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Case Report

Successful immunotherapy and irradiation in a HIV-positive patient with metastatic Merkel cell carcinoma

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ABSTRACT

This case report presents a HIV-positive 60-year old male with Merkel cell carcinoma of his right forearm and pulmonary sarcoidosis, who, after excisions and irradiations of the primary tumour site and subsequent lymph node metastases developed distant metastases. He received radiotherapy to symptomatic mediastinal lymph node metastases followed by Doxorubicin and, after two cycles, by the PD-1 inhibitor Pembrolizumab due to mixed response. Re-staging showed a para-mediastinal, radiotherapy-induced pneumonitis, which was treated by prednisolone due to clinical symptoms. In September 2017, the patient developed a solitary lymph node metastasis next to the right atrium, for which he received stereotactic radiotherapy. The systemic treatment with Pembrolizumab was replaced by the PD-L1 inhibitor Avelumab and is being continued since. The patient has been in complete remission for one year now and the HIV-infection is well-controlled.

1. Introduction

Merkel cell carcinoma is an aggressive, though radiosensitive tumour with an increasing incidence and mortality rate [1–3]. It in particular affects elderly, immune suppressed patients and develops in UV-exposed skin regions [4]. In case of distant metastases, the 1-year overall survival (OS) rate is approximately 44%, and the 5-year OS rate is about 18% [2]. The fact that the Merkel cell polyomavirus (MCPyV) and UV-light are oncogenetically relevant, and that a high PD-L1-expression (in MCPyV-positive tumours) or high tumour mutational burden (in MCPyV-negative tumours) are found was the rationale for the successful use of immunotherapy in this tumour entity [5–8].

2. Case report

We report on the remarkable medical history of a HIV-positive patient with metastatic Merkel cell carcinoma and pulmonary sarcoidosis, who, after various therapies, has been in complete remission with a PD-L1 inhibitor for one year now (Fig. 1).

The case describes a 60-year old Caucasian with no previous illnesses, ECOG 0–1, who was diagnosed with a Merkel cell carcinoma of the right forearm in 2014 and initially treated by excision biopsy (pT1, L1, V0, R1). Due to microscopic residual tumour cells, a second excision with a 2-cm lateral safety margin and a sentinel lymph node biopsy of the right axilla were performed. The resection margins and the sentinel lymph node did not show any proof of malignancy. Tumour staging was completed using an ^{18}Fluorodeoxyglucose positron emission tomography/-

