CASE REPORT

PD-1 inhibitor therapy of basal cell carcinoma with pulmonary metastasis

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Abstract Basal cell carcinoma (BCC) may be challenging to differentiate from basaloid squamous cell carcinoma (bSCC), both clinically and histologically. BCC constitutes one of the most common tumours and metastatic behaviour is extremely rare. In contrast, bSCC is a rare entity with an increased propensity for distant metastasis. If these conditions develop into inoperable metastatic disease, the therapeutic alternatives are different, but the use of PD-1 inhibitors may be a valid option for both. Here, we report a case with complex histology with a component initially classified as bSCC with lung metastases and treated with the PD-1 inhibitor cemiplimab resulting in radiological and clinical responses. Re-examination of the lung biopsy using routine histomorphology in combination with immunohistochemical staining for cytokeratin 14, cytokeratin17 and BerEp4 has, however, revealed a histopathological pattern of BCC, which is in concordance with a similar analysis of the cutaneous primary tumour in the face that the patient underwent surgery for more than 5 years earlier.

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Conflicts of interest
IJ, none; ML, Honoraria for lectures (Bristol Myers Squibb, MSD and Roche); LMA, none; ROB, Research grants (Bristol Myers Squibb, SkyLineDx, Inst.), Honoraria for lectures (Roche, Pfizer), Advisory Boards (Amgen, BD/BARD, Bristol Myers Squibb, MSD, Novartis, Roche, Sanofi Genzyme); LN, Research grants (Merck, Syndax Pharmaceuticals, Inst.), Honoraria for lectures (Pfizer, LeoPharma, Bristol Myers Squibb, MSD, Novartis), Advisory Boards (Bristol Myers Squibb, MSD, Novartis, Pierre Fabre, Sanofi Genzyme)

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What does this study add?
- Metastatic basal cell carcinoma (BCC) is responsive to PD-1 inhibitor therapy.
- Immunohistochemical staining against cytokeratin 14 and 17 may be helpful in tumours with overlapping histology, discriminating BCC from basaloid squamous cell carcinoma (bSCC), which subsequently may be of importance in the selection of systemic therapy if metastatic disease occurs.

Case report
A 66-year-old Caucasian man was admitted to the Dermatology and Pulmonary Medicine departments for further examination. In the past, the patient had undergone extensive and 10-fold repeated surgery due to a locally advanced basal cell carcinoma (BCC) of morpheid infiltrative type that engaged the skin of the left chin, with extension to the mucosa and bone tissue of the maxillary sinus. Recent follow-up examinations after surgery, which included clinical examinations, repeated biopsies and radiology, had not demonstrated any signs of local relapse of
disease. However, following a fall accident where he hurt himself badly, he was admitted for an acute CT scan that demonstrated tumour-like lesions in the left lung and a thickening of the pleura at the same side. Dermatological examination did not reveal any malignant skin lesions, but an FDG PET-CT scan confirmed the CT scan with FDG uptake in tumour-like lesions in the left upper lung lobe and pleura. The patient underwent biopsy of the pleural lesion where the pathology report described a basaloid epithelial tumour consistent with basaloid squamous cell carcinoma (bSCC), where primary or metastatic bSCC and BCC were included in the differential diagnosis. On clinical examination, no primary bSCC was identified in the usual primary tumour sites.

Subsequently, the patient initiated therapy with the hedgehog inhibitor vismodegib that resulted in a radiological partial response. Following 14 months of treatment with vismodegib, a new FDG PET-CT scan was performed that revealed residual disease with FDG uptake, especially in the lymph nodes of the left lung hili and the left upper lobe (Fig. 1). In parallel, the patient suffered from severe toxicity associated with the vismodegib treatment. He had lost almost 20 kg in bodyweight, suffered from fatigue, grade-3 diarrhoea, abdominal pain and decreased appetite. Considering the challenging clinical situation the patient was evaluated and included in the Early Access programme for the PD-1 inhibitor cemiplimab, that is, treatment with cemiplimab 350 mg IV every third week. After 3 months of therapy, a new FDG PET-CT scan was conducted, which demonstrated a partial remission with reduced FDG uptake that also was associated with an improved performance status with loss of abdominal pain, decreased diarrhoea and a weight gain of almost 10 kg. The patient then completed additional 9 months of cemiplimab therapy until the Early Access programme was closed. At this stage, repeated regular CT scans and FDG PET-CT scans had not demonstrated any obvious active disease, and a 3-month pause in therapy was decided as a reasonable approach.

