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Complete tumor response of a locally advanced lung large-cell neuroendocrine carcinoma after palliative thoracic radiotherapy and immunotherapy with nivolumab

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Highlights

- Complete tumor response of an L-LCNEC to radiotherapy and immunotherapy.
- There is a possible synergetic effect of radiotherapy with immunotherapy.
- Immunotherapy seems to be efficient in carcinoma-LCNEC.
- **Immunotherapy could be effective in the neoadjuvant setting in L-LCNEC**

Abstract

Lung large-cell neuroendocrine carcinoma (L-LCNEC) is a rare subset of lung carcinoma associated with poor overall survival. Due to its rarity, little has been established about its optimal treatment in the advanced stage. We report the case of a 41-year-old woman diagnosed with an unresectable locally advanced L-LCNEC who presented an impressive tumor response to immunotherapy with nivolumab after non-curative thoracic radiotherapy. Salvage surgery was then performed, and pathologic analysis of the resected piece revealed the absence of residual viable tumor cells. Based on this case report, we discuss the literature regarding the efficacy of inhibitors of programmed death-1 protein (PD-1) in L-LCNEC and their use in association with radiotherapy and in the neoadjuvant setting.

Keywords: Lung large-cell neuroendocrine carcinoma; locally advanced stage; PD-1 inhibitor; radiation therapy; salvage surgery; synergistic effect

1. Introduction

Lung large-cell neuroendocrine carcinoma (L-LCNEC) accounts for 2–3 % of all lung cancers. It is a high-grade neuroendocrine carcinoma with some cytological features of non-small-cell lung cancer (NSCLC), but it also has biological, clinical, and prognostic characteristics of small-cell lung cancer (SCLC). Diagnosis is based on histological features consistent with NSCLC and identification, by immunohistochemistry (IHC), of at least one neuroendocrine

marker. The prognosis is poor, with 5-year overall survival rates of 13–57% for all, 27–62% for early, and <5% for metastatic stages.

Because of its rarity, the optimal treatment strategy for L-LCNEC is poorly known. Most recommendations are based on small prospective or retrospective studies. For non-metastatic L-LCNEC, recommendations are similar to those for NSCLC, favoring a surgical approach whenever feasible and chemoradiotherapy in the locally advanced stage. First-line treatment of metastatic or locally advanced L-LCNEC not suitable for chemoradiotherapy consists mainly of a platinum–etoposide doublet chemotherapy, similar to treatment for SCLC, while treatment options remain undefined for subsequent lines. However, first-line chemotherapy has limited efficacy in L-LCNEC, unlike SCLC. Moreover, oncogenic drivers targetable with tyrosine kinase inhibitors (TKIs) are extremely rare, and data concerning the efficacy of immunotherapy with inhibitors of programmed death 1 protein (PD-1) are limited [1–3].

We report a case of locally advanced L-LCNEC with a complete tumor response after palliative thoracic radiotherapy and treatment with nivolumab, a PD-1 inhibitor. We also discuss the literature regarding the efficacy of PD-1 inhibitors in L-LCNEC, as well as their use in association with radiotherapy and in the neoadjuvant setting.

2. Case presentation

In January 2017, after complaining of cough and dyspnea, a 41-year-old woman was diagnosed with a left upper lobe L-LCNEC. She had no significant medical history but was a current smoker. Histological analysis of transthoracic biopsies of the primary lesion revealed features of NSCLC, as well as a diffuse positivity for synaptophysin and chromogranin A and a Ki67 index of 80% on IHC. The diagnosis of L-LCNEC was confirmed in an expert center (by M.R. at Hôpital Erasme, Belgium). IHC also showed PD-L1 expression in 1–5% of cancer cells, while there was no ALK or ROS-1 expression. Next-generation sequencing (NGS) did not reveal any TKI-targetable mutation. TNM classification (eighth edition), based on fluorodeoxyglucose positron-emission tomography combined with computed tomography (FDG-PET CT) and contrast-enhanced head computed tomography (CT), was cT4 cN2 cM0, consistent with stage cIIIB. T4 was based on tumor size (7.9 cm) and strong evidence of parietal and mediastinal involvement (lung mass repulsing the trachea, enclosing the

ascending aorta, and occluding the left pulmonary artery). N2 was based on a hypermetabolic enlargement of mediastinal lymph nodes in stations 4L and 5, without cyto/histological confirmation because the extent of the tumor made it inoperable and untreatable with upfront curative chemoradiotherapy.

