Clinical Oncology: Case Reports

Case Report

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Utilization of Dual Immunotherapy for Metastatic Pulmonary Pleomorphic Giant Cell Carcinoma: A Case Report

Breanna Hinman*, Godsfavour Umoru, Ethan Burns, Cynthia El Rahi, Jun Zhang

Abstract

Introduction: Pulmonary Pleomorphic Carcinomas (PPC) are a rare histologic subgroup of sarcomatoid Non-Small Cell Lung Carcinomas (NSCLC). They are characterized by more aggressive growth and elicit a poorer response to antitumor chemotherapy. Furthermore, PPC is associated with an increased likelihood of early metastasis as well as a high risk of relapse. Here, we report the clinical course of a patient with PPC treated with dual immune checkpoint inhibitor therapy and highlight the partial response observed with this approach.

Case Presentation: A 48-year-old male presented with metastatic high-grade pleomorphic giant cell carcinoma.

The liquid biopsy from the original brain lesion revealed no actionable mutations. Next generation sequencing results showed PD-L1 50% and Tumor Mutational Burden (TMB) of 13 mutations per megabase. He was initiated on nivolumab 3 milligrams (mg)/kilogram (kg) every 2 weeks and ipilimumab 1 mg/kg every 6 weeks in a 42-day cycle. He also underwent Stereotactic Radiosurgery (SRS) to the brain lesions. After completing two cycles of treatment, his repeat PET scan showed an overall interval partial response.

Conclusion: Dual immune-checkpoint inhibitor therapy is effective for the treatment of PPC and prospective clinical trials are warranted.

Keywords: Pulmonary pleomorphic carcinoma; PD-L1 expression; PD-1 inhibitors; PD-L1 inhibitors; Tumor mutational burden

Introduction

PPC is an uncommon subgroup of Non-Small Cell Lung Cancer (NSCLC), comprising less than one percent of cases [1]. Tobacco smoking and advanced age are risk factors for the development of PPC, and compared to other histologic classifications of NSCLC, pleomorphic carcinomas are characterized by more highly aggressive growth patterns, poorer response to systemic chemotherapy regimens, increased likelihood of early metastasis, and ultimately dismal outcomes [1,2]. At the time of this report, there are no known randomized clinical trials that have evaluated specific antineoplastic regimens for PPC, and treatment options are limited to retrospective studies and case reports. Given the paucity of specific chemotherapy options for PPC in available guidelines, there is a strong need for the exploration of efficacious treatment strategies in this patient population. Herein, we report the clinical course of a patient with PPC treated with dual immune checkpoint inhibitor therapy and highlight the partial response observed with this approach.

