

# Toxicity to immune checkpoint inhibitors presenting as pulmonary arterial vasculopathy and rapidly progressing right ventricular dysfunction

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## Abstract

**Introduction:** Immune Checkpoint Inhibitors (ICIs) are antitumor drugs associated with a number of serious immune-related adverse events (IRAEs). ICIs enhance anti-tumor immunity, thereby energized patient's immune system to fight cancer. IRAEs may affect functions of various organs, including heart, and may lead to morbidity and, to some extent mortality. Left ventricle (LV) myocarditis with dysfunction is a known side effect of this class of drugs. However, right ventricle (RV) myocarditis and pulmonary vasculitis are an unknown entity and has not been previously reported. Here, we present the first case of IRAEs causing selective RV involvement with dysfunctions, attributed to immune checkpoint inhibitors described till date in medical literature.

**Presentation of Case:** A 58-year male presented with history of low-grade fever and weight loss. On palpation, he had diffuse cervical lymphadenopathy. Histopathology evaluation of lymph node revealed metastatic lesions of Renal Cell Carcinoma (RCC).

**Conclusion:** Fatal cardiovascular adverse events can occur as a side effect of ICI. The combination of RV myocarditis with progressive pulmonary hypertension is fatal. Treatment with high dose corticosteroids and immunomodulators may help in patient survival. Physicians treating patients with ICIs should be aware of their lethal cardiotoxic side effects to reduce adverse cardiac outcomes. Because the number of patients exposed to this new immune therapy is expected to increase remarkably in the near future, our study encourages further work to define guidelines for cardiovascular monitoring and management.

**Keywords:** Immune checkpoint inhibitors; myocarditis; pulmonary vasculitis; renal cell carcinoma

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## Introduction

The development of immunotherapies in oncology over the past decade has revolutionised the management of advanced stage malignancies [1, 2]. The forefront of immunotherapy is represented by immune checkpoint inhibitors (ICIs), which inhibit molecules like monoclonal antibodies (mAbs) targeting ICIs {(e.g. cytotoxic T lymphocyte-associated antigen-4 (CTLA-4), programmed cell death-1 protein (PD-1) and its programmed cell death ligand-1 (PD-L1) and 2 (PD-L2)}. These ICIs have shown success in the treatment of solid and haematological tumours [2].

ICIs have transformed the treatment of various malignancies such as metastatic melanoma, bladder cancer, renal cancer, and non-small cell lung carcinoma (NSCLC) [1]. Ipilimumab, which targets CTLA-4 and PD-1 (nivolumab, pembrolizumab and cemiplimab) and PD-L1 (atezolizumab, durvalumab, avelumab and BMS-946559). Clinical studies conducted so far with these ICIs revealed significant responses in various cancers [3]. The combination of different ICIs showed improved overall survival (OS) in metastatic melanoma patients. Nivolumab (targeting PD-1) combined with ipilimumab (targeting CTLA-4) in resulted in >80% tumor regression in 30% of patients [4]. This ICIs combination also showed promising results in patients with recurrent glioblastoma and advanced renal cell carcinoma [5]. Further, it has been reported that chemotherapy combined with ICIs (dacarbazine combined with ipilimumab) enhanced survival in patients with advanced melanoma in comparison to dacarbazine alone [6]. Unfortunately, CTLA-4 inhibitors and PD-1 and PD-L1 blocking agents can produce a wide range of immune-related adverse affects (IRAEs) (e.g. cardiac toxicity) [7].

When ICIs were introduced as cancer treatments, little attention was paid to cardiac side-effects ranges from asymptomatic troponin-I elevations to conduction abnormalities of the heart. Several cases of LV myocarditis and fatal heart failure (HF) have been reported in melanoma patients treated with ICIs [8-10]. Several isolated cases of fulminant myocarditis and other cardiovascular disorders (pericarditis, vasculitis and AV blocks) were also reported [11-13]. Here we present a case of ICI-related cardio-toxicity diagnosed and managed at our hospital.

