Transthyretin Cardiac Amyloidosis Mimicking Immune Checkpoint-Induced Myocarditis in a Patient Treated with Atezolizumab and Bevacizumab for Advanced Hepatocellular Carcinoma: A Case Report

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Abstract
Checkpoint kinase inhibitors are increasingly used in oncology. The combination of atezolizumab and bevacizumab is currently the recommended first-line treatment for advanced hepatocellular carcinoma. Cardiac toxicities of immunotherapies are rare, but can lead to discontinuation of treatment. Transthyretin cardiac amyloidosis is a rare condition, but its incidence is probably underestimated. Its symptoms may suggest immunotherapy-induced myocarditis. When immune-mediated myocarditis is suspected, a thorough cardiac evaluation is necessary to confirm or refute the diagnosis of myocarditis and to avoid unnecessary interruption of immunotherapy. Cardiac magnetic resonance imaging may raise suspicion of transthyretin cardiac amyloidosis, the diagnosis being confirmed by technetium pyrophosphate bone scintigraphy.
Introduction

Sorafenib was for a decade the only systemic therapy that demonstrated efficacy in advanced hepatocellular carcinoma (HCC), with a median overall survival of 10.7 months in the SHARP trial [1]. Since 2017, other tyrosine kinase inhibitors have demonstrated efficacy or noninferiority in the treatment of advanced HCC: lenvatinib in first line [2], regorafenib in second line [3], and cabozantinib in second or third line [4]. In second-line therapy, ramucirumab, a VEGF receptor 2 inhibitor, improved overall survival compared to placebo in patients with alpha-fetoprotein serum level >400 ng/mL [5]. The initial results of phase III studies evaluating immunotherapy in advanced HCC have been disappointing. The Checkmate 459 study comparing nivolumab and sorafenib did not show a statistically significant benefit in overall survival in the first line, and the Keynote 240 trial comparing pembrolizumab and placebo in the second line was also a negative study [6, 7]. In these studies, however, a long responder profile could be distinguished, as is usually the case with checkpoint kinase inhibitors. The IMBRAVE-150 study is a first phase III study demonstrating the benefits of immunotherapy on overall survival changed in patients with advanced HCC. This study compared the combination of atezolizumab (anti-PD-L1, 1,200 mg every 3 weeks) and bevacizumab (anti-VEGF antibody 15 mg/kg every 3 weeks) with sorafenib. The combination showed a significant benefit in both overall survival (19.2 vs. 13.4 months, HR 0.66, \( p < 0.0009 \)) and progression-free survival (6.9 vs. 4.3 months, HR 0.65, \( p = 0.000 \)) [8]. More recently, the phase III HIMALAYA study demonstrated the superiority of the combination of durvalumab and tremelimumab versus sorafenib (primary objective) and the noninferiority of durvalumab alone versus sorafenib (secondary objective) [9]. The current challenges are to define predictive factors of response and to refine therapeutic strategies [10].

Most of patients treated with immune checkpoint inhibitors (ICIs) will experience at least one immune-related adverse event during treatment [11]. Myocarditis is a rare but classic example of these complications [12]. However, other diagnoses should be discussed in case of symptoms and initial workup suggesting myocarditis. We report the case of a patient treated with atezolizumab, presenting chest tightness and dyspnea, with a final diagnosis of transthyretin cardiac amyloidosis (ATTR-CA), enabling the reintroduction of the treatment.

Case Presentation

Figure 1 illustrates the timeline with the main events of the case report. A 76-year-old man with a medical history of essential hypertension and dyslipidemia was treated for viral hepatitis C in 2016, complicated by F1 portal hepatic fibrosis. During follow-up, an isolated
segment VI nodule of 25 mm was discovered in January 2021, without any distant lesion. Biopsies allowed the diagnosis of poorly differentiated HCC and F1 fibrosis in the extratumoral liver. Hyperselective lipidated transarterial chemoembolization was performed involving two vascular pedicles feeding the tumor (VI and VII). One month later, the re-evaluation CT scan showed the appearance of three new lesions suspected of HCC (LI-RADS 5). Treatment with atezolizumab and bevacizumab was started on May 2021, 1,200 mg and 15 mg/kg, respectively, every 3 weeks.

