Case Report

Truncating Titin (*TTN)* Variants in Chemotherapy-Induced Cardiomyopathy

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ABSTRACT

Chemotherapy-induced cardiomyopathy (CCMP) is a complication of chemotherapy treatment occurring in 9% of patients treated with the use of anthracyclines. Currently, risk stratification is based on clinical risk factors that do not adequately account for variable individual susceptibility. This suggests the presence of other determinants. In this case series, we describe 2 women with breast cancer who developed severe heart failure within months after chemotherapy. Genetic screening revealed truncating frameshift mutations in *TTN*, encoding the myofilament titin, in both women. To our knowledge, this is the 1st report of an association between truncating *TTN* variants and CCMP. Because truncations in *TTN* are the most common cause of familial and sporadic dilated cardiomyopathy, further research is needed to establish their prevalence in patients presenting with CCMP. (*J Cardiac Fail 2017;23:476–479*)
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Cardiotoxicity is a known complication of anticancer treatment, leading to chemotherapy-induced cardiomyopathy (CCMP). Anthracyclines are commonly associated with cardiotoxicity but remain essential in the treatment of multiple malignancies.[1] Clinical guidelines suggest limiting the maximum cumulative dose to lessen the incidence of CCMP while attempting to maintain the maximum antineoplastic effect.[1] Although these safety measures have been taken, the incidence of cardiotoxicity is currently 9%.[2] The prognosis of anthracycline-induced heart failure is poor, with a 60% mortality rate at 2 years.[3] However, with early recognition and treatment initiation, patient outcome can be significantly improved.[4]

Prediction models for the identification of high-risk patients use patient- and treatment-related variables.[5,6] Nevertheless, individual susceptibility is not explained adequately by these variables, indicating the presence of unidentified determinants.[7] As proper risk assessment enables focused monitoring of high-risk patients and early detection of myocardial dysfunction, it is of great importance to identify factors that modulate individual risk.

Case Series

Patient 1

A 43-year-old woman without a documented medical history was diagnosed with ductal adenocarcinoma (cT4N1M0) in her right breast in June 2014, for which she received taxotere (450 mg/m^2), adriamycin (300 mg/m^2), and cyclophosphamide (3000 mg/m^2). Five months later, she presented to the emergency department with complaints of dyspnea. Echocardiography displayed a borderline dilated left ventricle (LV) of 56 mm with poor systolic function (left ventricular ejection fraction [LVEF] 15%) and a restrictive filling pattern (grade III). Deformation imaging revealed a global reduction in longitudinal strain characteristic of chemotherapy-induced left ventricular (LV) dysfunction (Fig. 1A). Cardiac magnetic resonance imaging (MRI) confirmed these findings and showed no specific delayed enhancement patterns (Fig. 1B and C).

