Targeted Cancer Therapies With Pericardial Effusions Requiring Pericardiocentesis Focusing on Immune Checkpoint Inhibitors

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Case reports have reported immune checkpoint inhibitors (ICI), especially nivolumab, are associated with recurrent pericardial effusions. Our objective was to determine how often patients being treated with ICI develop hemodynamically significant pericardial effusion requiring pericardiocentesis compared with other cancer therapeutics and whether the survival of patients who underwent pericardiocentesis differs according to ICI use versus standard cancer therapeutics. Our institutional review board approved catheterization laboratory data collection for all pericardiocenteses performed and all patients receiving ICI from January 1, 2015 to December 31, 2017. Retrospective review of the electronic medical record was performed to identify cancer therapeutics given preceding pericardiocentesis. Log-rank analysis was performed to compare survival in patients requiring pericardiocentesis between those on ICI and those not on ICI. Overall, 3,966 patients received ICI of which only 15 pericardiocenteses were required, including 1 repeat pericardiocentesis in a patient on nivolumab. The prevalence of pericardiocentesis among patients on ICI was 0.38% (15/3,966). Eleven pericardiocenteses were performed after nivolumab infusion, 3 after pembrolizumab, and 1 after atezolizumab, with pericardiocentesis prevalences for each agent of 0.61% (11/1,798), 0.19% (3/1,560), and 0.32% (1/309), respectively. One hundred and twenty pericardiocentesis were performed on patients receiving other cancer therapeutics although no therapeutic agent was associated with more pericardiocenteses than nivolumab. In conclusion, the prevalence of hemodynamically significant pericardial effusions and ICI administration is uncommon, and survival durations after pericardiocentesis for patients receiving ICI and those not receiving ICI are similar, suggesting that frequent echocardiographic monitoring for pericardial effusions is not necessary. **(Am J Cardiol 2019;123:1351−1357)**

Pericardial effusions and their association with cancer are well described. Large pericardial effusions are often associated with neoplastic disease, and the presence of these effusions portends a worse prognosis.[1,2] There are 6 recently developed immune checkpoint inhibitors (ICI) that have been the Food and Drug Administration approved; nivolumab, pembrolizumab, atezolizumab, avelumab, ipilimumab, and durvalumab. These drugs inhibit negative feedback mechanisms on T cells such as programmed cell death protein 1 (PD-1), programmed cell death ligand 1, and cytotoxic T lymphocyte-associated protein 4. By inhibiting these pathways, ICI allow T cells to recognize and kill tumor cells. However, this success can sometimes be accompanied by severe immune-related adverse events, including a spectrum of cardiovascular events; arrhythmias, myocarditis, pericarditis, and pericardial effusion.[3−7] There have also been limited case reports and case series of nivolumab, a PD-1 inhibitor, and ipilimumab, a cytotoxic T lymphocyte-associated protein 4 inhibitor, causing pericardial effusions and, at times, cardiac tamponade.[4−10] The clinical significance of these immune-related adverse cardiac events is unknown. More importantly, the true incidence and association of pericardial diseases after cancer drug therapy is hard to prove. The primary objective of this study was to determine how often patients receiving ICI-developed hemodynamically significant pericardial effusions requiring pericardiocentesis and to determine whether survival in patients who underwent pericardiocentesis differed according to treatment with ICI versus non-ICI therapy.

Methods

All patients who had pericardiocentesis and all patients receiving any of the 6 US Food and Drug Administration-approved ICI during January 1, 2015, through December 31, 2017, were retrospectively identified through an Institutional Review Board-approved protocol at The University

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of Texas MD Anderson Cancer Center in Houston, Texas. The need for written informed consent was waived. Pericardiocentesis was performed in patients with clinical signs of cardiac tamponade and large pericardial effusions with echocardiographic evidence of increased pericardial pressures.[11–14] Echocardiographic parameters assessed for tamponade included right ventricular diastolic collapse, right atrial diastolic collapse, inferior vena cava size and collapsibility, and respiratory variation of mitral and tricuspid inflow velocities.[12–14]

The electronic medical records of all patients who had pericardiocentesis were manually reviewed. Data collected included age, gender, cancer diagnosis, cancer therapeutics received before pericardiocentesis, and pericardial fluid analysis (including cultures, gram stain, white blood cell count with differential, red blood cells, and cytology analysis). Survival time in days after pericardiocentesis was recorded. Survival was defined as days after pericardiocentesis until death. Standard descriptive statistics (mean and standard deviation or frequency and percentage) were used to describe baseline patient characteristics.

