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► To cite this version:

Melissa Y.Y. Moey, Rahim A Jiwani, Kotaro Takeda, Karyn Prenshaw, R Wayne Kreeger, et al.. Sipuleucel-T associated inflammatory cardiomyopathy: a case report and observations from a large pharmacovigilance database. ESC Heart Failure, 2021, 10.1002/ehf2.13400 . hal-03217725

HAL Id: hal-03217725







<https://hal.sorbonne-universite.fr/hal-03217725v1>

Submitted on 5 May 2021

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Sipuleucel-T associated inflammatory cardiomyopathy: a case report and observations from a large pharmacovigilance database

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Abstract

Aims The major cardiovascular (CV) adverse effects observed with sipuleucel-T from large multi-institutional clinical trials included thromboembolic events, myocardial infarction, and congestive heart failure in up to 0.3% of patients with CV risk factors. The incidence, outcomes, and mechanisms in real-world clinical settings of these CV adverse effects to date have not been fully elucidated. Our study identified a patient with sipuleucel-T-induced inflammatory cardiomyopathy, which led to the identification of CV adverse effects associated with sipuleucel-T from a large pharmacovigilance database and elucidation of its potential mechanisms.

Methods and results Using the MedDRA term 'cardiac disorders' (System Organ Class level), CV adverse events associated with sipuleucel-T versus all other drugs were reviewed from VigiBase, a large pharmacovigilance database. Disproportionality analysis was calculated by the information component (IC), a Bayesian disproportionality indicator. A positive IC₀₂₅ (IC 95% lower end credibility interval) value (>0) is the traditional threshold used in statistical signal detection at the Uppsala Monitoring Centre. From VigiBase, the total number of CV adverse drug reaction reported with sipuleucel-T was 306 out of a total of 22 980 104 adverse drug reactions in VigiBase on 10/25/2020. MedDRA preferred terms levels were grouped into major CV adverse drug reaction categories where we observed significant reports of myocardial ischaemia, supraventricular tachycardia (particularly atrial fibrillation/atrial flutter), congestive heart failure, and valvular disorders. Myocardial ischemia included acute myocardial infarction (IC₀₂₅ 2.3) with $n = 4/26$ (15%) of these individual case safety reports considered fatal. Among patients with 'cardiac failure congestive' (IC₀₂₅ 1.5), 11 of these 43 cases (26%) were fatal with 42 (98%) of these cases considered to be solely due to sipuleucel-T.

Conclusions Patients with CV risk factors who are receiving sipuleucel-T may be at higher risk for congestive heart failure, myocardial ischemia, and supraventricular tachycardia. Electrocardiograms during weekly sipuleucel-T infusions and left ventricular function monitoring with echocardiogram should be considered in these patients. Our findings are suggestive of another rare presentation of T-cell-mediated CV toxicity with cancer immunotherapy.

Keywords Prostate cancer; Immunotherapy; Sipuleucel-T; Cardiomyopathy; Cardiotoxicity; Cardio-oncology

Received: 18 August 2020; Revised: 25 February 2021; Accepted: 22 April 2021

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Background

Sipuleucel-T, marketed as Provenge[®], is an autologous cellular immunological agent¹ indicated in the treatment of metastatic castration-resistant prostate cancer (mCRPC).² Cardiovascular (CV) toxicities with sipuleucel-T are uncommon (0.3%).³ We report the first case of sipuleucel-T-induced inflammatory cardiomyopathy and describe the potential mechanisms. Through review of an international pharmacovigilance database, VigiBase, we also identified increased reporting of sipuleucel-T-associated CV toxicities.

Aims

In this study, we aimed to elucidate the mechanisms of sipuleucel-T-associated cardiomyopathy and to identify CV adverse effects associated with sipuleucel-T in the real world from VigiBase, the World Health Organization pharmacovigilance database.

Clinical case

A 64-year-old Caucasian male with well-controlled hypertension managed with lisinopril 10 mg daily was diagnosed with mCRPC in 2018. He received two doses of subcutaneous degarelix and underwent subsequent transurethral resection of his prostate followed by 6 cycles of docetaxel 75 mg/m² every 3 weeks along with pegfilgrastim completed 5 months later. He was initiated on enzalutamide 160 mg daily and quarterly intramuscular injections of leuprolide 40 mg shortly after. He had no complications with chemotherapy or hormonal treatment and had significant improvement with prostate-specific antigen (PSA) < 0.1 ng/mL on subsequent follow-up (*Figure 1*).

On 6 months of follow-up, he was started on sipuleucel-T every 2 weeks for a total of three infusions. Twenty-four hours after his second infusion of sipuleucel-T, he presented with dyspnea and chest pressure. On physical examination, he was afebrile, blood pressure of 145/82 mmHg, and heart rate of 74 b.p.m. with an oxygen saturation of 98% on room air. He had bilateral basilar rales, jugular venous pulse noted to be at least 8 cm with a positive hepatojugular reflex, and a grade 2/6 pansystolic murmur in the apical region without any radiation. He was warm without any lower extremity edema. Electrocardiogram showed new non-specific intraventricular conduction delay and non-specific T wave changes in V4 to V6. Troponin I peaked at 0.80 ng/mL (normal <0.03 ng/mL). Brain natriuretic peptide was 1062 pg/mL (normal <200 pg/mL).

