Sarcomatoid Lung Carcinoma and Immunotherapy: Report Of 3 Cases and Review of the Literature

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1. Abstract
The Pulmonary Sarcomatoid Carcinomas (PSC) represents only a small percentage of the cases of non-small cell lung cancer (0.1-0.4%). These tumours are more frequent in older patients with a heavy smoking habit and have been considered to be chemo-refractory tumours in advanced stages of the disease. Considering the few treatment possibilities of these patients, we have decided to present three cases, treated in our hospital and to carry out a bibliographic review of the immunotherapy (IO) efficacy in PSC. Currently the data of IO in patients with PSC is limited; however, the results in the real-world data show not only very good tumour response rates to treatment, but also remarkably long survival, compared to historical data for these neoplasms.

2. Introduction
The lung cancer cases and deaths are rising in the whole world. According to the GLOBOCAN data 2.09 million new cases (11.6% of total of new cancer cases) and 1.76 million deaths (18.4% of total of deaths cancer) of lung cancer were estimated (2021) [1]. Although there is some variability among different regions and distribution by sex, the main cause of lung cancer is the smoking habit (80% of the cases). The adenocarcinoma and the squamous cell carcinoma are the most frequent histological types of the non-small cell lung cancer (NSCLC). However, the term NSCLC includes a big number of neoplasms, each one with different morphology, molecular profile and clinical evolution [2]. Among all these entities, the Pulmonary Sarcomatoid Carcinomas (PSC) stand out, which represent a group of malignant neoplasms with a low prevalence [3]. The term of sarcomatoid carcinoma includes the pleomorphic carcinoma, carcinosarcoma, pulmonary blastoma, spindle cell carcinoma and giant cell carcinoma [2]. The PSC represents only a small percentage of the NSCLC cases (0.1-0.4%) which are more frequent in older patients with a heavy smoking habit. Until now, PSCs have been considered to be chemo-refractory tumours in advanced stages of the disease. However, several studies have shown a modest survival benefit in patients treated with adjuvant chemotherapy (CTH), after a complete surgical resection [4]. Considering the few treatment possibilities of these patients, we have decided to present three cases, treated in our hospital and to carry out a bibliographic review of the immunotherapy (IO) efficacy in PSC. All patients gave us their consent to access their medical records and to analyse their data in the current publication. The bibliographic review consisted of analysing the articles, published on PSC and IO and lung cancer, including clinical cases, series of cases, clinical trials and previous reviews (PubMed, Medline and Embase).
3.1. Case-1
A 75-year-old male smoker 53 pack-year, He began a study in February 2019 for a 2-month loss of 10 kg of weight and a whitish productive cough. The computed tomography (CT) scan showed a mass in the apical segment of Right Upper Lobe (RUL) with solid density of 49 x 40 x 40 mm. This mass has irregular edges contacting the pleural surface. Subsequently, the Positron Emission Tomography (PET) CT confirmed the pathological uptake of the lung mass in the RUL (SUVmax 17.9) of 4.7 x 3.9 x 5.1 cm. In addition, mediastinal lymphadenopathy with pathological uptake can be seen at the right para-aortic prevascular (SUVmax 4; 1.3 cm), right lower paratracheal (SUVmax 3.2; 1.1 cm) and right hilar level (SUVmax 2.7; 0.9 cm), (Figure 1A). The malignancy of the primary tumour was histologically confirmed by transthoracic biopsy (adenocarcinoma) and since the puncture of the subcarinal adenopathy was negative. The patient underwent surgery on Apr4-2019 by lateral thoracotomy, performing right upper lobectomy and lymphadenectomy. The result showed pulmonary lobectomy (RUL) with pleomorphic carcinoma, consisting mainly of a solid pattern adenocarcinoma, accompanied by a giant cell component measuring 6.5 x 6 cm with a microscopically affected border in the parietal pleura.

