

Triple Negative Oligometastatic Adrenal Lung Cancer: A Multimodal Therapeutic Strategy about a Case and a Review of the Literature

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Abstract

Background: Lung cancer is the leading cause of cancer deaths worldwide. About 30 to 50% of patients turn up with a metastatic disease at the time of diagnosis, and approximately 40% of patients treated for curative purposes will develop metastases throughout their lives. Some patients may have only one to five secondary lesions in a limited number of organs, realizing what is called an oligometastatic disease. Here, we describe the case of a patient with non-small-cells lung cancer Oligometastatic triple-negative, stage IV at the adrenal level having benefited from multimodal treatment including chemotherapy, surgery and local radiotherapy.

Case presentation: We report case of a 56-year-old patient with no notable history other than being a former smoker. A CT scan revealed the presence of a left pulmonary tumor class T1N2, a Guided CT biopsy revealed lung adenocarcinoma. The expansion report FIND a left adrenal metastasis without other secondary localization, particularly bone or cerebral. The clinical examination found patient PS 1, in good general. A molecular study complementary to the histological one showed an EGFR, ALK status, non-mute, PDL1 negative. The patient was receiving palliative chemotherapy cisplatinemetrexed type, with good premedication. After chemotherapy treatments, the reassessment indicated a partial response of more than 50% of the disease at the lung level, lymph node and adrenal, however, the patient would not tolerate maintenance-based Hematologic pemetrexed or the decision to discontinue systemic therapy. After a free interval of 5 months, the disease progressed at the adrenal and lung level but without new lesions compared to the CT scan at the start. The patient had received a second line of weekly paclitaxel chemotherapy after 4 months of treatment and stabilization of the disease, peripheral neuropathy secondary to treatment had set in and treatment ceased. The control after 3 months, showed no progression of the disease. Besides, the patient had benefited from an adrenalectomy at first. Two months after adrenalectomy, a lung resection was performed by thoracotomy and the. A month and a half after the patient had received a mediastinum radiotherapy by IMRT at a dose of 66 Gy. After a two-year follow-up, the last control showed no sign of progression of the disease, the patient was in good health showing no secondary complications signs.

Discussion and Conclusion: Oligometastatic lung cancers are rare but deserve to be well known because they can often benefit from the addition of treatments to loco-regional chemotherapy. Oligometastatic patients represent a heterogeneous group, and the data from the literature are the result of limited retrospective series. This class of patients requires maximum effort to preserve the maximum chances for complete remission of the disease and an extended survival.

Keywords: Lung; Adrenalectomy; Oligometastatic; Adenocarcinoma; EGFR; ALK status; Outcome

Abbreviations: EGFR: Epidermal Growth Factor Receptor; ALK: Anaplastic Lymphoma Kinase; PDL1: Programmed Death-Ligand 1; CT: Computed Tomography; RNA: Ribo-Nucleic Acid; PET: Positron Emission Tomography; NCCN: The National Comprehensive Cancer Network

Introduction

Lung cancer is the leading cause of cancer deaths worldwide. About 30% to 50% of patients turn up with a metastatic disease at the time of diagnosis, and approximately 40% of patients treated for curative purposes will develop metastases throughout their lives. If many patients have disseminated metastatic diseases, some may have only one to five secondary lesions in a limited number of organs, realizing what is called an oligometastatic disease [1,2].

A recent randomized survey, Gomez [3], has questioned this controversial entity. The standard of taking in charge metastatic cancers is a chemotherapy whose objective is palliative [4]. However, some patients affected by this disease [2] could benefit from a medical care with a curative aim calling for discussions during the multidisciplinary meetings to properly select the best patients. The ideal treatment for each location, dealing with the main tumor, the therapeutic sequence,

and specify the benefit in terms of survival and quality of life.

Here, we describe the case of a patient with non-small-cells lung cancer Oligometastatic triple-negative, stage IV at the adrenal level having benefited from multimodal treatment including chemotherapy, surgery and local radiotherapy.