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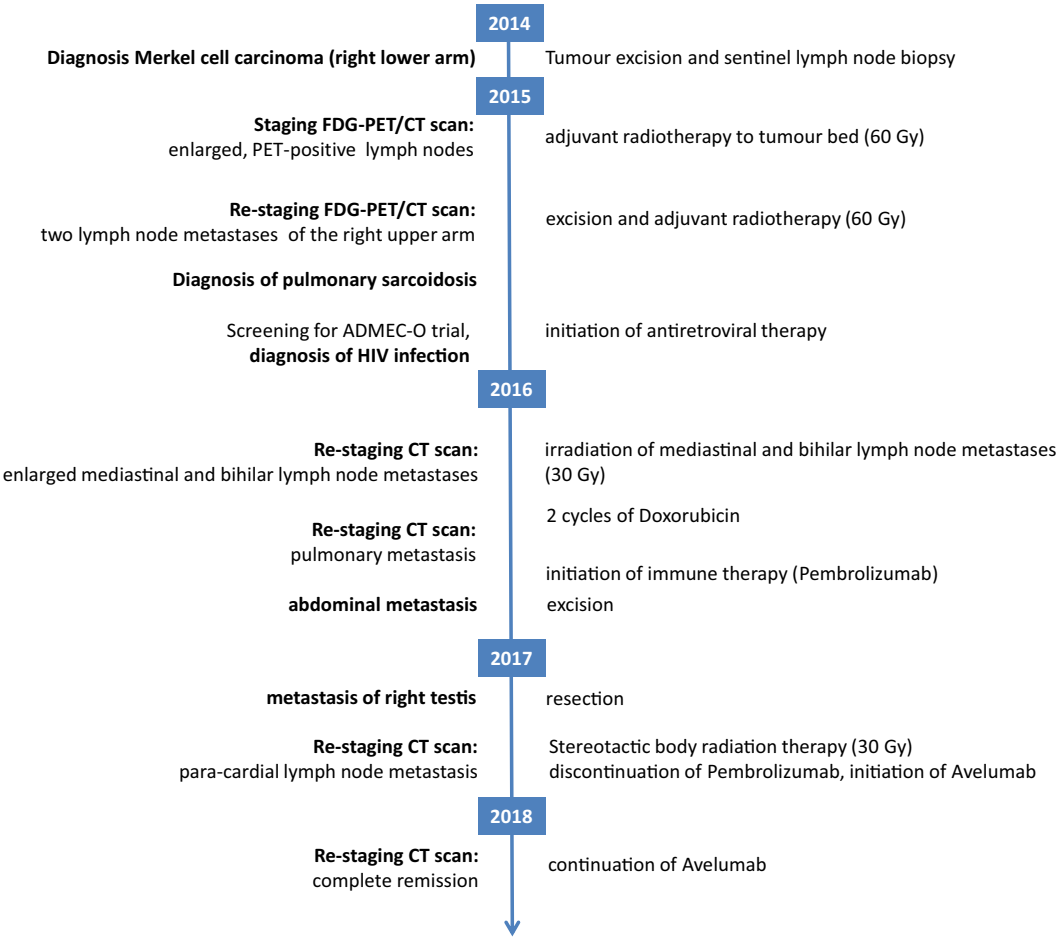

Fig. 1. Timeline showing the diagnoses, initiated therapies and detected relapses.

computed tomography (FDG-PET/CT) scan and showed FDG-avid cervical, axillar, iliacal and inguinal lymph nodes as well as FDG-PET-negative but slightly enlarged pathological mediastinal and hilar lymph nodes. Suspicious lymph nodes were investigated by endobronchial ultrasound (EBUS) guided biopsy, revealing no sign of inflammation, tumour cell infiltration or sarcoidosis of the paratracheal lymph node (level 2R) and of the subcarinal lymph node (level 7). After wound healing, adjuvant fractionated radiotherapy to the tumour bed was delivered (10 MeV electrons, 60 Gy total dose delivered in 25 fractions) from March till April 2015.

At nine-months follow-up, the patient presented with two suspicious non-movable, solid lesions, which were localised on his right upper arm proximal of the previously treated lesion. An FDG-PET/CT scan was performed for re-staging purposes revealing the two new lesions on the right upper arm to be FDG-PET-positive as well as cervical, axillary, mediastinal, iliacal and inguinal PET-positive lymphadenopathy, with a consistent glucose utilisation in comparison to the previous scan. Furthermore, small intrapulmonary nodules in both lungs were detected on CT. Therefore, a thorough pulmonary assessment was initiated, consisting of bronchoscopy with bronchoalveolar lavage, EBUS and a pulmonary function test (PFT). Histological analyses revealed a pulmonary sarcoidosis affecting the hilar and mediastinal lymph node levels 11R, 4R and 7 (stage II according to radiological diagnosis). There was no sign of tuberculosis or pulmonary metastases. The subsequently performed polymerase chain reaction for MOTT (mycobacteria other than tuberculosis) was positive, but in hybridisation no mycobacteria could be detected. The PFT revealed only a slight restriction of the diffusion capacity and of the ventilation distribution. Due to the lack of hypercalcaemia and any severe pulmonary limitations, no dedicated therapy for the pulmonary sarcoidosis was indicated. The two lesions on the right upper arm were excised in September 2015. During radiation treatment planning of the indicated adjuvant radiotherapy to the right upper arm, the patient developed another lesion proximal of the excised lesions at the right upper arm, which was excised in October 2015. Histological analysis revealed a lymph node metastasis of the Merkel cell carcinoma with extracapsular extension. Therefore, adjuvant radiotherapy was prescribed to the three tumour beds of the right upper arm and adjacent regional lymph node stations (50 Gy in 25 fractions to the tumour beds and lymph nodes, with a 10 Gy boost in 5 fractions to the tumour beds of the right upper arm).