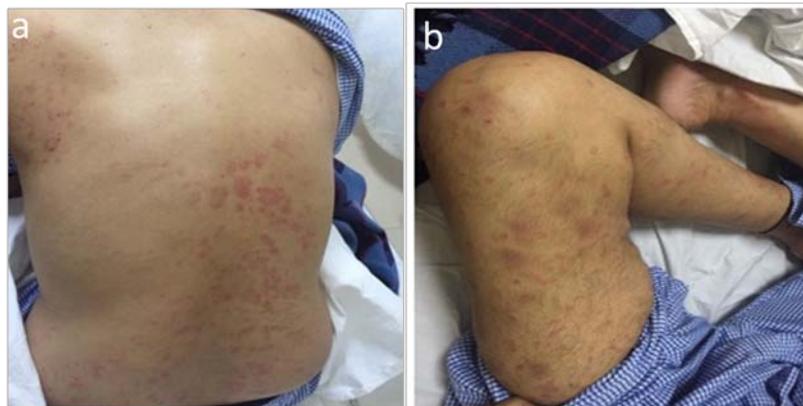
## Case Presentation

R.K.A, a 58-year male presented with history of low-grade fever and weight loss for the last 2 months, cough with haemoptysis for last 3 days. On examination, his vitals were stable. On palpation he had diffuse cervical lymphadenopathy. Biopsy of a lymph node was done. Histopathology sections showed features suggestive of metastatic lesions of Renal Cell Carcinoma (RCC). PET-CT scan revealed the location of primary tumour to be in the left kidney with metastasis. Patient underwent left nephrectomy and frozen section confirmed predominant clear cell type with small areas also showing papillary type of RCC. ECG and 2D Echo done before surgery was normal with no LV/RV systolic dysfunction and normal Pulmonary artery pressure (ePASP was 15 mm of Hg).

Post-surgery, chemotherapy was initiated with oral sunitinib, a multi-targeted Receptor Tyrosine Kinase (RTK) inhibitor. However, he developed symptoms of dyspnoea on exertion. A high-resolution computed tomography (HRCT) of the chest revealed nodular infiltrates in right upper as well as bilateral lower lung lobes. CT guided lung biopsy was done and the histology showed necrotizing granulomatous inflammation. Mycobacterial infection was suspected and treatment was

initiated for tuberculosis with five drug AKT regimen consisting of oral isoniazid (300 mg), rifampin (450 mg), pyrazinamide (750 mg) and ethambutol (800mg). Sunitinib was also continued. Unfortunately, there was no relief in symptoms, even after 3 cycles of sunitinib and a month on AKT regimen. Steroid therapy was also introduced and it leads to some improvement in symptoms.

After completion of 5 cycles, patient now developed extreme fatigue, diarrhea and blood profile showed severe pancytopenia. Sunitinib was discontinued in view of these side effects. Repeat HRCT did show decrease in pulmonary infiltrates and lymph node (LN) size. Sunitinib was re-introduced few weeks later, patient again developed pancytopenia. However, a month later, progression of disease was noticed on a PET-CT scan with cervical, mediastinal and abdominal lymph node involvement with deposits along multiple soft tissue planes and bones. Cytology of Pleural paracentesis was performed, which revealed malignant cells. AKT was stopped. 2D Echocardiogram was normal with no changes in pulmonary artery pressure (ePASP was 18 mm of Hg).



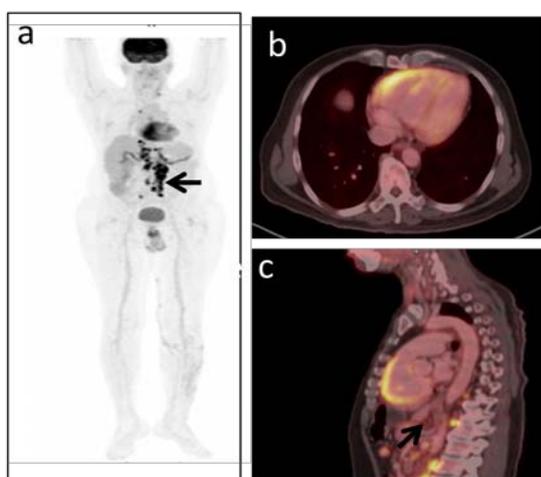
**Fig. 1** IRAE manifesting as pruritic skin rash (a: lesions on back of the patient skin; b: lesions on thigh)

