Case Report

Immune Checkpoint Blockade Is Associated With Durable Responses in Pulmonary Sarcomatoid Carcinoma

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Clinical Practice Points

- Pulmonary sarcomatoid carcinoma (PSC) is an aggressive variant of non–small-cell lung cancer associated with refractoriness to chemotherapy and radiation. The median overall survival for advanced PSC hitherto reported in the literature is 4 to 6 months.
- Recent reports indicate that PSC may be associated with high programmed death-ligand 1 tumor proportion score as well as a high tumor mutational burden, which are independent predictors of response to checkpoint blockade.
- In a retrospective review of new cases of advanced PSC diagnosed between June 2015 and June 2018 from 2 institutions, we identified 5 patients, all of whom were treated with pembrolizumab. All cases had a programmed death-ligand 1 score > 75%. Three received pembrolizumab in the front-line setting. Four patients experienced a response including 1 complete response. The fifth patient had prolonged disease stability. After a median of 13 months of follow-up, none of the patients had progressed, and 4 of 5 patients are alive at the time of this report. One patient died of complications from an aspergilloma without evidence of disease progression. The overall survival which is on-going ranges between 14+ and 33+ months.
- Programmed cell death protein 1 checkpoint blockade is associated with significant benefit in advanced PSC and should be considered for front-line therapy.

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Introduction

Pulmonary sarcomatoid carcinoma (PSC) is a variant of non–small-cell lung cancer (NSCLC) comprising 0.3% to 1.3% of all cases and characterized by mesenchymal differentiation.[1] Response to chemotherapy is poor, and 69% to 72% of patients with advanced PSC experience progression on front-line chemotherapy. The median progression free survival (PFS) and overall survival (OS) is 2 months and 4 to 6 months, respectively.[2,3]

Recently, targeted approaches were found to be feasible in 12% to 22% of PSC cases, with MET exon 14 skipping lesions associated with exquisite sensitivity to crizotinib.[4,5] The paradigm of front-line therapy of NSCLC has evolved to encompass immune therapy with checkpoint blockade. KEYNOTE-024 reported superior survival with pembrolizumab when compared with platinum-based doublet chemotherapy in patients with programmed death-ligand 1 (PD-L1) tumor proportion score (TPS) > 50%.[6] Various reports indicate that up to 90% of cases of PSC are PD-L1-positive by immunohistochemistry (IHC); most prominently in the sarcomatous component, which correlates with the presence of tumor-infiltrating lymphocytes and macrophages.[7]

Different malignancies with sarcomatoid de-differentiation share genomic alterations similar to that of PSC. Over 15% of PSC have recurrent mutations in TP53, CDKN2A, KRAS, CDKN2B, and NF1.[5] This is consistent with the mutational landscape of sarcomatoid pleural mesotheliomas and sarcomatoid renal cell carcinomas.[8,9]

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The presence of a high tumor mutational burden is an emerging marker of benefit from checkpoint inhibitor therapy. Forty-three percent of PSC cases have a high mutational burden (> 10 mutations per Mb), indicating that PSC may be uniquely well-suited to checkpoint blockade.[5] Sarcomatoid renal cell carcinomas are reported to have a higher mutational burden in the sarcomatous component, echoing findings in PSC, and sustained complete responses have been reported with immune checkpoint inhibitor (ICPI) therapy in this aggressive variant of renal cell carcinoma.[10]

Overall, it appears that sarcomatoid differentiation is associated with a high PD-L1 expression, immune infiltration, and mutational burden across different malignancies. We hypothesized that sarcomatoid histology may be a surrogate for a subset of NSCLC with the potential for highest benefit from checkpoint blockade. This study aims to report the patterns of response and survival in patients with PSC treated in the immunotherapy era.