Before the seventh infusion, the patient reported intermittent chest tightness, dyspnea, and pain in the right calf for 7 days. The electrocardiogram (ECG) showed repolarization disorders with a right precordial overshoot of 2–3 mm and a left precordial undershoot, with signs of left ventricular hypertrophy and a left bundle branch block. This left bundle branch block existed on the October 2020 cardiology workup. The CT scan did not find any pulmonary embolism. Troponins increased to 37 ng/mL without available history and N-terminal pro-BNP to 2,952 ng/mL, and creatine phosphokinase level was normal. In this context, the patient was hospitalized in cardiology. Echocardiography revealed diffuse hypokinesia more marked in the inferior and lateral walls and a depressed left ventricular ejection fraction (LVEF) of 35% associated with concentric left ventricular hypertrophy. Coronary angiography revealed atheromatous lesions without significant lesions explaining the alteration of the LVEF. The clinical evolution was favorable after intravenous diuretic treatment, followed by oral treatment and the introduction and titration of cardioprotective treatments. The diagnosis of immune-mediated myocarditis was suspected.

The cardiac magnetic resonance imaging performed after discharge showed an improvement in the LVEF to 52%, as well as a late gadolinium enhancement (LGE) of the basal and middle thirds and opposite the latero-apical wall of the left ventricle. There was a base-apex gradient and discrete latero-basal myocardial edema. The myocardial thickness was increased (13 mm septal). Tissue characterization abnormalities suggested anti-PDL1-related cardiac involvement, and the hypertrophy could be secondary to arterial hypertension, but cardiac amyloidosis was suspected as a differential diagnosis (Fig. 2).

Therefore, a bone scintigraphy scan was performed, revealing a Perugini grade III cardiac uptake without monodonal gammopathy allowing the diagnosis of ATTR-CA (Fig. 3). Treatment with beta-blockers and sartans was stopped. Treatment with atezolizumab and bevacizumab was rechallenged, with a re-evaluation scan performed in January 2022 showing stable lesions according to RECIST and no recurrence of signs of heart failure. The troponin level remained elevated during follow-up, before and after atezolizumab reintroduction, in favor of its relationship with amyloidosis.
The combination of atezolizumab and bevacizumab is the standard of care in first line systemic treatment of HCC [8]. In oncology, up to 60–80% of ICI-treated patients will experience at least one immune-related adverse event during treatment [11]. An international multicenter registry reported a rate of ICI-related myocarditis of 1.1–2.4% in the case of single ICI, and 2.4% in the case of a combination [12]. However, the true incidence of this cardiotoxicity is probably underestimated. The risk factors for ICI-related myocarditis are not well defined, as studies are limited by the low incidence of these events. The risk of myocarditis appears to be more important with anti-CTLA-4 monotherapy (3.3%) than with anti-PDL1 and PD1 agents (2.4% and 0.5%, respectively) [12]. The main known risk factor is the combination of ICI therapy, which increases the risk of developing myocarditis five times compared to monotherapy [13]. Other registries have also identified diabetes, obesity, autoimmune diseases, or preexisting cardiovascular risk factors as independent risk factors [14–16]. Myocarditis is not the only cardiac toxicity. Arrhythmias including atrial fibrillation (30%), conduction disorders (17%), pericarditis (13.6%), and tako-tsubo-like cardiomyopathy (14%) can also be immune mediated [17, 18].

The combination of ICI with VEGF inhibitors could increase the risk of cardiotoxicity. VEGF inhibitors can cause adverse cardiovascular side effects through the inhibition of the VEGF receptor and the platelet-derived growth factor receptor, which could lead to resting blood flow alteration to the myocardium [19].

The clinical presentation of myocarditis is variable, ranging from elevated cardiac biomarkers without symptoms to the development of rapid cardiac heart failure. Patients can present with nonspecific fatigue, chest pain, shortness of breath, lower extremity edema, palpitations,
irregular heartbeat, muscle pain, or syncope [17]. Most ICI-related myocarditis occurs within 3 months after starting treatment [12, 20, 21]. ECG is abnormal in about 90% of patients. Findings are nonspecific and variable, such as tachycardia, arrhythmias, and conduction disease [12]. Cardiac troponin is not specific for myocarditis, and it is the most sensitive test with elevated levels in 94% of patients with ICI-associated myocarditis [12]. The degree of troponin elevation has been associated with worse outcomes, and specifically troponin greater than 1.5 ng/mL at discharge has been associated with an increased risk of major adverse cardiac events [12]. Natriuretic peptides (brain natriuretic peptide/N-terminal pro-BNP) are elevated in 66% of patients with ICI-related myocarditis, particularly those with volume overload or heart failure, but sensitivity and specificity are limited for the diagnosis of myocarditis [12, 15].