Case Presentation

A 48-year-old male with a 40 pack-year smoking history and family history of hepatocellular carcinoma presented with seizure activity. Computed Tomography (CT) of the head and neck revealed a left temporo-occipital mass with perilesional edema. A full body Positron Emission Tomography (PET)/CT showed a dominate right upper lung mass measuring 6.4 x 4.3 cm and demonstrated a Standardized Uptake Value (SUV) of 6.9. Moreover, there were other bilateral pulmonary nodules and suspicious subcarinal adenopathy concerning for metastatic disease (Figure 1 A to C). The patient underwent a left temporal parietal craniotomy and resection of the intracranial mass. Initial suspicions were for a primary lung malignancy given the dominate lesion. However, immunohistochemical screening, positive staining for CK7, S100P, CK19, CK8/18, GATA3, and Inhibin, also suggested possible urothelial carcinoma, adrenal cortical carcinoma, and/or upper gastrointestinal/pancreatobiliary tract carcinoma in the differential diagnosis. He later received gamma knife Stereotactic Radiosurgery (SRS) to the right insula and to the postoperative resection cavity. He underwent endobronchial ultrasound with biopsy of a station 11R lymph node. Histopathologic examination revealed a high-grade pleomorphic giant cell carcinoma. Immunohistochemistry screening demonstrated 2% PD-L1 expression on tumor cells and a negative HER-2 overexpression score of 0. The tumor cells were positive for CK AE1/AE3, CK7, CK19, CK8/18, S100, GATA3, and Inhibin. Notably, tumor cells did not stain for CK20, PAX8, p63, p40, TTF-1, Napsin, ALK, PD-L1, androgene, calretinin, WT1, CEA, CDX2, OCT3/4, Arginase, HepPar, BHCG, SAL4, or CD117. Moreover, the brain lesion was absent for PD-L1 expression, and the liquid biopsy revealed no actionable mutations. He was ultimately started on nivolumab 3 milligram(mg)/kilogram(kg) every 2 weeks and ipilimumab 1 mg/kg every 6 weeks in a 42-day cycle. With regard to the duration of therapy, a total of 4 cycles of dual immunotherapy was initially planned. During the work-up for intermittent left amaurosis fugax, a transthoracic echocardiogram showed a large complex mitral mass with 2 separate components measuring up to 4cm in length. The mass was not biopsied, and the patient wasinitiated on therapeutic enoxaparin for two months. The cardiac mass finding did not result in any delay to ICI treatment. A repeat transthoracic echocardiogram 2 months later revealed a significant decrease in size (from 4 cm to 1 cm). After completion of cycle 2, next generation sequencing results showed PD-L1 50% and Tumor Mutational Burden (TMB) of 13 mutations per megabase. However, a repeat brain MRI showed a new metastatic lesion at the posterior right parietal lobe for which the patient received additional SRS. After completing two cycles of treatment, his repeat PET scan showed an overall interval partial response with a stable right suprahilar mass while the other pulmonary lesions showed an interval decrease in size (Figure 1 B, D).

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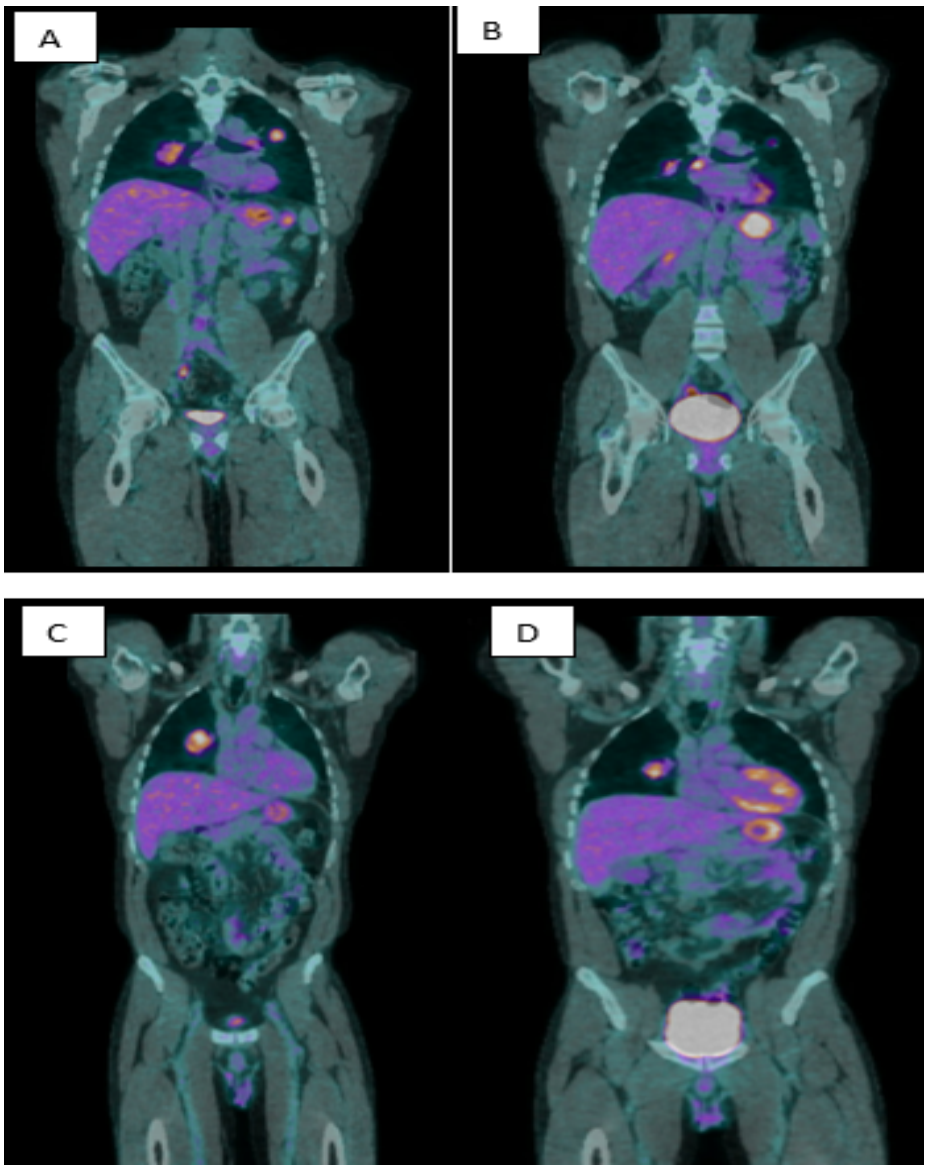