A transthoracic echocardiogram revealed a left ventricular ejection fraction (LVEF) of 36%, grade II diastolic

dysfunction, grade II mitral regurgitation due to dilated annulus, and mild aortic regurgitation. He received intravenous furosemide 40 mg daily with improvement in symptoms. Left heart catheterization showed 20% non-obstructive disease in the left anterior descending artery, left circumflex, and right coronary artery. Cardiac magnetic resonance imaging (cMRI) showed biatrial enlargement, moderate mitral regurgitation, and a dilated left ventricular with increased myocardial mass index (116 g/m², normal range: 42–85 g/m²) and global hypokinesis with an left ventricular ejection fraction (LVEF) of 32%. There was evidence of late gadolinium enhancement with a mottled mid-wall pattern in the distal septum and the basal inferolateral segment, which was suggestive of a non-ischemic cardiomyopathy representing myocardial edema or interstitial fibrosis suspicious for chemotherapy-related cardiomyopathy or infiltrative cardiomyopathy from amyloidosis (*Figure 2*).

The patient was discharged with a LifeVest and guideline-directed medical therapy for heart failure (HF) with reduced ejection fraction, which included carvedilol 3.125 mg twice a day and lisinopril 20 mg daily with follow-up in the Cardio-Oncology clinic. The patient received his last sipuleucel-T infusion 4 weeks after discharge. During this time, given the concern for cardiac amyloidosis based on cMRI, he was worked up as an outpatient with negative fat pad biopsy, bone marrow biopsy, and urine protein electrophoresis. Serum protein electrophoresis showed elevated serum kappa light chains however with normal kappa to lambda ratio. A nuclear study based on transthyretin protein protocol performed was equivocal for cardiac amyloidosis. He presented 4 months later with a 2 week history of orthopnea found to have new-onset atrial fibrillation and in acute decompensated HF.

An endomyocardial biopsy (EMB) was subsequently performed due to recurrent HF admission and concern for amyloidosis. The EMB showed several foci of predominant lymphocytic inflammation (*Figure 3*). Given possible immunotherapy-related myocarditis as observed with immune checkpoint inhibitors (ICIs),⁴ specific staining for T-cell subtypes CD4⁺ and CD8⁺ was obtained in addition to a non-standard of care stain for programmed cell death ligand-1 (PD-L1), which is overexpressed in ICI-related myocarditis.⁴ Cardiac amyloidosis was also evaluated with Congo red. Haematoxylin and eosin staining showed several foci of mature lymphocytic infiltration (*Figure 3A and 3B*) that were positive for both CD4⁺ and CD8⁺ (*Figure 3D–3F*). PD-L1 was not detected (*Figure 3F*). Congo red was negative (*Figure 3C*). He was discharged on carvedilol 6.125 mg twice a day, lisinopril 20 mg daily, furosemide 20 mg daily, and apixaban 5 mg twice a day. He did not have any recurrent hospitalizations. A repeat echocardiogram 1 month later showed persistent LVEF depression with an improvement to 45–50% at 6 months of follow-up.

Figure 1 Timeline of patient diagnosis and treatment of metastatic castration-resistant prostate cancer (mCRPC) and hospitalizations. Our patient was diagnosed with stage IVB prostate cancer in fall of 2018. He was subsequently started on degarelix, which was eventually discontinued due to side effects. He received 6 cycles of docetaxel and started on enzalutamide along with leuprolide. The patient eventually received sipuleucel-T 8 months following his initial diagnosis for mCRPC. Twenty-four hours following his second infusion of sipuleucel-T, he presented to the emergency department with new onset systolic dysfunction (Hospital Admission #1). He underwent coronary angiogram, which did not show obstructive disease. Cardiac magnetic resonance imaging showed late gadolinium enhancement suggestive of an infiltrative disorder. As an outpatient, he was worked up for amyloidosis, which was negative. He was discharged on lisinopril and carvedilol but presented 3 months later with recurrent symptoms and new onset atrial fibrillation (Hospital Admission #2). A myocardial biopsy was obtained during his second admission, which showed chronic myocardial inflammation. The patient was treated medically with lisinopril and carvedilol and continues to tolerate enzalutamide, leuprolide, and denosumab without any recurrent hospitalizations. ADHF, acute decompensated heart failure; AF, atrial fibrillation; HFrEF, heart failure with reduced ejection fraction; NSTEMI, non-ST elevation myocardial infarction; Q3w, every 3 weeks; Q6 mo, every 6 months; Qd, every day/daily; SPEP, serum protein electrophoresis; SQ, subcutaneous; UPEP, urine protein electrophoresis.

