

## Case Report

# Pembrolizumab in a patient with lung sarcomatoid carcinoma resulted in rheumatoid arthritis and limited benefit

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**Abstract:** Lung sarcomatoid carcinoma (SC) is a type of non-small cell lung carcinoma (NSCLC) with poor prognosis and chemo-resistance. Pembrolizumab achieved longer progression-free survival and overall survival than chemotherapy if PD-L1 expression surpasses 50% in NSCLC. However, its efficacy in lung SC is still unknown. We report a female patient with short efficacy with pembrolizumab, but occurrence of confirmed rheumatoid arthritis (RA) in lung SC. RA triggered by pembrolizumab is rarely reported. This patient had no RA before but had a positive family history. This case showed the efficacy of pembrolizumab in lung SC with high PD-L1 expression, and clinical trials containing more cases should be warranted to further evaluate its effect on lung SC. More importantly, oncologists should pay attention to screening of immune-associated family history and indices before anti-PD-1/PD-L1 therapy.

**Keywords:** Lung sarcomatoid carcinoma, pembrolizumab, PD-L1, rheumatoid arthritis, medical history

### Introduction

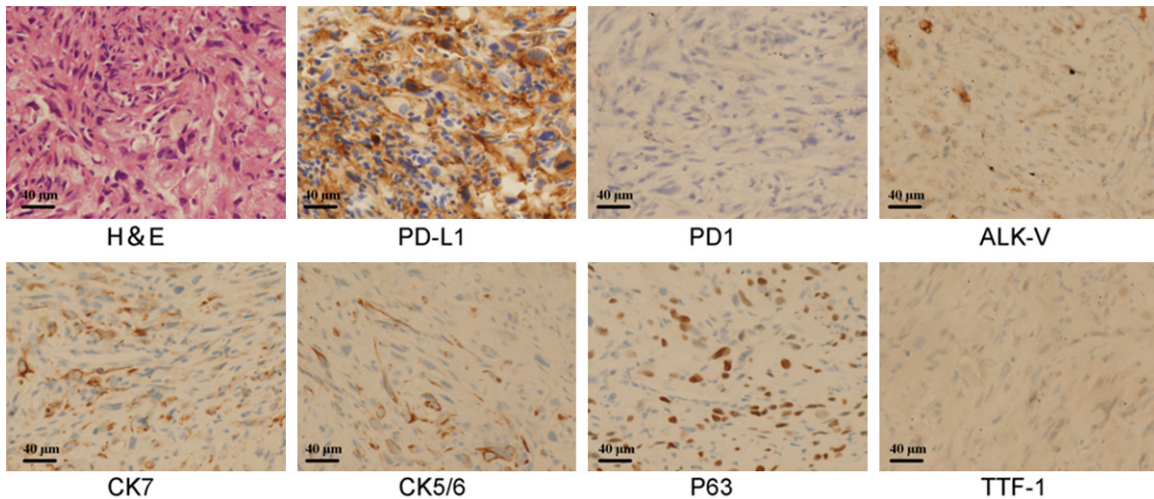
Lung sarcomatoid carcinoma (SC) is a rare kind of malignant tumor of non-small cell lung carcinomas (NSCLC) with poor prognosis. Preliminary efficacy of nivolumab in lung SC has been shown [1]. However, data about anti-PD-1/PD-L1 antibodies in SC are still lacking [1, 2], especially regarding pembrolizumab. We report a patient with high PD-L1 (> 50%) expression and a short efficacy after pembrolizumab. The occurrence of rheumatoid arthritis (RA), a rarely reported immune-related adverse event (irAE), was induced by pembrolizumab in lung SC.

