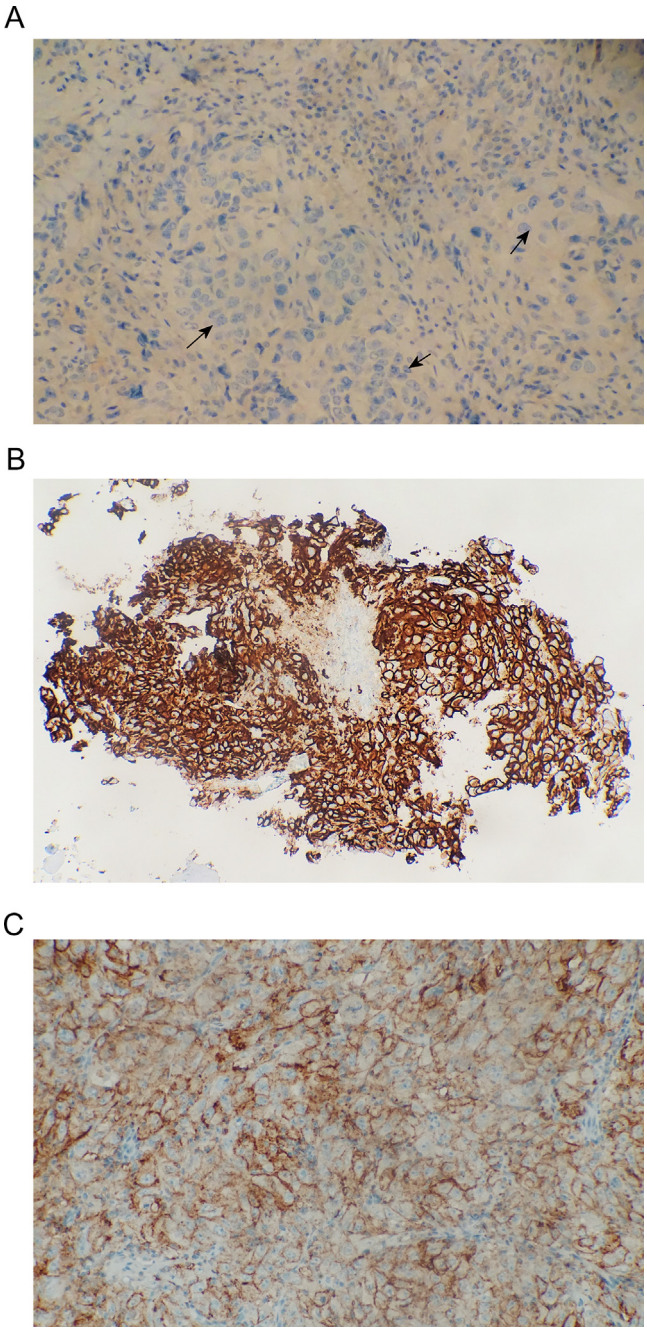

Fig. 1. Immunohistochemical staining of programmed death ligand-1 (PD-L1) in lung adenocarcinoma. Immunostaining was performed using 22C3 antibody and VENTANA BenchMark ULTRA platform. A: Initially PD-L1 negative tumor tissue (excised supraclavicular lymph node 2.5 × 1.5 × 1 cm, PD-L1 TPS < 1%, magnification x200), arrows indicate nests of PD-L1 negative tumor cells; B: PD-L1 highly positive tumor tissue after hypofractionated radiotherapy (transthoracic needle biopsy from previously irradiated mass in upper mediastinum, ca 0.5 cm, PD-L1 TPS 100%, magnification x100); C: PD-L1 highly positive metastasis in small intestine (resected duodenal metastatic mass ca 3 cm, PD-L1 TPS 100%, magnification x400).

3. Discussion

From the start of immunotherapy in nsclc, numerous biomarkers to predict benefit from this type of treatment have been evaluated. These include markers such as blood neutrophil–lymphocyte ratio (NLR) as well as tumor mutational burden (TMB) [6,7]. Nevertheless, so far, the most studied biomarker in nsclc immunotherapy is an immunohistochemical expression level of PD-L1 on tumor cells, since several phase III clinical studies have reported better treatment responses in patients with PD-L1 positive tumors [8,9]. Additionally, the most remarkable treatment efficacy with immune checkpoint inhibitors have been seen in nsclc patients with high PD-L1 tumor proportion score (i.e. TPS ≥50%) [8,9].