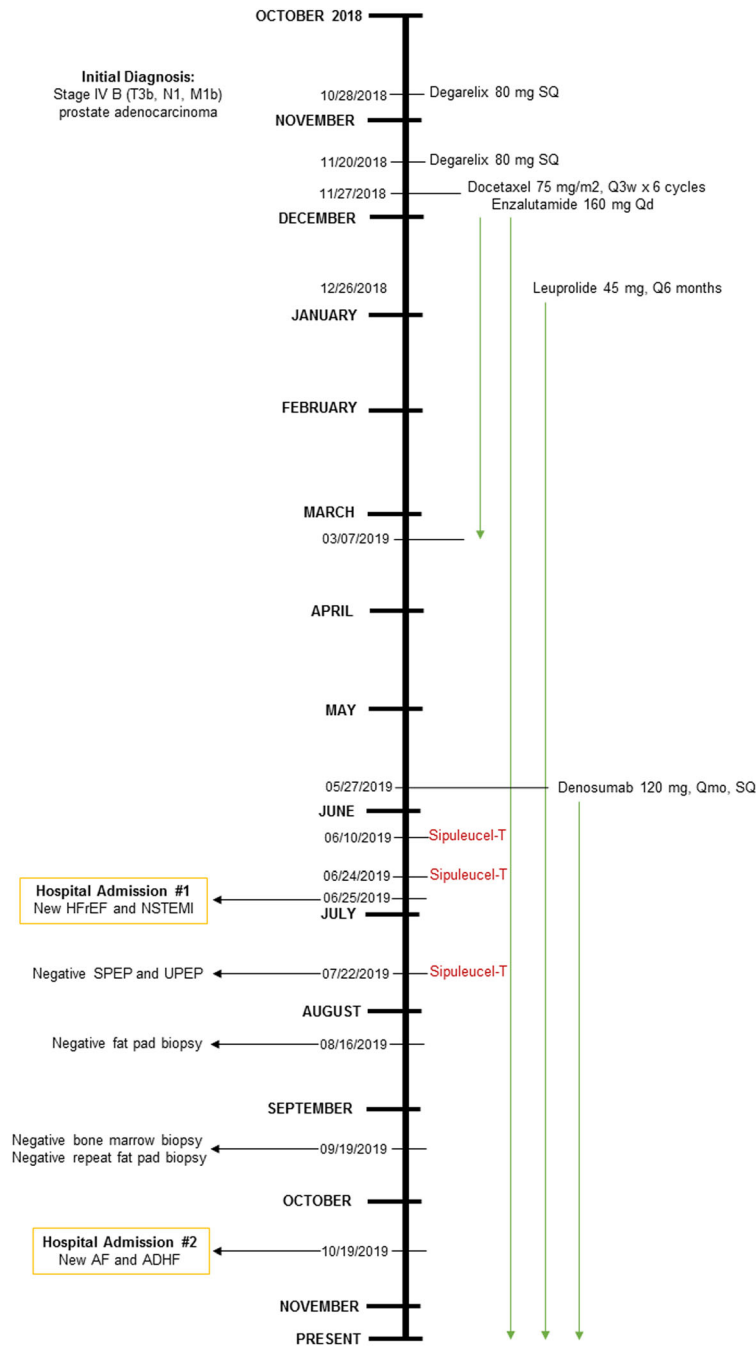
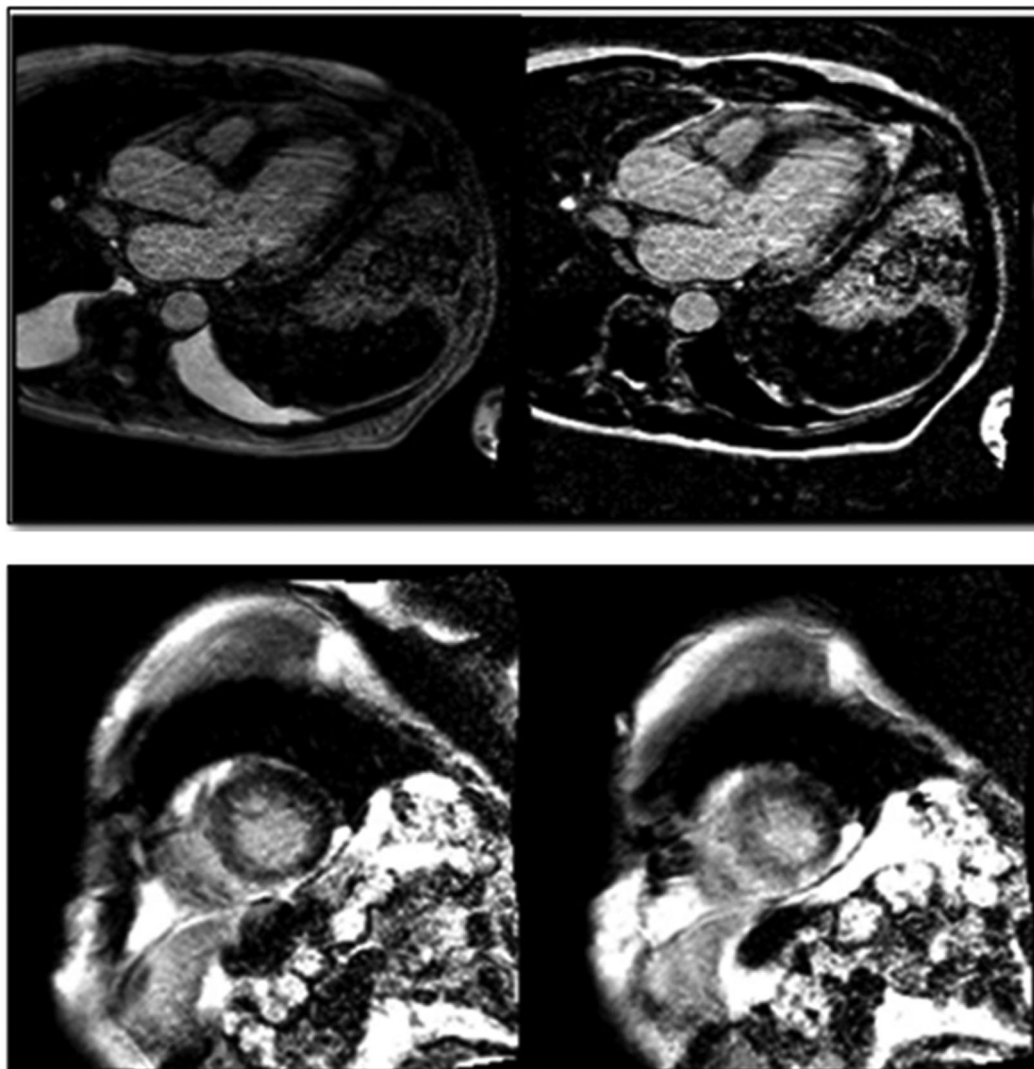


