Case report of elevation of high-sensitivity cardiac troponin T in the absence of cardiac involvement in immune checkpoint inhibitor-associated myositis

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Background
Immune checkpoint inhibitors (ICIs) have markedly improved outcome in various types of cancer. ICI-associated myocarditis is one of the most severe immune-related adverse events. In particular, high concentrations of cardiac troponin T (cTnT) are associated with a high risk of death and early detection and vigorous therapy with high-dose steroids may improve survival. However, chronic skeletal muscle disorders have been suggested as a non-cardiac source of elevated high-sensitivity cardiac troponin T (hs-cTnT) concentrations.

Case summary
Here, we present the case of a 72-year-old patient with metastatic melanoma treated with nivolumab and ipilimumab, who developed symptomatic myositis [creatine kinase (CK) max. 3113 U/L]. Due to substantially elevated concentrations of hs-cTnT (max. 1128 ng/L, normal <14 ng/L, Elecsys), the patient was referred to the cardio-oncology unit for evaluation of concomitant myocarditis. The patient did not report any cardiac symptoms and there were no clinical signs of congestion or rhythm abnormalities. Concentrations of NT-proBNP were within the normal range. Echocardiography showed normal cardiac dimensions and normal systolic and diastolic function. Cardiac magnetic resonance imaging confirmed these findings and also showed no evidence of acute or post-inflammatory myocardial tissue changes. Absence of relevant cardiomyocyte injury was supported by determination of normal levels of cardiac troponin I concentrations and made endomyocardial biopsy in this severely ill patient unnecessary.

Discussion
Our observation documents ICI-induced myositis as an alternative non-cardiac cause of hs-cTnT elevation. A global cardiologic approach employing clinical and cardiac magnetic resonance imaging data as well as NT-proBNP and cardiac troponin I helps to identify false positive hs-TnT elevation under ICI therapy.

Keywords
Case report • Immune checkpoint inhibitors • Immune-related adverse events • Myocarditis • Troponin • Biomarker • Myositis

ESC curriculum
6.9 Cardiac dysfunction in oncology patients • 2.3 Cardiac magnetic resonance

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Learning points

- Immune-related myositis is an important alternative non-cardiac cause of high-sensitivity cardiac troponin T (cTnT) elevation in cancer patients undergoing immune checkpoint inhibitor (ICI) treatment.
- A global cardiologic approach including clinical and cardiac magnetic resonance imaging data as well as NT-proBNP and cardiac troponin I helps to identify false positive hs-TnT elevation under ICI therapy.

Primary specialities involved other than cardiology section

Medical Oncology, Internal Medicine.

Introduction

Immune checkpoint inhibitors (ICIs) blocking inhibitory immune checkpoint receptors have become a cornerstone of cancer therapy due to their ability to induce sustained immune-mediated tumor suppression and improve patient survival. However, inflammatory syndromes including autoimmunity to self-antigens leading to immune-related adverse events (irAEs) have been reported across different types of ICIs. ICI-induced cardiotoxicity may involve all parts of the heart and is attributed to both inflammatory and non-inflammatory mechanisms. Inflammatory cardiotoxicity may manifest as myocarditis, perimyocarditis, pericarditis, left ventricular dysfunction without myocarditis, or coronary vasculitis. The incidence of ICI-related myocarditis is in the range of 1%. Although cardiotoxicity is overall rare, a high case fatality rate (35%) of ICI-induced myocarditis has been reported. Furthermore, among all irAEs, myositis and myocarditis have been identified as potential major causes of ICI-associated mortality. Importantly, simultaneous occurrence of myocarditis has been reported in up to 16.1% of patients presenting with ICI-associated myositis. Here, we describe the case of a melanoma patient developing myositis as irAE under ICI therapy exhibiting enhanced concentrations of hs-cTnI, in whom ultimately no evidence for cardiac involvement was found.