Fig. 1. Speckle tracking echocardiography and cardiac magnetic resonance imaging (MRI) of patient 1. (A) Deformation imaging showing the longitudinal strain curves of the left ventricular apical 4-, 2-, and 3-chamber views and the bulls-eye polar map displaying the peak systolic strain values of all 17 left ventricle (LV) segments. A severe impairment of all LV segments is seen with peak systolic strain values of −3% to −7%. Only the posterior wall shows some preservation of regional function, but it is nevertheless impaired. Global longitudinal strain is 6.2% (normal value −19.7%, 95% CI −20.4% to −18.9%). (B) Cardiac MRI short-axis views from base (top left) to apex (bottom right) showing the post-contrast delayed enhancement. Only nonspecific fibrosis at the insertion points of the right ventricle is seen. (C) Cardiac MRI 4-chamber view still frame of steady-state free precession (SSFP) sequence. The LV is moderately dilated with preserved wall thickness. The LV is moderately dilated with preserved wall thickness. The calculated LVEF was 12% based on global LV dysfunction.
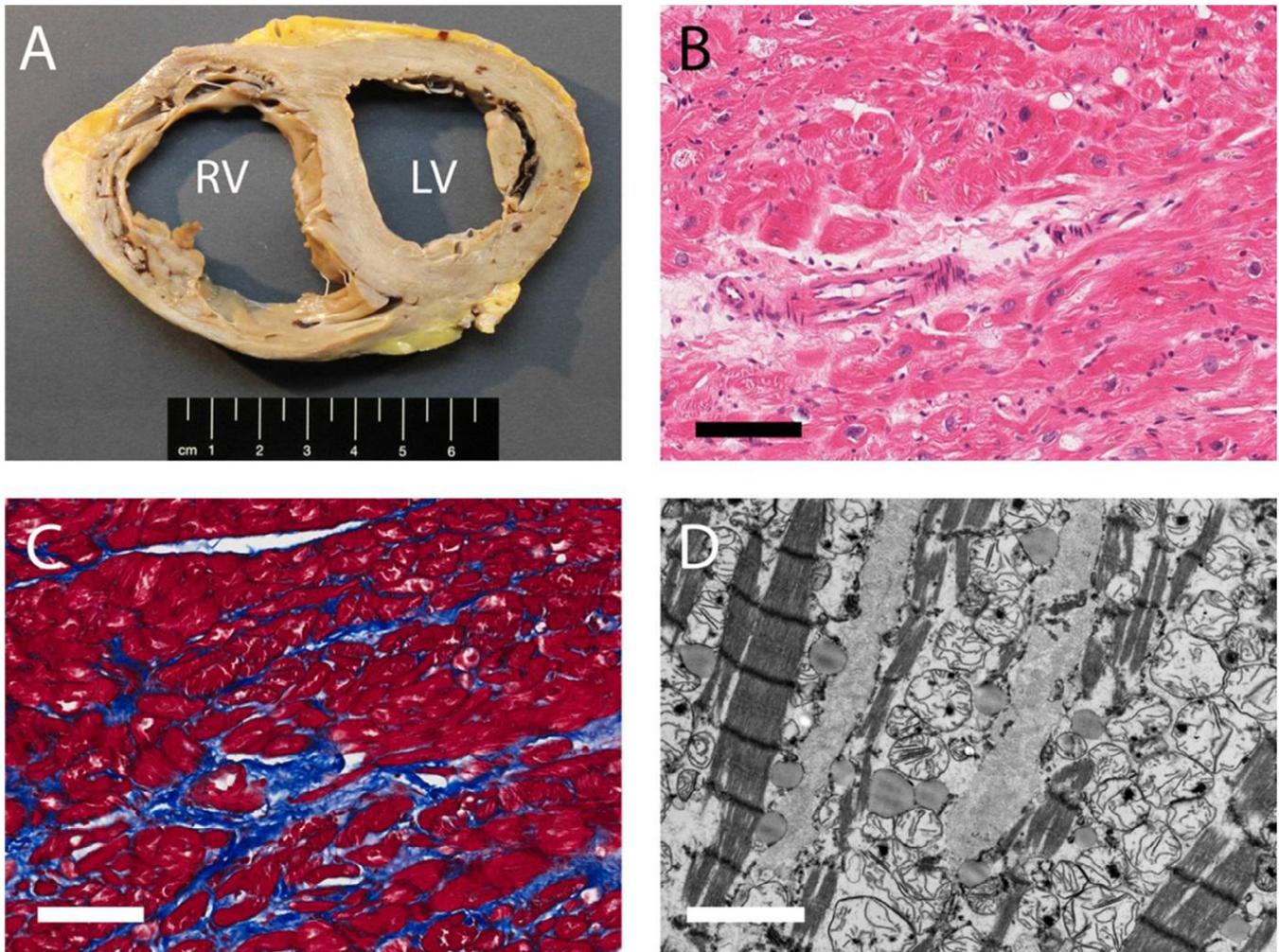
Fig. 2. Macroscopic, microscopic, and ultrastructural analysis of myocardial tissue of patient 1. (A) Gross view of the explanted heart: midventricular heart slice showing dilation of both ventricles. The ruler is located at the ventral side. (B) Histopathology of apical heart tissue removed during implantation of the left ventricular assist device. The cardiomyocytes are moderately hypertrophic. Bar = 100 μm. Hematoxylin and eosin stain. (C) In between the cardiomyocytes (*red*) there is mild to moderate interstitial fibrosis (*blue*). Bar =100 μm. Masson trichrome stain. (D) Electron microscopy of cardiomyocyte, showing loss of myofibrils and increased amount of mitochondria. Bar = 2 μm. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

She was diagnosed with CCMP, and heart failure treatment was initiated. The presence of a positive family history (see below) led to the suspicion of a genetic predisposition for dilated cardiomyopathy (DCM) that increased her risk of acquiring CCMP. Next-generation sequencing was performed to analyze 65 cardiomyopathy-associated genes (Supplemental Table S1). This revealed a heterozygous truncating frameshift mutation in *TTN* (NM_133432.3): c.27098del p.(Gly9033fs).