Figure 1: PET scan at diagnosis and after two cycles of dual ICI, coronal views. (A). 2.3 cm left upper lobe pulmonary nodule with SUV of 5.0. A 9 mm short axis right sided subcarinal lymph node demonstrates SUV of 2.7. (B). 1.4 cm left upper lobe nodule demonstrates an SUV of 3, decreased in size and avidity. The right subcarinal lymph node demonstrates an SUV of 6.6 and is now 1.3 cm x 0.7 cm in size. (C). Dominate right medial upper lobe nodule, 6.4 cm, with SUV of 6.9. (D). Necrotic right suprahilar measures 4.3 cm, with an SUV of 6.3.

The patient returned to his home country after receiving Cycle three, Day fifteen of nivolumab and was hospitalized for a traumatic head injury which resulted in a two-month delay of ICI treatment. A PET scan completed two weeks post resumption of nivolumab showed progressive disease. He was then switched to therapy with MAID (doxorubicin 15 mg/m^2 days 1-4, dacarbazine 250 mg/m^2 days 1-4, ifosfamide 2000 mg/m^2 days 1-3, and mesna). The patient transferred care back to our institution after receiving 3 cycles of MAID. His therapy was subsequently modified to omit dacarbazine and the doses of ifosfamide and doxorubicin were changed to 2000 mg/m^2 on days 1-4 and 25 mg/m^2 on days 1-3 respectively. PET imaging after cycle 4 showed continued improvement in the right suprahilar mass, mediastinal metastases, and bilateral pulmonary nodules with no evidence of new visceral metastases. Although there was no adequate detection of FDG within the CNS, brain MRI showed a progressive enhancing lesion at the left parietal lobe. At this time, the plan is for the patient to complete two more cycles of MAI and receive SRS for the progressive parietal lesion.

Discussion

This is a unique case of a young patient presenting with metastatic PPC that had a partial response to dual therapy with the Immune Checkpoint Inhibitor (ICI) agents nivolumab and ipilimumab. PPC is a rare histology that is often resistant to conventional chemotherapy with an Objective Response Rate (ORR) of 17% and Progression-Free Survival (PFS) of 2 months with first-line chemotherapy [3]. Patients with this histology often have a poor prognosis with a median overall survival between 5-10 months [3-7]. Moreover, guidelines do not provide any specific guidance for PPC, and these carcinomas are typically treated like other histologic subtypes of NSCLC. A

Table 1: ICI therapy utilized as either monotherapy or in combination with chemotherapy offers promising clinical efficacy for patients who highly express PD-L1.