Timeline

Both, high-sensitivity (hs) cardiac troponin T (cTnT) and high-sensitivity cardiac troponin I (hs-cTnI) are equivalent regarding the detection of cardiomyocyte loss and diagnosis of acute myocardial infarction. However, high concentrations of hs-cTnT, and much less frequently of hs-cTnI, have been reported in patients with chronic skeletal myopathies including Duchenne. Although the cause of cardiac troponin T detection remains incompletely understood, re-expression of cTnT in the diseased skeletal muscle and/or cross-reactivity of the hs-cTnT assay with circulating muscle epitopes may play a role. In contrast, rhabdomyolysis, an acute form of skeletal muscle damage, does not lead to disproportionally increased hs-cTnT concentrations. Here, we describe the case of a melanoma patient developing myositis as irAE under ICI therapy exhibiting enhanced concentrations of hs-cTnI, in whom ultimately no evidence for cardiac involvement was found.

Case presentation

A 72-year-old woman presented at the Clinic of Medical Oncology of the University Hospital of Basel (Switzerland) to receive the second course of a combination therapy with nivolumab and ipilimumab for the treatment of metastatic melanoma with liver, skin, and bone metastases. She was initially treated with single-agent nivolumab 5 weeks prior, which she tolerated well without showing any abnormal laboratory values. Due to rapid clinical progression of the disease with visible in-transit metastases, the therapy was intensified to a combination of nivolumab and ipilimumab 2 weeks later. The initial diagnosis of the primary melanoma was first made 10 months earlier. At that time, the patient was diagnosed with localized disease on the left posterior shoulder and underwent primary complete resection with 1 cm safety margins (Breslow 1.5 mm; Clark Level III). Sentinel cervical and axillary
lymph node biopsies showed no histological evidence of metastases (pT2a, pN0, cM0. Stage IB according to AJCC 8th edition). Seven months later, a positron emission tomography (PET) showed cutaneous/subcutaneous hypermetabolic tumours in the left shoulder and a hypermetabolic local lymph node in the left axilla. The patient underwent local resection and axillary lymph node dissection with histological confirmation of metastatic melanoma. Her past medical history was significant for bilateral breast cancer (right: pT1c, pN1mi cM0 G2; ER 95%, PR 15%, Her2 neg, Ki67 15%, and left: pT1c pN1a cM0 G2; ER 90%, PR 15%, Her2 neg, Ki67 <5%) diagnosed 19 months earlier, without evidence of recurrence. Previous medical history of the patient further included a basal-cell carcinoma on the right side of the neck 9 months earlier, which was treated locally, and hypertension, and non-insulin-dependent Type 2 diabetes mellitus. Regular medication included letrozole, perindopril, and vitamin D3.

At presentation, the patient reported progressive muscular pain and weakness, pain in both hips, dyspnoea, blurry vision, headache, and a hoarse voice. She was in a poor general condition, non-febrile, and with weakness, pain in both hips, dyspnoea, blurry vision, headache, and a hoarse voice. She was in a poor general condition, non-febrile, and with hypertension, and non-insulin-dependent Type 2 diabetes mellitus. Regular medication included letrozole, perindopril, and vitamin D3.

Based on the symptoms, the laboratory results, and the findings of the transthoracic echocardiography and the cMRI, an ICI-related myositis was diagnosed (Figure 1). At hospital admission, laboratory values showed the following values: hs-cTnT: 1128 ng/L (<14); N-terminal pro-b-type natriuretic peptide (NT-proBNP): 162 ng/L (<177); CK: 2844 U/L; CK-MB-mass: 153 µg/L; ALAT: 341 U/L; LDH: 1582 U/L; ASAT: 233 U/L; ALP: 86 U/L; GGT: 77 U, and CRP: 18 mg/L. A complete blood cell count was unremarkable. At that timepoint, the main symptoms were progressive dysphagia and weakness. Chest or muscle pain were not reported. Symptoms and findings were interpreted as potentially immune-related. Therefore, nivolumab was discontinued and treatment with prednisone 75 mg/d was initiated (corresponding to 1.5 mg/kg body weight). Due to the elevated hs-cTnT concentrations, a cardio-oncology consultation was arranged, where the patient reported general fatigue and moderate dyspnoea. The electrocardiogram showed a sinus rhythm (84 bpm) without abnormalities. No arrhythmias could be detected during the telemetric monitoring in the first 3 days after admission.

