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Case Report

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A burning heart: combined therapy of checkpoint-inhibitors and prednisolone in a patient with sarcoidosis

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Abstract

Patients with prior autoimmune diseases such as sarcoidosis require special care when treated with checkpoint inhibitors (CPIs), given the risk for reactivation of inflammation. Here, we address the clinical dilemma of initiating CPIs for recurrent metastatic carcinoma in a patient with extensive sarcoidosis, controlled after prolonged immunosuppressive therapy when the tumor recurrence was detected. To achieve the best possible outcome, the case was discussed by an interdisciplinary team comprising specialists in rheumatology, oncology, and CPI-related myocarditis. Literature on this topic was very limited. Based on the pharmacodynamics of CPIs and the pathophysiology of CPI-related autoimmune diseases, we concluded that initiating CPIs alongside low-dose prednisolone would effectively suppress any reactivation of sarcoidosis without interfering with CPIs in a relevant way.

Keywords: CPI, sarcoidosis, myocarditis, autoimmune disease, sudden cardiac arrest, prednisolone

PATIENT PRESENTATION

We present a 50-year-old man who presented with exertional dyspnea and chest burning after a short course of prednisolone for cardiac sarcoidosis that he received at an outside hospital. At that time, his vital signs were stable and the physical exam unremarkable. A 12-lead electrocardiogram revealed sinus rhythm with left bundle branch block. The echocardiogram revealed low normal left ventricular ejection (LVEF 53%), septal thinning, and hypokinesis. The patient had a history of surviving sudden cardiac arrest (SCA) in the context of ventricular fibrillation due to cardiac sarcoidosis. In addition, he had primary clear cell renal carcinoma (pT1bN0M0) that was treated with a laparoscopic partial R0 nephrectomy.

Given the persistence of symptoms after a course of immunosuppression (3 months: prednisolone 40 mg daily for 4 weeks followed by a taper), a fasting FDG PET-CT was performed and detected abnormal FDG uptake in the interventricular septum, suggesting ongoing myocardial inflammation [Figure 1A and B]. Therefore, the patient was initiated on long-term therapy for sarcoidosis using prednisolone. The treatment consisted of prednisolone 1 mg/kg body weight followed by a gradual reduction of 5mg of the total daily dose every 2 weeks to a maintenance dose of 5 mg daily.

The patient already had an implantable cardioverter-defibrillator (ICD) for secondary prophylaxis and received bisoprolol, valsartan, and amiodarone.

After the patient had been tapered off prednisolone, he underwent a second FDG PET-CT for follow-up to confirm continued suppression of metabolic activity in the heart. While there was complete resolution of cardiac FDG inflammatory activity, a recurrence of renal cell carcinoma with pulmonary metastasis and liver infiltration was detected. This caused the above-stated clinical conundrum. CPI therapy was indicated for renal carcinoma with metastatic lesions. However, this may lead to the reactivation of his cardiac sarcoidosis, which had previously triggered severe arrhythmias, resulting in cardiac arrest. In an interdisciplinary specialist discussion, we considered CPI therapy with axitinib and pembrolizumab for renal cell carcinoma while trying to find a method to mitigate the risk for reactivation of sarcoidosis.

INITIAL WORKUP- (E.G., ECG/LABORATORY ANALYSES/X-RAY/ECHO)

The patient's clinical presentation started with a survived SCA due to ventricular fibrillation in July 2019. Coronary angiography ruled out obstructive coronary artery disease while revealing mildly decreased LVEF. CT scan of the chest displayed a "galaxy sign", strongly suggesting sarcoidosis. This was confirmed with endobronchial ultrasound and cryobiopsy. Subsequent F18-FDG PET-CT scan [Figure 1A and B] displayed hypermetabolic activity in the heart, lymph nodes, lungs, skin, and bones (sacrum and thoracic spine), highlighting the cardiac involvement of sarcoidosis as the most likely cause for his severe arrhythmias and reduced left ventricular dysfunction. After a long course of immunosuppressive treatment with prednisolone, the desired therapeutical goal had been achieved with full suppression of metabolic activity in the myocardium. Unfortunately, by then, signs of recurring renal cell carcinoma with pulmonary metastasis were detected.