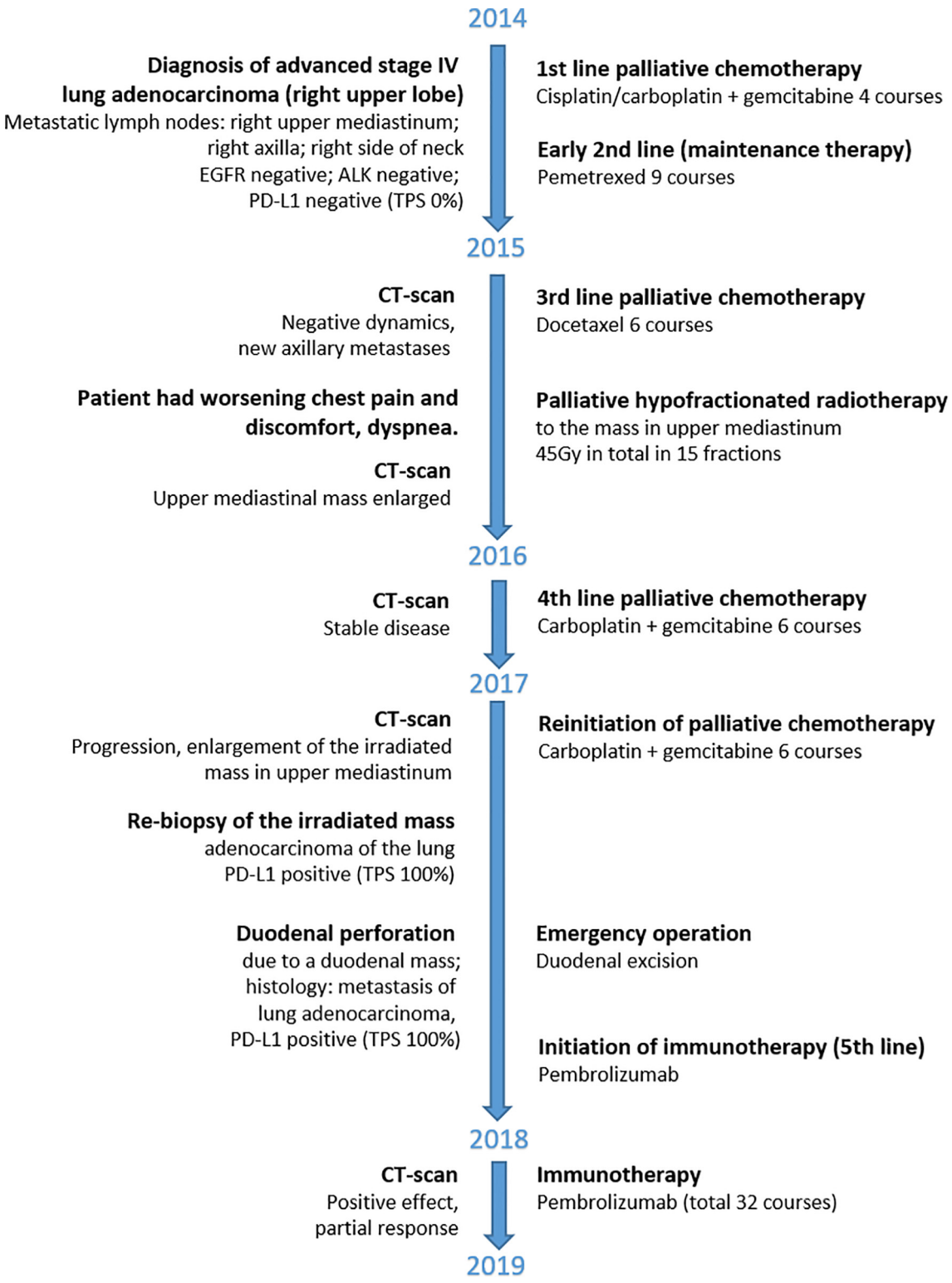

Fig. 2. The timeline of patient treatments.

Previous studies involving different world regions have revealed that approximately only one third of nsclc patients have tumors that express PD-L1 in high levels [3]. Moreover, in Europe, much smaller proportion of nsclc patients (11%) have tumors that express PD-L1 on ≥50% of cancer cells [10]. Latter has raised a number of questions whether tumor microenvironment can be changed and PD-L1 expression induced so that more nsclc patients could benefit from modern immunotherapy.

In nsclc, the effect of chemotherapy on tumor cell PD-L1 expression has been previously investigated in patients receiving neoadjuvant chemotherapy. However, the results are still controversial, showing decrease in PD-L1 expression [11], no significant changes

