Programmed death ligand-1 expression levels, clinicopathologic features, and survival in surgically resected sarcomatoid lung carcinoma

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Abstract

Aim: To determine the programmed death ligand-1 (PD-L1) expression rates in sarcomatoid lung carcinomas and to compare clinicopathologic features and survival rates of PD-L1-positive and negative patients.

Methods: PD-L1 expression was evaluated in 65 surgically resected sarcomatoid carcinomas. The clinicopathologic features of cases with PD-L1-positive and negative tumors were compared. Kaplan–Meier survival analysis was performed. Multiple Cox proportional hazard regression analysis was performed to determine independent predictors of overall survival.

Results: PD-L1 antibody positivity was found in 72.3% of surgically resected sarcomatoid lung carcinomas. Regarding histopathologic subtypes, PD-L1 expression was positive in 80.4% of pleomorphic carcinomas, 62.5% of spindle- and/or giant-cell carcinomas, and 16.7% of carcinosarcomas. Pleural invasion was observed in 68.1% of PD-L1-positive cases and 27.8% of PD-L1-negative cases ($P=0.008$). No difference in survival was found between PD-L1-positive and -negative tumors. The only factor significantly associated with poor survival was the pathological stage of the tumor.

Conclusions: This study reveals a high rate of PD-L1 positivity in a large number of sarcomatoid lung carcinoma cases with pleomorphic carcinoma, spindle- and/or giant-cell carcinoma, and carcinosarcoma subtypes. The only significantly different clinicopathologic feature in PD-L1-positive cases is pleural invasion. PD-L1 positivity is not a significant predictor of survival in sarcomatoid lung carcinomas.

KEYWORDS
carcinoma, carcinosarcoma, giant cell, survival analysis

1 INTRODUCTION

Sarcomatoid carcinomas are extremely rare lung tumors with survival rates and prognoses significantly worse than other non-small-cell carcinoma (NSCLC) types. Their prevalence is reported as 0.5% in large epidemiologic studies. According to the 2015 lung tumor classification of the World Health Organization (WHO), sarcomatoid carcinoma is categorized into five subtypes: pleomorphic carcinoma, spindle-cell carcinoma, giant-cell carcinoma, carcinosarcoma, and pulmonary blastoma. Sarcomatoid carcinomas are characterized by a highly aggressive behavior with distant metastases to unusual sites. Sarcomatoid carcinomas are also highly refractory to conventional chemotherapy and radiation therapy. Radical surgery remains the standard treatment for early localized disease, but in most cases,
recurrence rates are high. Traditional palliative chemotherapy is also associated with poor responses in advanced disease. In recent years, comprehensive genetic studies and clinical observations have to some extent clarified the key oncogenic bases of sarcomatoid carcinoma. Understanding its molecular pathogenesis has led to new approaches to immunotherapy in the treatment of this aggressive tumor.

Sarcomatoid carcinoma is characterized by higher levels of programmed death-1 ligand (PD-L1) expression than other types of NSCLC. Programmed death-1 (PD-1) is an advanced checkpoint molecule on the surface of activated T cells. Its ligand PD-L1, expressed in normal adult tissue components, activates the PD-1 protein on the T cells. This ligand-receptor binding between PD1 and PD-L1 ensures recognition of host cells by T lymphocytes, providing immune tolerance to host cells. Similar ligand-receptor binding occurs in cases of PD-L1 expressed in tumor cells, causing suppression of T-lymphocyte cytotoxicity. Overexpression of PD-L1 in tumor cells cripples the immune response to the tumor by inhibiting the cytotoxicity of CD8+ T cells in the tumor microenvironment. Checkpoint immunomodulation in the PD-1/PD-L1 pathway plays a vital role in tumor-induced immune suppression in the tumor microenvironment.

Antibodies against PD-L1, which block ligand-receptor binding, increase the activation of T lymphocytes and tumor cell cytotoxicity. Accordingly, tumor expression of PD-L1 acts as a potential biomarker with clinical utility. Treatments targeting the PD1/PD-L1 pathway have recently emerged as a promising therapeutic approach for these aggressive tumors, which are otherwise resistant to treatment.

This study aimed to determine the PD-L1 expression rates in patients with resected sarcomatoid lung carcinomas and to compare the clinicopathologic features and survival of PD-L1-positive and -negative cases.