Case Reports and Case Series													
Author/ Year	**Age/ sex**	**Ever Smoker**	**Histologic Subtype**	**Stage**	**PD-L1 TPS (%)**	**Surgery**	**Radiation**	**Prior Lines of Treatment**	**Treatment**	**Response**	**Duration of ICI treatment**	**irAE**	**Ref**
Kanazu et al., 2017	66/M	NR	Pleomorphic	IV	≥95	NR	Y	1	Nivolumab	PD	6 cycles/ discontinued	NR	[13]
Kanazu et al., 2017	59/F	NR	Pleomorphic	IIIA	80-90	N	NR	2	Nivolumab	PR	19 cycles/ ongoing	NR	[13]
Kanazu et al., 2017	83/M	NR	Pleomorphic	IIIA	60-70	N	N	3	Nivolumab	PR	10 cycles/ ongoing	NR	[13]
Marchand et al., 2017	55/M	Y	Pleomorphic	IV	90	N	N	1	Nivolumab	PR	9 cycles/ discontinued	Diabetes mellitus, Hypophysitis	[14]
Senoo et al., 2019	62/M	Y	Pleomorphic	IV	70	N	N	1	Nivolumab	PR	12 cycles/ ongoing	Hypophysitis	[15]
Ito et al., 2016	67/M	Y	Pleomorphic	IV	≥50	N	N	6	Nivolumab	PR	8 cycles/ ongoing	N	[16]
Salati et al., 2018	74/M	N	Pleomorphic	IV	≥50	Prior to ICI	N	2	Nivolumab	PR	28 months/ ongoing	Grade 1 Rash	[17]
Okamura et al., 2018	75/M	Y	Pleomorphic	IV	90	N	N	2	Nivolumab	CR	3 cycles/ ongoing	NR	[18]
Tozuka et al., 2018	82/M	Y	Pleomorphic	IIB	75	Prior to ICI	N	0	Pembrolizumab	PR	3 cycles/ discontinued	Agranulocytosis, Grade 1 pneumonitis, Ocular myasthenia gravis	[19]
Matsumoto et al., 2017	51/M	Y	Pleomorphic	IVB	≥50	Prior to ICI	N	0	Pembrolizumab	PR	3 cycles/ ongoing	N	[20]
Roesel et al., 2019	57/M	NR	Sarcomatoid	IV	80-90	Prior to ICI	N	1	Nivolumab	CR	3 months/ ongoing	NR	[21]
Roesel et al., 2019	60/M	NR	Sarcomatoid	IV	100	Prior to ICI	N	1	Nivolumab	PR	8 months/ ongoing	NR	[21]
Kakimoto et al., 2019	69/F	Y	Giant cell	IV	75	Post ICI	Y	0	Pembrolizumab	CR	4 cycles/ discontinued	Renal dysfunction Adrenal insufficiency	[22]
Ikematsu et al., 2017	71/M	Y	Sarcomatoid	IV	80	N	N	0	Pembrolizumab	PR	5 cycles/ ongoing	N	[23]
Hayashi et al., 2021	73/M	NR	Pleomorphic	IV	80-90	Prior to ICI	Y	0	Pembrolizumab	NR	2 cycles	NR	[24]
Hayashi et al., 2021	66/M	NR	Pleomorphic	IIIA	90-100	N	N	0	Pembrolizumab/ Carboplatin/ nab-paclitaxel àpembrolizumab maintenance	PR	4 cycles/ ongoing	NR	[24]
Hayashi et al., 2021	49/M	NR	Pleomorphic	IV	60-70	N	Y	1	Pembrolizumab	PR	11 months/ ongoing	NR	[24]
Rajdev et al., 2018	56/F	Y	Sarcomatoid	IIB	Unknown	N	Y	1	Nivolumab	PR	Ongoing	NR	[25]
Sukrithan et al., 2019	46/M	Y	Pleomorphic	IV	90	N	Y	2	Pembrolizumab	PR	22 months/ discontinued (death)	NR	[26]
Sukrithan et al., 2019	64/F	Y	Pleomorphic	IV	80	N	Y	0	Pembrolizumab	PR	11 months/ ongoing	NR	[26]
Sukrithan et al., 2019	57/M	Y	Sarcomatoid	IV	100	N	N	0	Pembrolizumab	SD	8 months/ ongoing	NR	[26]
Sukrithan et al., 2019	67/F	Y	Sarcomatoid	IV	>75	N	N	0	Pembrolizumab	PR	7 months/ ongoing	NR	[26]