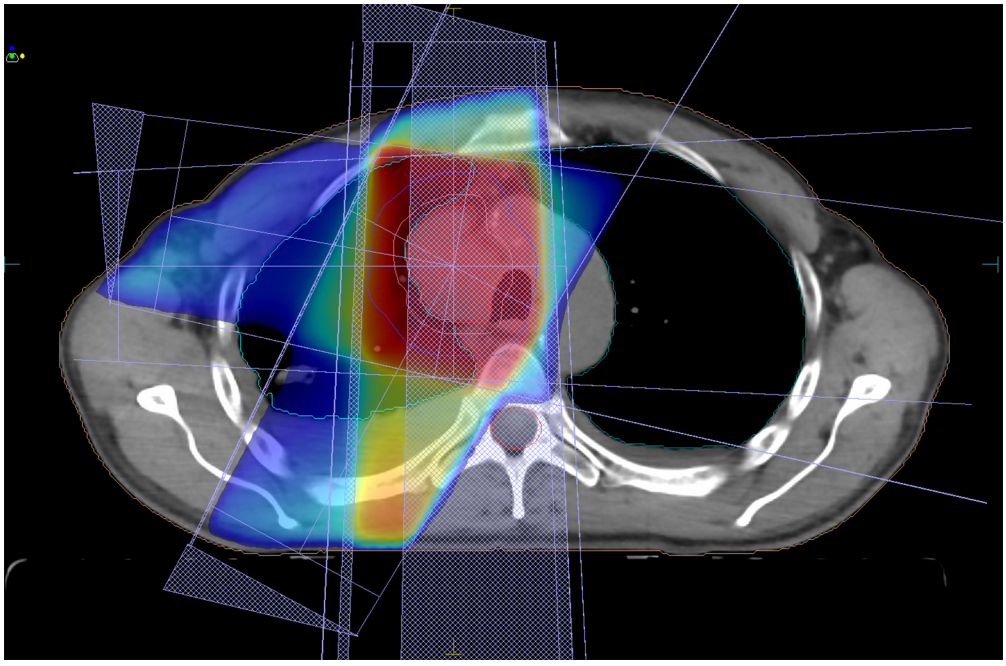

Fig. 3. Radiotherapy treatment plan for upper mediastinal mass Patient received hypofractionated radiotherapy, 45 Gy total in 15 fractions.

[12], upregulated PD-L1 expression [13], or mixed results [14]. These findings are also confused due to retrospective nature of reported studies as well as different and not clinically validated antibodies used for immunohistochemical detection of PD-L1. In contrast, studies on radiation-induced PD-L1 induction have been quite consistent. Growing number of preclinical studies indicate that irradiation induces PD-L1 expression on tumor cells. In general, radiotherapy-associated increases in tumor cell PD-L1 expression often occur early with peak levels detected within 24–96 h post-radiotherapy [15]. In nsclc cells, radiation-induced PD-L1 expression has been seen as early as 1–2 h after single dose of 6 Gy, whereas 4 h after irradiation no further increases were seen [16]. However, radiation-induced increase in PD-L1 expression in nsclc cells seems to be long-lasting since it has been reported 24 h after 2 fractions of 8.5 Gy and 72 h after 3 fractions of 2 Gy [17,18]. These preclinical findings of radiation-induced PD-L1 induction are supported by a published clinical case report, where gradually increased PD-L1 expression has been detected in a nsclc patient brain metastasis after repeated radiotherapy [19]. Additionally, some indirect evidence that radiotherapy may cause favourable changes in tumor microenvironment (e.g. induce PD-L1 expression) came from a published clinical study where compared to only immunotherapy-treated patients, longer progression-free survival (PFS) and overall survival (OS) were seen in patients that received prior pembrolizumab radiotherapy [20].

We present here the case, where radiotherapy not only resulted in a long-lasting treatment response but also could have induced PD-L1 expression in initially PD-L1 negative lung adenocarcinoma that was also evident in subsequently developed metastasis in small intestine. Due to increased PD-L1 expression, immunotherapy with pembrolizumab was very successful even after previously administered 4 lines of systemic chemotherapy regimens.

This report has several limitations. First, we were not able to compare PD-L1 expression in the same tissue since the supraclavicular lymph node was totally excised for initial diagnosis and high expression level of PD-L1 was detected later on in irradiated right upper mediastinal mass (upper mediastinal lymph nodes). Also, we cannot fully exclude the possibility that previous chemotherapy lines could also have selected a PD-L1 positive clone that finally resulted in disease progression. Lastly, although heterogeneity of PD-L1 expression in nsclc has been previously reported [21], we were not able to quantify this in our patient.

Conclusion

We showed here that radiotherapy may not only result in a long-lasting treatment response but also could induce PD-L1 expression in initially PD-L1 negative tumor enabling thereby subsequent effective immunotherapy with pembrolizumab despite of previously received 4 lines of systemic chemotherapy regimens. Without any doubt, radiotherapy is an important treatment modality that can be incorporated effectively into treatment schedules of metastatic nsclc. Whether radiotherapy should be added to medical treatments at initial treatment phase (e.g. to induce PD-L1 expression), after systemic treatment as consolidative local therapy or later on, should be clarified in future clinical trials.

Acknowledgement

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Conflict of interest

Jaanika Narits and Hannes Tamm declare no competing interests.

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