**TABLE 1** PD-L1 expression rates in patients with sarcomatoid lung carcinomas (n = 65)

| PD-L1 expression scores (%) | PD-L1 negative n = 18 (27.7 %) | PD-L1 positive n = 47 (72.3 %) | Positive |
|-----------------------------|---------------------------------|---------------------------------|----------|
|                             | 0                               | <25                             | 25-50    | ≥50                  |              |
| Pleomorphic Carcinoma (n = 51) | 4 (7.8)                        | 6 (11.8)                        | 1 (2.0)  | 40 (78.4)            | 41 (80.4)    |
| Adenocarcinoma with SCC and/or GCC (n = 28) | 2 (7.1)                        | 2 (7.1)                        | 1 (3.6)  | 23 (82.1)            | 24 (85.7)    |
| Squamous cell carcinoma with SCC and/or GCC (n = 15) | 2 (13.3)                        | 4 (26.7)                        | 0       | 9 (60.0)             | 9 (60.0)     |
| Large cell carcinoma with SCC and/or GCC (n = 7) | 0                              | 0                               | 0       | 7 (100.0)            | 7 (100.0)    |
| Adenosquamous carcinoma with SCC and/or GCC (n = 1) | 0                              | 0                               | 0       | 1 (100.0)            | 1 (100.0)    |
| Spindle and/or Giant cell carcinoma (n = 8) | 2 (25.0)                        | 1 (12.5)                        | 0       | 5 (62.5)             | 5 (62.5)     |
| Carcinosarcoma (n = 6) | 1 (16.7)                        | 4 (66.7)                        | 0       | 1 (16.7)             | 1 (16.7)     |
| Total (n = 65) | 7 (10.8)                        | 11 (16.9)                       | 1 (1.5)  | 46 (70.8)            | 47 (72.3)    |

Data are expressed as n (%). GCC, giant cell carcinoma; PD-L1, programmed cell death ligand-1; SCC, spindle cell carcinoma.

2 | MATERIALS AND METHODS

A retrospective study was designed for the evaluation of surgically resected sarcomatoid carcinomas of 67 patients diagnosed at the Pathology Departments of Health Sciences University, Atatürk Chest Diseases and Chest Surgery Education and Research Hospital, Ankara, Turkey and of the Faculty of Medicine of Gazi University, Ankara, Turkey between 2011 and 2018. Complete clinical and demographic data were retrieved from the hospital files of 65 of the 67 patients, who were thus included in this study. Hematoxylin-eosin and immunohistochemically stained slides were reassessed by two pathologists for diagnosis and subtyping. The lung tumors were classified according to the 2015 WHO classification.

The immunohistochemical study was performed on paraffin-embedded tissue sections with a thickness of 3-4 μm placed on poly-L-lysine-coated slides. The sections were kept in an incubator at 45°C for 24 h.

For immunohistochemical detection of PD-L1 antibody (SP263, rabbit monoclonal antibody, Ventana Medical Systems), standard antigen retrieval methods (deparaffinization, cell restoration, CC1 [64 min], preprimary peroxidase inhibitor–primary antibody) were employed. An OptiView DAB IHC Detection Kit (OptiView HQ Universal Linker, OptiView HRP Multimer; Ventana Medical Systems) was used in a BenchMark GX immunohistochemistry device (Ventana Medical Systems). Samples were counterstained for 4 min with hematoxylin II and postcounterstained for 4 min. Placenta was used as a positive control for PD-L1 staining.

PD-L1 expression was evaluated in terms of percentage of membranous or cytoplasmic staining and categorized as strong (>50%), moderate (25–50%), weak (<25%), and none (0%). Membranous and/or cytoplasmic staining of ≥25% was considered positive for PD-L1. Pleural invasion was classified according to the 7th edition of the TNM classification of lung cancer as follows: PL0: tumor with no pleural involvement beyond its elastic...
layer; PL1: tumor invading beyond the elastic layer of the visceral pleura but not exposed on the pleural surface; PL2: tumor exposed on the pleural surface; and PL3: tumor invading the parietal pleura. The pathological stage of surgically resected tumors was defined according to the TNM classification of lung cancer.\textsuperscript{16,17}

2.1 Statistical analysis

Descriptive statistics were expressed as numbers of cases and percentages. Categorical data for comparing the clinicopathologic features of patients with PD-L1-positive and PD-L1-negative sarcomatoid lung carcinomas were analyzed by a continuity-corrected chi-square or Fisher’s exact test. Comparisons between ordinal variables were performed with the Mann–Whitney U test. Because the expected frequency was below 5 in 50% of the cells in the comparison of categorical data regarding histological types, the \( P \)-values of the subanalyses were calculated according to Fisher’s exact test instead of the global chi-square test.