F: Female; M: Male; Y: Yes; N: No; NR: Not reported; ICI: Immune Checkpoint Inhibitor; PD-L1: Programmed Death Ligand 1; TPS: Tumor Proportion Score (TPS); CR: Complete Response; PR: Partial Response; SD: Stable Disease; PD: Progressive Disease; irAE: Immune-related Adverse Events; Ref: Reference

Retrospective Cohort and Observational Studies													
Author/ Year	**Population Studied**	**n**	**Men**	**Ever Smoker**	**Stage**	**Prior Lines of Treatment**	**PD-L1 TPS**	**Treatment**	**ORR**	**Median PFS in PPC Patients**	**Median OS in PPC Patients**	**irAE**	**Ref**
Miyashita et al., 2021	Common and uncommon NSCLC histologies	44 (10 PPC patients)	95%	95%	III: 32% IV: 48%	2: 50% ≥3: 34%	≥50%: 39% 1–49%: 23% Not available: 25%	Nivolumab: 50% Pembrolizumab: 36%	NR	7.7 months	9.5 months	8 patients experienced an irAE	[27]
Domblides et al., 2020	Pulmonary sarcomatoid carcinoma	37	73%	95%	III: 32% IV: 46%	2: 54% ≥3: 46%	Median PD-L1: 70%	Nivolumab: 87% Pembrolizumab: 8%	40.50%	NR	12.7 months	6 patients experienced an irAE	[28]
Lee et al., 2020	Pulmonary pleomorphic carcinoma	49	73.50%	73.50%	III: 27% IV: 60%	2: 77% ≥3: 18%	≥50%: 83.7%	Nivolumab: 14.3% Pembrolizumab: 81.6%	49%	7.2 months	22.2 months	13 irAE reported	[29]

NR: Not reported; PD-L1: Programmed Death Ligand 1; TPS: Tumor Proportion Score (TPS); ORR: Objective Response Rate; PRF: Progression-Free Survival; OS: Overall Survival; irAE: Immune-related Adverse Events; Ref: Reference

retrospective study by Karim and colleagues showed no significant difference in survival of patients treated with systemic chemotherapy alone compared to patients that did not receive any treatment [8]. Thus, novel treatment strategies are needed to address this unmet need.

