**OPINION REVIEW**

2674 Minimizing the risk of community spread of COVID-19 via institutional quarantine of high-risk travelers with serial viral RNA testing: A successful experience from Macao SAR, China

*Lio CF, Cheong HH, Lei CI, Lo IL, Lam C, Leong IH*

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**REVIEW**

2679 Balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension: State of the art

*Jin Q, Zhao ZH, Luo Q, Zhao Q, Yan L, Zhang Y, Li X, Yang T, Zeng QX, Xiong CM, Liu ZH*

2703 Advances in para-aortic nodal dissection in gastric cancer surgery: A review of research progress over the last decade

*Dong YP, Deng JY*

2717 Relevance on the diagnosis of malignant lymphoma of the salivary gland

*Zhang XY, Wang ZM*

---

**ORIGINAL ARTICLE**

**Clinical and Translational Research**

2727 Role of peripheral eosinophilia in acute exacerbation of chronic obstructive pulmonary disease

*Wu CW, Lan CC, Hsieh PC, Tzeng IS, Wu YK*

**Case Control Study**

2738 Effects of prostaglandin E combined with continuous renal replacement therapy on septic acute kidney injury

*Lei L, Wang MJ, Zhang S, Hu DJ*

**Retrospective Study**

2749 Modified technique of advanced core decompression for treatment of femoral head osteonecrosis

*Lin L, Jiao Y, Luo XG, Zhang JZ, Yin HL, Ma L, Chen BR, Kelly DM, Gu WK, Chen H*

2758 Initial experience with stereotactic body radiotherapy for intrahepatic hepatocellular carcinoma recurrence after liver transplantation

*Au KP, Chiang CL, Chan ACY, Cheung TT, Lo CM, Chok KSH*

2769 Correlation between age of onset and gastrointestinal stenosis in hospitalized patients with Crohn's disease

*Yang SB, Du SW, Wang JH*

2778 Adjuvant nab-paclitaxel plus gemcitabine vs gemcitabine alone for resected pancreatic ductal adenocarcinoma: A single center experience in China

*Yin ZZ, Zhao ZM, Tang WB, Jiang N, Zhang KD, Song YY, Wang Y, Li CG, Gao YX, Liu R*
## Contents

### Observational Study

2787  Case studies in psychotherapy training using Austria as an example  
*Neidhart E, Löffler-Stastka H*

### Prospective Study

2802  Correlation between crowdedness in emergency departments and anxiety in Chinese patients  

### SCIENTOMETRICS

2817  Bibliometric analysis of subject trends and knowledge structures of gut microbiota  

### CASE REPORT

2833  Acute myelomonocytic leukemia during pembrolizumab treatment for non-small cell lung cancer: A case report  
*Kim HB, Park SG, Hong R, Kang SH, Na YS*

2841  Metallic ureteral stent in restoring kidney function: Nine case reports  
*Gao W, Ou TW, Cui X, Wu JT, Cui B*

2849  Pheochromocytoma with delayed tumor thrombus detection in renal vein: A case report  
*Jia Z, Wang BJ, Li X, Zhang X*

2855  Laparoscopic repair of uterine rupture following successful second vaginal birth after caesarean delivery: A case report  
*Cui YQ, Liu W, Zhang H, He XQ, Zhang J*

2862  Missed diagnosis of femoral deep artery rupture after femoral shaft fracture: A case report  
*Ge J, Kong KY, Cheng XQ, Li P, Hu XX, Yang HL, Shen MJ*

2870  Posterior reversible encephalopathy syndrome and heart failure tacrolimus-induced after liver transplantation: A case report  
*Liu JF, Shen T, Zhang YT*

2876  Significant benefits of pembrolizumab in treating refractory advanced pulmonary sarcomatoid carcinoma: A case report  
*Chen P, Yu M, Zhang JL, Chen WY, Zhu L, Song Y, Jiang CY, Zhang S*

2885  Two sequential surgeries in infant with multiple floor of the mouth dermoid cysts: A case report  
*Liu NN, Zhang XY, Tang YY, Wang ZM*
ABOUT COVER

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The WJCC is now indexed in Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports/Science Edition, PubMed, and PubMed Central. The 2020 Edition of Journal Citation Reports® cites the 2019 impact factor for WJCC as 1.013 (5-year impact factor: N/A), ranking WJCC as 120 among 165 journals in medicine, general and internal (quartile in category Q3).