DIAGNOSIS AND MANAGEMENT

CPIs are effective antineoplastic agents but have many potential pathophysiological effects[1-4], including the potential for reactivating quiescent sarcoidosis[1]. The mechanism of CPIs involves antagonizing two T-cell expressed proteins to enhance immune defense against cancer cells: Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and Programmed Cell Death Protein 1 (PD-1)[2,3,5]. The interaction of PD-1 with its ligand, programmed death ligand 1 (PD-L1), controls the induction and maintenance of immune tolerance in the tumor environment[1,2,5]. On the other hand, CTLA-4 interaction with its ligand (CD28) works earlier

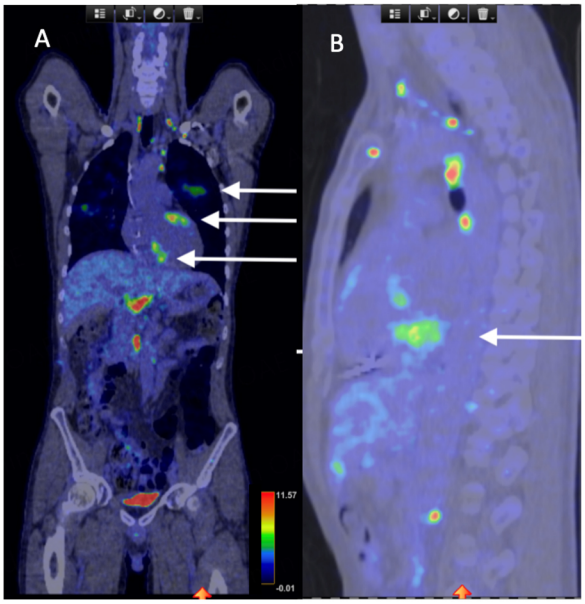

Figure 1. Pre-treatment 18-FDG-PET-CT: (A) 18-FDG-PET-CT coronal view ventral slice: Prior to treatment of sarcoidosis. Visible hypermetabolic activity in the heart, lymph nodes, lungs, and bones (sacrum and thoracic spine). (B) 18-FDG-PET-CT sagittal view: Visible hypermetabolic activity in the heart and lungs.

in tolerance induction. While multiple mechanisms of action have been proposed for CTLA-4, the most accepted include prevention of co-stimulation of CD4+ T cells in the lymph node and inhibition of peripheral autoimmunity via regulatory T cells. Therefore, the antagonist action of CPIs on CTLA-4 and PD-1 leads to a double inhibition of immune regulation, resulting in a disruption of the body's self-tolerance mechanisms[1,5]. Disruption of the body's self-tolerance in patients undergoing CPI therapy increases the risk for adverse autoimmune-related events, such as myocardial inflammation[6].

In contrast, anti-sarcoidosis treatment with agents such as glucocorticoids (prednisolone) induces anti-inflammatory and immunosuppressive effects, which may result in drug interference with CPIs.

We evaluated the risks and benefits of administering a higher dose of prednisolone and its potential to attenuate the efficacy of CPIs in the management of renal cell carcinoma. Concurrently, we considered the possibility that CPI therapy could precipitate a recurrence of the patient's cardiac sarcoidosis, potentially resulting in life-threatening cardiac arrhythmias, similar to the patient's initial clinical presentation. Additional research is necessary to better understand the pathophysiology of simultaneous administration of steroids and CPIs in patients with an autoimmune disease.

Considering the mechanisms and the patient's individual clinical status, it was concluded in our interdisciplinary discussion that a low dose of prednisolone would effectively safeguard the patient from CPI-mediated sarcoidosis reactivation while maintaining the efficient antineoplastic effect of CPIs.

FOLLOW-UP- CLINICAL OUTCOME/ANY COMPLICATIONS

After 4 months of treatment with CPIs and a maintenance dose of prednisolone 5mg daily, the patient presented for a follow-up PET-CT scan to screen for any potential reactivation of myocardial inflammation due to reactivation of sarcoidosis or CPI myocarditis in general. The PET CT [Figure 2A and B] did not reveal any reactivation of cardiac sarcoidosis with a low maintenance dose of prednisolone 5 mg daily.

