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World J Clin Cases 2020 January 6; 8(1): 1-244





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The WJCC is now indexed in PubMed, PubMed Central, Science Citation Index Expanded (also known as SciSearch®), and Journal Citation Reports/Science Edition. The 2019 Edition of Journal Citation Reports cites the 2018 impact factor for WJCC as 1.153 (5-year impact factor: N/A), ranking WJCC as 99 among 160 journals in Medicine, General and Internal (quartile in category Q3).

RESPONSIBLE EDITORS FOR THIS ISSUE

Responsible Electronic Editor: *Yan-Xia Xing*

Proofing Production Department Director: *Yun-Xiaojuan Wu*

NAME OF JOURNAL

World Journal of Clinical Cases

ISSN

ISSN 2307-8960 (online)

LAUNCH DATE

April 16, 2013

FREQUENCY

Semimonthly

EDITORS-IN-CHIEF

Dennis A Bloomfield, Bao-Gan Peng, Sandro Vento

EDITORIAL BOARD MEMBERS

<https://www.wjnet.com/2307-8960/editorialboard.htm>

EDITORIAL OFFICE

Jin-Lei Wang, Director

PUBLICATION DATE

January 6, 2020

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INSTRUCTIONS TO AUTHORS

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<https://www.wjnet.com/bpg/gerinfo/240>

PUBLICATION MISCONDUCT

<https://www.wjnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>



Pembrolizumab - emerging treatment of pulmonary sarcomatoid carcinoma: A case report

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Informed consent statement: Consent to publish was obtained from the patient in the study.

Conflict-of-interest statement: The authors declare that they have no competing interests.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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Abstract

BACKGROUND

Few studies have addressed the efficacy of pembrolizumab in pulmonary sarcomatoid carcinoma (PSC), a rare, previously rapidly fatal subtype of non-small-cell lung cancer.

CASE SUMMARY

We report the case of a 69-year-old man presented with respiratory distress caused by a large left upper lung lobe mass diagnosed as PSC with programmed death-ligand 1 expressed on more than 50 percent of tumor cells. The patient was started on pembrolizumab and, after 5 cycles, there was a more than 80 percent decrease in the size of the tumor mass. Further decrease was seen at the end of 10 cycles. The patient has been tolerating pembrolizumab well, with no limiting side-effects. Fourteen months after first coming into the hospital, he remains asymptomatic.

CONCLUSION

Pembrolizumab appears as a viable emerging treatment for PSC.

Key words: Pembrolizumab; Pulmonary sarcomatoid carcinoma; Programmed death-ligand 1; Platinum-based chemotherapy; Non-small-cell lung cancer; Overall survival;

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Manuscript source: Unsolicited manuscript

Received: September 11, 2019

Peer-review started: September 11, 2019

First decision: October 24, 2019

Revised: November 5, 2019

Accepted: November 14, 2019

Article in press: November 14, 2019

Published online: January 6, 2020

P-Reviewer: Vanoli A

S-Editor: Dou Y

L-Editor: A

E-Editor: Wu YXJ



Case report

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Core tip: Pulmonary sarcomatoid carcinoma (PSC) is classified as a rare, aggressive subtype of non-small-cell lung cancer. In recent years, pembrolizumab, a humanized monoclonal IgG-kappa isotype antibody against the programmed death-1 receptor, has become the first-line treatment for NSCLE with programmed death-ligand-1 (PD-L1) expression on at least 50% of tumor cells. We report the case of an elderly man diagnosed with invasive PSC with PD-L1 greater than 50%. The patient experienced a highly positive response to pembrolizumab. The recommendation to treat PSC with pembrolizumab is supported by the small number of published papers available in the English literature.

Citation: Cimpeanu E, Ahmed J, Zafar W, DeMarinis A, Bardarov SS, Salman S, Bloomfield D. Pembrolizumab - emerging treatment of pulmonary sarcomatoid carcinoma: A case report. *World J Clin Cases* 2020; 8(1): 97-102

URL: <https://www.wjnet.com/2307-8960/full/v8/i1/97.htm>

DOI: <https://dx.doi.org/10.12998/wjcc.v8.i1.97>

INTRODUCTION

Pulmonary sarcomatoid carcinoma (PSC) represents a high-grade histologic subtype of non-small-cell lung cancer (NSCLC), accounting for only about 1% of NSCLC and 0.4% of all lung cancers in the United States^[1,2]. Most are diagnosed at advanced stages and have an aggressive clinical course and lower overall survival than other histologic subtypes, even on the rare occasions when discovered incipiently^[2]. Management of metastatic disease has been challenging, owing to high rates of resistance to conventional platinum-based chemotherapy, which, up to recently, was the preferred treatment option for all metastatic types^[2-4]. While response to pembrolizumab in the more common subtypes of NSCLC has been reported by several studies, very few have addressed the efficacy of pembrolizumab in PSC. We report a case of excellent response to pembrolizumab in a patient with PSC characterized by programmed death-ligand 1 (PD-L1) expression greater than 50%.