Figure 2 Cardiac magnetic resonance imaging. (A) Three-chamber view. Left panel (magnitude) and right (phase sensitive inversion recovery late gadolinium contrast) study demonstrating increased signal intensity in the inferolateral and distal septal regions. (B) Short-axis view. There is mottled increased signal intensity on phase sensitive inversion recovery sequence in the distal septal area.

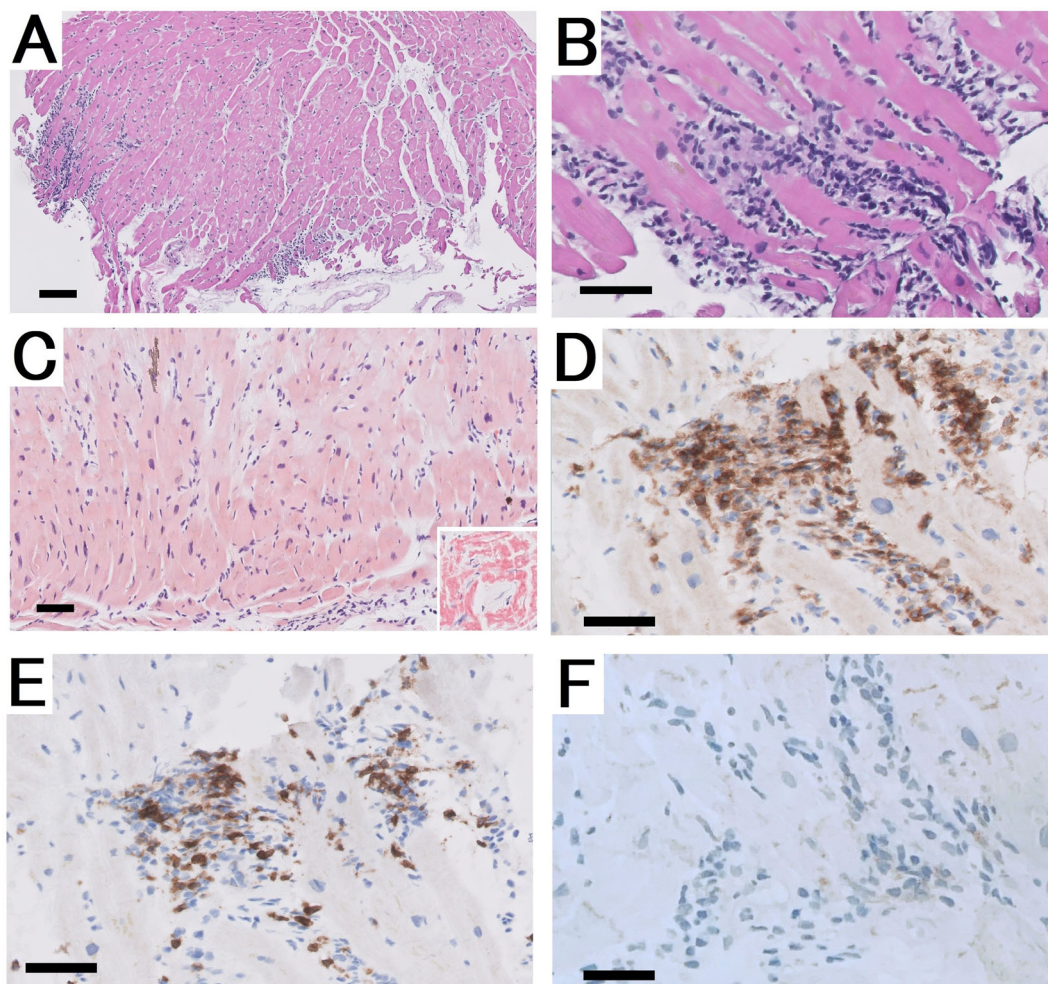


Methods

We searched for adverse drug reactions (ADRs) reported in VigiBase (*NCT03530215*), the World Health Organization database containing individual case safety reports from more than 130 countries since 1967.⁵ VigiBase is managed by the Uppsala Monitoring Centre (Uppsala, Sweden). The use of confidential, electronically processed patient data was approved by the French National Commission for Data Protection and Liberties (Commission Nationale de l'Informatique et des Libertés; reference number 1922081). Using the MedDRA term 'cardiac disorders' (System Organ

Class level), we searched for CV adverse events associated with sipuleucel-T versus all other drugs in the database. Disproportionality analysis was calculated by the information component (IC), a Bayesian disproportionality indicator, which has been previously described.⁶ A positive IC_{025} (IC 95% lower end credibility interval) value (>0) is the traditional threshold used in statistical signal detection at the Uppsala Monitoring Centre. To identify the co-occurrence of relevant CV-ADR associated with sipuleucel-T ($IC_{025} > 0$), individual extracted cases were reviewed and the UpSet technique⁷ was used to visualize set intersections.