Material and Methods

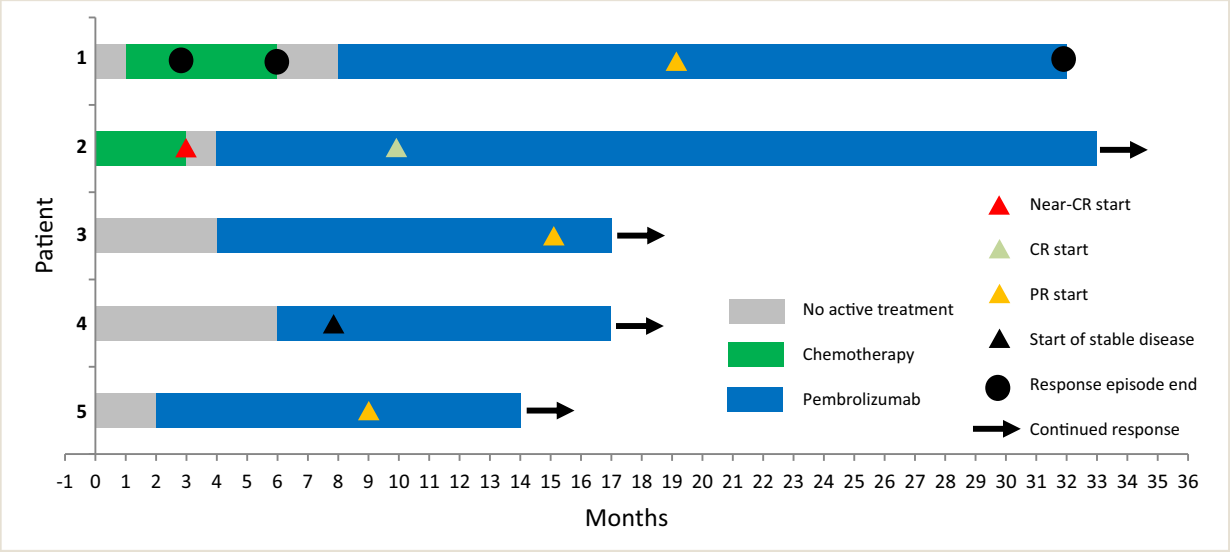
We conducted a retrospective review of surgical pathology and treatment records for all cases of advanced PSC diagnosed between June 2015 and June 2018 at 2 institutions in Bronx, NY. Clinical response was characterized according to Response Evaluation Criteria in Solid Tumors, version 1.1. IHC testing for PD-L1 was performed on formalin-fixed paraffin-embedded tissue using the 22C3 companion diagnostic test (Ventana). Another cohort of patients with advanced PSC diagnosed between June 2012 and June 2015 who were treated in the pre-immunotherapy era was also identified.

Results

The clinical course of the identified cohort of patients with newly diagnosed advanced pulmonary sarcomatoid carcinoma is summarized in Figure 1. The median age of the cohort was 57 years. All cases were smokers with a median of 30 pack-years and a PD-L1 TPS ≥ 75%. Sixty percent were female. All patients were treated with ICPI, including one in the third-line setting. One patient experienced a complete response, 3 patients had a partial response, and the fifth patient had prolonged stable disease with clear-cut benefit by imaging and clinical progress. This represents an overall response rate of 80% and clinical benefit rate of 100%. After a median follow-up of 13 months, none of the patients had experienced progression, compared with a PFS of 2 months reported with conventional chemotherapy. Four of 5 patients were alive at the time of this report. One patient succumbed to an infectious complication after 23 months of treatment, with sequential computed tomography (CT) scans having revealed no evidence of progression. Three patients continue on pembrolizumab with minimal adverse effects. One patient with a complete response is now being observed off-treatment after 2 years on pembrolizumab. Ongoing PFS ranged from 11+ months to 29+ months, and ongoing OS ranged between 14+ and 33+ months. The median OS and PFS have not been reached. One of 3 patients who had sequencing of the MET gene showed mutations associated with exon 14 skipping, and this patient experienced a partial response to pembrolizumab.