CASE PRESENTATION

Chief Complaints

A 69-year-old man presented with one week's duration of respiratory distress and diffuse, intermittent and non-radiating left upper chest pain.

History of present illness

The patient began experiencing occasional dry cough two months prior to presentation but denied having any other symptoms.

History of past illness

There was a past medical history of 60 pack-year smoking, hypertension, diabetes mellitus type II, hypothyroidism, Parkinson's disease and depression.

Physical examination

The patient had labored and irregular breathing but did not use the accessory muscles of respiration. There was tenderness to palpation of the left chest wall and dullness to percussion in the left upper lung field, with decreased breath sounds, rhonchi and slight wheezing. There was mild diffuse abdominal tenderness, without guarding.

Laboratory examinations

Laboratory workup revealed white blood cell count 22.9 K/uL, hemoglobin 10.8 g/dL, hematocrit 37.0%, platelet count 943 K/uL, erythrocyte sedimentation rate 130, serum potassium 5.4 mmol/L and serum calcium 11.6 mg/dL.

Imaging examinations

Chest computed tomography (CT) demonstrated a solid, heterogeneous, partially necrotic mass occupying the left upper lobe, encasing the left subclavian artery and extending into the left mediastinum (Figure 1A, 1B). Abdominal and pelvic CT showed hepatomegaly. There was extensive destruction of the left first rib, with less severe involvement of the left second rib, but no evidence of mediastinal, hilar or axillary adenopathy.

FINAL DIAGNOSIS

Biopsy of the mass revealed a poorly differentiated neoplasm composed predominantly of spindle cells, with rare epithelioid cells and large bizarre nuclei (Figure 2A). The immunohistochemical analysis of the lesion demonstrated that the neoplastic cells were positive for cytokeratin-7 (CK-7) (Figure 2B) but negative for thyroid transcription factor-1, p40, CK20, prostate-specific antigen, and MelanA. In addition, immunohistochemical stains for mesothelial origin, specifically Calretinin, CK5/6 and podoplanin (D2-40) were negative. The negative p40 and CK5/6 also ruled out sarcomatoid squamous cell carcinoma. The neoplastic cells tested positive for PD-L1, with a tumor proportion score greater than 50% (Figure 2C). No mutations in epidermal growth factor receptor (EGFR) exons 18, 19 or 21 and KRAS codons 12, 13 or 61 were present. An exon 20 insertion was identified but the mass was EGFR T790M-negative. Anaplastic lymphoma kinase (ALK) and receptor tyrosine kinase (ROS) translocations were not performed since EGFR and KRAS mutations are mutually exclusive with these translocations. The tumor was classified as stage IIIa (T4N1M0) PSC.

TREATMENT

IV fluids, Pamidronate and antibiotics were administered, and the patient's condition stabilized. Given multiple medical comorbidities, surgical debulking was not feasible. As the tumor was causing airway compromise, palliative radiation therapy was initiated. The patient was also started on pembrolizumab (200 mg) every 21 d.

OUTCOME AND FOLLOW-UP

A repeat CT scan of the chest after 5 cycles of pembrolizumab showed a decrease of more than 80 percent in the size of the tumor mass (Figure 1C, 1D).

Positron emission tomography-CT (PET-CT) scan at the end of 10 cycles showed an even further decrease (Figure 3). The patient has been tolerating pembrolizumab well, with no limiting side-effects and a plan was made to continue the same treatment. At present, 14 mo after first coming into the hospital, he remains asymptomatic.

DISCUSSION

When diagnosed, PSCs are frequently bulky, peripherally located and already metastatic, with poor prognosis^[1]. For a patient like ours, with stage III tumor, overall survival is estimated at 5.8 mo, whereas for stages I-II it is 16.9 mo and for stage IV 5.4 mo^[5]. The typical patient has a history of heavy smoking^[1]. PSCs are more widespread in Caucasians (89%) and males (59%)^[5]. The mean age at diagnosis is 70 years^[5]. Our patient fits these exact demographics - male, Caucasian, heavy smoker, in his late 60 s and with an advanced malignancy. Improved survival in PSC is seen when tumors are localized, amenable to complete surgical resection, 4 cm or less in size, and when patients are not underweight or anemic^[6]. Our patient was not underweight but lacked other positive prognostic factors. He was, in fact, anemic and had a large, locally-invasive tumor, which put him at increased risk for a less favorable outcome.