The cohort of patients who had pericardiocentesis was then split into patients who received ICI and those who did not. Of note, at our institution all patients have some form of cancer therefore all those requiring pericardiocentesis had active malignancy. The total number of patients receiving both ICI and non-ICI was able to be obtained through a query in our electronic medical record. Separate descriptive statistics were obtained for each group. Kaplan-Meier survival comparisons between these 2 groups were performed using the log-rank (i.e., Mantel-Cox) method using IBM SPSS version 24 statistical software. Statistical significance was defined as p value <0.05. In the survival analysis, 47 patients were censored, 43 from the non-ICI cohort, and 4 from the ICI cohort.

Results

A total of 3,966 patients received ICI, 82,517 patients received a cancer therapeutic other than ICI, and a total of 135 pericardiocentesis procedures were performed during the study period. The 135 pericardiocenteses were performed in 122 patients, of whom 13 patients had a second pericardiocentesis for recurrent pericardial tamponade (Table 1). Of the 122 patients who had pericardiocentesis, the majority were male and white (Table 1). The most common underlying malignancies were lung cancer followed by leukemia, breast cancer, and lymphoma (Table 1). The baseline characteristics of the patients who underwent pericardiocentesis after receiving ICI and those who underwent pericardiocentesis without receiving ICI were similar (Table 1); the only substantial difference was that most of those patients receiving ICI (57%) had an underlying lung cancer, whereas only 19% of patients in the cohort without ICI had lung cancer.

Of the 3,966 patients on ICI, 14 required pericardiocentesis (Table 2) of which 1 patient received 2 pericardiocenteses whereas on nivolumab. The overall rate of hemodynamically significant pericardial effusion in the 3,966 patients receiving ICI was 0.38% (Table 3). Of note, 11 pericardiocenteses were performed during nivolumab therapy, 3 were performed after pembrolizumab infusion, and 1 was performed after atezolizumab infusion, with pericardiocentesis rates of 0.61%, 0.19%, and 0.32%, respectively (Tables 2 and 3). No pericardiocenteses were required for patients receiving ipilimumab, avelumab, or durvalumab. No other cancer therapeutic had a higher number or incidence of pericardiocenteses than nivolumab. Notably, nivolumab was also the most prescribed ICI, and the incidence of pericardial tamponade in patients given nivolumab was still less than 1%, as with pembrolizumab and atezolizumab (Table 3). None of the patients that required pericardiocentesis were on combination ICI therapy which included 529 of the 3,966 patients. The average time from initiation of ICI to day of pericardiocentesis was 101 days with a standard deviation of 67 days. The time from ICI initiation to pericardiocentesis ranged from as little as 6 days to as long as 240 days with a median of 91 days.

The patients not receiving ICI who required pericardiocentesis were on various cancer therapeutics which are detailed in Table 2. The prevalence of pericardiocentesis

Table 1
Demographic and clinical characteristics of patients who had pericardiocentesis