Echocardiography can reveal abnormal regional wall motion or decreased systolic function. However, in an international retrospective registry, 51% of patients with ICI-associated myocarditis had a normal LVEF. Importantly, 38% of severe forms such as fulminant myocarditis occurred in patients with a normal LVEF [12, 22]. Cardiac magnetic resonance imaging is superior to echocardiography for the diagnosis of myocarditis, allowing tissue characterization in the presence of myocardial edema, fibrosis, and inflammation. Myocardial inflammation and edema can be visualized using techniques such as LGE and T2-weighted imaging. Wall motion abnormalities may be global or regional. However, cardiac magnetic resonance imaging may not be readily available and severely ill patients may not tolerate the test. Similar to echocardiographic studies, 61% of the patients had a preserved LVEF of >50% in CMR. LGE was present in 48% of the patients, of which 43% had preserved LVEF [23]. Endomyocardial biopsy is the gold standard for the diagnosis of ICI myocarditis, but is not performed routinely because of the risk of cardiac perforation. It should be considered in patients with high clinical suspicion of ICI-associated myocarditis and negative or ambiguous noninvasive imaging. If endomyocardial biopsy is performed, histopathological analysis typically reveals interstitial fibrosis and inflammatory infiltrates in the myocardium with lymphocytic T cells and macrophages [24].

When immune-mediated cardiac toxicity is suspected, it is important to consider differential diagnoses to avoid unnecessary discontinuation of ICI. In fact, a low troponinemia elevation can be present in several other cardiac pathologies, such as sarcomeric hypertrophic cardiomyopathy or ATTR-CA, in which LGE is frequent on CMR. These pathologies can be suspected on echocardiography. Our patient had a final diagnosis of ATTR-CA. This is an infiltrative cardiomyopathy caused by extracellular deposition of insoluble transthyretin (TTR) amyloid fibrils in the myocardium. TTR is a plasma protein synthesized in the liver that is the transporter of thyroxine and retinol-binding protein. Two types of ATTR-CA have been identified: wild type, caused by age misfolding of TTR, and hereditary type which is an autosomal dominant disease responsible for the changes in the protein TTR. The wild type is the most frequent form of amyloidosis and predominantly affects men over 60 years of age.

Symptoms are nonspecific, such as dyspnea, fatigue, weakness, chest pain. Diagnosis is frequently delayed due to comorbidities, aspecific symptoms, and lack of recognition of this clinical entity. On the ECG, patients may develop a low QRS voltage or a pseudoinfarction pattern. The most common phenotype in echocardiogram is the presence of increased left ventricular wall thickness, atrial enlargement, and signs of elevated filling pressure. The LVEF is initially preserved and decreases as the disease progresses. Even when the ejection fraction is preserved, an alteration of the global longitudinal strain and a relative apical sparing can be observed and is very sensitive for the diagnosis of cardiac amyloidosis. Cardiac magnetic resonance shows various patterns of LGE: global subendocardial LGE, global transmural LGE, atrial LGE, and suboptimal myocardial nulling. CMR has a sensitivity and a specificity of, respectively, 80% and 94% for the diagnosis of CA [23]. Radionuclide bone scintigraphy employing technetium pyrophosphate (99mTc-PYP) is a recent diagnostic method for ATTR-CA, which can detect cardiac TTR deposition [25]. Histology reveals a deposit of amyloid fibrils.
with red congo coloration. However, the algorithm based on bone tracer scintigraphy and the search for monoclonal or light chain protein is very effective in reaching the diagnosis of TTR amyloidosis and noninvasive diagnosis [26].

**Conclusion**

At baseline and during follow-up, a baseline ECG and troponin I or T should be considered, as well as screening echocardiography in patients with a history of cardiovascular disease and those with a history of exposure to other cardiotoxic therapies. When cardiac toxicity is suspected, exhaustive complementary examinations should be performed to avoid unnecessary discontinuation of ICI.

**Statement of Ethics**

This clinical case is not report of a clinical study. Written informed consent was obtained from the patient for publication of this case report and any accompanying images. This retrospective review of patient data did not require ethical approval in accordance with local/national guidelines.

**Conflict of Interest Statement**

None of the authors declared conflicts of interest.

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**Author Contributions**

Study design: Yann Touchefeu; data collection and interpretation: Pierrine Le Bras, Louise Plard, Christèle Le Gouill, Nicolas Piriou, and Yann Touchefeu; manuscript writing and manuscript editing and approval to submit: Pierrine Le Bras, Louise Plard, Nicolas Piriou, and Yann Touchefeu.

**Data Availability Statement**

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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