Oral axitinib (small molecule tyrosine kinase inhibitor) was started in place of sunitinib and it lead to symptom relief and weight gain. However, the progression of disease was noticed with enlargement of cervical lymph nodes and only a partial mediastinal Lymph Node response was observed. Nivolumab (anti PD-1 monoclonal antibody) was added to low dose axitinib (2.5 mg). This combination lead to a dramatic response within 3 weeks and complete resolution of cervical lymph node involvement was noticed. However, two months later, he developed generalised non pruritic skin rash (Fig 1) and the biopsy showed lymphocytic small vessel vasculitis. 2D Echo done now showed features of RV myocarditis with dysfunction (RVEF of 30%) with the involvement of the apex and free wall with pulmonary artery hypertension (PAP of 113 mm of Hg). Troponin-I was mildly elevated done was normal. N-terminal pro b-type natriuretic peptide (NT-proBNP) level was observed to be 1150 pg/dl viral markers. Suspecting drug toxicity, nivolumab was stopped and steroids were re-introduced (Table 1).

**Table-1** Table showing progressive 2D Echocardiographic deterioration in patient on checkpoint inhibitors.

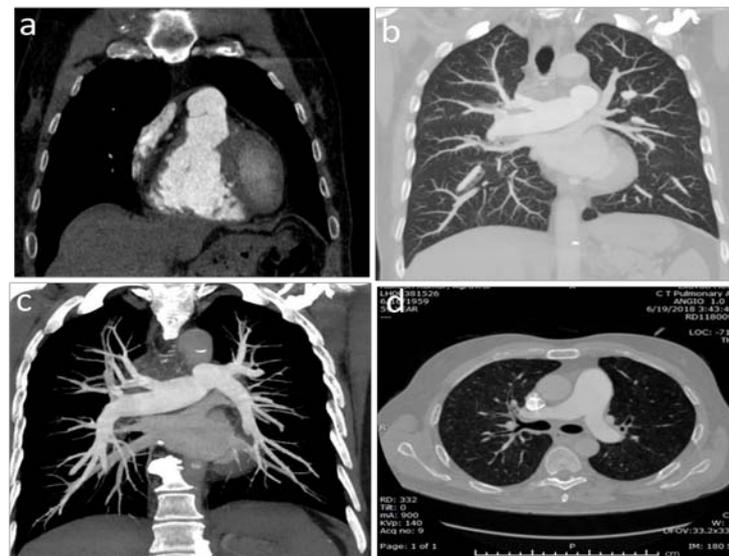
Time period	LV function	GLS	RV function	ePASP	Therapy
1).On treatment initiation	60%	-20	Normal	Normal	Axitinib
2).At 2 months	55%	-19	Normal	Normal	Axitinib
3).At six months	53%	-18	Normal	38	Axitinib/AKT
4).At 8 months	55%	-19%	Moderate RVEF 40% RV hypokinesia	48	Axitinib/ Nivolumab
5).At 1 year	52%	-18	Moderate RVEF 30% RV hypokinesia	113	Axitinib Nivolumab /

(ePASP: estimated pulmonary artery systolic pressure [mmHg], LV: Left Ventricular. RV: Right ventricular, RVEF: Right ventricular ejection fraction).



**Fig. 2** FDG-PET body scan (a) showing abnormal tracer uptake in the right ventricular wall (black arrow). Proximal pulmonary artery favouring myocarditis with pulmonary vasculitis (b). Also, there is an evidence of metastatic lymphadenopathy in the abdomen (c) (black arrow).

Whole body FDG PET with CT scan superimposition demonstrated curvilinear high-grade tracer uptake along the pulmonary trunk extending to the apical and free wall of RV and proximal pulmonary artery favouring myocarditis with pulmonary vasculitis. Also, there is an evidence of metastatic lymphadenopathy in the abdomen (Fig. 2). The metastatic lesions in the liver, lungs, subcutaneous tissue, and skeletal system showed complete metabolic and morphologic resolution. There is no evidence of local recurrence in the operative bed of the left renal fossa. Improvement was observed in skin lesions after high dose corticosteroids. However, dyspnoea, fatigue remained unresponsive even after initiating treatment with ambrisentan, sildenafil, inhaled milrinone and high flow Oxygen. HRCT Thorax and pulmonary CT angiogram results did not reveal pulmonary thromboembolism or other pulmonary parenchymal lesions (Fig 3). In spite of our best efforts, symptoms continued to progress and the patient succumbed due to progressive right heart failure.