Induction chemotherapy combining cisplatin and etoposide was provided to the patient. CT performed after three cycles showed tumor progression, with an increase in size of the primary pulmonary tumor and the left hilar adenopathies, partially constricting the left main bronchus and pulmonary artery, and extending to the ascending aorta and esophagus. Due to the extent of the radiation field, curative chemoradiation was still not possible. However, because of parietal pain and the risk of esophageal and vascular compression, palliative thoracic radiotherapy was administered on the left pulmonary mass and mediastinum (13 x 3 Grays).

Two weeks after completion of radiotherapy, second-line systemic therapy with nivolumab (3 mg/kg every 2 weeks) was started. Despite limited data on the efficacy of immune checkpoint inhibitors (ICIs) in L-LCNEC, we followed NSCLC treatment guidelines and preferred nivolumab over second-line chemotherapy because of the poor efficacy of chemotherapy and the absence of strong recommendations for second-line and further treatments in L-LCNEC. CT evaluation after four cycles showed a partial tumor response, with a significant decrease in the left lung mass and mediastinal involvement. Additional tumor regression was observed after eight and 14 cycles.

In light of the impressive radiological tumor response, and considering the patient's young age and good performance status (ECOG 0), a complete tumor assessment was performed in order to evaluate the feasibility of salvage surgery. PET-CT showed a hypermetabolic lesion of 4.6 cm in the left upper lobe, extending to the hilum. There was no more sign of mediastinal invasion or of bronchial, vascular, or esophageal tumor compression.

Endobronchial ultrasound followed by mediastinoscopy confirmed the absence of mediastinal involvement. Brain MRI excluded brain metastases. TNM classification became ycT2a ycN0 ycM0, consistent with stage ycIb. Hence, a left upper lobectomy with venous graft bypass between the left pulmonary artery and the inferior lobar artery together with mediastinal lymph-node dissection were performed in December 2017, 7 months after the initiation of nivolumab. Because of insufficient perfusion of the remaining left lower lobe, a left pneumonectomy had to be performed. Histological analysis of the resected lung and

lymph nodes showed an absence of viable tumor cells, while pulmonary necrosis and fibrosis were observed. Therefore, pathological TNM classification (eighth edition) was ypT0 ypN0 (R0). Nivolumab was not continued after the surgery and no other adjuvant treatment was planned. In August 2018, 8 months after the surgical resection, the patient was still in complete remission and free of treatment.

3. Discussion

Though considered as first choice in first-line treatment of advanced-stage L-LCNEC, the platinum–etoposide doublet is less effective in L-LCNEC than in SCLC. Recently, it has been demonstrated that L-LCNEC is a biologically heterogeneous group of tumors comprising two main subsets based on genomic signatures: an SCLC-like subset (*P53+RB1* co-mutation/loss and other SCLC-type alterations) and an NSCLC-like subset (lack of co-altered *TP53+RB1* and a nearly universal occurrence of NSCLC-type mutations (*STK11*, *KRAS*, and *KEAP1*)) [4]. A retrospective review of 79 stage IV L-LCNEC cases showed that tumors with a wild-type *RB1* gene and RB1 protein expression had longer overall survival and progression-free survival when treated with a platinum–gemcitabine or platinum–taxane doublet as compared to the standard platinum–etoposide chemotherapy, while no association was found for L-LCNEC with an *RB1* mutation or lost RB1 expression [5]. Analysis of our patient’s tumor by NGS revealed a G105C mutation in *TP53*, while there was no mutation in *STK11* and *RB1*, which was compatible with an NSCLC-like subtype. The absence of *RB1* mutation is a possible explanation for the poor response to cisplatin–etoposide in our patient, even though prospective randomized clinical trials are required to guide the treatment of L-LCNEC according to genomic subtypes. Highlighting the complexity of L-LCNEC, a recent genomic and molecular profiling of 75 L-LCNEC cases confirmed the existence of two L-LCNEC subtypes with mutational patterns close to those of SCLC or NSCLC, but demonstrated that this was not correlated with the neuroendocrine profile: type I L-LCNECs showed inactivation of *TP53* and *STK11* and/or *KEAP1* genes, as in NSCLC, but presented a neuroendocrine profile close to that in SCLC, while type II L-LCNECs were enriched for bi-allelic inactivation of *TP53* and *RB1*, as in SCLC, but differed from SCLC in reduced neuroendocrine markers, high activity of the NOTCH pathway, and upregulation of immune-related pathways [6].

