Metastatic cutaneous apocrine adenocarcinoma responsive to the programmed cell death protein 1 inhibitor pembrolizumab

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Dear Editor,

An 83-year-old man was referred to our skin cancer unit because staging whole computed tomography (CT) scans (Fig. 1A) revealed multiple lung and mediastinal lymph node metastases of cutaneous apocrine carcinoma (Fig. 2A), which had been treated by a wide surgical excision and lymph node dissection (with metastases in 13 of 17 removed lymph nodes) 3 months before. The patient was staged as metastatic apocrine carcinoma and was discussed in our multidisciplinary tumour board. After considering several factors including the lack of significant comorbidities, excellent Eastern Cooperative Oncology Group status, lack of effective established treatments and promising effect of programmed cell death protein 1 (PD-1) inhibitors on several forms of solid cancers, a decision to initiate a treatment with pembrolizumab was made. He received a dose of 2 mg/kg body weight intravenously every 3 weeks. Treatment was well tolerated without adverse effects. CT scans after the first 4 cycles (at week 12) indicated stable disease according to the iRECIST criteria with a sum of measures (SOM) of 54 for 3 target lesions compared to the baseline SOM of 56 [1]. Treatment was continued and re-staging after further 4 cycles (week 24) revealed partial remission. After, overall, 16 cycles (48 weeks from baseline), the patient showed ongoing partial response with a SOM of 35 (>30% decrease). The enlarged mediastinal and hilar lymph nodes decreased to normal size (Fig. 1B), and the lung metastases remained stable. Currently, the patient is continuing the treatment.

Immunohistochemistry for PD-L1 (clone 28-8; Abcam), PD-1 (clone NAT 105; Cell Marque AK) and

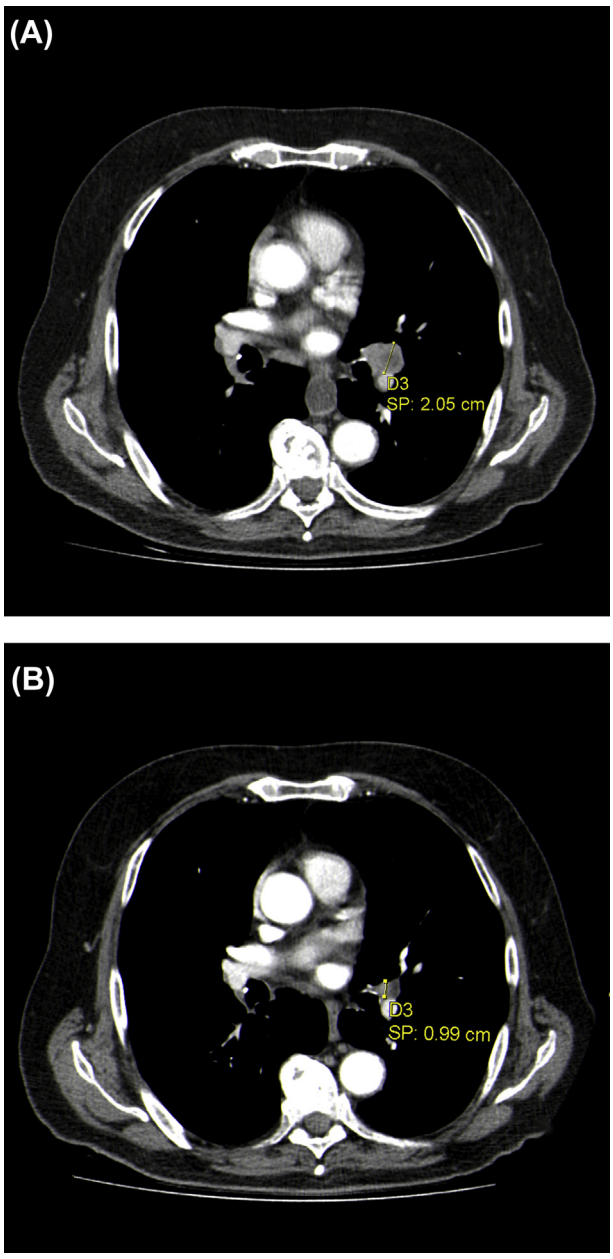

Fig. 1. Enlarged hilar lymph node at baseline CT (A) with decrement to normal size after 16 cycles of pembrolizumab (B) (marking D7 with diameter in centimetres). CT, computed tomography.

epidermal growth factor receptor (EGF-R) (clone 3C6; Roche) was analysed in the primary tumour on serial sections using a Roche-Ventana Benchmark™ Ultra automated stainer. The evaluation of immunohistochemistry was performed semiquantitatively. Normal tonsil was used as on-slide positive control. A predominantly cytoplasmic immunoreactivity in about 60% of the tumour cells for PD-L1 (Fig. 2B) and a moderately intense immunoreactivity in about 70% of the tumour cells for EGF-R were found, whereas the tumour was negative for PD-1.