To corroborate these better-than-expected outcomes compared with conventional chemotherapy, we identified a cohort of advanced PSC (n = 6) diagnosed between June 2012 and June 2015 in the pre-ICPI era. Two-thirds were male with a median age of 62 years and a median smoking history of 40 pack-years. The median OS was 5.6 months. No patient survived beyond 1 year, compared with 100% in the ICPI cohort. Outcomes for patients treated with conventional chemotherapy alone are in line with

Figure 1 Swimmer Plot of PSC Case Responses to Immunotherapy. Bar Colors Indicate Periods of Treatment. Arrows Indicate Continuing Response



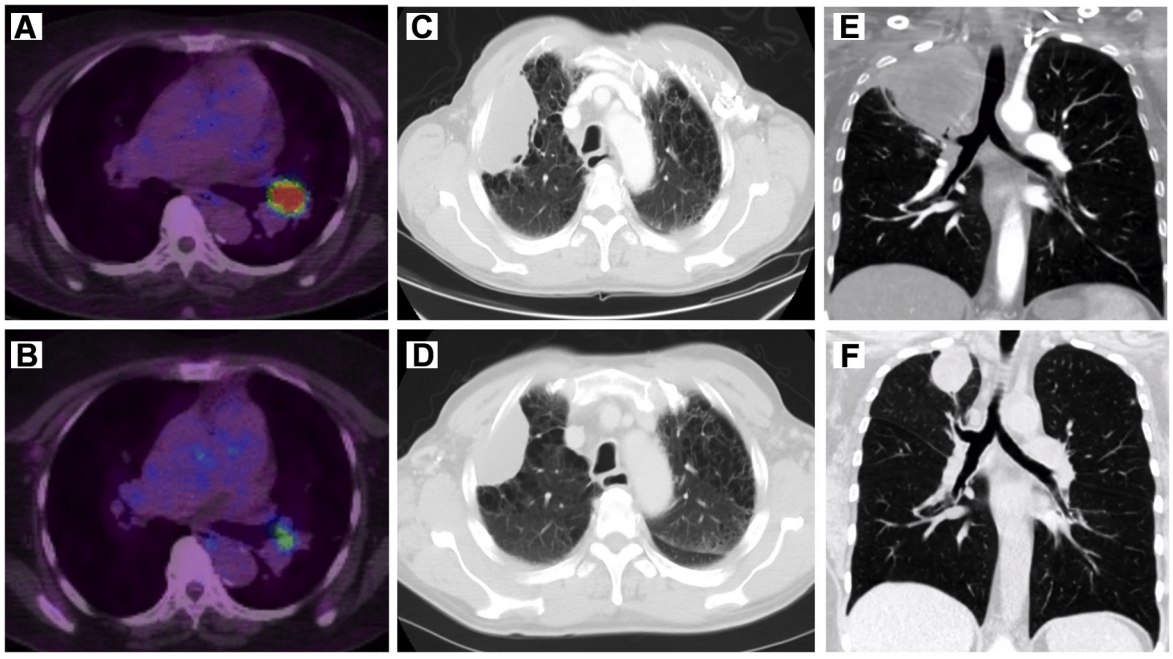
Abbreviations: CR = complete response; PR = partial response; PSC = pulmonary sarcomatoid carcinoma.

Table 1 Summary of Cases of Pulmonary Sarcomatoid Carcinoma Treated With Immune Checkpoint Inhibitors