Figure 3 Endomyocardial biopsy of the right ventricular septum. (A) Haematoxylin and eosin staining of myocardium (low magnification) showing several foci of lymphocyte infiltration. Scale bar, 100 μ m. (B) Haematoxylin and eosin staining (high magnification) showing small mature lymphocytes infiltrating in the interstitial area. Scale bar, 50 μ m. (C) Congo red staining showing no amyloid deposition. Inset: positive control. Scale bar, 50 μ m. (D–F) Immunohistochemistry for CD4 (D), CD8 (E), and programmed cell death ligand-1 (F). Infiltrating lymphocytes are positive for CD4 or CD8, and negative for programmed cell death ligand-1. Scale bar, 50 μ m.



Results

The total number of CV-ADR reported with sipuleucel-T versus all other drugs was 306 and 22 980 104, respectively, on 10/25/2020. There were 18 MedDRA terms of 'cardiac disorders' associated with sipuleucel-T (positive $IC_{025} > 0$) (Table 1). MedDRA preferred terms levels were grouped into major CV-ADR categories where there were significant reports of myocardial ischemia, supraventricular tachycardias (SVTs) (atrial fibrillation/atrial flutter), congestive HF (CHF), and valvular disorders. All of these CV-ADRs were considered severe. Myocardial ischemia included acute myocardial infarction ($IC_{025} = 2.3$) with $n = 4/26$ (15%) of these individual case safety reports considered fatal. Among patients with 'cardiac failure congestive' ($IC_{025} = 1.4$), 11 of these 43 cases (26%) were fatal with 42 (98%) of these cases suspected to be

solely due to sipuleucel-T. Other CV-ADRs were not significantly associated with sipuleucel-T (Table 1). Among the major CV-ADR categories, these occurred independently with minimal overlap among each major CV-ADR category. Myocardial ischemia occurred independently in 84.4% ($n = 65/77$) of all cases, SVT 77.2% ($n = 44/57$), CHF 75% ($n = 36/48$), and valvular disorders 62.5% ($n = 5/8$). SVT was rarely associated with CHF ($n = 6/48$, 12.5%) and myocardial infarction ($n = 6/77$, 7.79%) (Figure 4).

Discussion

We describe the first reported phenomenon of a T-cell-mediated sipuleucel-T-induced cardiomyopathy. This is further corroborated by our pharmacovigilance analysis that

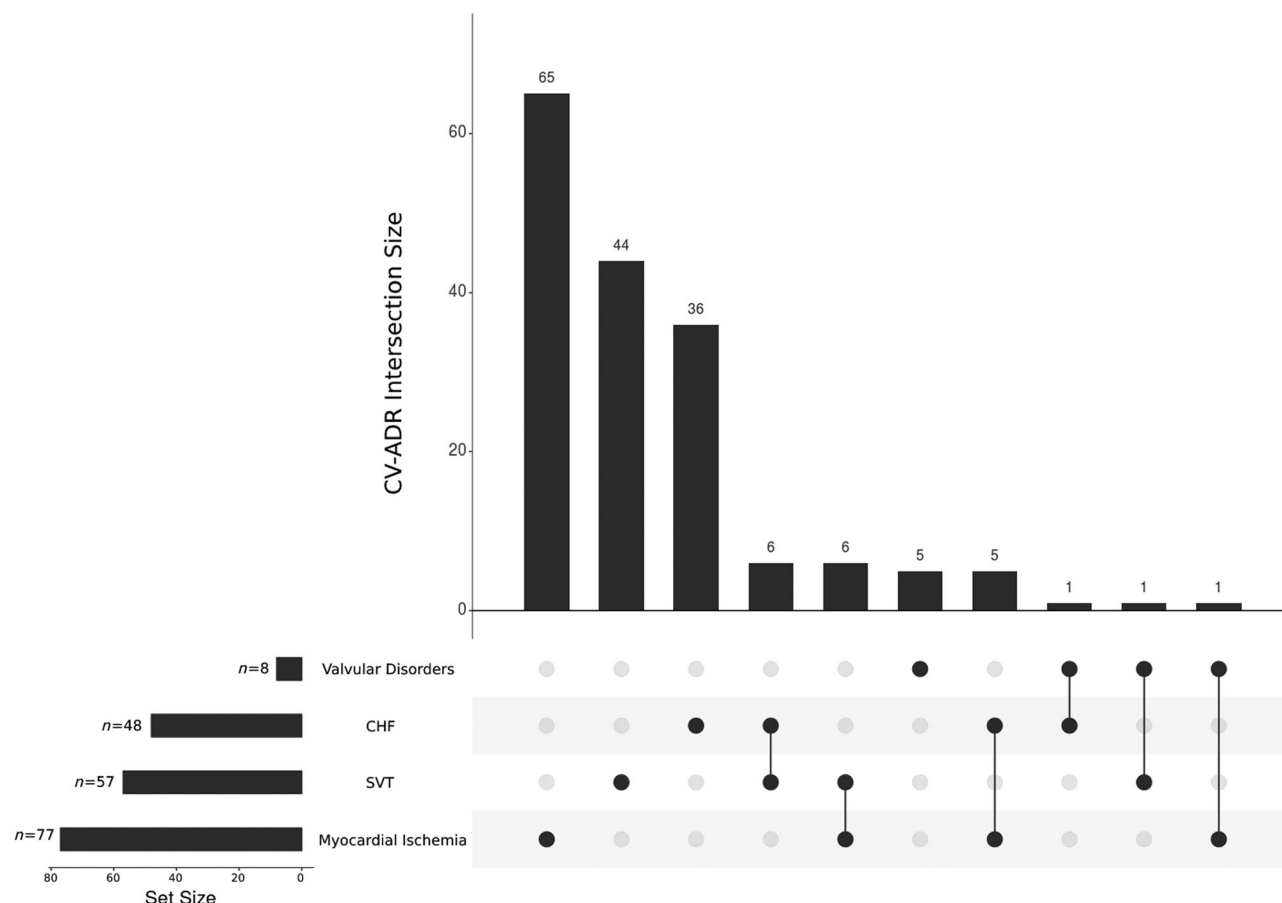
Table 1 Cardiovascular adverse events (detected as individual case safety reports) reported with sipuleucel-T in comparison with the full VigiBase database on 10/25/2020