Characteristic	Immune checkpoint inhibitor given	
	Yes (n = 14)	No (n = 108)
Pericardiocenteses	15	120
Patients receiving two pericardiocenteses	1	12
Age (Years)		
Mean	57.4	50.4
Standard deviation	12.1	16.0
Male	8 (57%)	59 (55%)
Female	6 (43%)	49 (45%)
White	8 (57%)	52 (48%)
Hispanic	2 (14%)	13 (12%)
Black	1 (7%)	11 (10%)
Asian American	0	7 (6%)
Middle Eastern	0	2 (2%)
Other	3 (21%)	23 (21%)
Malignancy type		
Renal cell carcinoma	1 (7%)	8 (7%)
Breast cancer	0	15 (14%)
Lung cancer	8 (57%)	20 (19%)
Leukemia	2 (14%)	25 (23%)
Melanoma	0	2 (2%)
Thyroid cancer	0	1 (1%)
Lymphoma	2 (14%)	12 (11%)
Esophageal cancer	0	5 (5%)
Ovarian cancer	0	3 (3%)
Thymoma	0	1 (1%)
Neuroendocrine cancer	0	1 (1%)
Unknown	0	1 (1%)
Multiple myeloma	0	2 (2%)
Sarcoma	0	4 (4%)
Tongue cancer	0	1 (1%)
Skin cancer	0	1 (1%)
Mesothelioma	1 (7%)	0
Pancreatic cancer	0	2 (2%)
Gastric cancer	0	1 (1%)
Hepatocellular carcinoma	0	1 (1%)
Rectal cancer	0	1 (1%)
Uterine cancer	0	1 (1%)

Table 2
Cancer therapeutic use before pericardiocentesis

Therapy type	No. of pericardiocenteses
Checkpoint inhibitors	**15 (11%)**
Nivolumab	11
Pembrolizumab	3
Atezolizumab	1
Platinum-based therapy	**14 (10%)**
Cisplatin	3
Oxaliplatin	5
Carboplatin	6
Alkylating agents	**12 (9%)**
Ifosfamide	1
Melphalan	3
Cyclophosphamide	2
Melphalan/thiotepa	1
Melphalan/busulfan	1
Cyclophosphamide/melphalan/thiotepa	1
Busulfan	2
Temozolomide	1
Microtubule-Targeting	**11 (8%)**
Docetaxel	4
Eribulin	1
Ixabepilone	2
Vincristine	3
Vinorelbine	1
Monoclonal antibodies	**10 (7%)**
Cetuximab	1
Trastuzumab	1
Brentuximab	2
Rovalpituzumab tesirine	1
Rituximab	3
Lorvotuzumab	1
Ramucirumab	1
Anthracyclines	**3 (2%)**
Doxorubicin	3
Antimetabolites	**40 (30%)**
Fluorouracil	6
Capecitabine	6
Gemcitabine/capecitabine	2
Pemetrexed	4
Gemcitabine	5
Fluorouracil/gemcitabine	1
Azacitidine	6
Fludarabine	5
Cytarabine	1
Decitabine	1
Gemcitabine, clofarabine	1
Capecitabine/fluorouracil	1
Clofarabine	1
Tyrosine kinase inhibitors	**26 (19%)**
Sunitinib	1
Cabozantinib	3
Crizotinib	3
Bosutinib	1
Ruxolitinib	2
Crenolanib	2
Sorafenib	2
Crizotinib/dasatinib	1
Pazopanib	2
Ponatinib	1
Erlotinib	2
Vandetanib/everolimus	1
Afatinib	1
Regorafenib	1
Nintedanib	1
Lenvatinib	1
Axitinib	1
No therapy before pericardiocentesis	**14 (10%).**

Some patients received cancer therapeutics from different classes concomitantly therefore were included in each class of cancer therapeutic. None of the patients receiving ICI were receiving medications from a separate class of cancer therapeutic.

Table 3
Pericardiocentesis and use of checkpoint inhibitors

Measure	Value
Number of pericardiocenteses	135
Number of pericardiocenteses in patients on checkpoint inhibitors	15
Number of patients receiving checkpoint inhibitors	3,966
Number of patients receiving nivolumab	1,798
Number of patients receiving pembrolizumab	1,560
Number of patients receiving atezolizumab	309
Prevalence of pericardiocentesis with checkpoint inhibitor use	0.38% (15/3,966)
Nivolumab prevalence of pericardiocentesis	0.61% (11/1,798)
Pembrolizumab prevalence of pericardiocentesis	0.19% (3/1,560)
Atezolizumab prevalence of pericardiocentesis	0.32% (1/309)