PD-1 inhibitors, such as nivolumab or pembrolizumab, are ICIs proven to improve survival in advanced-stage NSCLC [7,8], but data on their efficacy in L-LCNEC are rare and limited mainly to a few case reports/series. In a first report, a metastatic L-LCNEC presented a surgically confirmed complete response to a PD-1 inhibitor associated with a CTLA-4 inhibitor, another ICI [9]. A second paper reported two cases of metastatic L-LCNEC treated with nivolumab in sixth- and third-line treatments, with significant tumor reduction [7]. In a third case report, a significant and durable tumor response was obtained with pembrolizumab in third-line treatment of a metastatic L-LCNEC with low PD-L1 expression but high tumor mutation burden (TMB) [1]. Finally, a fourth paper reported two cases of L-LCNEC treated with nivolumab in second line, one presenting complete response and the other stable disease [10]. Similarly, our case also supports the idea that immunotherapy might be effective in L-LCNEC, even if PD-L1 tumor expression is low. Of note, L-LCNEC response to ICIs has also been correlated with high TMB, independently of PD-L1 expression [1]. Retrospective analysis of our patient's tumor revealed a high TMB in two different laboratories (27.74 mutations/Mb at Hôpital Erasme and 33.86 mutations/Mb at University Hospital Antwerp, Belgium), which may explain our patient's good response to nivolumab. Clinical trials are ongoing to evaluate ICI efficacy in neuroendocrine cancers, including L-LCNEC, and the correlation of tumor response to biomarkers such as PD-L1 expression and TMB.

In this context of limited data on the efficacy of PD-1 inhibitors in L-LCNEC, even less is known about their use in association with radiotherapy. Preclinical studies showed synergistic efficacy of radiotherapy combined with ICI, irrespective of the tumor type. Radiation may interfere with the tumor's capacity to evade immune detection by generating inflammation, modifying the tumor microenvironment, activating dendritic cells, and causing tumor infiltration by lymphocytes. On the other hand, immunotherapy associated with radiation might enhance its abscopal effect, potentially reducing the metastatic progression rate. Without associated treatments stimulating immune reaction, the abscopal effect is rare (around 50 documented cases in the literature) [11]. Immunotherapy combined with radiotherapy in NSCLC is currently under investigation in several clinical trials. PACIFIC, a phase III trial, showed that durvalumab, a PD-L1 inhibitor, administered for 12 months as consolidation after curative chemoradiotherapy improved survival in locally advanced NSCLC. The trial included only two cases of L-LCNEC, with no specific details on their outcome [12]. Although strong evidence is lacking, our case supports the hypothesis of a

synergistic effect of sequential treatment by radiotherapy and immunotherapy. Indeed, the radiation dose administered was insufficient to ensure complete tumor response. Moreover, the low PD-L1 tumor expression was not predictive of a sustained response to ICI, although PD-L1 expression is known to be heterogeneous, possibly underestimated on small biopsies, and has not yet been correlated with L-LCNEC response to ICI. We hypothesize that tumor destruction and microenvironmental modifications caused by radiotherapy triggered a robust response to ICI by massively releasing tumor antigens, hence triggering a more sustained immune reaction.