In parallel, a viral screening was initiated for the inclusion of the patient in the ADMEC-O trial for adjuvant treatment of metastatic Merkel cell carcinoma investigating Ipilimumab *versus* placebo (*www.clinicaltrials.gov*, NCT02196961). This screening revealed an HIV infection (human immunodeficiency virus) with advanced immunosuppression (CD4 cells 174/μl, CDC 1993 stage A3), and a viral load of 127,000 copies/ml. Consequently, antiretroviral therapy (ART) with Emtricitabine [nucleoside reverse transcription inhibitor (NRTI)], Tenofovir (NRTI) and Dolutegravir (integrase inhibitor) was initiated in December 2015, together with antibiotic prophylaxis of Pneumocystis jirovecii pneumonia.

In March 2016, the patient suddenly developed a dry cough and shortness of breath when exercising. Initially, Levofloxacin was prescribed by the general practitioner. Due to persistent symptoms, the patient presented himself at the hospital in April 2016. A chest CT scan was performed and showed smaller cervical lymph

nodes but enlarging mediastinal and bihilar lymph nodes (see Fig. 2A), which was suggested to be an immune-reconstitution syndrome due to the ART. However, bronchoscopy and EBUS were recommended for confirmation. Cytological examination of lymph nodes in levels 2, 7 and 10 revealed lymph node metastases of the Merkel cell carcinoma. Again, there was no evidence for granuloma, tuberculosis or other pathogens.

After multidisciplinary discussion in the tumour board, palliative radiotherapy to the mediastinal and hilar lymph nodes to a total dose of 30 Gy in 10 fractions was prescribed (see Fig. 2B). Radiotherapy was followed by chemotherapy with pegylated liposomal Doxorubicin (20 mg/m^2 body surface area). This systemic treatment was chosen based on a retrospective analysis of a small series of five patients with metastatic Merkel cell carcinoma treated with radiotherapy and liposomal Doxorubicin, which showed good albeit only short-term response with acceptable side effects [9].

After 2 cycles of Doxorubicin, a CT scan was performed and revealed a metastasis in the lower lobe of the left lung in June 2016, while the bihilar and mediastinal lymph nodes had decreased in size. Considering the mixed response to Doxorubicin, chemotherapy was replaced by immunotherapy with the anti-programmed death-1 (PD-1) receptor antibody Pembrolizumab (2 mg/kg body weight every 3 weeks, off-label). Ten weeks later, a cutaneous abdominal metastasis was resected. While CT re-staging showed a reduction of the mediastinal and hilar lymph nodes as well as of the pulmonary metastasis, signs of para-mediastinal pneumonitis were also detected (Fig. 2C). The patient reported shortness of breath moderately affecting the activities of daily living (New York Heart Association (NYHA) class II) and intermittent dry cough without pyrexia (grade 2 pneumonitis according to CTCAE). Differential diagnoses included an immune-induced pneumonitis, infectious pneumonia, sarcoidosis or radiotherapy-induced pneumonitis. Interdisciplinary discussion supported the latter, since the extent of radiological findings corresponded well to the radiation fields (see Fig. 2B and C). Furthermore, the patient did not show any symptoms of inflammation. Therefore, in accordance with guidelines for treatment of radiation-induced pneumonitis, prednisolone was prescribed for 6 weeks and the patient reported decreasing symptoms.

In March 2017, the patient was diagnosed with a metastasis of the right testis, which was surgically resected. Thereafter, a whole body CT scan showed a complete remission (see Fig. 2D). Therefore, immune therapy with Pembrolizumab was continued without side effects with monthly clinical and three-monthly radiological follow-up visits. Also, HIV viral load significantly decreased during ART below 50 copies/ml (42 copies).