Case Presentation

This is the case of a 56-year-old patient with no notable history other than being a former smoker (50 Packets-years but weaning for 20 years). He had episodes of hemoptysis with loss of weight and normal clinical

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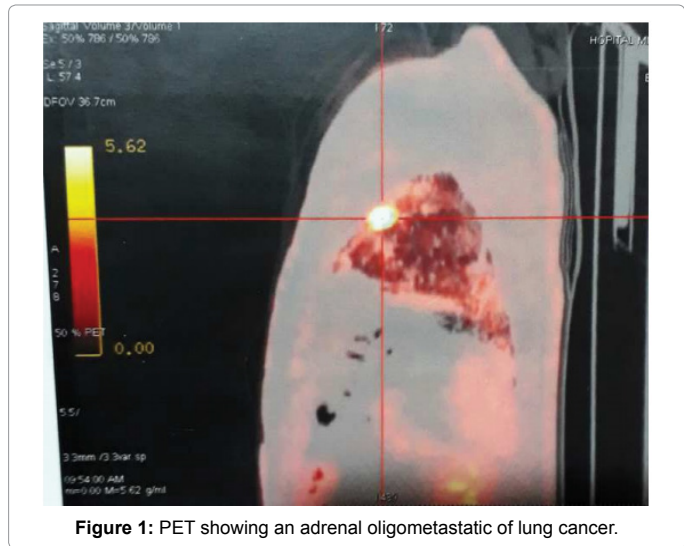
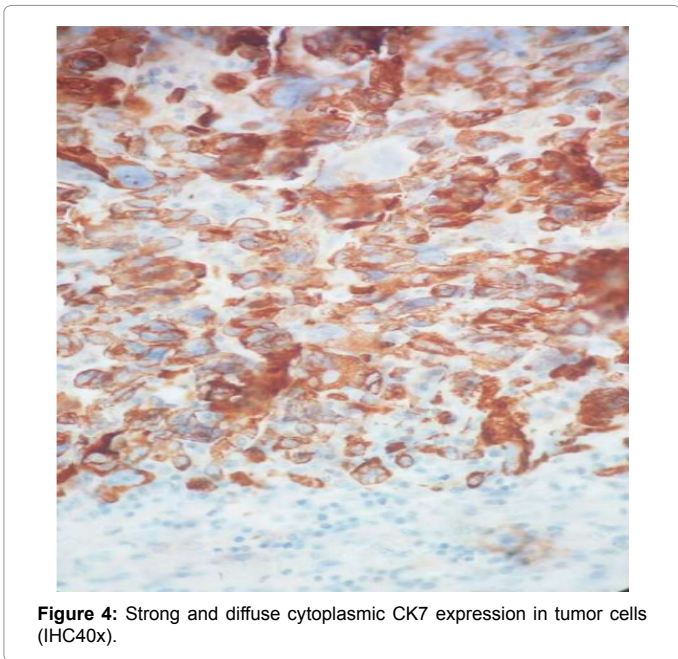
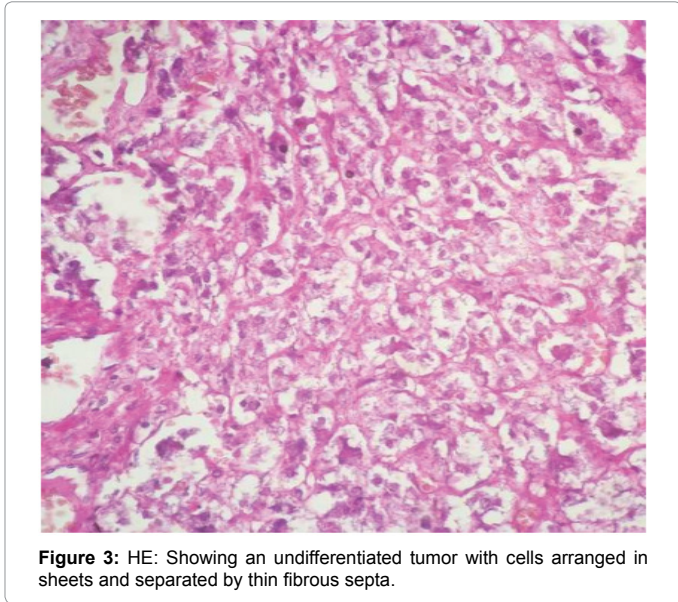
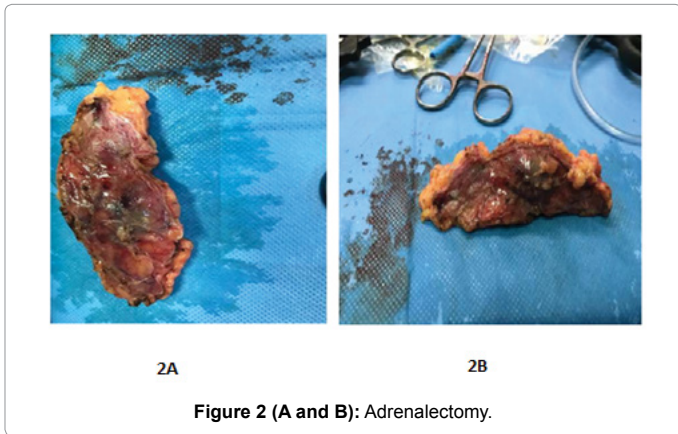
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examination. A CT scan revealed the presence of a left pulmonary tumor class T1N2, a Guided CT biopsy revealed lung adenocarcinoma. The expansion report FIND a left adrenal metastasis without other secondary localization, particularly bone or cerebral.