Case	Date of Diagnosis	Age, y	Gender	Race	Smoking (Pack-years)	Histologic Subtype	TPS, %	Prior Lines of Therapy	Systemic Therapy	Mutational Status	Best Response to ICPI (% Change)	CNS Involvement	PFS, mo	OS, mo
1	June 2015	46	Male	White	30	Pleomorphic	90	2	Cisplatin and etoposide; gemcitabine and docetaxel; pembrolizumab	EGFR/ALK/MET wt, NOTCH3 R2031, TP53 R249S,CREBBP E1724,K1176, JUN amplification, PBRMI1 A137	Partial response (−47%)	Yes	23	31
2	October 2015	56	Female	White	40	Spindle cell	80	1	Cisplatin and pemetrexed followed by maintenance pembrolizumab	EGFR wt	Complete response	No	29+	33+
3	February 2017	64	Female	Black	50	Pleomorphic	>90	0	Pembrolizumab alone	EGFR/ALK/ROS1/ MET wt, MSS, TMB 15/Mb, AKT2, AXL, CCNE1, and KRAS amplification; CDKN2A loss, EP300 Q852, FUBP1 E320, KDM6A splice-site, KRAS G12D, TP53 G245R, WT1 D427Y	Partial response (−33%)	No	13+	17+
4	February 2017	57	Male	Hispanic White	30	N/A	100	0	Pembrolizumab alone	EGFR wt	Stable disease (−21%)	No	11+	17+
5	May 2017	67	Female	Black	24	N/A	>75	0	Pembrolizumab alone	EGFR/ALK/ROS1 wt. MET exon 14 splice site, FGFR1 amplification, MYST3 amplification, TP53 G105V	Partial response (−30%)	No	12+	14+

+ indicates ongoing responses.
Abbreviations: CNS = central nervous system; ICPI = immune checkpoint inhibitor; OS = overall survival; PFS = progression-free survival; TPS = tumor proportion score; wt = wild-type.

Figure 2 A, Positron Emission Tomography Scan From April 2017 for Patient 3 Showing a Hypermetabolic Left Lung Mass. B, Repeat Positron Emission Tomography Scan From August 2017 for Patient 3 Consistent With a Partial Response, 2 Months After Starting Pembrolizumab. C, Computed Tomography (CT) of the Thorax From October 2017 for Patient 4 Showing a Right Lung Mass 2 Months After Starting Pembrolizumab. D, Repeat CT of the Thorax From July 2018 Showing Stable Disease in Patient 4, 11 Months After Starting Pembrolizumab. E, CT of the Thorax From June 2017 in Patient 5 Showing a Large Right Lung Mass Prior to Treatment. F, Repeat CT of the Thorax From November 2017 in Patient 5 Showing a Partial Response, 4 Months After Starting Pembrolizumab



previously published reports of poor efficacy, highlighting markedly improved survival noted with ICPI therapy. The pertinent aspects of individual cases are described below and summarized in Table 1.

Patient 1

A 46-year-old male with a 30 pack-year smoking history presented with back pain in June 2015 and was found to have a large fluorodeoxyglucose-avid left lung mass with nodal uptake. Pathology and imaging confirmed a stage IIIA PSC with pleomorphic features. He underwent concurrent radiotherapy and cisplatin/etoposide chemotherapy from July to September 2015, but experienced progression of disease, with a new left adrenal metastasis. Gemcitabine and docetaxel were started in October 2015. However, in December 2015, he developed infiltration of T3-T4 vertebral bodies and enlargement of the adrenal metastasis. Subsequently, in January 2016, he developed seizures secondary to hemorrhagic brain metastases. Whole brain radiation therapy was administered with subsequent stereotactic radiosurgery in April and November of 2016 to residual lesions. Further testing of the biopsy specimen yielded a TPS of 90%. In February 2016, pembrolizumab was initiated at a dose of 200 mg every 3 weeks. In January 2017, a positron emission tomography (PET)/CT scan showed a partial response, with 36% reduction in the size of target lesions. By December 2017, a repeat PET scan showed that responses had deepened further to a 47% decrease in the size of the mass with no further progression of his intracranial or extracranial disease. In December 2017, he developed an epidural abscess, aspergilloma, and bacteremia in the setting of the known necrotic chest tumor. Despite aggressive treatment, he died from sepsis in January 2018.