However, a new scan after the pause in therapy revealed a relapse in disease with marked increased FDG uptake in a lesion in the pleura of the left lung (Fig. 2). Since cemiplimab was not reimbursed and available in Sweden at this time, the patient instead started treatment with the PD-1 inhibitor pembrolizumab 200 mg IV every third week. After 3 months of therapy, the pleural lesions were slightly larger and the patient had

**Figure 1** (a) FDG PET-CT scan with positive FDG uptake at baseline before initiation of cemiplimab. Note the FDG uptake in lymph nodes in the left lung hili (white arrow). (b) FDG PET-CT scan with reduced FDG uptake in the lymph nodes (white arrow) following 3 months of cemiplimab therapy.

**Figure 2** (a) FDG PET-CT scan demonstrating relapse of disease in the pleura of the left lung (white arrow) after 3 months of pause of therapy that followed a previous treatment period of cemiplimab for 1 year. (b) FDG PET-CT scan demonstrating further disease progression in the pleura of the left lung (white arrow) with increased size and FDG uptake following 3 months of pembrolizumab therapy, that is, PD-1 refractory disease.
developed a severe diarrhoea of grade 3 that was judged to be an immune-related adverse event. The patient was prescribed prednisolone 1 mg/kg orally to that he responded well, and the pembrolizumab treatment was stopped. As the patient in the latest FDG PET-CT scan only had one tumour lesion with FDG uptake, he has been referred for thoracic surgery. Following the uncertainties with the metastases judged to have complex characteristics, a pathological re-examination of the pleural biopsy has been performed using additional immunohistochemical staining against BerEp4, cytokeratin 14 (CK14) and cytokeratin 17 (CK17) as suggested by Linskey and co-workers. The most commonly used staining, BerEp4 alone is unreliable for differentiation between BCC and bSCC, and the addition of CK14 or CK17 will increase the diagnostic certainty. BCC is usually positive for all three markers whilst bSCC would be negative with few exceptions. Both the primary tumour from the face and the lung metastasis demonstrated a strong positivity in BerEp4, CK14 and CK17, and negativity in S100, respectively, which together with the growth pattern of BCC in the patient’s face including the maxillary sinus, oriented the histological diagnosis towards BCC (Fig. 3).

**Discussion**

BCC constitutes one of the most common skin tumours, but metastatic BCC is extremely rare, ranging between 0.0028% and 0.55% of all patients with BCC. Recent evidence has suggested that PD-1 inhibitors are effective treatments in not only melanoma but also in non-melanoma skin cancers in the advanced setting. Here, we present a case with complex histology where the histopathological pattern indicated a potential overlap between BCC and bSCC, similar to what has been described previously. The patient had received the hedgehog inhibitor vismodegib as first-line therapy, based on a diagnosis of previous metastatic BCC but was switched to the PD-1 inhibitor cemiplimab due to both concern for inadequate clinical efficacy, potentially related to what was suspected to be a bSCC tumour component and severe toxicity with impact on quality of life. In tumours with overlapping morphology of BCC and bSCC, immunohistochemical staining against BerEp4, CK14 and CK17 add value in the standard panel in order to optimize the management of patients with potential metastatic BCC or metastatic bSCC, where the use of systemic therapies may be different.

Following approxmtely one year of cemiplimab therapy, clinical disease control was obtained with radiological partial remission in parallel with improved quality of life and decreased toxicity. This clinical course is very similar to what recently has been reported in patients with locally advanced BCC post-hedgehog inhibitor therapy where cemiplimab therapy has been associated with an overall response rate of 31% and durable responses extending 12 months in a majority of patients in parallel with manageable toxicities. With the termination of the Early Access programme for cemiplimab in SCC, the patient had a pause in therapy for approximately three months. However, a new scan at this time point revealed increased tumour size and FDG activity in one of the tumour lesions of the pleura eventually leading to restart of PD-1 inhibitor therapy. This time the PD-1 inhibitor pembrolizumab was chosen due to reimbursement issues, but the therapy was less successful with progress in

![Figure 3](https://example.com/f3.png)
a pleural tumour lesion and immune-related toxicity that finally led to termination of the PD-1 inhibitor treatment. Whether the two different PD-1 inhibitors, cemiplimab and pembrolizumab have different effects in metastatic BCC is not known, it could also be that the resistance developed independently of the PD-1 therapy switch. In current conditions, metastatic surgery or radiotherapy may be an option that could be considered, although data are scarce on the clinical benefit of local therapy in PD-1 refractory disease.7

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The patient in this manuscript has given written informed consent to the publication of the case details.

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