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RESEARCH REPORT

Immune checkpoint inhibitors-associated pericardial disease: a systematic review of case reports

Alessandro Inno[1] · Nicola Maurea[2] · Giulio Metro[3] · Andreina Carbone[2] · Antonio Russo[4] · Stefania Gori[1]

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Abstract

Treatment with immune checkpoint inhibitors (ICIs) can be complicated by cardiovascular toxicity, including pericardial disease. To date, no prospective studies specifically investigated the optimal treatment of ICI-associated pericardial disease, and the available evidence is based on case reports and series only. We performed a systematic review of case reports and series including 20 publications for a total of 28 cases of ICI-associated pericardial disease. In this review, pericardial disease was reversible in the majority of cases (75%), although 2 deaths were reported. The majority of cases were life-threatening (G4, 53.6%) or severe (G3, 21.4%), requiring pericardiocentesis. Higher rates of improvement were associated with administration of corticosteroids (86.7% vs 61.5%), presence of other immune-related adverse events (90.9% vs. 64.7%), and non-malignant effusions (86.7% vs 42.8%). ICIs were discontinued in the majority of cases and then restarted in 7 patients with no recurrence of pericardial disease. Based on these results, ICI-associated G3–G4 pericardial disease as well as G2 pericardial disease with moderate–severe effusion should be treated with ICIs discontinuation and high-dose steroids, also performing pericardiocentesis, pericardial drainage or pericardial window in case of cardiac tamponade. For G2 with small effusion or G1 pericardial disease, ICIs might be continued and colchicine or NSAIDs could be considered. For patients requiring ICIs discontinuation, a rechallenge with ICIs seems to be feasible after resolution or meaningful improvement of pericardial disease.

Keywords Pericarditis · Pericardial effusion · Cardiac tamponade · Cardiotoxicity · Immune checkpoint inhibitors · Rechallenge

Introduction

Over the last decade, immune checkpoint inhibitors (ICIs) have revolutionized the treatment of cancer and extended survival across several tumor types [1]. ICIs are monoclonal antibodies directed against immune checkpoint proteins such as cytotoxic T-lymphocyte antigen 4 (CTLA-4), programmed cell death protein 1 (PD-1) or programmed death-ligand 1 (PD-L1), that are involved in key negative regulatory pathways of the immune system [2]. ICIs work by unleashing the brakes on the immune system, thus eliciting an anti-tumor immune response. On the other hand, they may also induce immune-related adverse events (irAEs) that potentially involve any organ or system, including the cardiovascular system [3, 4].

Pericardial disease in the form of pericarditis, pericardial effusion or cardiac tamponade represents one of the clinical manifestations of ICI-associated cardiovascular toxicity [5]. An observational retrospective pharmacovigilance study reported 95 cases of ICI-related pericardial disease. In this study, pericardial disease had a median time to onset of 30 days (IQR 9–90) and it was severe in 81% of cases with a fatality rate of 21% [6]. The exact incidence of ICI-associated pericardial disease is unknown. In a single-institution retrospective study on 2,830 patients treated with ICIs,

✉ Alessandro Inno
alessandro.inno@sacrocuore.it

1 Oncologia Medica, IRCCS Ospedale Sacro Cuore Don Calabria, Via don A. Sempreboni 5, 37024 Negrar di Valpolicella, Verona, Italy

2 Divisione di Cardiologia, IRCCS Fondazione G. Pascale, Napoli, Italy

3 Oncologia Medica, Ospedale Santa Maria della Misericordia, Azienda Ospedaliera Di Perugia, Perugia, Italy

4 Oncologia Medica, Dipartimento di Discipline Chirurgiche, Oncologiche E Stomatologiche, Policlinico Universitario "A. Giaccone", Palermo, Italy

pericardial toxicity was uncommon with an incidence rate of approximately 0.1% [7], but a retrospective Italian study reported a non-negligible 6.7% incidence of pericardial effusion among 60 patients treated with ICIs for non-small cell lung cancer (NSCLC) [8].