Cardiac adverse event	MedDRA preferred term level	ICSR with sipuleucel-T ($n_{total} = 3943$)	ICSR in full database ($n = 22\ 980\ 104$)	IC ($IC_{0.25}$)	Serious adverse events	Fatal events	Suspected due to sipuleucel-T only
Myocardial ischaemia	Acute myocardial infarction	26	17 700	2.9 (2.3)	26	4	23
	Coronary artery occlusion	8	9723	2.0 (0.8)	8	2	7
	Myocardial infarction	42	143 746	0.8 (0.3)	42	13	42
Supraventricular tachycardia	Coronary artery disease	10	25 890	1.1 (0.1)	10	0	9
	Atrial fibrillation	49	60 507	2.2 (1.8)	48	10	41
	Atrial flutter	6	5136	2.2 (0.9)	6	1	5
Congestive heart failure	Cardiac failure congestive	43	67 656	1.8 (1.4)	43	11	42
	Dilatation ventricular	4	1161	2.7 (0.9)	4	1	3
	Diastolic dysfunction	4	1531	2.6 (0.8)	4	0	3
Valvular disorders	Tricuspid valve incompetence	5	5017	2.0 (0.5)	5	1	5
	Mitral valve incompetence	6	9522	1.6 (0.2)	6	1	4
Miscellaneous	Extrasystoles	7	8639	1.9 (0.7)	6	0	5
	Tachycardia	50	137 211	1.1 (0.6)	36	4	44
	Ventricular extrasystoles	6	7010	1.9 (0.6)	6	1	6
	Left ventricular hypertrophy	4	2659	2.2 (0.5)	4	1	4
	Cardiac disorder	20	55 766	1.0 (0.3)	9	4	20
	Cardiomegaly	6	8828	1.7 (0.3)	6	0	4
	Sinus tachycardia	6	9899	1.6 (0.2)	6	1	4

IC, information component; ICSR, individual case safety report.

An $IC_{0.25} > 0$ (information component 95% credibility interval lower end) is considered significant.

Figure 4 Intersection of major cardiovascular adverse drug reaction (CV-ADR) categories associated with sipuleucel-T. Myocardial ischemia occurred independently 84.4% ($n = 65/77$) of all cases, supraventricular tachycardia (SVT) 77.2% ($n = 44/57$), congestive heart failure (CHF) 75% ($n = 36/48$), and valvular disorders 62.5% ($n = 5/8$). SVT was rarely associated with CHF ($n = 6/48$, 12.5%) and myocardial infarction ($n = 6/77$, 7.79%).



revealed an over-reporting of CHF with sipuleucel-T with ~15% fatality.

Although CV toxicities from sipuleucel-T were uncommon among clinical trials,³ we demonstrate through VigiBase that there was significant over-reporting of myocardial ischemia, SVT, and CHF with sipuleucel-T versus all other drugs. While reports from VigiBase are non-homogeneous with the inability to definitively verify the cases with clinical, laboratory, or radiological tests, we suspect that these CV-ADRs may have been one of the manifestations of an inflammatory-mediated cardiomyopathy.⁸ Our observation of lymphocytic inflammation on myocardial biopsy suggests that sipuleucel-T invoked an inflammatory cascade that resulted in a T-cell-mediated cardiomyopathy with similar features to observed cases of immune-related CV toxicities such as with influenza vaccination^{9,10} and ICIs.⁴

In fact, preclinical production studies of sipuleucel-T demonstrated an immune priming response followed by immune boosting with subsequent infusions, similar to classic vaccine-mediated cellular and humoral responses.¹¹

Antigen-presenting cells, detected by CD54, were significantly up-regulated after the first dose with the most robust response at week 4, along with antigen-presenting cell activation-associated cytokines, which is followed by T-cell activation-associated cytokines in the second and third infusion preparations.¹¹ Particularly, from peripheral blood samples obtained from patients receiving sipuleucel-T, both T-cell helper 1 (interferon and tumour necrosis factor- α) and 2 [interleukin (IL)-5 and IL-13]-specific cytokines were elevated, supporting the mechanism of sipuleucel-T-mediated cellular and humoral responses. Acting in concert with interferon and tumour necrosis factor- α , an increase in IL-17 levels was also observed, which has been implicated in the pathophysiology of autoimmune diseases.¹² Specific responses measured by anti-PA2024 and anti-PAP antibody titres were sustained at least until week 26.¹¹ This may have resulted in cytokine cascade,^{9,10} which resulted in T-cell recruitment and myocardial injury in our patient.

