Sipuleucel-T Immunotherapy-related Cardiomyopathy: A Novel Observation

Melissa Y.Y. Moey[1] MD MSc, Rahim Jiwani[2] MD, Kotaro Takeda[3] MD, Lauren M. Vaughan[2] MD, Karyn Prenshaw[3] MD, Darla K. Liles[4] MD, Dennis L. Morris[1] MD, Wayne R. Kreeger[1] MD, Constantin B. Marcu[2] MD and Sivakumar Ardhanari[1] MD

[1]Department of Cardiovascular Disease, [2]Department of Internal Medicine and [3]Department of Pathology, [4]Department of Hematology and Oncology at Vidant Medical Center/East Carolina University

INTRODUCTION

Sipulecuel-T (Provenge) is an autologous active cellular immunotherapy containing blood mononuclear cells activated by a recombinant prostatic acid phosphatase (PAP) antigen to granulocyte-macrophage colony-stimulating factor (GMCSF) that is indicated in castration-resistant prostate cancer[1]. Thromboembolic and myocardial infarction events have been reported with sipuleucel-T however are very rare (0.01%)[2]. We describe a case of suspected sipuleucel-T related cardiomyopathy and provide insight into its possible immune-related mechanisms.

CASE PRESENTATION

A 64 year old Caucasian male presented to the emergency department with progressive weakness for several days and orthopnea. He denied chest pain, lightheadedness/dizziness, syncope, dyspnea on exertion, lower extremity edema, unintentional weight gain, nausea, vomiting.

Physical Exam:
- Cardiovascular: JVP at clavicle at 45° angle, irregularly irregular rate and rhythm, no murmurs/gallops/rubs
- Lungs: clear to auscultation bilaterally, no wheezes/crackles/rhonchi
- Extremities: no lower extremity edema

Past Medical History:
- Stage IV castration-resistant prostate adenocarcinoma
  - Xtandi (enzalutamide) – 11/12/2018 to present
  - Taxotere (docetaxel) – 11/20/2018 to 02/07/2019
  - Lupron (leuprolide) – 01/03/2019 to present
  - Xgeva (denosumab) – 05/23/2019 to present
  - Provenge (sipuleucel-T) – 06/10/2019 to 07/22/2019
- Non-ischemic cardiomyopathy (EF of 32% in 06/2019)
- Hypertension, well controlled

Past Surgical History: transurethral resection of the prostate
Past Social History: never smoker or illicit drug use

Medications:
- Carvedilol 3.125 mg BID
- Lisinopril 20 mg QD
- Furosemide 40 mg BID
- Leuprolide Q6 months
- Denosumab Q4 weeks

Labs:

WBC: 7.41k/uL	Na: 139 mEq/L
Hgb: 11.6 g/dL	K: 3.7 mEq/L
Hct: 35.6 %	Cl: 104 mEq/L
Plt: 200 k/uL	HCO3: 24 mEq/L
	BUN: 19 mg/dL
	Cr: 1.03 mg/dL

06/20/19
Received 1st Provenge (Sipuleucel-T) infusion

06/25/19
New-onset HFrEF and NSTEMI (TnI of 0.8 ng/mL)

07/01/19 – 09/20/19
SPEP and UPEP
Fat pad biopsy
Bone marrow biopsy

10/19/19
New-onset AF
Acute decompensated HF

Echocardiogram:
- EF of 35-40%
- Diastolic dysfunction, grade II
- Grade II mitral regurgitation

Cardiac catheterization:
- LM: normal
- LAD: 20% disease
- LCx: 20% disease
- RCA: 20% disease

Cardiac MRI (Figure 2):
- LGE in distal septum and basal inferolateral segment

SPEP and free κ and λ:
- Free κ – 34.2 (3.3-19.4)
- κ:λ ratio – 1.52 (0.26-1.65)

^{99m}Tc-PYP:
- Grade 1 mild uptake
- H:CL ratio 1.2
- Equivocal study

? Cardiac Amyloidosis ?