Patient 2

A 56-year-old female with a 40 pack-year smoking history presented in October 2015 with a 2-month history of productive cough, weight loss, and diffuse joint pains. A CT scan showed a 6.0 × 7.1 cm right upper lobe mass with chest wall invasion. Also noted were multiple bilateral lung nodules ranging from 0.5 cm to 2.7 cm in size, representing stage IV disease. CT-guided core biopsy revealed epithelioid and spindle cells staining positive for AE1/AE3, CAM5.2, WT-1, and desmin, confirming the diagnosis of PSC. The patient was treated with 4 cycles of cisplatin and pemetrexed between October 2015 and December 2015; subsequent chest x-ray in January 2016 showed a near complete response. In the interim, IHC for PD-L1 staining became available with a TPS of 80%. In February 2016, pembrolizumab was initiated at a dose of 200 mg every 3 weeks as maintenance therapy. A CT scan from August 2016 showed a full complete response, which has continued to this date. Pembrolizumab was stopped in April 2018 with the initiation of surveillance.

Patient 3

A 64-year-old female with end-stage renal disease on hemodialysis since November 2016 and a 50 pack-year smoking history was admitted to the hospital in February 2017 with worsening dyspnea. She was found to have a spiculated left upper lobe nodule and a soft tissue hilar mass obstructing the lingular bronchus along with an entero-enteric fistula. Pathology from a small bowel resection was consistent with stage IV pleomorphic variant of PSC. Pembrolizumab was initiated in June 2017 at a dose of 200 mg every 3 weeks after further tissue testing revealed a TPS $>$ 90%. By May 2018, a follow-up scan showed a partial response with 33% decrease in the size of target lesions; this partial response is currently ongoing (Figure 2A and B).

Patient 4

A 57-year-old male, current smoker with a 30 pack-year smoking history, chronic obstructive pulmonary disease, and schizophrenia presented to the emergency department in February 2017 and was found to have a right upper lobe mass on CT scan. PET/CT in August 2017 demonstrated a hypermetabolic pleural-based right upper lobe mass measuring 8.4 $\times$ 4.5 cm, along with significant uptake in the right upper lobe nodule, right paratracheal nodes, and left adrenal gland. Biopsy confirmed stage IV PSC with a TPS of 100%. Pembrolizumab was started at a dose of 200 mg every 3 weeks in August 2017. A CT scan in October 2017 showed stable disease with repeat imaging in April 2018 showing a slight decrease in the size of the mass (Figure 2C and D). The patient continues to be on pembrolizumab therapy without any serious side effects other than a skin rash localized to the dorsum of the right hand.

Patient 5

A 67-year-old female with a 24 pack-year smoking history presented in May 2017 for a second opinion regarding a recent diagnosis of stage IV NSCLC. A CT scan in June 2017 demonstrated a right upper lobe mass that was biopsied, revealing poorly differentiated adenocarcinoma with sarcomatoid areas of lung, and a TPS greater than 75%. She was started on pembrolizumab at a dose of 200 mg every 3 weeks in July 2017. A PET/CT scan in February 2018 confirmed a partial response with decrease in size and activity of the mass (30% decrease in target lesions). A PET/CT scan in May 2018 revealed a 5% increase in the size of the mass compared with a previous scan but with continued reduction in the standardized uptake value from 19.1 to 15.1, indicating disease stability. (Figure 2E and F)

Discussion

In this cohort of advanced PSC treated with ICPI therapy, a response rate of 80% was observed, including 1 complete response in a patient who had maintenance therapy after a good response to front-line platinum-based chemotherapy. At a median follow-up of 13 months, the median OS was not reached, and on-going OS ranged between 14+ and 33+ months. This compares favorably with a cohort of patients treated in the pre-immunotherapy era who experienced a median survival of 5.6 months. Several limitations must be considered when interpreting these results. The rarity of this subtype limits sample size, and the retrospective nature of the study restricts broad generalizability. Also, a majority of patients continue to be on treatment without any signs of progression, which precludes a definitive description of the clinical course. The final survival data may well exceed that reported in this case series.

Conclusion

Sarcomatoid histology may be indicative of a subset of NSCLC with a high tumor mutational burden, a rich immune infiltrate, and high TPS score, identifying a group of patients with clinical benefit from checkpoint blockade.

Disclosure

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