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Clinical Case Seminar **A3 (1-6)**

Challenges and perspectives in the multidisciplinary management of well-differentiated lung neuroendocrine tumours: a case report

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Abstract

Neuroendocrine tumours of the lung represent a distinct subgroup of primary lung neoplasms, characterized by particular morphologic, ultrastructural, immunohistochemical and molecular peculiarities and different biological behavior. A detailed pathological diagnosis including immunohistochemistry, Ki-67, mitotic rate and necrosis status can be helpful to identify the different subtypes. The optimal management of advanced well-differentiated lung neuroendocrine tumors is still debated and can be very challenging for the clinician. Currently, no established therapeutic algorithm exists for patients with unresectable or metastatic typical carcinoids and atypical carcinoids. To highlight the importance of a multidisciplinary management we report the case of a patient affected by unresectable lung neuroendocrine tumors, who has benefited from integration strategy, resulting in complete surgical excision of the tumour.

Key-Words: Neuroendocrine tumours; carcinoids; multidisciplinary management

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Introduction

Neuroendocrine tumors (NETs) arise from neuroendocrine cells in various anatomic sites, most commonly the gastrointestinal and pulmonary systems. Bronchopulmonary or lung NETs represent approximately 25% of primary lung neoplasms and 20%–25% of primary NETs (1).

In the 2015 World Health Organization classification, lung NETs form a cluster of diseases that can be subdivided into prognostic subtypes with possible implications for choice of therapy (2).

Over the years, several reports have commented on the risk of overinterpreting lower respiratory tract carcinoid tumors, either typical or atypical as small-cell carcinomas in small biopsy tissue fragments or cytologic samples (3).

A detailed pathological diagnosis including immunohistochemistry, Ki-67, mitotic rate and

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necrosis status can be helpful to identify the different subtypes.

Successful treatment of lung NETs relies on accurate and timely diagnosis.

The optimal management of advanced well-differentiated lung NETs is still debated, due to their relative rarity and the lack of prospective randomized studies. Therefore, the management of advanced lung NETs should be discussed by a multidisciplinary team (4).

Currently, no established systemic treatments exist for patients with unresectable or metastatic typical carcinoids and atypical carcinoids.

Therapeutic options for advanced pulmonary carcinoids include chemotherapy, Somatostatin (SST) analogs (SSAs), Interferon, Everolimus, or the new option of Peptide Receptor Radionuclide Therapy (PRRT) (5).

To highlight the importance of a stepwise multidisciplinary approach to effectively manage the disease, we present the case of an unresectable pulmonary NET, treated with integration modality, resulting in a complete surgical excision.

Case Report

In December 2014, a 49 years old male patient, current smoker, with family history of SCLC (small cell lung cancer) in good clinical conditions (Performance status ECOG 0), referred to our hospital suffering from cough and fever. The radiological work-up with a contrast-enhanced computed tomography (CT) scan had revealed complete atelectasis of the upper lobe of left lung, with a solid lesion of 7 x 4 cm determining obstruction of segmental bronchus for the superior lobe, with mediastinal lymph node involvement. The bronchoscopy had evidenced an infiltrative-growing mass that obstructed the left upper lobe.

The pathology report, performed in a small peripheral hospital, was consistent with a poor differentiated carcinoma of the lung with neuroendocrine features (NSE+; Cromogranin+; CD 56+).

No further pathological data were available. A pathological revision in our hospital was suggested but patient refused the option.

The disease staging was completed with a fluorodeoxyglucose (^{18}FDG) Positron Emission Tomography (PET) scan, that confirmed a clinical stage cT2bN3M0 (Stage IIIB-TNM 7th Edition) with a Standardized Uptake Value (SUV) max in left mass of 4.3. The extension of the disease and the high volume to irradiate increased risk of severe toxicities from concomitant radiotherapy and chemotherapy. Consequently, in January 2015 he started sequential a program of chemo-radiotherapy with three courses of Cisplatin-Etoposide at standard doses. After the conclusion of chemotherapy tumor re-staging with contrast-enhanced CT demonstrated a stable

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disease according to RECIST 1.1 criteria (left lung lesion 75 mm versus 70 mm; reduction of mediastinal lymph nodes short-axis diameter >30%). ^{18}FDG-PET scan was performed and a modest increase of the FDG uptake (SUV max: 5.6 vs. 4.3) was reported.