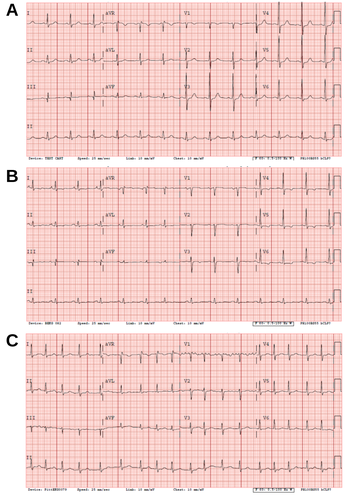

Figure 1. Electrocardiogram at A) baseline, B) June 2019 and C) October 2019

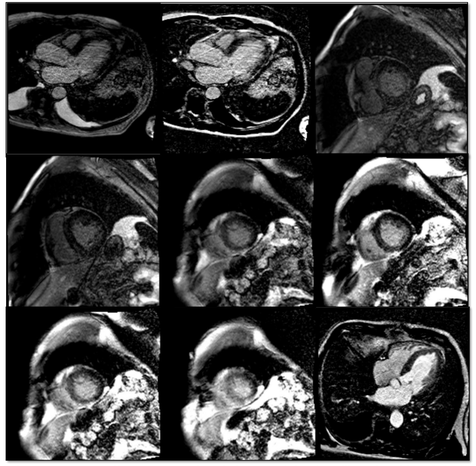

Figure 2. Cardiac MRI. The left ventricle is dilated with global hypokinesis and EF of 32%. Evidence of LGE with a mottled mid wall pattern in the distal septum and basal inferolateral segment (non-ischemic pattern representing myocardial edema or interstitial fibrosis).

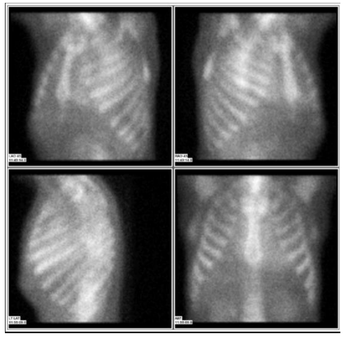

Figure 3. 99mTc-PYP scan for cardiac amyloidosis. Semiquantitative visual scoring showed grade 1 mild uptake activity in the region of the heart with quantitative analysis showing a H/CL ratio of 1.2. This was indicative of an equivocal study with no definitive suggestion for presence of ATTR cardiac amyloidosis.

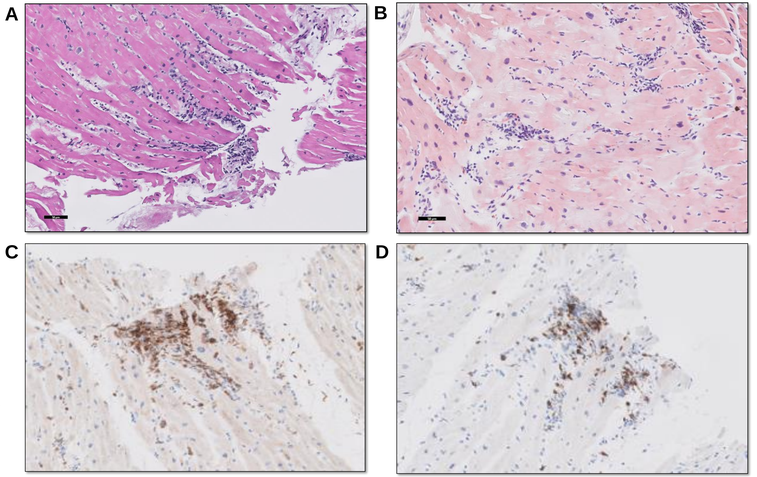

Figure 3. Endomyocardial biopsy. **A)** Right ventricular septum demonstrating myocardium with chronic inflammation. **B)** Endomyocardial biopsy with negative staining on Congo red special stain. **C)** Inflammatory cells demonstrate a mixed pattern strongly staining CD4+ and **D)** CD8+ T cells.

DISCUSSION

- Sipuleucel-T cardiotoxicity is rare with post-marketing analyses demonstrating 0.01% risk of thromboembolic events and myocardial infarction[2].
- Cardiomyopathy observed in our patient may have been a result of an increased immune response secondary to sipuleucel-T as evidenced by chronic inflammation predominant in CD4+ and CD8+ T cells. This may have caused a similar effect seen in autoimmune myocarditis[3] or increased propensity for viral myocarditis[4] leading to cardiomyopathy.
- Limitations to this study include lack of myocardial biopsy and viral testing during the sentinel event in June 2019 and lack of baseline echocardiogram prior to sipuleucel-T
- In summary, close monitoring of cardiotoxicity in patients receiving immunotherapy is warranted and additional studies are needed to evaluate its pathophysiology.

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