With the diagnosis of pleomorphic lung carcinoma pT3pN0cM0 (stage IIB - TNM 8th ed.) and microscopically affected border (R1), adjuvant CTH and radiotherapy (RT) treatment was decided. The patient received 2 cycles of carboplatin / vinorelbine that is suspended, due to poor hematologic tolerance (persistent grade 2 neutropenia). In the PET-CT for planning the RT treatment appeared a lesion suspected of metastasis in the liver (segment 7) of approximately 1.8 cm (SUVmax 4.2), (Figure 1B). The biopsy confirmed that it was a metastasis of the previously diagnosed pleomorphic carcinoma. The mutational status was: EGFR not mutated, ALK and ROS1 not translocated, and programmed death ligand-1 (PD-L1) by immunohistochemistry (IHC) 22C3 of 20%. Considering that the liver progression of the disease occurred during the CTH treatment, the patient was treated in a second-line with nivolumab for 5 doses and he achieved a complete radiological response (Figure 1C). It was necessary to suspend the IO treatment in November 2019 because of the persistent grade 2 pneumonitis; however, now, 16 months later, there is no evidence of disease progression.

3.2. Case-2
This is a 62-year-old male patient, with a history of chronic hepatitis due to HCV since 1998, treated with interferon and ribavirin (currently the disease cured). He is an active smoker (56 packyear). He was diagnosed with lung cancer in the context of the study due to spondylodiscitis (L3-L4). The CT scan showed a peripheral RUL lung lesion with tracts to the pleura, measuring 3.6 x 1.5 cm and a satellite micronodule in the upper portion. The malignancy of the lesion was histologically confirmed by transthoracic biopsy (adenocarcinoma). After the resolution of the infectious process, a PET-CT confirmed the pathological uptake of the pulmonary lesion (SUVmax 3) and a left supraclavicular...
adenopathy (SUVmax 5.4; 1.3cm). The N3 was discarded by a biopsy. The negative mediastinum was confirmed by the endobronchial ultrasound (EBUS) and a right upper lobectomy and a lymphadenectomy were performed. The results were of a lobectomy specimen with a pleomorphic carcinoma. The 70% of the tumour was represented by a giant cell component and the 30% left - by adenocarcinoma. The neoplasm was poorly differentiated with 4 cycles of carboplatin / vinorelbine followed by post-opera- disease. The mutational status has been described in (Table 1). The tive RT (PORT) with a total dose of 56 Gy which ended in March patient began a treatment in January 2020 within a clinical trial 2019. In December of the same year, he presented supra and in- with anti-PD-L1 plus antiangiogenic agent, achieving a sustained fradiaphragmatic and pulmonary lymph node progression of the partial response of the disease.

Table 1: Clinical characteristics of the patients previously described. COPD: Chronic Obstructive Pulmonary Disease; CTH: Chemotherapy; FISH: Fluorescence in situ hybridization; HCV: Hepatitis C virus; HBP: High blood pressure; IHC: Immunohistochemistry; IO: Immunotherapy; MSI: Microsatellite Instability Status; N/A: Not applicable; PORT: Post-operative radiotherapy; OS: Overall survival; PFS: Progression-free survival; PSC: Pulmonary sarcomatoid carcinoma; RUL: Right upper lobe; TMB: Tumor Mutational Burden. In the case 1, the progression of the disease occurred during the adjuvant treatment and this is the reason because this was considered first-line of metastatic disease.

<table>
<thead>
<tr>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td><strong>Male</strong></td>
<td><strong>Male</strong></td>
</tr>
<tr>
<td>Sex</td>
<td>76</td>
<td>62</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>Dyslypemia</td>
<td>HCV Spondylodiscitis</td>
</tr>
<tr>
<td>Smoking habit</td>
<td>53 pack-year</td>
<td>56 pack-year</td>
</tr>
<tr>
<td>Histological type</td>
<td>Pleomorphic carcinoma</td>
<td>Pleomorphic carcinoma</td>
</tr>
<tr>
<td><strong>IHC</strong></td>
<td>CK AE1-AE3 + focal TTF1 + Vimentin +</td>
<td>NapsinA + CK5 / 6 – TTF-1 + p40 –</td>
</tr>
<tr>
<td><strong>TMB</strong></td>
<td>TMB 11 mts / Mb. Alterations in TP53, SMARCA, KEAP1 MSI</td>
<td>TMB 18 mts / Mb. Alterations in BRAF N581S, NF1 E244*, CTNNB1 D32H, KEAP1 R415C, RBM10 E264fs*4, TP53 I162F, MSI</td>
</tr>
<tr>
<td>PD-L1 (IHC 22C3)</td>
<td>20%</td>
<td>6%</td>
</tr>
<tr>
<td>Stage at the diagnosis</td>
<td>IIB</td>
<td>IIIA</td>
</tr>
<tr>
<td>Surgical treatment</td>
<td>Lobectomy (RUL)</td>
<td>Lobectomy (RUL)</td>
</tr>
<tr>
<td>Adjuvant CTH</td>
<td>Carboplatin Vinorelbine*</td>
<td>Carboplatin Vinorelbine</td>
</tr>
<tr>
<td>PORT</td>
<td>No</td>
<td>56 Gy</td>
</tr>
<tr>
<td>Time to relapse</td>
<td>1.5 months</td>
<td>15 months</td>
</tr>
</tbody>
</table>
### 3.3. Case-3