In April 2015 the therapeutic program was completed with the sequential radiotherapy using the Intensity-modulated radiotherapy (IMRT) technique with a dosage of 50 Gy on tumor mass and mediastinal lymph nodes and a 10 Gy boost on the primary tumor.

Contrast-enhanced CT and ^{18}FDG-PET scan performed in July 2015, after sequential chemo-radiotherapy completion, documented a substantial stable disease.

Given the relative low sensitivity to chemo-radiotherapy, after discussion in the multidisciplinary team, the pathological revision was considered indispensable to continue therapeutic program. Tumor was reclassified as carcinoid (absence of necrosis, no evidence of mitotic figures, and a low mitotic index→Ki-67 3%). However, mitotic count was performed in a small field area and the presence of necrosis was not evaluable. Consequently, the distinction between typical and atypical carcinoid remained unclear.

In August 2015 a ^{68}Gallium (Ga^{68}) PET was performed, showing high expression levels of Somatostatin receptor in the upper lobe of the left lung.

Consequently a Peptide Receptor Radionuclide Therapy (PRRT) with ^{177}Lutetium (Lu)-Dotatoc was programmed and started in October 2015

A ^{18}FDG-PET scan after 3 courses of ^{177}Lu-Dotatoc PRRT revealed a good metabolic response with a ~ 50% reduction of FDG uptake in the left lung lesion (SUV max of 7.5 vs. 14.5 in July 2015).

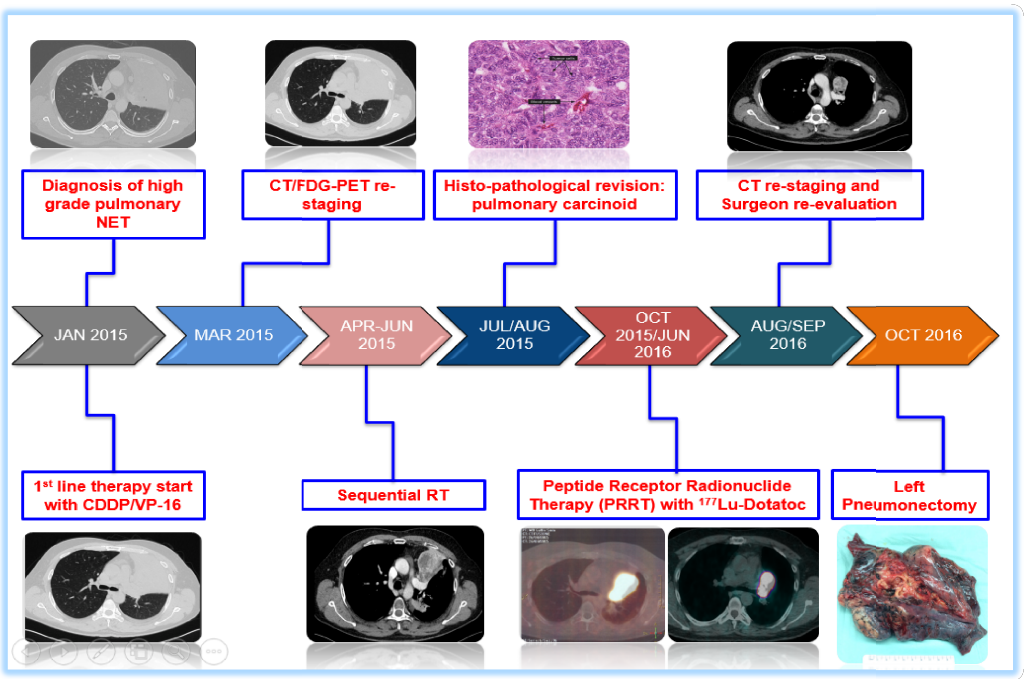

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Fig.1 Clinical course

^{177}Lu-Dotatoc PRRT was continued up to 6 courses, with good tolerance and no relevant adverse events. The CT/^{68}Ga-PET restaging after PRRT treatment documented a significant reduction of tumor extension (47 x 29 mm) compared with baseline, with partial atelectasis of upper lobe of the left lung and no pathological lymph nodes, with a with substantial stability of SUV max values in the primary tumor, compared with August 2015.