The clinical examination found patient PS 1, in good general condition with clinical examination without any peculiarity. The biological assessment was correct on the hematological, liver, renal and metabolic as well as respiratory studies. A molecular study complementary to the histological one showed an EGFR, ALK status, non-mute, PDL1 negative. The patient was receiving palliative chemotherapy cisplatinemetrexed type, with good premedication. After chemotherapy treatments, the reassessment indicated a partial response of more than 50% of the disease at the lung level, lymph node and adrenal, however, the patient would not tolerate maintenance-based Hematologic pemetrexed with thrombocytopenia and neutropenia grade III and IV and grade IV asthenia or the decision to discontinue systemic therapy. After a free interval of 5 months, the disease progressed at the adrenal and lung level but without new lesions compared to the CT scan at the start. The patient had received a second line of weekly paclitaxel chemotherapy after 4 months of treatment and stabilization of the disease, peripheral neuropathy secondary to treatment had set in and treatment ceased. The control after 3 months, showed no progression of the disease.

Facing this evolutionary profile of this oligometastatic disease and after discussions with the multidisciplinary staff, a multimodal therapeutic strategy was developed. The PET scanner (Figure 1) eliminated the presence of other secondary locations apart from cervical fixation of probably inflammatory origin to monitor. Besides, the patient had benefited from an adrenalectomy at first (Figures 2A and 2B).

The anatomopathological and the immunohistochemical studies revealed a metastasis of an adenocarcinoma of lung origin (Figures 3-5). Two months after adrenalectomy, a lung resection was performed by thoracotomy and the histological study confirmed the result of the initial biopsy (Lung ADENOCARCINOMA) (Figure 6). A month and a half after the patient had received a mediastinum radiotherapy by IMRT at a dose of 66 GY. After a two-year follow-up, the last control showed no sign of progression of the disease, the patient was in good health showing no secondary complications signs.



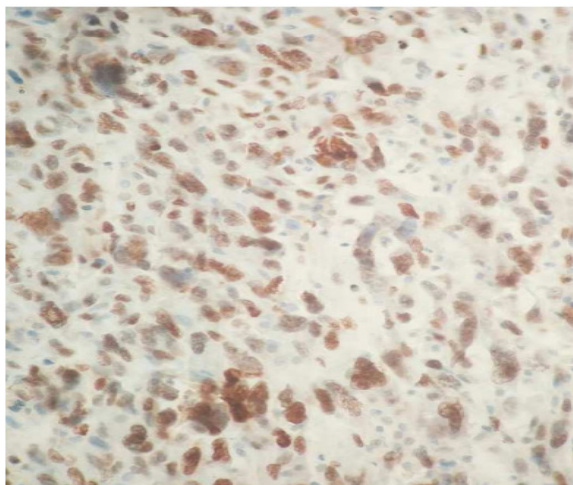


Figure 5: Tumor cells showed nuclear stain for TTF1 (IHC40x).