Unique to our case was the observation of CD4⁺ and CD8⁺ T cells within focal inflammatory areas on myocardial biopsy.

Notably, sipuleucel-T increases the frequency of CD4⁺ and CD8⁺ T cells within prostate tissue 2 to 3 weeks after treatment, particularly at the tumour margin.¹³ Whether sipuleucel-T may induce a generalized inflammatory response that can affect additional organs has not yet been reported in preclinical sipuleucel-T-treated animal models.¹³ These pre-clinical findings of an increased immune response at week 2 with the most robust response at week 4 are consistent with the timeline to development of our patient's inflammatory cardiomyopathy, further corroborating the high likelihood of sipuleucel-T exposure as the suspected cause.

We did not observe an increased expression of PD-L1 in the myocardium as previously demonstrated in ICI-related myocarditis.⁴ This is likely due to a variation in the mechanism of action whereby ICI exhibits a generalized immune blockade whereas sipuleucel-T induces a destruction specific to prostate cancer cells. However, the phenomenon of 'antigen spread' with sipuleucel-T where additional prostate cancer-associated tumour antigens involved in PSA processing and oncologic downstream signalling were targeted has also been observed.¹⁴ We suspect that cross-reactivity and/or shared antigen recognition within the myocardium by sipuleucel-T is likely low, however possible in pro-inflammatory environments such as patients with CV risk factors.¹⁵

Our patient had LVEF recovery within 6 months on guideline-directed medical therapy only. This suggests that the immune-mediated mechanisms were likely transient, with reversion to a balanced non-inflammatory environment following completion of sipuleucel-T treatment. Nonetheless, our patient experienced a severe reaction reflecting our pharmacovigilance results in which approximately 15% of patients with sipuleucel-T-associated CHF associated suffered fatal outcomes. While our patient was concomitantly receiving androgen-deprivation therapy (ADT) with enzalutamide and leuprolide, the likelihood of ADT resulting in cardiomyopathy was low in the differential. Cardiotoxicities reported with ADT include cardiometabolic disturbances (hypertension, hyperglycemia, and hyperlipidemia) and risk of arrhythmias from prolonged QTc¹⁶ and are generally not associated risk of HF; in clinical trials, HF was reported to be <1%.^{17,18} Docetaxel has also not been associated with HF despite prolonged use.¹⁹ Our patient tolerated ADT and docetaxel for several months but developed acute onset of symptoms with sipuleucel-T, correlating with the timeline of the immune modulating mechanism of sipuleucel-T and potential crosstalk between pathways making sipuleucel-T the most plausible culprit of our patient's inflammatory cardiomyopathy.

In comparison with the familiarity of cardiotoxicities associated with anthracyclines and anti-human epidermal growth factor receptor (HER2) therapy, prostate cancer therapy-induced cardiac adverse events are underrecognized. There have been concerns regarding adequate reporting and potential under recognition of adverse cardiac events with

prostate cancer therapies as the studies were not designed to detect cardiotoxicities.²⁰ Therefore, we encourage consideration of monitoring in patients with CV risk factors with serial electrocardiograms during weekly infusions and obtaining a baseline echocardiogram in patients receiving sipuleucel-T. Additional studies investigating the complex immune-mediated mechanisms in patients receiving immunotherapy and optimal management to avoid off-target organ inflammation without affecting the salutary effects of immunotherapy are highly warranted.

Limitations

Our study is not without limitations. As there are no current guidelines regarding obtaining baseline cardiac diagnostic testing prior to initiation of prostate cancer treatment, our patient did not have a baseline echocardiogram for comparison. The patient did not have any cardiac symptoms or complaints that would have suggested baseline systolic or valvular dysfunction; therefore, it is assumed that his baseline cardiac function was normal prior to and during his non-immunotherapy treatment for mCRPC. Another limitation of our study was the lack of viral genome data from EMB. The patient did not have any viral or infectious symptoms at the time of his admission in addition to negative blood cultures and respiratory viral panel; an infectious or viral-associated cardiomyopathy was very low in the differential. In addition, limitations with VigiBase reporting are voluntary, and thus, not all data fields are included in every report, and quality might be variable.

Acknowledgements

The supplied data from VigiBase® come from various sources. The likelihood of a causal relationship is not the same in all reports. The information does not represent the opinion of the World Health Organization.

Conflict of interest

None declared.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Supporting Information.

Figure S2. Supporting Information.