No patients receiving ipilimumab, avelumab, or durvalumab required pericardiocentesis.

during the study period was uncommon for all categories of cancer therapeutics. The highest prevalence was for ICI at 0.38% (15/3,966) followed by antimetabolites at 0.24% (40/16,354), tyrosine kinase inhibitor (TKI) at 0.22% (26/11,984), monoclonal antibodies 0.20% (10/5,120), and the rest of the groups of medications having less than 0.14% prevalence. The incidence of pericardiocentesis on ICI was 0.35% (14/3,966) compared with an incidence of non-ICI cancer therapeutic pericardiocentesis of 0.11% (94/82,517). The 14 patients who required pericardiocentesis before starting cancer therapeutics were excluded from this incidence calculation as the number for the denominator of how many patients with cancer who are not on therapy was not available from the electronic medical record. This translates to a relative risk of pericardiocentesis in ICI-treated patients compared with non-ICI cancer therapeutic of 3.1 with a p value <0.001 using Fischer's exact test 1-sided.

The 15 pericardial fluid analyses in the patients who were on ICI are described in Table 4. Malignant cells were present in roughly half (53%) of the pericardial fluid analyses. Of note, in the 1 patient requiring repeat pericardiocentesis, the pericardial fluid from the repeat pericardiocentesis did not have malignant cells but, rather, showed chronic inflammatory cells. This case was the only case of ICI-associated pericardiocentesis with chronic inflammatory cells in the pericardial fluid.

The survival rates after pericardiocentesis in the cohorts were similar with 38% survival in the non-ICI group compared with 29% survival in the ICI group. The survival did

Table 4
Pericardial fluid analysis in patients on immune checkpoint inhibitors

Patient number	Immune checkpoint inhibitor		Pathology report		
			Malignant cells present	Acute inflammatory cells present	Chronic inflammatory cells present
1	Nivolumab		No pathology report available		
2	Nivolumab		0	0	0
3	Nivolumab		+	0	0
4	Nivolumab		+	0	0
5	Pembrolizumab		0	+	0
6	Nivolumab		+	0	0
7	Pembrolizumab		0	+	0
8	Nivolumab		+	0	0
9	Nivolumab		0	+	0
10	Pembrolizumab		+	0	0
11	Nivolumab		+	0	0
12	Nivolumab	First pericardiocentesis	+	0	0
		Second pericardiocentesis	0	0	+
13	Nivolumab		+	0	0
14	Atezolizumab		0	+	0

	Fluid analysis									
			White blood cell differential (%)							
Patient number	Appearance	White blood cells (/μl)	Lymphocytes	Segmented neutrophils	Basophils	Eosinophils	Histiocytes	Red blood cells (/μl)	Glucose (mg/dl)	Protein (g/dl)
1	No fluid analysis available									
2	No fluid analysis available									
3	No fluid analysis available									
4	No fluid analysis available									
5	No fluid analysis available									
6	Bloody	14,224	15	76	n/a	1	3	672,000	54	4.2
7	Bloody	1,599	28	59	n/a	n/a	13	1,030,000	90	5.3
8	Bloody	3,336	43	7	n/a	n/a	24	27,000	75	3.5
9	Clear	28	56	n/a	n/a	n/a	11	373	115	3.2
10	Bloody	2,076	n/a	4	n/a	n/a	74	461,000	71	6.4
11	Hazy	5,037	81	3	n/a	n/a	13	1,000	67	3
12 (first)	Hazy	130	42	n/a	n/a	n/a	12	498	88	4.6
12 (second)	Bloody	165	80	13	1	n/a	5	83,000	84	5
13	Bloody	1,339	2	73	n/a	n/a	17	538,000	160	4.5
14	Clear	124	30	28	n/a	n/a	28	14	111	4.9