Kaplan–Meier survival analysis with the log-rank test was used to determine overall survival prognosis. The crude survival rates, 1-, 3-, and 5-year cumulative survival rates, and mean expected life duration were also calculated with 95% confidence intervals (CI). Multiple Cox proportional hazard regression analysis was performed to determine the best independent predictor(s) of overall survival after adjustment for clinically important factors. Any variable for which the univariable test gave a \( P \)-value < 0.25 was accepted as a candidate for the multivariable model. The relative risks and 95% CIs for each independent variable were also calculated. Data analysis was performed using IBM SPSS Statistics version 17.0 (IBM Corporation). A \( P \)-value of less than 0.05 was considered statistically significant.

3 RESULTS

This study included surgically resected sarcomatoid carcinomas of 65 patients. The patients’ median age was 61 years (range: 36–80 years), and the gender distribution was 60 (92.3%) males and 5 (7.7%) females.
In 47 (72.3%) of the samples, more than 25% of the tumor cells were stained with the PD-L1 antibody (PD-L1-positive group). Of those, 46 exhibited high (≥50%) and 1 moderate (25-50%) staining intensity. PD-L1 antibody staining was negative in 18 cases (PD-L1-negative group). Of those, 11 exhibited weak (<25%) and seven exhibited no staining. Positive staining with PD-L1 antibody was detected in 80.4% of pleomorphic carcinomas, 62.5% of spindle- and/or giant-cell carcinomas, and 16.7% of carcinosarcomas (Table 1). Immunohistochemical staining in sarcomatoid lung carcinoma sections is shown in Figure 1.

The demographic and clinicopathologic characteristics of PD-L1-positive and negative patients are displayed in Table 2. Pleural invasion was significantly higher in PD-L1-positive than in negative cases. PD-L1 expression was significantly lower in carcinosarcomas and significantly higher in pleomorphic carcinomas. Age and gender distribution, smoking status, tumor size, lymph node metastasis, and tumor pathological stage did not differ significantly between PD-L1-positive and -negative cases.

Table 3 presents the survival rates and risk factors related to overall survival. Overall mean life expectancy in sarcomatoid lung carcinoma was 53.6 months (95% CI: 41.9-65.2). The Kaplan–Meier survival analysis showed age, gender, smoking history, tumor size, lymph node metastasis, pleural invasion, histopathologic subtype, and PD-L1 expression did not significantly affect overall survival. The only factor significantly associated with overall survival was the pathological stage of the tumor (P = 0.004). Stage III tumors were associated with worse prognosis than stage I and II tumors (P = 0.015 and 0.004, respectively). The Kaplan–Meier overall survival curves of PD-L1-positive and negative cases are shown in Figure 2.
### Table 3: Results of univariate survival analyses