Another whole body CT scan acquired in September 2017 revealed a solitary lymph node metastasis next to the right atrium. Therefore, it was decided to replace the systemic treatment with Pembrolizumab by the PD-ligand 1 (PD-L1) blocking antibody Avelumab (10 mg/kg body weight every 2 weeks, off-label). The first application was followed by a stereotactic irradiation of the lymph node metastasis to a total dose of 30 Gy in 6 fractions of 5 Gy. Radiotherapy was reasonably well tolerated despite extensive overlap with previous irradiation fields. In December 2017, the CT scan showed a good response and a previously discussed surgical intervention for the para-cardial lymph node was abandoned.

The systemic treatment with Avelumab is still being continued. On all three-monthly CT scans obtained since December 2017, the para-cardial lymph node metastasis has been decreasing in size and no new metastatic sites have developed. CD4 cells rose to 238/μl in January 2018 and HIV viral load continues to be nearly completely suppressed under ART (25 copies/ml). In April 2018, interferon gamma release test for tuberculosis remained negative after recovery of cellular immunity with CD4 cells >200/μl.

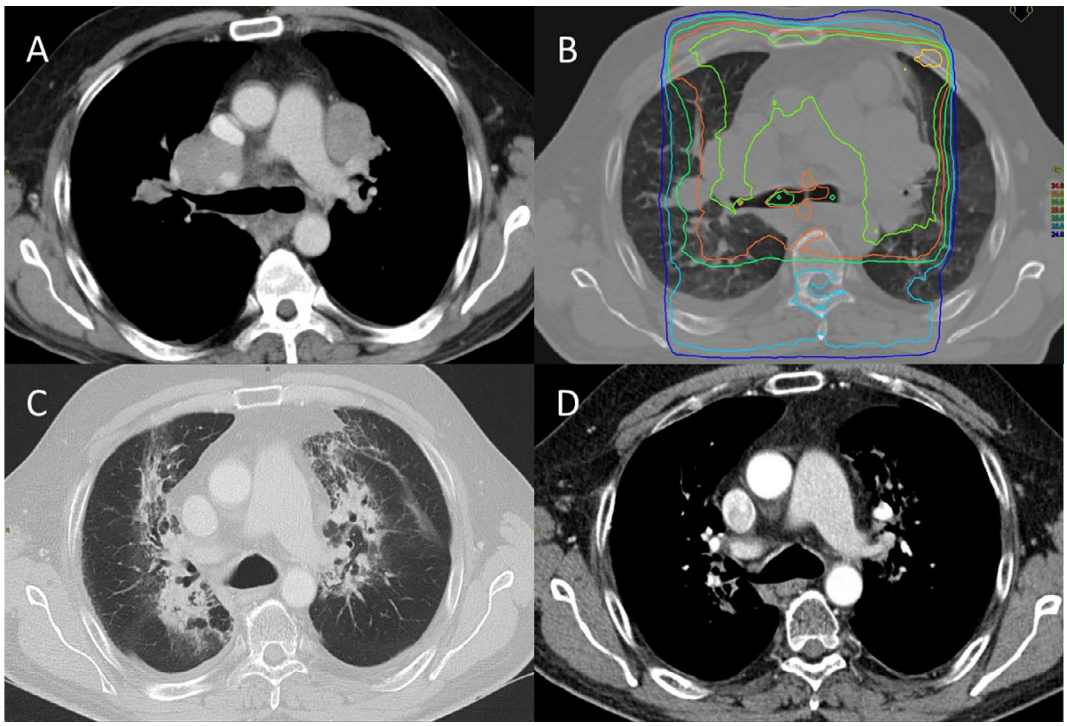

Fig. 2. (A) Transverse view of a CT scan depicting the (FDG-PET-positive) mediastinal lymphadenopathy, which was proven tumour positive and referred for palliative irradiation in March 2016. (B) Radiation treatment plan encompassing the affected hilar and mediastinal lymph nodes (30 Gy total dose in 10 fractions of 3 Gy). The coloured lines represent the various isodose lines (see legend). (C) When the patient presented with shortness of breath (NYHA class II, CTCAE grade 2), the CT scan (lung setting) revealed ample radiological changes corresponding with a pneumonitis after irradiation, combined with immunotherapy and underlying HIV-infection as well as sarcoidosis (December 2016). (D) Complete remission of the mediastinal lymphadenopathy was diagnosed in March 2017.