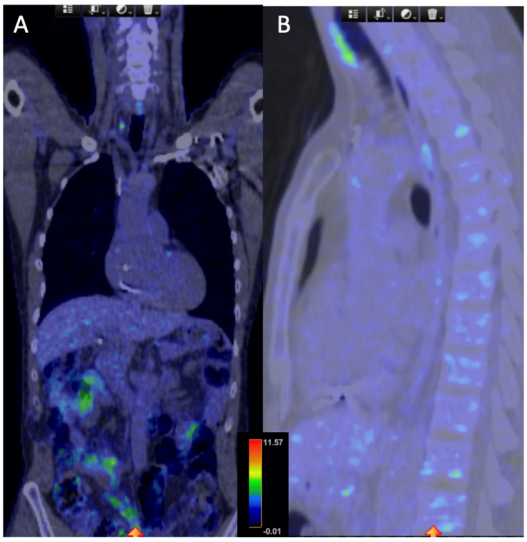

Figure 2. Post-CPI-treatment 18-FDG-PET-CT: (A) 18-FDG-PET-CT coronal view ventral slice: full suppression of hypermetabolic activity in the heart, lungs, and lymph nodes indicating remission of the disease. (B) 18-FDG-PET-CT sagittal view: in comparison to PET-CT prior to sarcoidosis treatment, no potential CPI associated reactivation is visible, displaying regression of prior hypermetabolic activity.

Minor, nonspecific, and not significantly elevated metabolic activity was reported at the base of the left ventricle. The report also provided evidence of successful CPI therapy, with total remission of the renal cell carcinoma recurrence and complete regression of pulmonary and hepatic lesions after therapy.

Furthermore, no other autoimmune manifestations of CPI therapy, which have been reported in the literature[6], were found in our patient after comprehensive diagnostic follow-up.

The patient has undergone nephrectomy of the affected kidney after 10 months of CPI therapy. Histopathological evaluation of the kidney revealed no vital neoplastic cells and the presence of necrotic tissue with a chronic inflammatory reaction correlating with immunotherapy. No signs of metastasis on staging CT. The patient will undergo a follow-up abdominal CT scan after six months.

Thus, we consider the combination of low-dose prednisolone and CPI therapy in this individual patient successful in the short term. We do not have any long-term data on the patient yet.

CONCLUSION(S)- TAKE HOME MESSAGES/LEARNING POINTS

In conclusion, our case presentation addresses the clinical dilemma of the use of CPI therapy in a patient with a history of severe autoimmune disease. Based on our experience, we suggest that low-dose prednisolone maintenance therapy with 5mg daily may be a safe compromise to prevent patients with a history of severe autoimmune disease from recurrent flares, when they undergo CPI therapy. While this combination therapy should not be used lightly, given the opposing effects of CPIs and prednisolone, we suggest that in individual cases with prior autoimmune diseases resulting in life-threatening complications including ventricular fibrillation in sarcoidosis, a combination therapy of CPI and low-dose prednisolone may be a reasonable compromise to pursue the best possible outcome. Collection of long-term outcomes data in larger cohorts will be necessary to address this challenging clinical scenario to provide further guidance for the medical community. In addition, further research is necessary to address similar scenarios in which patients with other types of autoimmune disease require CPI treatment.

DECLARATIONS

Authors' contributions

Wrote the first draft of the manuscript: Wilke F, Suwalski P
Contributed to manuscript writing and editing and care of the patient: Heidecker B
Contributed to reviewing and editing the manuscript: Landmesser U, Miller EJ, Moslehi J

Availability of data and materials

All data used for analyses in this study will be made available in a de-identified manner upon request via email to the corresponding author. Data will be shared only with academic staff.

Financial support and sponsorship

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Conflicts of interest

Bettina Heidecker is an inventor of patents that use RNA for the diagnosis of myocarditis. Patent protection is being processed for MCG for diagnosis and measurement of therapy response in inflammatory cardiomyopathy. The remaining authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

The ethics committee of the Deutsches Herzzentrum der Charité (DHZC) Universitätsmedizin Berlin approved the study (EA4/193/17). The presented patient provided written informed consent to participate in the study. Data from the study can be made available upon request from the principal investigator PD Dr. med. Bettina Heidecker in a de-identified form. A data use agreement must be signed beforehand. Access is only granted to academic staff.

Consent for publication

The patient provided consent for publication.

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