|                                | Crude survival ratio (%) | Survival rates (%) | Mean life expectancy (95% CI) (months) | Log-Rank | P-value |
|--------------------------------|--------------------------|--------------------|----------------------------------------|----------|---------|
| **Age (years)**                |                          |                    |                                        |          |         |
| <60                            | 57.7                     | 69.2               | 54.5                                   | 54.5     | 0.337   |
| ≥60                            | 45.9                     | 73.0               | 48.5                                   | 34.0     | 0.562   |
| **Gender**                     |                          |                    |                                        |          |         |
| Male                           | 51.7                     | 72.4               | 51.6                                   | 41.3     | 0.252   |
| Female                         | 40.0                     | 60.0               | 40.0                                   | 40.0     | 0.615   |
| **Smoking status**             |                          |                    |                                        |          |         |
| Smoker                         | 54.5                     | 54.5               | 54.5                                   | -        | 0.295   |
| Nonsmoker                      | 50.0                     | 75.0               | 51.3                                   | 41.6     | 0.587   |
| **Tumor size (cm)**            |                          |                    |                                        |          |         |
| ≤3                             | 58.3                     | 83.3               | 62.5                                   | 50.0     | 0.521   |
| >3                             | 49.0                     | 68.6               | 48.1                                   | 40.1     | 0.470   |
| **Lymph node metastases**      |                          |                    |                                        |          |         |
| Absent                         | 56.5                     | 71.7               | 57.2                                   | 46.8     | 0.856   |
| Present                        | 35.3                     | 70.6               | 38.5                                   | 30.8     | 0.355   |
| **Pleural invasion**           |                          |                    |                                        |          |         |
| PL0                            | 59.3                     | 85.2               | 57.1                                   | 50.0     | 2.528   |
| PL1, PL2, PL3                  | 44.4                     | 61.1               | 46.4                                   | 36.1     | 0.112   |
| **Pathological stage**         |                          |                    |                                        |          |         |
| I                              | 66.7                     | 93.3               | 56.0                                   | 56.0     | 11.106  |
| II                             | 59.3                     | 77.8               | 68.8                                   | 50.0     | <0.04   |
| III                            | 28.6                     | 47.6               | 21.8                                   | 21.8     |         |
| **Histopathologic subtype**    |                          |                    |                                        |          |         |
| Pleomorphic carcinoma          | 49.0                     | 71.4               | 49.5                                   | 38.3     | 0.645   |
| Spindle and/or giant cell carcinoma | 50.0                 | 62.5               | 46.9                                   | 46.9     | 0.724   |
| Carinosarcoma                  | 66.7                     | 83.3               | 66.7                                   | 66.7     |         |
| **PD-L1**                      |                          |                    |                                        |          |         |
| Negative                       | 61.1                     | 94.4               | 69.6                                   | 47.7     | 2.750   |
| Positive                       | 46.7                     | 62.2               | 43.1                                   | 38.8     | 0.097   |
| Overall                        | 50.8                     | 71.4               | 50.8                                   | 41.5     |         |

CI, confidence interval; PD-L1, programmed cell death ligand-1, PL pleural invasion.

1 Stage I versus stage III (P = 0.015).
2 Stage II versus stage III (P = 0.004).

*p* significant at level of *p* < 0.01.

Table 4 presents the factors associated with overall survival and factors that might be clinically related to overall survival. The multivariate Cox proportional hazard regression analysis showed that only the pathological stage was independently associated with prognosis. When the effects of other factors were kept constant, the mortality rate was 3.203 times (95% CI: 1.141-8.996) higher in patients with stage III than in patients with stage I sarcomatoid lung carcinoma (P = 0.027). When correction was made according to other factors, pleural invasion and PD-L1 positivity were not found to be significantly associated with prognosis.

### DISCUSSION

This study found PD-L1 positivity in 72.3% of patients with surgically resected sarcomatoid carcinomas. The PD-L1 positivity rate was higher in the pleomorphic carcinoma subgroup (80.4%) and relatively low in the spindle-cell carcinoma (62.5%) and carcinosarcoma (16.7%) subgroups. No difference in survival was found between PD-L1-positive and -negative tumors. The only factor independently associated with lower overall survival was an advanced pathological stage of the tumor.
TABLE 4 Results of multiple Cox regression analysis

|                  | RR  | 95% CI         | P-value |
|------------------|-----|----------------|---------|
| Pleural invasion |     |                |         |
| PL0              | 1.00| -              | -       |
| PL1, PL2, PL3    | 1.218| 0.551-2.692   | 0.626   |
| Pathological stage|     |                |         |
| I                | 1.000| -              | -       |
| II               | 1.012| 0.349-2.938   | 0.983   |
| III              | 3.203| 1.141-8.996   | 0.027*  |
| PD-L1            |     |                |         |
| Negative         | 1.000| -              | -       |
| Positive         | 2.038| 0.822-5.052   | 0.124   |

CI, confidence interval; PD-L1, programmed cell death ligand-1; PL, pleural invasion; RR, relative risk.

*p significant at level of *p < 0.05.