Platinum-based chemotherapy has proven disappointing in PSC, with most patients (69%) experiencing disease progression and overall survival being only slightly increased compared to the non-platinum group (7.0 *vs* 5.3 mo)^[3]. Compared to patients not receiving any treatment, platinum-based chemotherapy resulted in a median overall survival of only 51 d longer^[7]. Decreased survival in PSC has been largely attributed to its aggressive nature as well as chemoresistance^[1]. The marginal performance of available treatment options warranted a need for new therapeutic

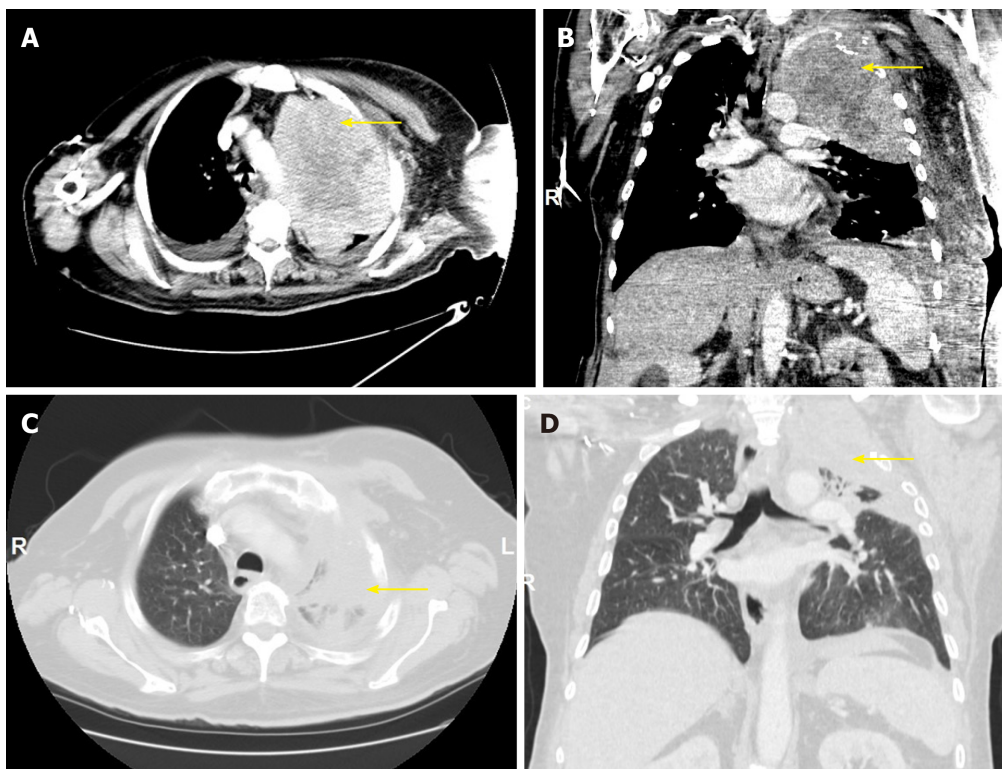


Figure 1 Chest computed tomography. A, B: Prior to initiation of pembrolizumab, with yellow arrows pointing to a left upper lobe primary measuring 14.1 cm × 10.6 cm × 14.9 cm. C, D: After 5 cycles of pembrolizumab, with yellow arrows pointing to a markedly decreased left upper lobe mass measuring 8.0 cm × 7.7 cm × 6.8 cm.

strategies.

The introduction of pembrolizumab, a monoclonal IgG4 kappa isotype antibody against the Programmed Death 1 pathway, for NSCLC lacking targetable EGFR or ALK mutations has resulted in improved overall survival and progression-free survival for NSCLC with PD-L1 on at least 50% of tumor cells^[4,8]. Pembrolizumab has become the first-line treatment for such tumor^[4]. KEYNOTE studies (021, 024 and 189) all showed improved treatment response when pembrolizumab was added to platinum-based chemotherapy^[4,9,10]. In addition, patients on pembrolizumab benefited from increased overall survival, greater response rate, longer duration of response and fewer adverse effects secondary to treatment^[10]. However, the application of pembrolizumab for PSC has been minimally reported. On a Pubmed search, there are three other individual cases published supporting our contention that pembrolizumab is effective in this previously rapidly fatal tumor^[11-13]. There are six other cases in which a form of immunotherapy has been used, however, the outcome is unclear^[14,15].