She successfully underwent left ventricular assist device implantation. Unfortunately, in July 2015, a computerized tomographic scan displayed numerous lesions in both liver and lumbar vertebrae, highly suggestive of hepatic and bone metastases. Her clinical condition worsened rapidly, and she died within days. Postmortem analysis confirmed metastatic disease as the cause of death. Further examination of the heart showed dilated ventricles (Fig. 2A) with hypertrophy of cardiomyocytes predominantly in the LV wall (Fig. 2B) and mild to moderate

diffuse interstitial fibrosis (Fig. 2C). An increase of mitochondria and loss of myofibrils was observed with the use of electron microscopy (Fig. 2D).

The mother of the patient developed heart failure symptoms at the age of 55 years and was diagnosed with DCM. A nuclear heart scan exposed an LVEF of 29%. Coronary angiography excluded stenosis in the coronary arteries. Ten months after treatment initiation, she had made a remarkable recovery with an LVEF of 55%. Genetic analysis of the truncating *TTN* variant identified in her daughter revealed that she was heterozygous for this variant as well.

Patient 2

A 49-year-old woman without a documented medical history was diagnosed with a ductal adenocarcinoma (T2N1M0) in February 2007. She received adjuvant radiotherapy (28 × 1.8 Gy with a boost of 13.7 Gy) and chemotherapy consisting

of adriamycin (240 mg/m^2), cyclophosphamide (2400 mg/m^2), paclitaxel (960 mg/m^2), and trastuzumab.

In September 2007, she developed progressive signs of left-sided decompensation. Echocardiography displayed a moderately dilated left ventricle (59 mm) with poor systolic function (LVEF 20%). Trastuzumab was discontinued, and heart failure treatment was initiated. Within 10 months, her LVEF had improved partially to 41%.

During a hospital admission 6 years later, she developed severe left and right decompensation after fluid administration (LVEF 7%, tricuspid annular plane systolic excursion 11 mm) and was referred to our hospital for heart transplant eligibility screening. Subsequently, her clinical condition improved to New York Heart Association functional class II with an LVEF of 23% and normal right ventricular function. MRI 4 months later displayed further improvement (LVEF 34%, RVEF 55%).

Genetic testing revealed a heterozygous truncating frameshift mutation in *TTN* (NM_133432.3): c.56184_56185delinsT p.(Glu18728fs). Her family history was negative for cardiomyopathies and sudden cardiac death.

Discussion

To our knowledge, this is the 1st report of an association between truncating titin variants (*TTN*tv) and CCMP. *TTN*tv are the most frequent identifiable genetic cause of DCM, with detection rates of 25% in familial and 18% in sporadic cases.[8] In addition, these mutations are present in 10% of women with peripartum cardiomyopathy, suggesting that these cardiomyopathies have a shared genetic cause.[9] With our observation that *TTN*tv carriers present with CCMP, we speculate that carriers may have an increased risk of developing cardiac dysfunction after superimposed stress, eg, increased hemodynamic demands during pregnancy or treatment with cardiotoxic chemotherapy. Considering the prevalence of *TTN*tv in the general population (0.5%)[10,11] and the number of women with breast cancer that are treated with cardiotoxic agents worldwide, genetic testing of *TTN* might identify a large group of patients susceptible to CCMP. Interestingly, the 2 *TTN*tv carriers described here had a disproportionately severe CCMP phenotype (LVEF <20%) compared with other patients with cardiotoxicity.[2]

We identified 2 other studies that investigated if a genetic predisposition for DCM could be a risk factor for CCMP. Wasielewski et al[7] sequenced 48 cardiomyopathy-associated genes in 21 patients with CCMP and identified pathogenic mutations in *MYH7* in 2 patients. An *MYH7* mutation was also found in a patient described by Shipman et al.[12]

In conclusion, this case series supports the hypothesis that a genetic predisposition for DCM increases susceptibility for CCMP. Because *TTN*tv are the most common cause of familial and sporadic DCM, further research is needed to establish their prevalence in patients with CCMP. The absence of a positive family history does not exclude an underlying genetic susceptibility. Future studies investigating the prevalence of pathogenic variants in cardiomyopathy-associated genes in a larger cohort of CCMP patients is warranted.

Disclosures

None.

Supplementary Data

Supplementary data related to this article can be found at doi:10.1016/j.cardfail.2017.03.003.

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