ICIs have demonstrated significant efficacy and tolerable safety profiles across the spectrum of NSCLC histologic subtypes. A recognized predictor of ICI response is the degree of programmed death-ligand 1 (PD-L1) expression, although this response varies across tumor types. PPC histology has been shown to display PD-L1 expression at a higher rate than other NSCLC histologies. Kim et al. reported that 90.2% of patients with pulmonary pleomorphic carcinomas had positive PD-L1 expression [9, 10]. Chang et al. reported that 70.5% of PPC patients had high PD-L1 expression [11]. Although uncommon NSCLC histologies have been included in large clinical trials, specific characterization is infrequently reported [12-13]. Retrospective studies, case reports, and case series (Table 1) have shown that ICI therapy utilized as either monotherapy or in combination with chemotherapy offers promising clinical efficacy for patients who highly express PD-L1 (PD-L1 ≥50%) [14-30]. Miyashita et al. performed a retrospective analysis that included propensity score-matched patients with common NSCLC histology and uncommon histology, including 10 patients with PPC treated with ICI monotherapy [28]. Results from this study found that median ORR, PFS, and OS were not significantly different based on the dichotomization of common versus uncommon histology groups. Subgroup analysis of pleomorphic carcinoma showed a median PFS and OS were 7.7 months and 9.5 months, respectively, and was similar to the primary group [28]. Domblides et al. performed a retrospective study of 37 patients with pulmonary sarcomatoid carcinoma with a median PD-L1 expression of 70% that received ICI as second-line therapy or beyond [29]. The ORR and median OS were 40.5% and 12.7 months, respectively. The ORR was higher in patients who were PD-L1 positive [29]. Lee et al. performed a retrospective analysis of 49 pulmonary pleomorphic carcinoma that were treated with PD-1/PD-L1 inhibitor therapy [30]. The ORR, median PFS, and OS were 49.0%, 7.2 months, and 22.2 months, respectively [30]. The outcome differences between the results by Domblides and Lee et al. may be due to differences in the number of patients included with high PD-L1 expression.

TMB is another important cancer biomarker that has been utilized to predict responsiveness to ICI. Like PD-L1 expression, TMB can vary between patients and cancers. High TMB (TMB-H) is associated with a higher proportion of patients with better response to ICI monotherapy compared to patients with non-TMB-H carcinomas [31]. Dual ICI therapy has also been associated with improved clinical outcomes in patients with NSCLC and TMB-H [32]. A genomic profiling study of 125 PPCs by Schrock et al demonstrated intermediate to high TMB status in 43% of patients, showing this is an important biomarker of interest in this patient population [33]. There are fewer data available evaluating TMB status and ICI responsiveness in PPC patients compared with PD-L1 expression. A case report and a retrospective cohort study have demonstrated that patients with TMB-H status may have higher response rates to ICI therapy [29]. Domblides et al. included 8 patients who had TMB status assessed [29]. The median TMB was 18 mutations per megabase, with 87.5% of the cases displaying a high TMB. This study found a higher TMB was associated with a trend toward higher survival, with a median 18-month OS in TMB-H populations versus a 1.8-month OS in low TMB populations.

This is the first known report describing the utilization of dual ICI therapy in a patient with metastatic pulmonary pleomorphic giant cell carcinoma. Partial response was the best response achieved. Akin to the previously described literature, our patient had PD-L1 expression of 50% and a Tumor Mutational Burden (TMB) of 13 mutations per megabase, which may have culminated in the partial response observed. It is important to highlight the differences in PD-L1 expression between the CNS lesion, lymph node, and NGS results for this patient. These differences are reflective of the known heterogeneity of a tumor specimen. Although we were unable to determine if the eventual progression on immunotherapy was due to the 2-month delay in therapy while the patient was hospitalized for a traumatic head injury, we found the partial response to be encouraging given the poor response of this disease state to traditional chemotherapy options.

Conclusion

There is an unmet need to find novel treatment strategies for PPC, a subtype of NSCLC that is notoriously resistant to conventional chemotherapy, has a paucity of standardized recommendations for clinical management, and a strong under representation in clinical trials. This study adds to the limited literature regarding the potential benefit of adding ICI therapy in PD-L1 high expressing PPCs and is to our knowledge, the first employing the utilization of dual ICI therapy. Prospective studies are needed to corroborate findings limited by case reports and case series, and there is also a continued need to identify potentially targetable biomarkers to guide treatment or predict therapeutic response.

Availability of Data and Materials

Data sharing not applicable to this case report as no datasets were generated or analyzed for this study.

Conflicts of Interests

The authors declare that there is no conflict of interest regarding the publication of this article.

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