RESPONSIBLE EDITORS FOR THIS ISSUE

Electronic Editor: Yan-Xia Xing; Production Department Director: Yun-Xiaojuan Wu; Editorial Office Director: Jin-Lei Wang.
Significant benefits of pembrolizumab in treating refractory advanced pulmonary sarcomatoid carcinoma: A case report

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Author contributions: Chen P, Yu M, and Zhuang S reviewed the literature and contributed to manuscript drafting; Zhang J-L and Chen WY contributed to manuscript drafting; Zhu L and Song Y analyzed and interpreted the imaging findings; Chen P, Yu M, Zhuang S, and Jiang CY were responsible for revising the manuscript for important intellectual content; all authors provided final approval for the version to be submitted; Chen P and Yu M contributed equally to this work.

Informed consent statement: Informed written consent was obtained from the patient for publication of this report and any accompanying images.

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

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the author contributions section has been completed.

Abstract

BACKGROUND
Pulmonary sarcomatoid carcinoma (PSC), a rare subtype of non-small cell lung cancer (NSCLC), is poorly differentiated and highly aggressive. Treatment is limited, and the prognosis is poor. Pembrolizumab is an anti-programmed death (PD)-1 antibody with good efficacy in NSCLC. Recent studies have demonstrated that PD-ligand 1 (PD-L1) overexpression is common in PSCs, which suggests that anti-PD-L1 treatment is an ideal option. However, the response to pembrolizumab in PSC has not been studied.

CASE SUMMARY
We present a PSC case with PD-L1 overexpression that significantly benefited from pembrolizumab. A 73-year-old Chinese male was detected with a right lung lesion. Pathological analysis of the right upper lobectomy confirmed PSC. The PD-L1 test revealed overexpression (TPS: 90%). Multiple metastases occurred 1 mo after surgery, representing stage IV PSC. Neither first-line chemotherapy nor second-line antiangiogenic agents showed any benefit. Radiotherapy (1200 cGy) was administered to relieve chest wall pain. The patient received the PD-1 inhibitor pembrolizumab (100 mg) as third-line therapy; however, because of fever and severe infection, he refused to receive immunotherapy any longer. Thus, only one dose of pembrolizumab was administered. Deep sustained remission of most of the metastases was achieved except for lesions in the right adrenal gland, which first shrank and then progressed. The patient died because of disease progression in the right adrenal gland. He achieved a progression-free...
survival time of 8 mo and an overall survival time of 9 mo with third-line pembrolizumab.

CONCLUSION
Our findings highlight and offer direct evidence of the efficacy of pembrolizumab in PD-L1-overexpressing PSCs. Combined radiotherapy and immunotherapy may enhance treatment efficacy.

Key words: Pulmonary sarcomatoid carcinoma; Immunotherapy; Programmed death-ligand 1; Pembrolizumab; Radiotherapy; Case report

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Core tip: This is a report of a patient with programmed death-ligand 1 (known as PD-L1)-overexpressing pulmonary sarcomatoid carcinoma with a good response to pembrolizumab, indicating that pembrolizumab is an important treatment for pulmonary sarcomatoid carcinoma patients with PD-L1 overexpression. In this case, the patient received low-dose radiotherapy before pembrolizumab, which suggests that the combination of radiotherapy and immunotherapy may elevate treatment efficacy.

URL: https://www.wjgnet.com/2307-8960/full/v8/i13/2876.htm
DOI: https://dx.doi.org/10.12998/wjcc.v8.i13.2876

INTRODUCTION
Pulmonary sarcomatoid carcinoma (PSC) comprises a rare group of non-small cell lung cancer (NSCLC). According to the Surveillance, Epidemiology, and End Results database, PSC accounts for 0.52% of all NSCLC cases[1]. PSC is characterized by poorly differentiated, highly aggressive, and highly metastatic properties, and its prognosis is much poorer than that of other NSCLC subtypes[2,3]. Moreover, PSCs are not sensitive to conventional chemotherapy[4,5]; thus, developing novel therapeutic strategies is essential. Programmed death 1 (PD-1) and PD-ligand 1 (PD-L1) inhibitors have clinical efficacy in NSCLC[6-8]. In general, the efficacy of immunotherapy parallels the level of PD-L1 expression. Recently, studies have demonstrated that PD-L1 overexpression is common in PSCs, ranging from 53% to 69.2%, which makes immunotherapy a promising treatment option for PSCs. However, studies of immunotherapy in PSC are very limited to date, and only a few reports can be found[9-11]. Here, we present one patient with PSC, who developed deep sustained remission for most metastatic lesions except for right adrenal lesions, after treatment with one dose of the PD-1 inhibitor pembrolizumab.