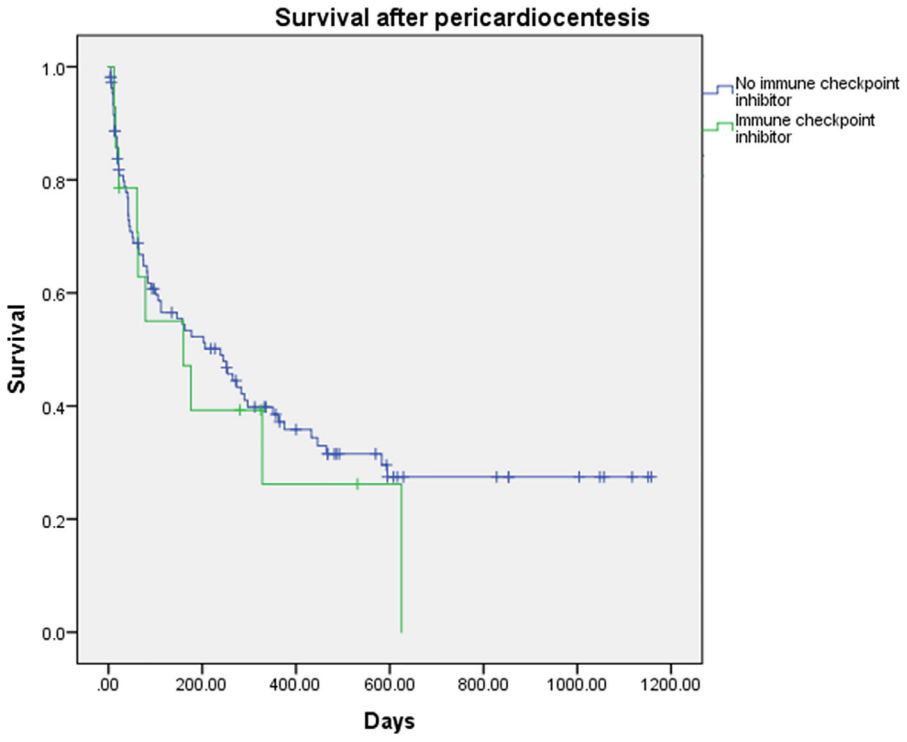
n/a: not available.

not significantly differ between the cohorts with and without ICI when compared by Kaplan-Meier log-rank test ($p = 0.538$; Figure 1). The survival analysis censored 45 patients of which 41 were in the non-ICI group compared with 4 in the ICI group. Six patients either transitioned to hospice care or returned to their home country after treatment and lacked survival data.

Discussion

Despite increasing case reports and case series of ICI-associated pericardial effusions, our cohort of patients given ICI shows that the development of hemodynamically significant pericardial effusions and their recurrence is uncommon for all ICI. Nivolumab had the highest incidence and prevalence of pericardiocenteses, but nivolumab also has a high rate of use among ICI, and the prevalence of pericardiocenteses in patients receiving nivolumab was marginally higher than that of pembrolizumab or atezolizumab (Table 3). None of the patients on combination ICI therapy required pericardiocentesis which is in contradiction to the current reported increase in cardiac toxicities with combination therapy.[15] Of note, the only patient who had recurrent hemodynamically significant pericardial effusion in the ICI group was on nivolumab. These findings are congruent with most of case reports associating nivolumab with pericardial effusions.[4,5,16] Although the incidence of pericardiocentesis is uncommon for those on ICI, the relative risk of 3.1 for pericardiocentesis compared with other cancer therapeutics, including other targeted therapies, is statistically significant. This suggests that patients on ICI are more likely to need pericardiocentesis but the mechanism or reason why is still unclear.

In fact, pericardial effusions from ICI lack an established mechanism, but a potential explanation exists. With activation of the immune system, T cell infiltration in cancer cells has



Overall Comparisons

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	0.379	1	0.538

Test of equality of survival distributions for the different levels of ICluse.