### Case report

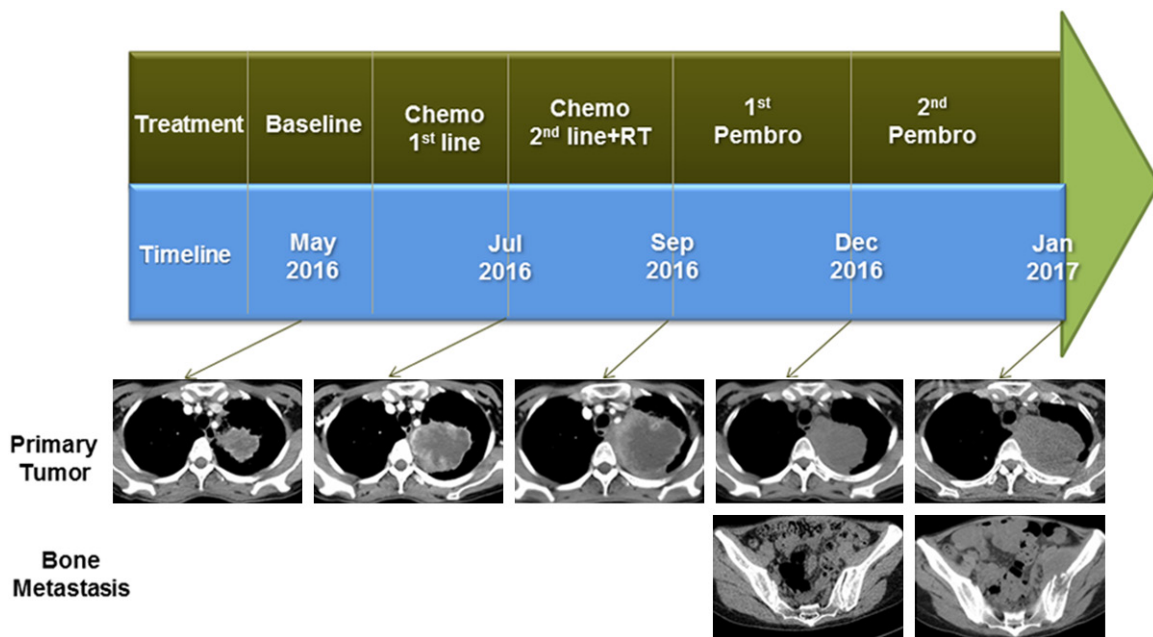
A 49-year-old Chinese female non-smoking patient was diagnosed with stage IIIa NSCLC in June 2016. The patient was confirmed by percutaneous puncture biopsy of the lung as SC. Immunohistochemical analysis showed positive PD-L1 (> 50%), weakly positive ALK-V, and negative staining for ROS-1 and PD-1 (Figure

1). ALK-V was negative by next generation sequencing (NGS). Because of the poor performance status (PS 2), therapy first included two circles of paclitaxel plus cis-platinum but not with concurrent radiotherapy, on which she had shown progression. Therapy was then switched to one circle of pemetrexed chemotherapy and local radiotherapy (25 F/5000 cGy/5 weeks). Computed tomography scan in September 2016 revealed progressive disease and then she began to receive pembrolizumab treatment in October 8, 2016 (Figure 2). For the next 10 days after the first pembrolizumab treatment, the patient complained with multiple and symmetrical arthralgia, articular dyskinesia, and morning stiffness. Laboratory testing showed an erythrocyte sedimentation rate of 120 mm/h (reference range (RR): 0-26 mm/h), C-reactive protein of 91.7 mg/L (RR: 0-5 mg/L), rheumatoid factor (RF) of 82.2 IU/mL (RR: 0-20 IU/mL) and anti-cyclic citrullinated peptides (CCP) of 51.7 IU/ml (RR: 0-17 IU/ml). Ultrasound and MRI examination showed active inflamma-

## Pembrolizumab with lung SC resulted in RA



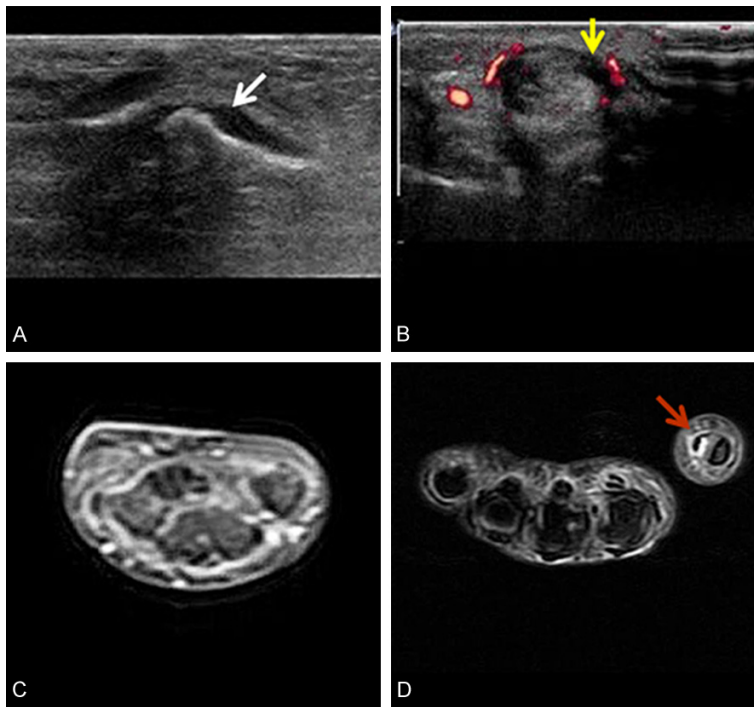
**Figure 1.** H&E staining and immunohistochemistry with PD-L1, PD1, ALK-V, CK7, CK5/6, P63, and TTF-1. H&E staining exhibiting poorly differentiated cells with spindle cells, immunohistochemistry result showing positive for PD-L1, weakly positive for ALK-V, CK7, CK5/6, and P63, and negative for PD1 and TTF-1. H&E staining and immunohistochemistry indicated non-small cell lung carcinoma with spindle cell carcinoma.