In non-small-cell lung carcinoma, PD-L1 immunohistochemistry has become a standard biomarker of patient response to PD/PD-L1 blockade, and immune checkpoint inhibitors have become the standard treatment for advanced disease. Accordingly, the clinical significance of PD-L1 measurements in sarcomatoid lung carcinomas has gradually increased. However, the relationship between PD-L1 expression in sarcomatoid lung carcinoma and outcomes of treatments targeting the PD1/PD-L1 pathway is still being investigated.

Case reports published in the last decade have suggested that treatments targeting the PD1/PD-L1 pathway are promising for the treatment of sarcomatoid lung carcinoma. As more data have accumulated, immune checkpoint inhibitors have been shown to be advantageous in the management of these aggressive tumors. A recent retrospective analysis of 125 patients concluded that PD-1/PD-L1 inhibitors show outstanding efficacy for pleomorphic lung carcinomas. A pooled analysis of the literature on immunotherapy response in advanced pulmonary sarcomatoid carcinomas found that immune checkpoint inhibitors are associated with disease control in about 20% of patients for 2 years and that PD-L1 expression significantly correlates with tumor response and progression-free survival after immunotherapy.

PD-L1 levels in sarcomatoid lung carcinoma were first reported by Velcheti et al in their study which included 13 sarcomatoid carcinoma cases. That study reported a PD-L1 positivity rate of 69.2% in sarcomatoid carcinoma. Subsequently, several studies reported high rates of PD-L1 upregulation in sarcomatoid lung carcinoma, ranging from 25.5 to 90.2%. Some have also reported that PD-L1 levels are associated
TABLE 5  Comparison of the findings of this and previous studies regarding PD-L1 expression in pulmonary sarcomatoid carcinoma

| Author | Number of cases | Histopathologic subtype | Rate of PD-L1 positivity (%) | PD-L1 clone | Prognostic impact |
|--------|----------------|-------------------------|-------------------------------|-------------|------------------|
| Velcheti et al 7 | 13 | 10 giant cell carcinoma, one carcinosarcoma, one pleomorphic carcinoma | 69.2 | 5H1 | N/A |
| Kim et al 27 | 41 | All pleomorphic carcinoma | 90.2 | E1L3N | No association |
| Chang et al 28 | 122 | All pleomorphic carcinoma | 70.5 | CD274 | PD-L1(+) associated with poor prognosis |
| Vieira et al 29 | 75 | Nine carcinosarcoma, 59 pleomorphic carcinoma, four giant-cell carcinoma, one spindle cell carcinoma | 53.5 | 5H1 | No association |
| Yvorel et al 30 | 36 sarcomatoid carcinoma | 31 pleomorphic, carcinoma, five other histopathologic subtypes | 75 | E1L3N | PD-L1(+) associated with poor prognosis |
| Imanishi et al 31 | 26 | All pleomorphic carcinoma | 76.9 at ≥1% cut-off, 69.2 at ≥5% cut-off | E1L3N | High PD-L1 expression associated with favorable prognosis |
| Lococo et al 32 | 43 | Eight pleomorphic carcinoma, 35 other histopathologic subtypes | 25.5 | 28-8 | PD-L1(+) associated with poor prognosis |
| Yang et al 33 | 148 | N/A | 36.5 | 28-8 | No association |
| Agackiran et al (Current report) | 65 | 51 pleomorphic carcinoma, eight spindle and/or giant cell carcinoma, six carcinosarcoma | 72.3 | SP-263 | No association |

Our study also had a high rate of patients with positive immune staining with PD-L1 antibody. PD-L1 positivity was highest in the pleomorphic carcinoma group and lowest in the carcinosarcoma group. Among pleomorphic carcinomas, positive staining was present in all cases with large-cell and adenosquamous carcinoma components. The positivity rates of pleomorphic carcinomas with adenocarcinoma and squamous cell carcinoma components were 85.7 and 60%, respectively. A comparison of the findings of this and previous studies regarding PD-L1 expression in pulmonary sarcomatoid carcinoma is presented in Table 5.