A transthoracic echocardiography was performed on the day of the patient’s admission and showed a left ventricle with normal dimensions and normal left ventricular ejection fraction (63%, reference ≥54%). There were no abnormalities regarding the left ventricular regional motility and no relevant valvulopathy. Diastolic function was normal, and there was no pericardial effusion. Cardiac magnetic resonance imaging (cMRI) was performed after the weekend on the third day of hospitalization and confirmed the findings obtained by echocardiography showing normal left ventricular dimensions and normal global and regional function. Furthermore, a previous myocardial infarction could be excluded, and there was neither evidence of a myocardial oedema nor evidence of acute or post-inflammatory myocardial tissue alterations. There were no signs of a metastatic infiltration, and no indication of scar or myocardial oedema as evidenced by the absence of late gadolinium enhancement and normal T2 (Figure 2).

Cardiac TnI assessed 5 days after admission using a sensitive assay was <10 ng/mL [reference <40 ng/mL]. Under ongoing therapy with prednisone, CK and hs-cTnT concentrations dropped during the course of the hospitalization (Figure 1).

Based on the symptoms, the laboratory results, and the findings of the transthoracic echocardiography and the cMRI, an ICI-related myositis with no associated myocarditis was diagnosed. We considered myasthenia gravis as differential diagnosis. We did not measure antibodies against acetylcholine receptor due to lack of specific therapeutic options.

**Figure 1** Course of creatine kinase, high-sensitivity cardiac troponin T, and cardiac troponin I over time.
The pathophysiologic mechanism leading to ICI-associated myositis probably due to progressive myositis, the patient was transferred to a palliative care unit where she died 2 days later.

In a recently published series of 35 patients requiring ICI therapy and exhibiting irAEs, invasive diagnostics with endomyocardial biopsy (EMB) may be mandatory to avoid withdrawing (ICI therapy in case of dismissed) or withholding (high-dose steroids in case of confirmed myocarditis) potentially life-saving therapy. Considering the poor general condition of our and many other cancer patients requiring ICI therapy and exhibiting irAEs, invasive diagnostics of any kind requires careful consideration. Although EMB was discussed as additional option to exclude myocarditis, the negative read-out of cTnI on top of the clinical and imaging information obtained by cMRI prompted us to ultimately forgo EMB in this patient, who showed rapid progression of the tumour even under ICI therapy.

The presented case has several limitations. Because no biopsy or autopsy was performed, we cannot completely exclude smouldering myocarditis in our patient. However, the discrepancy between a highly elevated hs-cTnT and a normal cTnI makes this highly unlikely. In addition, increase in cTnI even in smouldering myocarditis up to 13 times the upper limit of normal has also been reported. Although we measured cTnI only at a later time point, we would not expect different findings otherwise, as cTnI and hs-cTnT show similar dynamics in acute myocardial infarction with a trend to an even earlier increase of cTnI.

**Discussion**

ICI play an increasingly important role in the treatment of numerous types of cancer. Beside other cardiovascular complications as myocardial infarction, takotsubo cardiomyopathy and cardiorenal failure, ICI-associated myocarditis is a severe condition with a high risk of a fatal outcome. Overall the prevalence of ICI-associated myocarditis is low. The pathophysiologic mechanism leading to ICI-associated myocarditis is not yet fully understood. Currently, it is thought to be caused by the infiltration of predominant CD4+/CD8+ T lymphocytes and few macrophages (CD68+ cells). Furthermore, elevated levels of tumour necrosis factor-α, granzyme B, and interferon-γ produced by activated T cells might contribute to cardiac injury. The most likely explanation is the ‘shared antigen’ between tumour and cardiomyocytes, with muscle-specific antigens (desmin and troponin) detected in the tumour.

Of all laboratory tests, troponin is generally the most sensitive marker for suspected myocarditis. In a recently published series of 35 patients with ICI-associated myocarditis, almost all patients (i.e. 94%) had elevated troponin at the time of presentation. In addition, a high cTnT level of ≥ 1.5 ng/ml (fourth generation troponin T assay) was associated with a four-fold higher incidence of major adverse cardiac events and high-dose steroid administration led to a more sustained decrease in cTnT and a lower event rate than lower steroid doses. These observations attribute a role to cTnT not only in the diagnosis of ICI-associated myocarditis but also in its prognostication. Especially in patients responding well to ICI therapy, future treatment decisions depend on the careful evaluation of irAEs, their significance regarding patient outcome, and the potential consequences of re-exposition of the patient to ICI therapy. Therefore, and because the simultaneous occurrence of myocarditis has been reported in up to 16.1% of the patients presenting with an ICI-associated myositis, the screening for and the identification of myocarditis are of cardinal importance.