For PSCs with mutated EGFR, EGFR tyrosine kinase inhibitors (TKIs) can be a more suitable treatment option^[16]. Third generation EGFR-TKIs have proven efficacious in tumors with EGFR mutations in exons 19 and 21 as well as exon 20 T790M mutations^[17]. Osimertinib, a third-generation EGFR-TKI, is particularly indicated for EGFR-mutant NSCLC with an acquired T790M resistance mutation, progressing during or following treatment with EGFR-TKIs^[17]. Our patient lacked EGFR targetable mutations. The tumor was in fact positive for an EGFR exon 20 insertion, which is seen in about 9% of all EGFR-mutated tumors and has been linked to de-novo resistance to EGFR-TKI^[18]. For these reasons, EGFR-TKIs were not an appropriate choice.

CONCLUSION

The efficacy of pembrolizumab in the treatment of PSC has not been adequately studied. In our patient, it was proven a highly beneficial form of treatment. He continued to be asymptomatic, more than 14 mo after presentation. To date, this is one of the most sustained responses of PSC to an immune checkpoint inhibitor reported in the English literature. For PSC patients with PD-L1 expression on 50% or more of tumor cells, pembrolizumab is a viable option.

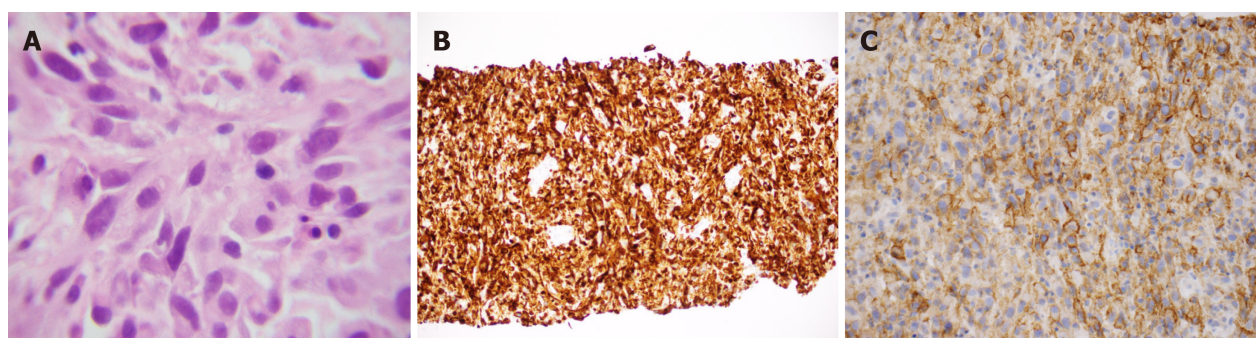


Figure 2 Histological lung section. A: Hematoxylin and eosin staining showing sarcomatoid carcinoma, with visible spindle cells and rare epithelioid cells (magnification, 100 ×); B: Immunohistochemical staining showing sarcomatoid carcinoma with neoplastic cells positive for CK7 (magnification, 200 ×); C: Hematoxylin and eosin staining showing sarcomatoid carcinoma, with cells positive for programmed death-ligand-1 and tumor proportion score greater than 50% (magnification, 400×).

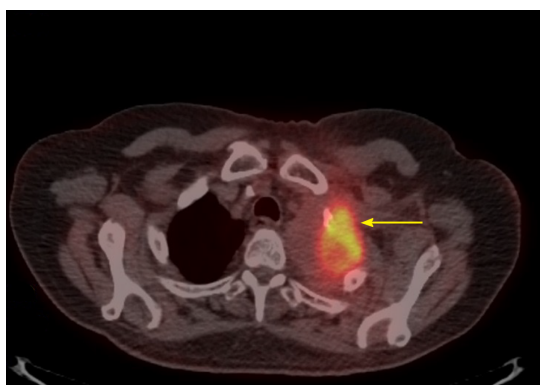


Figure 3 Chest positron emission tomography - computed tomography (lung window) after 9 cycles of pembrolizumab, with the yellow arrow pointing to a fluorodeoxyglucose-avid 5.5 cm × 4 cm mass in the left upper lobe, with central necrosis and a maximum standardized uptake value of 8.6, consistent with malignancy. Inferiorly and in its continuation, there is a second lesion measuring 2.3 cm × 1.8 cm with a maximum standardized uptake value of 7.2, interpreted as a remnant from the initial tumor.

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