Figure 1. Kaplan-Meier survival plot comparing days of survival postpericardiocentesis of patients on checkpoint inhibitors versus noncheckpoint inhibitor cancer therapeutics.

been observed to cause an initial increase in tumor size believe to be from inflammation, also called pseudoprogression.[17] This tumor behavior informs the monitoring of and indications for stopping ICI: an initial increase in tumor size should be followed by monitoring for eventual improvement as opposed to inappropriate early discontinuation of ICI.[17] There is speculation that pericardial effusions from ICI are a form of pseudoprogression of micrometastases in the pericardium.[16] If so, then the development of pericardial effusion may be a sign that the immune system is being activated to fight the cancer. However, our study showed no difference in mortality between patients who underwent pericardiocenteses on ICI and those not on ICI. This lack of effect on survival may be due to several reasons. The pericardial effusion may be related not to the ICI but to the progression of the malignancy itself. If so, one would expect similar mortality between the cohorts with and without ICI. Of note, 8 of the 15 (53%) ICI-associated pericardiocenteses did show malignant cells in the pericardial fluid suggesting that their etiology could be the malignancy itself. In addition, if pericardial effusions do develop owing to an immune response to micrometastases, then one would expect most ICI-treated cases to have malignant cells in the pericardial fluid. In fact, only 4 of the 15 (27%) cases of ICI-associated pericardiocentesis showed acute inflammatory cells in the pericardial fluid. Endomyocardial biopsies of patients developing ICI-related myocarditis have shown T cell infiltration. However, the cell counts from the pericardial fluid in most of the cases we evaluated were not predominantly lymphocytic, as one would expect if ICI immune stimulation were causing the effusion. Another possible explanation is that over-stimulation of the immune system causes hemodynamically significant pericardial effusions with the same poor prognostic significance as in most other cardiac diseases.

The retrospective study design has inherent limitations including selection bias and information bias. Also, malignancies themselves are known to cause pericardial effusions of which we cannot exclude the possibility that some or all of the hemodynamically significant effusions that developed were due to the cancer itself. Large pericardial effusions develop due to various reasons with one of the most common being malignancy itself.[2] We cannot prove a causal relation between ICI and the development of pericardial effusions. Also, because the limited sample size, in which only 15 pericardiocenteses were performed among 3,966 patients, it is difficult to come to conclusions other than that pericardial effusion is an uncommon event when comparing the cohorts with and without ICI. This study did not address other immune-related adverse events, such as myocarditis, that may develop with ICI. It is possible that some of the patients