3. Discussion

Here, we report on successful systemic therapy of a HIV-positive patient with metastatic Merkel cell carcinoma treated with radiotherapy and immune checkpoint inhibitors.

In phase II clinical studies, the PD-1-antibody Pembrolizumab as well as the PD-L1-antibody Avelumab have shown continuing anti-tumour activity with response rates of 55–60% in first line and 35% in second line therapies along with acceptable side effects in patients with metastasised Merkel cell carcinoma [10–13]. The biologics license application for Avelumab (10 mg/kg body weight, biweekly) for the treatment of metastatic Merkel cell carcinoma has been granted by the U.S. Food and Drug Administration (FDA) in March 2017 and by the European Medicines Agency (EMA) in September 2017. Although it has been shown that mono-chemotherapy, such as liposomal Doxorubicin, is not only less toxic but also as effective as combination chemotherapy for the treatment of metastatic Merkel cell carcinoma [9], chemotherapy cannot be recommended any longer as treatment of first choice. As presented in this case report, chemotherapy was ineffective and the replacement of Pembrolizumab by Avelumab again resulted in a clinical response, which in fact is still continuing to date. Immunosensitising effects for Avelumab, caused by the afore delivered hypofractionated radiotherapy, are likely [14].

Despite the known association between the development of a Merkel cell carcinoma and immunosuppression, HIV infection is an exclusion criteria for the clinical studies on PD-(L)1 blockage [4]. Disease exacerbation or the development of increased or novel severe side effects of the immune checkpoint inhibitors are suspected.

In a preclinical model in HIV-infected macaques, it was shown that PD-1-blockage leads to an increased immune response including increased proliferation and increased functionality of HIV-specific CD8-postive T-cells, which resulted in a significant reduction of viremia and in prolonged survival of the animals with an overall good treatment tolerance [15]. To date, there is very limited knowledge on the clinical use of immune checkpoint inhibitors in HIV-positive patients. In a small study including ten HIV-positive patients treated with ART and immune checkpoint inhibitors, no increased toxicity was found [16]. Immune-mediated side effects included myositis (N = 1) and colitis (N = 1). Viral load remained stable, and only small changes in the CD4-positive cell count were found [16]. Recently, a phase I clinical trial on the use of a PD-L1 antibody in HPV-positive patients receiving antiviral therapy has been initiated (*www.clinicaltrials.gov*, NCT02028403). Recently, seven cases of HIV-positive patients with metastatic non-small cell lung cancer simultaneously treated with ART and Nivolumab or Pembrolizumab have been reported [17]. Three of the seven patients showed partial response to immune checkpoint inhibitors. Importantly, none of the seven patients experienced any grade 3 or grade 4 immune-related adverse events or toxicity. In our case, a significant decline in viral load was shown and the combination of ART (Emtricitabine, Tenofovir, Dolutegravir) and Pembrolizumab was tolerated well. Even though, the causality of the severe radiation pneumonitis was not fully elucidated and may well be linked to the combination of radiation therapy, immunotherapy and underlying HIV-infection.

Autoimmune diseases are among the frequent exclusion criteria in clinical trials including immune checkpoint inhibitors because of potential exacerbations. It remains controversial, whether this also relates to sarcoidosis. A small number of case reports are reporting the development of "sarcoidal granuloma" under systemic treatment with checkpoint- and PD-1-antibodies, but data on their genesis are equivocal [18,19]. In this case, an exacerbation of the pre-existing sarcoidosis in the context of an immune constitution syndrome after ART, or following Pembrolizumab, was not detectable.

Prospective studies investigating the effects of immune checkpoint blockage in patients who have been systematically excluded from previous clinical trials [20], such as patients with immunosuppression or autoimmune diseases, are urgently needed.

Conflict of interest

All authors declare that there are no competing interests.

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