**Figure 2.** CT evaluation of corresponding anti-cancer treatment across the time line. Lung sarcomatoid carcinoma was resistant to chemotherapy and radiotherapy, and benefit from pembrolizumab limitedly. Chemo: chemotherapy; RT: radiotherapy; Pembro: pembrolizumab.

tion in the tendon sheath and joints (**Figure 3**). After the rheumatologist's consultation, the patient was confirmed as RA. She had no history of RA or arthritis before, but her father was a RA patient. Then she was administered with prednisone, hydroxychloroquine and leflunomide. The symptoms were relieved significantly after 1 week. The second pembrolizumab treat-

ment was conducted in December, 2016. She totally received two circles of pembrolizumab. Curative effect was evaluated as stable disease before the second pembrolizumab treatment, but then progressive disease at January 2017 (**Figure 2**). Unfortunately, she died of respiratory failure caused by severe lung infection in February 28, 2017.



**Figure 3.** Ultrasound and MRI examinations of left wrist and hand. A. Ultrasound imaging of proximal interphalangeal joint of index finger showing synovitis (white arrow). B. Doppler ultrasound of flexor tendon sheath of thumb showing tenosynovitis (yellow arrow). C. MRI (enhanced T1-weighted image) of left wrist joint showing extensive synovitis. D. MRI (T2-weighted image) showing tenosynovitis involving flexor tendon of thumb (red arrow).

family history is very likely a factor to trigger RA in this patient. Therefore, this patient who has family history should receive pembrolizumab treatment cautiously. Regarding the pathophysiology, pembrolizumab can activate cytotoxic T-lymphocytes, which may cause disorders of immune tolerance and then induce an abnormal immune response. Greisen reported RA patients had a high concentration of soluble PD-L1 level compared with healthy volunteers [7]. Wan found PD-L1 level in serum soluble form is correlated with RF level significantly in RA patients [8]. These indicated that PD-L1 expression might correlate with occurrence of RA. In this case, PD-L1 expression was above 50%, but no PD-L1 expression was reported in two other cases of RA related to pembrolizumab [3].

### Discussion

As far as we know, this is the third case with irAE of RA induced by pembrolizumab [3]. Up to now, the number of reported RA cases caused by pembrolizumab is only two, which were reported by Rakiba Belkhir in 2017 [3]. Additionally, there have been limited case reports about arthritis [4, 5]. Arthritis was divided into many types and RA is just one of the six main types [6]. In accordance with the 2010 American College of Rheumatology (ACR)/European League against Rheumatism (EULAR) criteria, these cases of arthritis can't be diagnosed as RA. In this case, RA is diagnosed according to 2010 ACR/EULAR criteria with multiple symmetrical symptomatic arthritis, positive RF and anti-CCP, ultrasound and MRI examinations of hand and wrist.

The etiology of RA induced by pembrolizumab remains elusive. Epidemiological data showed RA genetic susceptibility, which indicated that positive family history might increase risk of developing RA in patients who receive anti-PD-1/PD-L1 therapy. We considered that positive

Data involving anti-PD-1/PD-L1 antibodies is very limited in SC. Nivolumab showed preliminary efficacy in lung SC [1] but effectiveness of pembrolizumab is still unknown. In this case, duration of stable disease after first pembrolizumab treatment was very short and about three months. Then disease progressed quickly with primary lesion and bone metastasis (Figure 2). Three reasons might account for this. First, lung SC is very aggressive and maybe has shorter PFS compared to other NSCLC. Second, high expression of PD-L1 might be caused by driver genes. The abundance of mutations of PIK3CA, DDR2, TP53, and MAP2K1 are 49.5%, 21.5%, 14.9%, and 21.6% by NGS, respectively. These genes can promote PD-L1 expression directly or indirectly [9, 10]. Single inhibition of PD-1/PD-L1 but not driver genes was insufficient for tumor control. Third, it was not possible to exclude cytotoxicity of radiotherapy before pembrolizumab. Interestingly, this case and two others of RA induced by pembrolizumab all achieved stable diseases [3]. Correlation between RA and anti-tumor effect to pembrolizumab are yet to be studied.

## Pembrolizumab with lung SC resulted in RA

We report a rare case of RA triggered by pembrolizumab and highlight the importance of RA-related medical history and indices screening before PD-1/PD-L1 inhibitor therapy. Additionally, our case offered diversity of efficacy regarding the anti-PD-1/PD-L1 therapy and suggested the necessity of further study containing more cases on effects in lung SC.

### Disclosure of conflict of interest

None.

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