CASE PRESENTATION
Chief complaints
A 73-year-old Chinese male patient was initially admitted to the hospital due to a space-occupying lesion in the right lung found during a routine health examination.

History of present illness
The patient did not experience any symptoms or discomfort before this examination.

History of past illness
The patient had a clear medical history.

Personal and family history
The patient had a long-term smoking history for approximately 45 years (20 cigarettes...
per day) without quitting until the disease was detected. He had no personal or family history of other diseases.

**Physical examination upon admission**

At admission, the patient was conscious, body temperature was 36.3 °C, with a regular heart rate of 68 bpm, respiratory rate of 16 breaths per minute, and blood pressure of 120/70 mmHg. He reported no history of weight loss during recent months. The patient’s Eastern Cooperative Oncology Group (referred to as ECOG) Performance Status (PS) score was 0. His right upper lung breathing sounds were weak. The other physical examinations were normal.

**Laboratory examinations**

The results of routine laboratory tests including routine blood examination, blood biochemistry, routine urine examination, fecal occult blood, and tumor markers were all within normal limits.

**Imaging examinations**

Computed tomography (CT) of the chest revealed a space-occupying lesion in the apical segment of the upper lobe of the right lung.

**FINAL DIAGNOSIS**

Pathology after right upper lobe pneumonectomy and lymphadenectomy revealed the following: centrally low differentiated carcinoma in the right upper lobe, (dominant with spindle cell/sarcomatoid carcinoma, adenocarcinoma also present), diameter of 63 mm, with pleura and chest wall invasion, pT3N0M0. Immunohistochemistry (IHC): PCK (+, partial cells), epithelial membrane antigen (+, partial cells), thyroid transcription factor 1 (+, for adenocarcinoma), Napsin A (+, for adenocarcinoma), smooth muscle actin (+, partial cells), p63 (+), cytokeratin K5/6 (-), S-100 (-), desmin (-), stabilin-2 (-). IHC for PD-L1 (clone SP142 by Ventana Medical System) showed strong expression in tumor cells (tumor proportion score [TPS]: 90%) (Figure 2). Next-generation sequencing analysis of the tumor sample revealed no mutation, rearrangement, or infusion. At 1 mo after surgery, CT revealed bilateral lung and adrenal gland metastases, and bone destruction was also found in the right second to third ribs and the left fifth rib, with soft tissue lesion formation in the right second to third ribs, representing stage IV (cT3N0M1b) PSC (Figure 1).

**TREATMENT**

Systemic treatments were subsequently administered. On June 5, 2018, first-line chemotherapy was administered consisting of paclitaxel 220 mg and carboplatin 380 mg d1 q21d. At the same time, the patient complained of heavy pain in his right chest, with a numerical rating scale (NRS) score of 8, and oral morphine hydrochloride sustained-release tablets 30 mg q12h were prescribed. Starting on June 12, 2018, radiotherapy of the right chest wall was administered to relieve the pain, with 200 cGy each time. After chemotherapy, the patient experienced grade 4 leukopenia (0.8 × 10^9/L) and grade 2 nausea and vomiting according to the Common Terminology Criteria for Adverse Events version 4.0. Rapid enlargement of the left supraclavicular lymph nodes revealed progressive disease. Because of concerns that the patient could not tolerate toxic cell chemotherapy, second-line therapy was administered with the anti-angiogenic agent anlotinib 12 mg po qd1-14 q3w starting from June 14, 2018. Unfortunately, grade 3 hypertension with systolic blood pressure 160 mmHg, grade 2 nausea/vomiting, fatigue and loss of appetite was observed; therefore, anlotinib was discontinued on June 26, 2018. At the same time, radiation treatment also stopped, with the patient receiving a total of 1200 cGy. On June 30, 2018, the patient experienced cough with white sputum, white blood cell count: 14 × 10^9/L, C-reactive protein: 78.2 mg/L, and procalcitonin: 0.05 ng/mL, and auscultation revealed wet rales in both lungs. Consequently, the antibiotics piperacillin and sulbactam were administered, and the infection gradually resolved. However, the patient again developed disease progression to the thyroid, oropharynx left anterior wall, hypopharynx left wall, left chest wall, bilateral lungs, neck lymph nodes, ribs, and adrenal glands. His PS score was 2 at that time. Because the tumor progression was so rapid and high PD-L1
expression was observed in this patient, a combination of isocyclophosphamide and pembrolizumab was planned on July 11, 2019. The patient exhibited severe allergic reactions, including tightness, throat edema, and redness after mesna was injected, which was administered to prevent urinary tract toxicity of isocyclophosphamide; therefore, treatment was suspended. The patient gradually recovered, and 100 mg of the anti-PD1 agent pembrolizumab (Keytruda) was given on July 17, 2019 (Figure 3). At 2 d after administration, the patient experienced a fever of 39.8 °C with cough and
sputum; blood culture revealed *Staphylococcus aureus*, and sputum culture showed *Candida albicans*. As the patient also experienced grade 2 respiratory insufficiency and loss of appetite, immunotherapy was stopped. After 6 wk of linezolid antibiotics and fluconazole antifungal treatment, the patient recovered. Gradually, the patient’s pain was relieved to NRS 0; no analgesic was needed, and his PS score recovered to 0. However, the patient refused to continue immunotherapy. On September 18, 2018, a controlled CT scan showed shrinkage of all the lung metastases, both sites of rib bone destruction and the thyroid and adrenal gland metastases. Accordingly, partial response (PR) was achieved for this patient. No late toxicity was observed.