1. Comment

Cutaneous apocrine adenocarcinoma is a rare form of sweat gland cancer with main sites of predilection on the trunk and the head/neck region. The established therapy for a localised tumour is wide local excision with a 1–2 cm clear margin. The most important predictor of survival is the lymph node status with positive lymph nodes associated with a poor prognosis. For metastatic disease, no effective treatment is currently established. The 5-year overall survival is less than 10% [2,3].

Clinical trials cannot practically be conducted for apocrine gland carcinoma because of the rarity of this malignancy. Accordingly, there are no guidelines for the treatment of metastatic disease. Evidence of successful chemotherapeutic regimens or more recently human epidermal growth factor receptor 2 is limited in the literature to isolated case report or specific cancers [3,4]. Inhibition of the PD-1 achieves a high effective anti-tumour activity in several forms of cutaneous cancers including not only melanoma and Merkel cell carcinoma but also cutaneous squamous cell carcinoma [5,6].

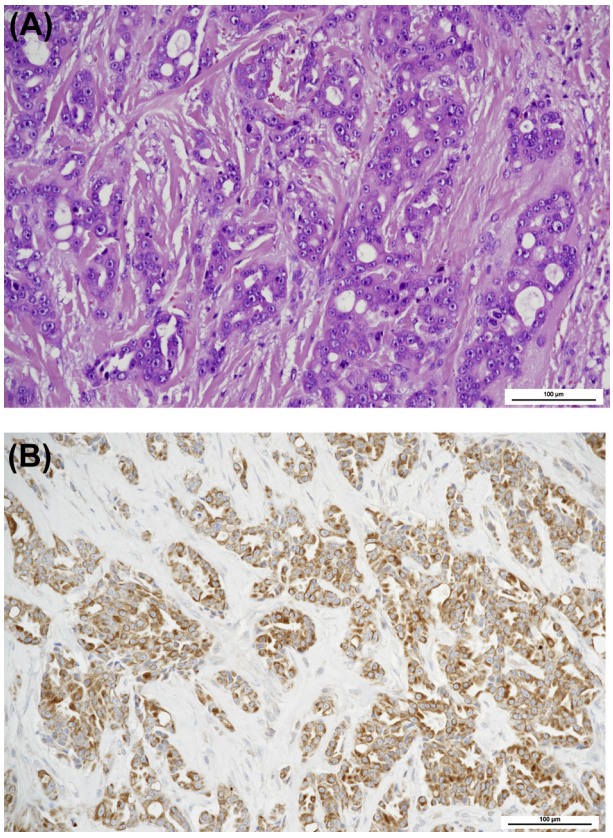

Fig. 2. The tumour cells are arranged in glandular formations and characterised by eosinophilic cytoplasm and large nuclei with prominent nucleoli Hematoxylin and Eosin (HE) (A). Strong membranous and cytoplasmic reactivity for PD-L1 is demonstrable by immunohistochemistry (3,3-diaminobenzidine tetrahydrochloride), in this area in all tumour cells (B).

The decision to initiate treatment with the PD-1 antibody pembrolizumab as first-line therapy in our patient was based on the following rationale: first, treatment is generally well tolerated with less side-effects compared to other proposed cytotoxic or targeted therapies. Second, cytotoxic drugs may negatively influence the immune system, which in turn may cause a less efficient immune response of PD-1 antibodies in a second line. Third, because this treatment has a well-documented high anti-tumoural efficacy in many forms of solid cancers. As we did not perform any adjuvant therapy (i.e. radiotherapy) before and during treatment, the observed signs of regression of the mediastinal lymph nodes and the stable disease in the lungs can be regarded as partial response to the applied therapy. To the best of our knowledge, this is the first report showing an ongoing partial response of metastatic cutaneous adenocarcinoma after 1 year of treatment. Notably, for the use of pembrolizumab in non−small cell lung cancer, the proof of PD-L1 expression by validated immunohistochemistry is required and should reveal immunoreactivity in more than 50% of tumour cells (equalling a strong positivity). This was demonstrable in our case. Interestingly, an intense cytoplasmic immunoreactivity was found which may be caused by the apocrine differentiation of the tumour cells.

In conclusion, although metastatic cutaneous apocrine carcinoma is rare, it represents a major therapeutic challenge. Our case suggests that inhibition of PD-1 may be considered as first-line therapy for patients with metastatic disease.

Author contributions: I.Z. and M.R. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. I.Z. contributed to study concept and design; J.S. and I.Z. contributed to acquisition, analysis and interpretation of data; I.Z., M.R., J.S., R.G. and M.U. contributed to drafting of the manuscript; S.L. contributed to review of the histology, immunohistochemical analysis and photomicrographs; K.S.-Z. and S.L. contributed to critical revision of the manuscript for important intellectual content; K.S.-Z. contributed to statistical analysis; J.S. and M.R. contributed to administrative, technical or material support; I.Z. contributed to study supervision.

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Conflict of interest statement

None declared.

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