As previously described, hs-cTnT is not always specific for cardiac damage. The majority of patients with skeletal myopathies do present with elevated hs-cTnT levels. Importantly, this appears not to be the case for troponin I. Although these patients usually exhibit mildly to moderately elevated levels of troponin T (median: 24 ng/L; interquartile range: 11–54 ng/L), higher levels in isolated cases under inflammatory conditions are also described (>1000 ng/L). These observations support that suspicion of myocarditis should not be raised purely based on increased cTnT, but that simultaneous determination of cTnI, in particular in cases with highly elevated CK levels, should be included into routine assessment of these patients.

Information from ECG, biomarkers, and cardiac imaging are all integrated to diagnose myocarditis. Besides late gadolinium enhancement, an enhanced T2 signal in cMRI may indicate myocarditis. However, the results may be normal in patients with ICI-induced myocarditis, in whom cardiac function may be maintained and late gadolinium enhancement or oedema may be absent on cMRI. Hence invasive diagnostic with endomyocardial biopsy (EMB) may be mandatory to avoid withdrawing (ICI therapy in case of dismissed) or withholding (high-dose steroids in case of confirmed myocarditis) potentially life-saving therapy. Considering the poor general condition of our and many other cancer patients requiring ICI therapy and exhibiting irAEs, invasive diagnostics of any kind requires careful consideration. Although EMB was discussed as additional option to exclude myocarditis, the negative read-out of cTnI on top of the clinical and imaging information obtained by cMRI prompted us to ultimately forgo EMB in this patient, who showed rapid progression of the tumour even under ICI therapy.

![Figure 2](image-url) Late gadolinium enhancement showed no evidence of myocardial infarction or focal fibrosis. T2 mapping of the myocardium showed normal T2 values and no evidence of a myocardial oedema.
In summary, we present a case of severe ICI-associated myositis. In our case, a false positive hs-cTnT led to the suspicion of possible concomitant myocarditis. Through a combination of clinical findings (absence of arrhythmia or typical sings of congestive heart failure or lung oedema), biomarkers (normal NT-proBNP and cTnI) and imaging studies (normal echocardiography and no signs of myocardial oedema or late gadolinium enhancement on cMRI) a myocarditis as cause of the patient’s serious condition could ultimately be excluded.

Our observation provides additional evidence for the potential lack of specificity of hs-cTnT for cardiomyocyte injury in ICI-associated myositis. In this scenario, a global cardiologic approach with a combination of clinical findings, biomarkers (including cTnI), and imaging studies is needed not only for informed treatment decisions regarding immuno-suppressive therapy or re-exposure to ICI but also to avoid unnecessary invasive diagnostics in these severely ill patients. Although nowadays, we routinely measure cTnI repetitively in patients with suspected ICI-induced myocarditis, newer imaging modalities may also hold promise for improved non-invasive diagnosis or rule-out of myocarditis, e.g. 68Ga-DOTATOC PET/CT.19

Lead author biography
Sacha I. Rothschild is Professor of Medical Oncology at the University of Basel, and Head of Clinical Research Medical Oncology at the University Hospital Basel, Switzerland. His areas of clinical focus are thoracic oncology and the treatment of head and neck tumors, and he conducts clinical and translational research in thoracic oncology – a field in which he is widely published. Prof. Rothschild is also Vice President of the Swiss Group for Clinical Cancer Research (SAKK), Director of Studies for the ‘CAS Personalized Molecular Oncology’ program at the University of Basel and Associate Editor of Thoracic Oncology, Frontiers in Oncology. He also holds memberships with several professional bodies including the American Association for Cancer Research (AACR), American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO) and International Association for the Study of Lung Cancer (IASLC).

Supplementary material
Supplementary material is available at European Heart Journal – Case Reports online.

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We thank the patient and her family for letting us present her case in this report.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The authors confirm that written consent for submission and publication of this case report including images and associated text has been obtained from the patient in line with COPE guidance.

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