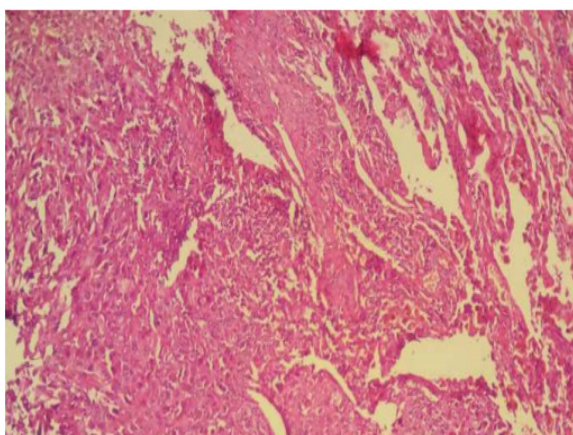


Figure 6: Photomicrograph showing a lung parenchyma infiltrated by a solid adenocarcinoma. Hematoxylin eosin staining, 20x.

Discussion

The therapeutic care of patients with non-small cell lung carcinoma Stage IV Patients calls for Palliative Chemotherapy when Targeted Anti EGFR or Anti Therapies ALK and immunotherapy are not possible. The prognosis of patients is unclear and the rate of response to a standard chemotherapy doublet based on platinum salts does not exceed 20% to 30% [4]. The concept of oligometastatic disease was described in 1995 by Hell-man and Weichselbaum about breast cancer [2]. It is a metastatic disease developed (less than five lesions), more favorable prognosis, accessible to local treatment, thus justifying curative care aiming at lengthening not only the survival but also the improvement of the quality of life [1,5]. The biological rationale Underlying the oligo- or polymetastatic development of a tumor is still poorly understood.

The identification of genetic signatures linked in part to interferon could explain this oligometastatic potential [6]. In addition, recent work has made it possible to classify patients into two phenotypes according to the expression of microRNAs (miR-200c): Those among whom the disease progresses towards a diffuse polymetastatic recurrence and those whose relapse shows up in the form of some metastases [7].

In a consensual way, a patient is said to be oligometastatic when he presents from one to five metastases all accessible to local treatment. This description implies a criterion that of the indolence of the tumor. The new classification of the IASLC takes account of this situation. Four situations can be described [8]:

- A patient with 5 or fewer metastases in a limited number of organs, all accessible to local radical treatment.
- A metastatic patient becoming oligometastatic after a systemic treatment.
- A patient with one to five metachronous recurrences after curative treatment of the lesion initially accessible to local radical treatment.

The most frequently discussed situation in the medico-surgical field and in the literature is the unique synchronous brain metastasis. Our reported case is found in this configuration but with adrenal metastasis instead of a cerebral one.

A recent meta-analysis included 757 patients from 20 different origins with non-small cell lung carcinoma with one to five synchronous secondary locations or metachrones, treated by surgical metastasectomy or irradiation, in combination with a curative treatment of the primitive lesion; the same strategy was adopted for our patient. The average duration of the overall survival was 26 months, the 1-year and 5-year survival rates were 70.2% and 29.4% [9]. However, most of the data stem from small non-randomized series, with great heterogeneity in the selection of patients and the therapeutic strategy used.

The number of metastatic sites is known to be an independent prognosis factor and the presence of a single metastatic site appears as a favorable prognostic factor for survival [10].

Earlier recommendations, ACCP 2013 [11], and recent test data [12] insist on the N0 or maximum N1 character of the patients. A precise ganglion staging is imperative. The CT scan associated with EBUS or EUS or even mediastinoscopy are imperative to rule out patients with N2 involvement which was the case with our five-year survival of our N2 negative patients for example; treated with a curative intent indicating 58% versus 0% in the N2 positive group. A good “performance status” also seems to be a logical criterion for selecting these patients who will undergo an aggressive multimodal treatment, NCCN 2017 [13]. It is important to remember that our patient was in a very good general condition with indolent illness which motivated a maximum perseverance even though it was an N2 to PET.