A 70-year-old male patient with multiple comorbidities, including hypertension and hypercholesterolemia, hypertensive heart disease, severe chronic obstructive pulmonary disease and stable chronic alcoholic liver disease. He is a former smoker (40 packyear). He was operated on 27-May-2014 through atypical segmentectomy in RUL for infiltrating papillary lung adenocarcinoma with sarcomatoid features of 1 cm (pT1a). The control CT scan from September 2017 revealed a cystic lesion with a solid pole in the apical segment of the left lower lobe associated with a subpleural nodule in the contralateral lower lobe. A PET-CT confirmed the presence of the cystic lesion (7.8 x 4 cm) with a very thin wall with a solid pole of 5 mm metabolically undetermined. Additionally, several nodular lesions in the soft tissues were observed with a pathological uptake. The most important were located at the anterior pericardial (1.3 cm, and image of the metabolic response of the disease (B)).

### 4. Discussion

The PSC is a rare entity considered of poor prognostic until now [5-6]. The majority of cases corresponding to elderly patients, smoking men with a large, peripheral or central mass in upper pulmonary lobes. The treatment, the prognosis and the survival data of these patients published so far, come from retrospective studies, series of cases and database analysis. These data demonstrate that PSC is a chemo-refractory tumour in advanced stages; nevertheless, an optimal surgery [7] and an adjuvant-CTH do have a positive impact on the disease-free survival (DFS) and on the overall survival (OS) [4]. However, these results are disparate. For example, in the Surveillance, Epidemiology and End Results (SEER) cohort, with 1640 patients with PSC, the results

<table>
<thead>
<tr>
<th>Site of relapse</th>
<th>Liver</th>
<th>Lung, Thoracic and abdominal adenopathies</th>
<th>Soft tissue and bone</th>
</tr>
</thead>
<tbody>
<tr>
<td>1º line of treatment</td>
<td>Carboplatin Vinorelbine*</td>
<td>Clinical trial: Anti-PD-L1 + Antiangiogenic agent</td>
<td>Carboplatin Paclitaxel</td>
</tr>
<tr>
<td>Type of response</td>
<td>Progression disease</td>
<td>Partial response</td>
<td>Stable disease</td>
</tr>
<tr>
<td>2º line of treatment</td>
<td>Nivolumab</td>
<td>N/A</td>
<td>Atezolizumab</td>
</tr>
<tr>
<td>Type of response</td>
<td>Complete response</td>
<td>N/A</td>
<td>Partial response</td>
</tr>
<tr>
<td>Last dose of IO</td>
<td>Nov-19</td>
<td>Ongoing</td>
<td>Mar-20</td>
</tr>
<tr>
<td>OS</td>
<td>36 months</td>
<td>44 months</td>
<td>77 months</td>
</tr>
</tbody>
</table>

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**Figure 2:** PET scan image of a patient with sarcomatoid lung carcinoma showing a systemic relapse of the disease before to start immunotherapy (A) and image of the metabolic response of the disease (B).
showed a median survival of 7 months and a 5-year OS 19.5%. The patients, who received adjuvant-CTH after a complete resection, had a significant improvement in survival (Hazard Ratio [HR] 0.78; 95% CI 0.620.98), with a higher benefit in T3 to T4 (p=0.04) and N-positive (p <0.01) cases [4]. While in the study, published by Lin Y et al. no improvement was evidenced with adjuvant treatment, probably due to the small sample [8]. In this study, the median of OS was 19.1 months, and the 5-year survival rate was 17.4%. In the study by Maneenil et al. with a total of 127 patients, the median DFS of cases who underwent complete surgical resection and perioperative CTH was approximately 8.19 months. The benefit of perioperative CTH seems to be seen exclusively in patients with stages II-III [9-10]. In advanced disease, the treatment of CTH does not appear to significantly improve OS and may not be useful [11].