The US Food and Drug Administration (FDA) has approved four PD-L1 immunohistochemistry tests, which use four different PD-L1 antibodies (28-8, 22C3, SP263, and SP142) on two different platforms (manufactured by Dako and Ventana Medical Systems), each with its own scoring system. While 22C3 (Dako), 28-8 (Dako), and SP263 (Ventana) immunohistochemical assays are comparable regarding PD-L1 staining, the SP142 assay (Ventana) reveals fewer stained tumor cells. In this study, SP263 was used to assess PD-L1 expression in sarcomatoid lung carcinoma. SP263 is a rabbit monoclonal primary antibody against PD-L1. The SP263 test has been approved by the FDA as a complementary diagnostic test for nivolumab and a concomitant diagnostic test for pembrolizumab in non-small-cell carcinoma. Clone SP263 has the highest concordance rate on all immunohistochemical platforms. The cutoff value of PD-L1 positivity is usually a concern for interpreting the study results. Based on the findings of previous studies, PD-L1 expression is considered positive if ≥25% of the tumor cells exhibit membranous and/or cytoplasmic staining with SP263 clone.14,15

In this study, PD-L1 positivity was significantly higher in tumors with pleural invasion (PL1, PL2, and PL3) than in those without pleural invasion (PL0). Naito et al analyzed PD-L1 expression in 35 surgically resected pleomorphic carcinomas and found a significant correlation between parietal-pleural invasion and high PD-L1 expression. This finding is in line with our study, which used a larger sample size and examined not only pleomorphic carcinomas but also spindle- and/or giant-cell carcinomas and carcinosarcomas.

The crude survival rate in our study population was 50.8%, and the mean life expectancy was 53.6 months (95% CI: 41.9-65.2). The crude and 1-, 3-, and 5-year survival rates were lower in the PD-L1-positive than in the PD-L1-negative group. However, the differences were not statistically significant. Similarly, although the mean life expectancy in the PD-L1-positive group was approximately 20 months shorter than in the PD-L1-negative group, the difference was not statistically significant. The pathological stage of the tumor was the only factor independently associated with prognosis.

This study found no statistically significant relationship between PD-L1 positivity and prognosis in cases of surgically resected sarcomatoid lung cancer. Previous studies have reported rather conflicting results. Chang et al,28 Yvorel et al,30 and Lococo et al32 reported that PD-L1 overexpression is associated with negative survival outcomes. In contrast, in line with our study, Kim et al,27 Vieira et al,29 and Yang et al33 found no association between PD-L1 expression and prognosis. The only study reporting an association between high PD-L1
expression and favorable prognosis is that of Imanishi et al. It should be noted, however, that these studies differ in terms of histological subtypes of tumors, immunohistochemical clones used, and cutoff values determined in immunohistochemical studies. In our study, PD-L1 expression was investigated in sarcomatoid lung carcinoma specimens that included not only pleomorphic carcinomas but also other histopathologic subtypes. The anti-PD-L1 clone used to assess PD-L1 positivity was SP263, which is known to have the highest concordance rate on all immunohistochemical platforms.

This study investigated PD-L1 expression and clinicopathologic features of surgically resected sarcomatoid lung carcinomas. A large number of sarcomatoid lung carcinoma cases, which were not limited to pleomorphic carcinomas but included other histopathologic subtypes (spindle- and/or giant-cell carcinoma and carcinosarcoma) were examined. PD-L1 positivity was studied with PD-L1 SP263 clone antibody for the first time in sarcomatoid lung carcinomas. High PD-L1 expression in sarcomatoid lung carcinomas shown in the present study, in conjunction with previous studies on PD-1/PD-L1 pathway in sarcomatoid lung carcinomas, herald drugs targeting PD-1/PD-L1 pathway will be an effective treatment option. Major limitation of the study is the retrospective study design. Prospective studies are needed to reveal the efficiency of immunotherapy in sarcomatoid lung carcinomas.

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CONFLICT OF INTEREST
The authors have no conflict of interest to declare.

ETHICS STATEMENT
The study was approved by the Medical Expert Board of Health Sciences University, Atatürk Chest Diseases and Chest Surgery Education and Research Hospital, Ankara, Turkey (07.11.2017/572). Due to the retrospective nature of this study, informed consent was waived.

AVAILABILITY OF DATA AND MATERIAL
The dataset used and/or analyzed during the present study is available on reasonable request.

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AÇIKKIRAN ET AL.

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