References

- Cheever M, Higano C. PROVENGE (sipuleucel-T) in prostate cancer: the first FDA-approved therapeutic cancer vaccine. *Clin Cancer Res* 2011; **17**: 3520–3526.
- Kantoff PW, Higano CS, Shore ND, Berger ER, Small EJ, Penson DF, Redfern CH, Ferrari AC, Dreicer R, Sims RB, Xu Y, Frohlich MW, Schellhammer PF. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N Engl J Med* 2010; **363**: 411–422.
- Higano CS, Armstrong AJ, Sartor AO, Vogelzang NJ, Kantoff PW, McLeod DG, Pieczonka CM, Penson DF, Shore ND, Vacirca J, Concepcion RS, Tutrone RF, Nordquist LT, Quinn DI, Kassabian V, Scholz MC, Harmon M, Tyler RC, Chang NN, Tang H, Cooperberg MR. Real-world outcomes of sipuleucel-T treatment in PROCEED, a prospective registry of men with metastatic castration-resistant prostate cancer. *Cancer* 2019; **125**: 4172–4180.
- Johnson DB, Balko JM, Compton ML, Chalkias S, Gorham J, Xu Y, Hicks M, Puzanov I, Alexander MR, Bloomer TL, Becker JR, Slosky DA, Phillips EJ, Pilkinton MA, Craig-Owens L, Kola N, Plautz G, Reshef DS, Deutsch JS, Deering RP, Olenchock BA, Lichtman AH, Roden DM, Seidman CE, Koralnik IJ, Seidman JG, Hoffman RD, Taube JM, Diaz LA Jr, Anders RA, Sosman JA, Moslehi JJ. Fulminant myocarditis with combination immune checkpoint blockade. *N Engl J Med* 2016; **375**: 1749–1755.
- Lindquist M. VigiBase, the WHO global ICSR database system: basic facts. *Drug Inf J* 2008; **42**: 409–419.
- Salem JE, Manouchehri A, Moey M, Lebrun-Vignes B, Bastarache L, Pariente A, Gobert A, Spano JP, Balko JM, Bonaca MP, Roden DM, Johnson DB, Moslehi JJ. Cardiovascular toxicities associated with immune checkpoint inhibitors: an observational, retrospective, pharmacovigilance study. *Lancet Oncol* 2018; **19**: 1579–1589.
- Lex A, Gehlenborg N, Strobel H, Vuilleumot R, Pfister H. UpSet: visualization of intersecting sets. *IEEE Trans Vis Comput Graph* 2014; **20**: 1983–1992.
- Lyon AR, Yousaf N, Battisti NML, Moslehi J, Larkin J. Immune checkpoint inhibitors and cardiovascular toxicity. *Lancet Oncol* 2018; **19**: e447–e458.
- Saraiya N, Singh S, Corpuz M. Fatal influenza myocarditis with incessant ventricular tachycardia. *BMJ Case Rep CP* 2019; **12**: e228201.
- Kim YJ, Bae JI, Ryoo SM, Kim WY. Acute fulminant myocarditis following influenza vaccination requiring extracorporeal membrane oxygenation. *Acute Crit Care* 2019; **34**: 165–169.
- Sheikh NA, Petrylak D, Kantoff PW, dela Rosa C, Stewart FP, Kuan LY, Whitmore JB, Trager JB, Poehlein CH, Frohlich MW, Urdal DL. Sipuleucel-T immune parameters correlate with survival: an analysis of the randomized phase 3 clinical trials in men with castration-resistant prostate cancer. *Cancer Immunol Immunother* 2013; **62**: 137–147.
- Kuwabara T, Ishikawa F, Kondo M, Kakiuchi T. The role of IL-17 and related cytokines in inflammatory autoimmune diseases. *Mediators Inflamm* 2017; **2017**: 3908061.
- Laus R, Yang DM, Ruegg CL, Shapero MH, Slagle PH, Small EJ, Burch P, Valone FH. Dendritic cell immunotherapy of prostate cancer: preclinical models and early clinical experience. *Cancer Res Ther Control* 2001; **11**: 1–10.
- GuhaThakurta D, Sheikh NA, Fan LQ, Kandadi H, Meagher TC, Hall SJ, Kantoff PW, Higano CS, Small EJ, Gardner TA, Bailey K, Vu T, DeVries T, Whitmore JB, Frohlich MW, Trager JB, Drake CG. Humoral immune response against nontargeted tumor antigens after treatment with sipuleucel-T and its association with improved clinical outcome. *Clin Cancer Res* 2015; **21**: 3619–3630.
- Willerson JT, Ridker PM. Inflammation as a cardiovascular risk factor. *Circulation* 2004; **109**: II2–II10.
- Salem JE, Yang T, Moslehi JJ, Waintraub X, Gandjbakhch E, Bachelot A, Hidden-Lucet F, Hulot JS, Knollmann BC, Lebrun-Vignes B, Funck-Brentano C, Glazer AM, Roden DM. Androgenic effects on ventricular repolarization: a translational study from the international pharmacovigilance database to iPSC-cardiomyocytes. *Circulation* 2019; **140**: 1070–1080.
- Scher HI, Fizazi K, Saad F, Taplin ME, Sternberg CN, Miller K, de Wit R, Mulders P, Chi KN, Shore ND, Armstrong AJ, Flaig TW, Fléchon A, Mainwaring P, Fleming M, Hainsworth JD, Hirmand M, Selby B, Seely L, de Bono JS. Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med* 2012; **367**: 1187–1197.
- Beer TM, Armstrong AJ, Rathkopf DE, Loriot Y, Sternberg CN, Higano CS, Iversen P, Bhattacharya S, Carles J, Chowdhury S, Davis ID. Enzalutamide in metastatic prostate cancer before chemotherapy. *N Engl J Med* 2014; **371**: 424–433.
- Zamorano JL, Lancellotti P, Rodriguez Muñoz D, Aboyans V, Asteggiano R, Galderisi M, Habib G, Lenihan DJ, Lip GYH, Lyon AR, Fernandez TL, Mohty D, Piepoli MF, Tamargo J, Torbicki A, Suter TM, ESC Scientific Document Group. 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: the Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). *Eur Heart J* 2016; **37**: 2768–2801.
- Witteles RM, Telli M. Underestimating cardiac toxicity in cancer trials: lessons learned? *J Clin Oncol* 2012; **30**: 1916–1918.