The 2015 World Health Organization (WHO) classification of tumors of the lung gave some new recommendations for molecular testing, according to already known histologic components, for example the analysis of EGFR, ALK, ROS1 and KRAS4. The studies showed that there is a significant percentage of PSC patients with driver mutations for which there are currently targeted treatments [6, 12]. For example, the case of a series of Chinese patients (N = 58), published in 2019, in which an analysis is performed through Whole-exome sequencing. The results showed some mutations in TP53 (74%), KRAS (24%), SMARCA4 (14%), MET (12%), EGFR (10%), among others. The median tumor mutation burden (TMB) was 8.6 muts/Mb; 37.9% and 12.1% of patients had a TMB > 10 muts/Mb and > 20 muts/Mb, respectively [13].

For many years now, even before the introduction of IO into routine clinical practice, retrospective studies have been developed, in which the expression of PD-L1 is analysed in possibility for this pathology [17]. There are several cases of pa-

Subsequently, a Korean study analysed the differences of the PD-L1 expression between the sarcomatous and the carcinomatous areas of the tumour in 41 patients. The PD-L1 expression was significantly higher in sarcomatous than in the carcinomatous areas of the tumour (P = 0.006) and the positive cases were infiltrated by higher quantity of CD8+ TILs compared with the negative cases (P = 0.006) [15]. It is important to bear in mind that all of these are retrospective studies, with significant variability in the number of cases included [16].

The efficacy of IO in patients with NSCLC has been demonstrated in some large randomized studies. These results have allowed the approval of the IO for both squamous and non-squamous NSCLC, as well as first and second-line of treatment. Considering these data and the expression profile of PD-L1 in patients with PSC, it has been suggested that IO could be considered as a treatment. Eighteen patients were enrolled and received durvalumab 1500 mg and tremelimumab 75 mg every 4 weeks, followed by durvalumab 750 mg every 2 weeks until the progression of the disease or unacceptable toxicity. The primary endpoint of the study was the ORR and the secondary endpoints were PFS, OS and toxicity. Fifteen of 18 patients were evaluated for the analysis of the primary endpoint, the ORR was 26.7% (95% CI: 7.8–55.1). With a median follow-up of 12 months, the median PFS was 5.9 months (95% CI:1.1–11.9) and the median OS was 15.4 months (95% CI: 11.1 - not reached). The toxicity profile was acceptable and manageable. Only 2 patients discontinued the treatment due to adverse events grade ≥ 3. Based on all these data, we concluded that IO may be an optimal management option in patients with recurrent or metastatic PSC. However, it is necessary to design international prospective studies that allow the recruitment of a significant number of patients, in which to evaluate the role of IO and thus confirm the data already published.

5. Funding

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anlotinib in a patient with PD-L1 overexpression and the coexistence of KRAS exon 2 mutation [21]. This is the reason why we have been motivated to treat our patients with IO in a second-line, achieving a good objective response rates (ORR) and a long survival. There is a British publication that evaluated the responses and the survival in 90 patients with PSC, treated with IO. The percentage of cases with radiological complete or partial
response was 54.5%, stable disease 15.9% and progressive disease 29.6%. The median PFS was 7 months. Sixty-six patients had some information about the PD-L1 status. Among them the 74.2% had overexpression (≥50%) with a positive relationship between the PD-L1 level and the radiological response [22]. Another study showed 40.5% of ORR and 64.8% of disease control, regardless of PD-L1 status. The median OS was 12.7 months (range: 0.3-45.7 months). The median of PD-L1 expression was 70%. The correlation between the PD-L1 expression and the ORR was confirmed (58.8% in PD-L1+ vs 0% in a negative case) p=0.44 [23]. Despite all these data, there is only one clinical trial in PSC patients, treated with IO. This is a phase II, multicenter, open-label, single-arm Korean study that evaluated the role the treatment with durvalumab plus tremelimumab in frontline for recurrent or metastatic PSC patients (NCT03022500) [24].