The mutational status of patients is certainly an important prognostic factor. Subjects with an EGFR mutation have a better overall prognosis, but it is difficult to predict for the moment if they will benefit from an aggressive care as compared to a maintenance treatment in accordance with their mutation. In the randomized series, Gomez [3], the existence of an interest mutation is a factor that increases the progression-free survival, but the analysis is conducted on all patients in the trial (including consolidation and maintenance group). It is therefore not possible to say whether an EGFR mutated patient will benefit from a local treatment associated with a systemic treatment. The case presented is a triple negative, carrying no EGFR, ALK and does not express PDL1.

The treatment of lung oligometastatic cancer is multimodal. The sequence therapy will often meet the priority of treating certain symptomatic locations, but the key point of the discussion is that it is a metastatic disease therefore it requires a systemic treatment. Another major point is the control of this systemic disease, as illustrated by

the randomized trial published in the *Lancet Oncology* by Gomez [3]. The “maximalist” care of a patient in an Oligometastatic situation implies a non-progression under systemic treatment. It seems that this “chemo-selection” is an additional criterion in the selection of patients. It is important to note here that our patient never developed a new metastatic localization undergoing a systemic treatment and that the only progression after ceasing the disease maintenance under pemetrexed due to poorly tolerated treatment limited to a reactivation of the disease regarding the same targets as the starting point, primary lung injury and adrenal injury.

The treatment of the primary tumor, which ideally is a T1-3 tumor N0-1 at a WHO patient 0-1, is logically a classic surgical treatment of a lobectomy type with radical mediastinal dissection. Here again the development of assisted thoroscopic and robotic surgery techniques has reduced the morbidity and stay duration. The prognostic factors observed are the N0 character, the quality of the resection, the histology adenocarcinoma and stages I-II [14,15]. However, our patient has benefited from a metastectomy combined with an external radiotherapy at the mediastinal level due to its N2 lymph node status and to limit post-surgical secondary complications.

Adrenal metastases are the most widely studied sites but in general clinical cases in a monocentric study reporting thirty-seven cases, the Prognostic role of mediastinal lymph node involvement appears to be major [16]. The five-year survival was 34% for patients operated on by adrenalectomy, 0% for those not operated ($p=0.002$).

In this study, there was no difference according to whether adrenal metastases were synchronous or metachronous, in contrast, survival was significantly higher in patients operated on for homolateral adrenal metastasis compared with patients operated for contralateral metastasis (83% vs. 0%). This difference is probably since adrenal homolateral metastases would correspond to lymphatic and non-haematogenic migration. Our case had a synchronous homolateral adrenal metastasis and the evolution was consistent with the literature data since after two years of recession there was no adrenal gland recurrence. Non-surgical treatment of the initial lesion, radiotherapy or radio-chemotherapy is an alternative. It is highly recommended in the locally advanced forms. Several cohorts of non-surgically treated patients have survived longer with a good local control of thoracic disease by radio chemotherapy [17,18].

In the randomized series published by Gomez [3], the treatment of the lesion only 3 out of 25 patients in the local consolidation group; for our patient the decision was to merge between a surgery for lung injury and an external radiotherapy for lymph node involvement. No randomized phase III trial treatment for patients with curative purposes has been envisaged so far, or even which technique has been used or again what it has done. Two randomized phase II trials are currently being resorted to: the SABR-COMET trial (Stereotactic Ablative Radiotherapy for Comprehensive Treatment of Oligometastatic Tumors).

NCT01446744 and NCT01725165 that assess the effectiveness of surgery or consolidation radiotherapy after induction chemotherapy in the non-small cell lung carcinoma (II).

Conclusion

Oligometastatic lung cancers are rare but deserve to be well known because they can often benefit from the addition of treatments to loco-regional chemotherapy. Oligometastatic patients represent a heterogeneous group, and the data from the literature are the result of

limited retrospective series; it is therefore difficult to assess the overall survival in this situation.

These treatments are often capable of leading to long, comparable survivals to those observed in non-metastatic resectable forms that have been demonstrated through the study of this clinical case and their identification could be assisted by biological differences concerning the expression of microRNAs.

This class of patients requires maximum effort to preserve the maximum chances for complete remission of the disease and an extended survival.

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Availability of Data and Materials

All data generated or analyzed during this study are included in this published article. The authors presented all the necessary information about their case report in the manuscript. However, about the literature review, all used literature was referenced appropriately in the “References” section.

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