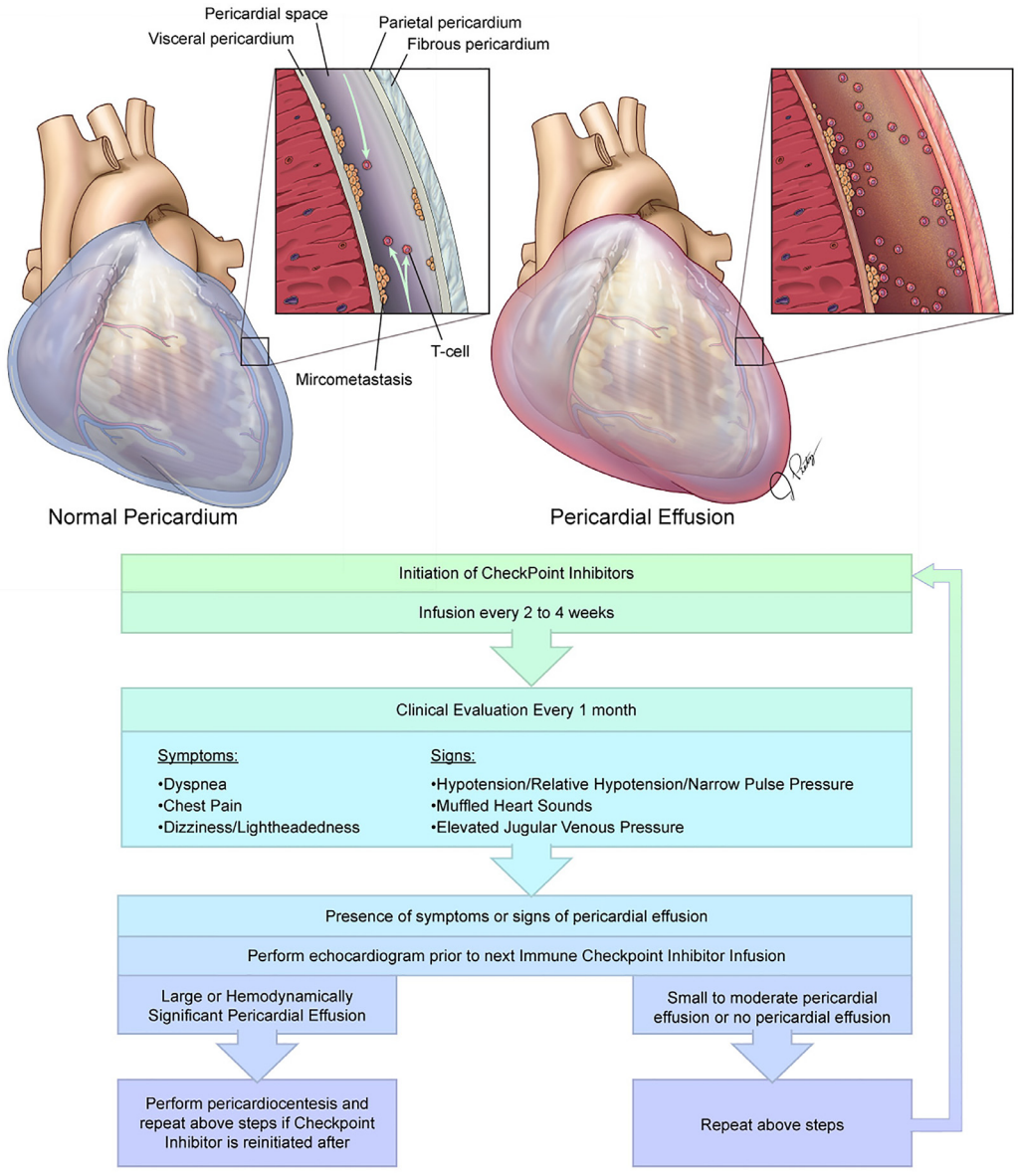


Figure 2. (Top) Illustration of the proposed mechanism of checkpoint inhibitor induced pericardial effusion by T cell infiltration of micrometastases in the pericardial space. (Bottom) Suggested clinical algorithm for identification and management of checkpoint inhibitor associated pericardial effusions.

who developed hemodynamically significant pericardial effusions also had myopericarditis that was not clinically evident, which may be a milder variant of the fulminant myocarditis recently described with ICI.

ICI have a prevalence of hemodynamically significant pericardial effusions in less than 1% of cases. Given the low prevalence, routine echocardiographic monitoring for pericardial effusions in patients on ICI has unclear benefit at this time. Healthcare providers should periodically clinically monitor these patients and, if indicated per clinical parameters, such as tachycardia, dyspnea, muffled heart sounds, and elevated jugular venous pressure, perform echocardiography for suspected pericardial disease (Figure 2). Further investigation and evaluation of pericardial fluid in patients on ICI should focus on mechanisms to determine if the hypothesis of T cell infiltration of micrometastases is correct.