**Fig. 3** HRCT thorax (a,b) and Pulmonary CT angiogram (c,d) revealed no pulmonary thromboembolism or other pulmonary parenchymal lesions.

## Discussion

Modulation of the human immune system has transformed cancer therapy, and immune checkpoint inhibition is one of the many successful forms to treat malignancies [14]. Cancer immunotherapy with immune checkpoint inhibitors such as monoclonal antibodies targeting cytotoxic T lymphocyte associated antigen 4 or CTLA-4 and programmed cell death 1 or PD-1 and its ligand PD-L1, have revolutionized the treatment of many malignancies. Solid and haematological tumours are known to have high recurrences with poor prognosis. Immune checkpoint inhibitors (ICI) act on anti-tumour immunity, and can induce cancer regression, thereby improving survival in different cancers [8,15]. However, several case studies have unveiled a wide range of side effects from activation of immune system with IC'Is [8]. These side effects are more commonly referred to as immune-related adverse events (IRAEs) affecting skin, muscle, joints, renal, CVS, CNS, ophthalmic, gastrointestinal tissue and endocrine systems [12,15-17]. IRAEs are generally low grade and easily manageable when detected in a timely manner<sup>18</sup>.

Cardiotoxicity usually manifests as myocarditis with predominant left ventricular dysfunction. Vasculopathy can affect vessels of any size but is more common in larger vessels such as temporal (giant cell) arteritis or aortitis [17]. Histopathological analysis in humans has revealed predominant infiltration by T lymphocytes and macrophages, indicating immune complex mediated response as the main mechanism [12,17]. Pre-existing auto-immune diseases, co-existent cardiac disease or use of more than one ICI's together can predispose patients to cardiac toxicity [19].

Pulmonary vasculopathy causing pulmonary hypertension has only been described in a single case report, but it was also associated with left ventricular myocarditis [20]. The patient under discussion had rapidly progressive pulmonary hypertension. Pulmonary embolism as the cause for severe pulmonary hypertension was excluded by pulmonary CT angiography. Inflammation of pulmonary artery was confirmed on Whole body PET with CT scan superimposition, with

demonstration of curvilinear high-grade tracer uptake along the pulmonary trunk. Skin biopsy of lesions had demonstrated predominant lymphocytic small vessel vasculitis. Clinical features, skin histopathology and imaging (Echocardiographic and CT-PET scans) correlation indicated that vasculitis was most likely the cause for pulmonary hypertension.

2D-Echocardiography was performed at regular intervals to study the disease progression. The findings showed no evidence of LV dysfunction on chemotherapy. However, progressive RV dysfunction, attributed to RV myocarditis, was noted during the course of treatment with immune checkpoint inhibitors. To the best of our knowledge, this is the first report of selective RV involvement with cardiotoxicity attributed to immune checkpoint inhibitors, described in medical literature. The patient under discussion presented with predominant sub acute, progressive right ventricular myocarditis (confirmed on 2 D Echo and FDG PET scan) (Fig 2). Selective viral RV myocarditis has been described [21, 22]. According to existing consensus statements, patients with threatened or established vasculitis or myocarditis, ICI therapy should be immediately stopped and immunosuppression with other agents such as intravenous methylprednisolone should be commenced. The complex pathophysiology of RV immune-mediated myocarditis and RV dysfunction associated with progressive pulmonary arterial hypertension ultimately proved catastrophic.

## Conclusion

Although uncommon, potentially fatal cardiovascular adverse events can occur as a side effect of ICI. Small vessel vasculitis as a complication of ICIs has been well documented. Evidence of vasculitis can be in form of skin lesions. However, vasculitis involving larger vessels such as pulmonary artery, resulting in pulmonary hypertension is indeed rare. The combination of RV myocarditis with progressive pulmonary hypertension is fatal. Treatment with high dose corticosteroids and immunomodulators may help in patient survival. Physicians treating patients with ICIs should be aware of this potentially lethal cardiotoxic side effect and multidisciplinary approach is often required to reduce adverse cardiac outcome.

## Statement of Ethics

All the procedures followed were in accordance with the ethical standards of our Institutional ethics committee on human experimentation. Informed consent was obtained from the patient for publication of this case report.

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## Disclosure Statement

The authors have no relevant conflicts of interest to report.

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