Complete tumor responses to PD-1 inhibitors alone in NSCLC are rare. For instance, in CheckMate 57, a phase III trial comparing nivolumab to docetaxel in second-line treatment of advanced-stage NSCLC, only 4/292 cases of non-squamous NSCLC (1%) presented a complete response to nivolumab [7]. Nevertheless, the complete response rate to ICI in L-LCNEC is unknown and may be higher than in other NSCLC subtypes, possibly due to high TMB, as in our patient's tumor. To support this, it has recently been reported that, in a small cohort of 37 patients with L-LCNEC, TMB was significantly higher in L-LCNEC than in unselected NSCLC and SCLC cases, while it did not differ by L-LCNEC genomic subtype [13]. We may also speculate that high TMB may be responsible for a stronger synergistic effect of radiotherapy and ICI.

Although nivolumab was initially prescribed in a non-curative perspective in our patient, we retrospectively considered it as a neoadjuvant treatment before a radical surgical resection because of the impressive tumor response. However, the benefit of immunotherapy in the neoadjuvant setting, combined or not with radiotherapy, is poorly known in NSCLC. A recent trial evaluated the feasibility and safety of PD-1 inhibition before surgical resection in early-stage NSCLC. Results were encouraging, showing few side effects, no delay in surgery, and a major pathological response to two doses of nivolumab in 45% of the resected tumors [14]. Large-scale prospective trials are still ongoing to confirm these results and evaluate potential survival benefits. A case series also reported initial data on five advanced-stage (four metastatic and one stage IIIA) NSCLC resections after ICI. The conclusion of this study was that pulmonary resection after immunotherapy is feasible without major complications. As previously mentioned, the study reported the case of a patient with L-LCNEC who benefited from lobectomy with lymph-node dissection after responding to immunotherapy combining

PD-1 and CTLA-4 inhibitors, with no evidence of residual cancer [9]. As opposed to our case, there was no association with radiotherapy, but rather with another ICI.

4. Conclusion

The L-LCNEC case we report is of special interest because of the complete response to nivolumab after palliative thoracic radiotherapy in this rare subset of lung cancer characterized by a poor prognosis. ICI efficacy in L-LCNEC has not yet been evaluated, but might constitute a breakthrough in terms of survival. The association between immunotherapy and radiotherapy might also represent a new therapeutic approach in NSCLC based on their synergistic effects. Finally, the use of immunotherapy in a neoadjuvant setting might allow surgical resection of tumors initially considered inoperable. Still, these new therapeutic perspectives will raise a number of questions. The first and main concern will be the possibly increased risk of high-grade toxicity caused by combined therapies. Second, the therapeutic sequence of therapies will be subject for debate. And last but not least, the optimal duration of immunotherapy when combined with radiation or administered as induction before surgery will need to be established.

Disclosure statement

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Figure legends

Figure 1: Evaluation by fluorodeoxyglucose positron-emission tomography combined with computed tomography (FDG PET-CT). (A) At diagnosis. The upper left lobe mass was considered as the primary tumor while the hilar mass was considered as regional lymph-node invasion. *Color online.* (B) At the time of surgical feasibility assessment after three cycles of cisplatin and etoposide in first-line therapy, palliative thoracic radiotherapy in second-line therapy, and 14 cycles of nivolumab in third-line therapy. The primary tumor has reduced in terms of both hypermetabolism and size, and the hilar mass has disappeared. *Color online.*

Figure 2: Pathology. (A) At the time of diagnosis. *Left upper picture:* hematoxylin and eosin (HE) staining shows neoplastic cells with morphological characteristics of non-small-cell lung cancer. *Right upper picture:* immunohistochemistry reveals diffuse expression of synaptophysin, leading to the diagnosis of lung large-cell neuroendocrine carcinoma. Picture magnification: 20x; scale bar: 50 μm . *Color online.* (B) At the time of surgery. *Left lower picture:* HE staining shows normal lung tissue adjacent to a necrotic area of former cancer tissue, with no residual viable cancer cells. *Right lower picture:* HE staining shows a necrotic area of former cancer tissue, with no residual viable cancer cells. Picture magnification: 20x; scale bar: 50 μm . *Color online.*