Disclosures

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Supplementary materials

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1. Colombo A, Olson HG, Egan J, Gardin JM. Etiology and prognostic implications of a large pericardial effusion in men. *Clin Cardiol* 1988; 11:389–394.
2. Ben-Horin S, Bank I, Guetta V, Livneh A. Large symptomatic pericardial effusion as the presentation of unrecognized cancer: a study in 173 consecutive patients undergoing pericardiocentesis. *Medicine* 2006;85:49–53.
3. Mahmood SS, Fradley MG, Cohen JV, Nohria A, Reynolds KL, Heinzerling LM, Sullivan RJ, Damrongwatanasuk R, Chen CL, Gupta D, Kirchberger MC, Awadalla M, Hassan MZO, Moslehi JJ, Shah SP, Ganatra S, Thavendiranathan P, Lawrence DP, Groarke JD, Neilan TG. Myocarditis in patients treated with immune checkpoint inhibitors. *J Am Coll Cardiol* 2018;71:1755–1764.
4. Nesfeder J, Elsensohn AN, Thind M, Lennon J, Domsky S. Pericardial effusion with tamponade physiology induced by nivolumab. *Int J Cardiol* 2016;222:613–614.
5. Kushnir I, Wolf I. Nivolumab-induced pericardial tamponade: a case report and discussion. *Cardiology* 2017;136:49–51.
6. de Almeida DVP, Gomes JR, Haddad FJ, Buzaid AC. Immune-mediated pericarditis with pericardial tamponade during nivolumab therapy. *J Immunother* 2018;41:329–331.
7. Dasanu CA, Jen T, Skulski R. Late-onset pericardial tamponade, bilateral pleural effusions and recurrent immune monoarthritis induced by ipilimumab use for metastatic melanoma. *J Oncol Pharm Pract* 2017; 23:231–234.
8. Yun S, Vincelette ND, Mansour I, Hariri D, Motamed S. Late onset ipilimumab-induced pericarditis and pericardial effusion: a rare but life threatening complication. *Case Rep Oncol Med* 2015;2015:794842.
9. Chu YC, Fang KC, Chen HC, Yeh YC, Tseng CE, Chou TY, Lai CL. Pericardial tamponade caused by a hypersensitivity response to tuberculosis reactivation after anti-PD-1 treatment in a patient with advanced pulmonary adenocarcinoma. *J Thorac Oncol* 2017;12:e111–e114.
10. Shaheen S, Mirshahidi H, Nagaraj G, Hsueh C-T. Conservative management of nivolumab-induced pericardial effusion: a case report and review of literature. *Exp Hematol & Oncol* 2018;7:11.
11. Sagristà-Sauleda J, Angel J, Permanyer-Miralda G, Soler-Soler J. Long-term follow-up of idiopathic chronic pericardial effusion. *N Engl J Med* 1999;341:2054–2059.
12. Singh S, Wann LS, Schuchard GH, Klopfenstein HS, Leimgruber PP, Keelan MH Jr. Brooks HL. Right ventricular and right atrial collapse in patients with cardiac tamponade—a combined echocardiographic and hemodynamic study. *Circulation* 1984;70:966–971.
13. Himelman RB, Kircher B, Rockey DC, Schiller NB. Inferior vena cava plethora with blunted respiratory response: a sensitive echocardiography sign of cardiac tamponade. *J Am Coll Cardiol* 1988;12:1470–1477.
14. Burstow DJ, Oh JK, Bailey KR, Seward JB, Tajik AJ. Cardiac tamponade: characteristic doppler observations. *Mayo Clin Proc* 1989;64:312–324.
15. Puzanov I, Diab A, Abdallah K, Bingham CO, 3rd, Brogdon C, Dadu R, Hamad L, Kim S, Lacouture ME, LeBoeuf NR, Lenihan D, Onofrei C, Shannon V, Sharma R, Silk AW, Skondra D, Suarez-Almazor ME, Wang Y, Wiley K, Kaufman HL, Ernstoff MS. Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. *J Immunother Cancer* 2017;5:95.
16. Kolla BC, Patel MR. Recurrent pleural effusions and cardiac tamponade as possible manifestations of pseudoprogression associated with nivolumab therapy- a report of two cases. *J Immunother Cancer* 2016;4:80.
17. Di Giacomo AM, Danielli R, Guidoboni M, Calabro L, Carlucci D, Miracco C, Volterrani L, Mazzei MA, Biagioli M, Altomonte M, Maio M. Therapeutic efficacy of ipilimumab, an anti-CTLA-4 monoclonal antibody, in patients with metastatic melanoma unresponsive to prior systemic treatments: clinical and immunological evidence from three patient cases. *Cancer Immunol Immunother* 2009;58:1297–1306.