Based on the favorable response with ^{177}Lu-Dotatoc PRRT, imaging restaging, age, good clinical conditions, tumor histology and disease staging, the case was revaluated by the multidisciplinary team and in October 2016 the patient underwent a left pneumonectomy.

The pathology report showed a complete pathologic response to ^{177}Lu-Dotatoc PRRT, with no evidence of active disease in the resected lung. A standard follow up program was started.

Discussion

With the term lung NETs, in the 2015 WHO classification are included a series of different histo-pathological entities, including: SCLC and combined SCLC; Large cell neuroendocrine carcinoma (LCNEC) and combined LCNEC; and Carcinoid tumors, consisting of Typical Carcinoid (TC) and Atypical Carcinoid (AC) tumors. Pulmonary carcinoids (PCs) represent ~30% of all well-differentiated NETs throughout the body, whereas LCNEC and SCLC accounts for ~90% of all poor-differentiated neuroendocrine carcinomas (1,2,5,6,). The implementation of the WHO classification in daily practice can be difficult due to: infrequent exposure in general pathology practice; recognized inter-observer variation, even among experienced pathologists; the requirement of surgical resected tissue for assessment of all morphological criteria, making diagnosis based on small biopsy and cytological specimens tenuous; the difference between the pulmonary, thyroid, and gastrointestinal classification system for NETs with regard to advised nomenclature and mitosis/Ki67 evaluation (7).

Ki-67 index is a useful diagnostic marker for neuroendocrine tumors. The role of Ki-67 is mainly to separate the high-grade neuroendocrine tumours from the carcinoids.

Conflicting results have been reported in separating typical from atypical carcinoid tumors (2). Consequently is not recommended in this setting (8).

Somatostatin receptor imaging may be useful to determine the disease burden in such patients.

Whenever available, the use ^{68}Ga-DOTATE PET should be preferred to SRS (Somatostatin receptor scintigraphy) for the study of patients with low/intermediate grade NETs (5). ^{68}Ga-DOTATE PET may be used not only for disease staging, but also to evaluate patients suitable for Peptide Receptor Radionuclide Therapy (PRRT).

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The optimal management of advanced well-differentiated lung NETs is still debated, due to their relative rarity and the lack of prospective randomized studies and their management should be discussed by a multidisciplinary team (4). Therapeutic options for advanced pulmonary carcinoids include Somatostatin (SST) analogs (SSAs), Interferon, Everolimus, chemotherapy or Peptide Receptor Radionuclide Therapy (PRRT) (5).

Conclusions and Future Perspectives

The present case underlines the importance of a detailed pathological diagnosis of lung NETs to identify the histotype and define therapeutic strategy, suggesting that second-opinion may be useful in selected cases, especially in small biopsies.

A multidisciplinary management of lung NETs represent the best approach to personalize treatment and obtain the better results.

PRRT with ^{177}Lutetium is an intriguing therapeutic strategy for low/intermediated grade SSTR-expressing lung NETs and could be an option as neoadjuvant therapy in patients with unresectable pulmonary carcinoids.

The therapeutic landscape of lung NETs is rapidly evolving and the promising results of recent clinical trials RADIANT-4 and LUNA (9,10) have supported the introduction of Everolimus, a new therapeutic option in advanced/metastatic setting.

Conflicts of Interest: There is no potential conflict of interest, and the authors have nothing to disclose. This work was not supported by any grant.

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