### OUTCOME AND FOLLOW-UP

On November 30, 2018, another CT scan showed significant regression of all metastases except the lesions in the right adrenal gland, which were slightly larger, and a continuous PR was assessed. Considering that the lesion in the right adrenal gland was becoming larger while no late immunotherapy toxicity was observed, we advised the patient to receive further treatment, such as puncture biopsy, local radiotherapy for his right adrenal gland lesion and pembrolizumab. However, the patient refused. The patient’s ECOG status significantly deteriorated starting from March 2019, and a subsequent CT scan reassessment (March 12, 2019) showed disappearance of the metastatic lesions in the neck lymph nodes, thyroid, oropharynx and hypopharynx; the lesions in the bilateral lungs and chest walls also displayed sustained reduction, but the lesion in his right adrenal gland had become much larger. We advised the patient to receive further treatment, but he refused. Finally, on April 24, 2019, the patient died from disease progression. The tumor changes are characterized in Figure 4. The patient did not receive a CT scan from March 2019 to April 2019. Third-line pembrolizumab resulted in a progression-free survival (PFS) of 8 mo and an overall survival (OS) of 9 mo for this patient.

### DISCUSSION

PSC is a rare subtype of NSCLC that is not sensitive to conventional chemotherapy, and the prognosis is much poorer than that of other types of NSCLC\(^\text{(16,17)}\). Fortunately, immunotherapy is offering new treatment possibilities for this disease. PD-L1 overexpression is very common in PSC\(^\text{(18)}\). The mechanism of action of immunotherapy is a multiple-step process related to inflammation. Once inflammation accelerates, an extensive systemic inflammatory response may occur, and the efficacy may be sustained and thorough\(^\text{(19)}\). One study reported that a PSC patient treated with pembrolizumab achieved a PR\(^\text{(20)}\). Another PSC patient with small intestinal metastasis achieved a PR after 3 mo of immunotherapy. Due to pneumonia, immunotherapy was discontinued, and the disease was still well controlled during reexamination 7 mo later\(^\text{(21)}\). The present patient obtained 8 mo of control of most of his lesions after only one administration of pembrolizumab. This outcome shows that PSC is sensitive to immunotherapy.

Radiotherapy is widely used in limited disease with perfect local tumor control; for advanced disease, radiation is traditionally used for palliative purposes. Currently,
increasing attention has been paid to the combination of radiotherapy and immunotherapy\cite{22,23,24}. Tumor cell death after radiotherapy can release neoantigens\cite{23,24}, and anti–PD-1/PD-L1 therapy can augment the radiation-induced immune response, even causing an abscopal effect. In the PACIFIC study, patients in the durvalumab group had longer PFS and OS than those in the controlled group. Additionally, a secondary analysis of KEYNOTE-001 revealed that PFS and OS were significantly longer for patients who had previous extracranial radiation before pembrolizumab than for patients who did not have previous radiation. Elevated PD-L1 expression may continue for 7 d at the end of radiotherapy; consequently, if PD-L1 inhibitors are used within this time, efficacy may be increased. Based on subgroup analysis in the PACIFIC study, a better PFS was observed when durvalumab was initiated within 2 wk of radiation compared with durvalumab > 2 wk after radiation. Previous studies have suggested that high ablative doses are highly effective; however, a high dose of radiotherapy may lead to lymphopenia and thereby reduce the effectiveness of immunotherapy. At present, researchers tend to believe that a lower dosage, such as 2000 cGy, is sufficient to achieve a sensitization effect. As we all known, PSC is a type of tumor which is not sensitive to radiotherapy. For this patient, he receives radiotherapy from June 12 to June 26, totally 1200 cGy to relieve chest wall pain, a CT scan between the end of radiotherapy and start of immunotherapy showed tumor progression. And after pembrolizumab, a controlled CT revealed that the tumor shrank obviously. So, the clearance of the tumor is probably due to immunotherapy or due to the combination of radiotherapy and immunotherapy.

In our case, the patient experienced different efficacies with regard to his metastases: most of the metastases were perfectly controlled, though the lesion in the right adrenal gland first shrank and then progressed. Intratumor heterogeneity (ITH) was believed to be present in this patient. Indeed, recent studies have revealed that ITH can exist within a single patient and even a single tumor. During “tumor progression,” some cancer cells may develop additional mutations, leading to the emergence of subclones; at the same time, cancer cells may lose functional T-cells and...
Pembrolizumab for refractory advanced PSC

Chen P et al.

To the best of our knowledge, this is the first report of pembrolizumab administration for metastatic PSC in which most of the lesions achieved a perfect response for 8 mo after only one dosage of only 100 mg. There are some notable characteristics of this patient. First, this was a 73-year-old patient. It is known that immunotherapy will be less effective for old patients than young patients, and old age may also be a factor for hyperprogression disease after immunotherapy. Second, the patient was at PS 2 when the immunotherapy was taken; most clinical trials will exclude patients with poor PS scores, and studies suggest that patients with poor PS scores experience less treatment efficacy. Third, PD-L1 was overexpressed in this patient, and he experienced severe adverse events. Some studies have shown that severe adverse events after immunotherapy are associated with better efficacy and longer periods of tumor control. Fourth, the patient received pembrolizumab only once at 21 d after radiotherapy, the dosage of which was 1200 cGy, and most of his lesions were perfectly controlled. It is believed that the radiotherapy plays a very important role in sustained tumor control; efficacy may be increased with a shorter interval between radiotherapy and immunotherapy. Fifth, the patient experienced different efficacies for his metastases, and ITH was believed to exist in this patient. A longer tumor control time may have occurred if the patient had received radiotherapy of the right adrenal gland and continued immunotherapy. This case provides valuable insights into the use of immunotherapy in PSC. First, the poor prognosis of this disease makes it necessary to search for new treatment options. Second, high PD-L1 expression enables deep and sustained remission with immunotherapy. Finally, radiotherapy followed by immunotherapy may be a promising choice to improve treatment efficacy. Further studies should be performed to explore the optimization of treatment for this disease. The finding also raises some questions about the appropriate usage of immunotherapy, namely, what is the appropriate dosage, how often should it be used, and is there some method to reduce adverse events. At present, it is recommended that PD-1 and PD-L1 inhibitors be administered every 2 or 3 wk, as it is known that, the terminal half-life of pembrolizumab is 26 d. It should be determined whether changing the immunotherapy schedule to a longer time is a safe, effective, and cost-saving strategy while reducing patients' adverse events. It seems that a lower frequency or lower dosage may yield the same effectiveness, especially for patients with PD-L1 overexpression or when immunotherapy was followed after radiotherapy.

Nevertheless, there were some limitations. First, the PD-L1 test was used for SP142; Dako 22C3 is the standard diagnostic method for pembrolizumab, and SP142 is relatively lower in sensitivity. Regardless, the patient showed high expression by SP142, which may detect the true high expression of PD-L1. Second, PD-L1 expression was assessed using tissue obtained before chemotherapy and radiotherapy. Therefore, true PD-L1 expression after chemotherapy and radiotherapy was unclear. Moreover, the relationship between PD-L1 expression after chemotherapy and radiotherapy and the effectiveness of pembrolizumab are worthy of investigation. Third, when the right adrenal lesion progressed, rebiopsy was not performed; consequently, it is unknown whether there were differences in pathology or biology between lesions in the
CONCLUSION

PSCs with PD-L1 overexpression may achieve a good response and survival benefit from pembrolizumab. The combination of radiotherapy and immunotherapy may be a promising treatment in PSC. More studies should be performed to obtain a deeper understanding of this disease and to find more optimized treatments.

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