Although several well-established guidelines on irAEs are available, no recommendation is specifically provided for the management of pericardial disease [9, 10]. Since there are no prospective studies investigating the optimal management of ICI-associated pericardial disease, the available evidence is limited to case reports and series. We performed a systematic review of case reports with the aim to assess the available evidence on the treatment of ICI-associated pericardial disease.

Materials and methods

Published studies were identified by searching PubMed until May 2020 for the following combination of terms: ('Neoplasms' OR 'cancer' OR 'tumor') AND ('checkpoint inhibitors' OR 'checkpoint blockade' OR 'checkpoint inhibition' OR 'anti-CTLA4′ OR 'anti-PD1′ OR anti-PDL1′ OR 'nivolumab' OR 'pembrolizumab' OR 'ipilimumab' OR 'atezolizumab' OR 'durvalumab' OR avelumab' OR 'cemiplimab') AND ('pericarditis' OR 'pericardial toxicity' OR 'pericardial effusion' OR 'cardiac tamponade' OR 'cardiac toxicity' OR 'cardiac adverse event' OR 'cardiac irAE' OR 'cardiac complication' OR cardiac side-effect'). Three reviewers (A.I., G.M., A.C.) independently performed the study selection and data extraction. Case reports or case series of pericardial disease in cancer patients receiving ICIs were included if they reported data on the treatment and outcome related to pericardial complication. Severity of pericardial disease was graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0 [11], as reported in Table 1. When not specifically stated by the authors, NCI-CTCAE grading was inferred based on clinical information. Associations among categorical variables were evaluated by the Fisher's exact test.

Results

The search strategy identified 116 records. An additional publication was included from authors' knowledge. All records were screened by abstract review, and 20 publications including 28 cases of pericardial disease were selected (Fig. 1) [7, 12–30]. A descriptive summary of the 28 cases is reported in Table 2.

Main characteristics of patients are summarized in Table 3. Median time to onset of pericardial disease was 70 days (IQR 44–116) after the start of ICIs, although some cases of early toxicity occurring within the first week of treatment, or late toxicity occurring after ≥ 1 year of ICIs treatment [23, 24] or even after treatment completion [16, 23, 29], were described.

Among the 28 included cases, patients were mostly male (64.3%), with lung cancer (89.3%), and treated with anti-PD-1/PD-L1 as single agent (89.3%). Pericardial effusion cytology and/or pericardial biopsy was positive for malignant cells in 7 (25%) patients. Pericardial disease was severe (G3) or life-threatening (G4) in the majority of the cases (75%). No patients with G1 pericardial disease were included. Although pericardial disease was largely reversible with a recovery or improvement rate of 75%, 2 deaths (7.1%) related to this condition were reported.

Pericardiocentesis, surgical drainage or pericardial window was performed in 19 out of 21 patients (90%) presenting with G3–G4 pericardial disease, and in 1 out of 6 patients (17%) presenting with G2 pericardial disease. Overall, corticosteroids were administered in 56% of cases. The most common corticosteroid schedule was prednisone 1 mg/kg/day. Colchicine and/or non-steroidal anti-inflammatory drugs were used in a minority of cases (4 patients), obtaining recovering or improvement of pericardial disease in 3 of them (75%).

Table 1 NCI-CTCAE v. 5.0 grading of pericardial disease

CTCAE term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Pericardial effusion	–	Asymptomatic effusion size small to moderate	Effusion with physiologic consequences	Life-threatening consequences; urgent intervention indicated	Death
Pericardial tamponade	–	–	–	Life-threatening consequences; urgent intervention indicated	Death
Pericarditis	Asymptomatic, ECG or physical findings (e.g., rub) consistent with pericarditis	Symptomatic pericarditis (e.g., chest pain)	Pericarditis with physiologic consequences (e.g., pericardial constriction)	Life-threatening consequences; urgent intervention indicated	Death

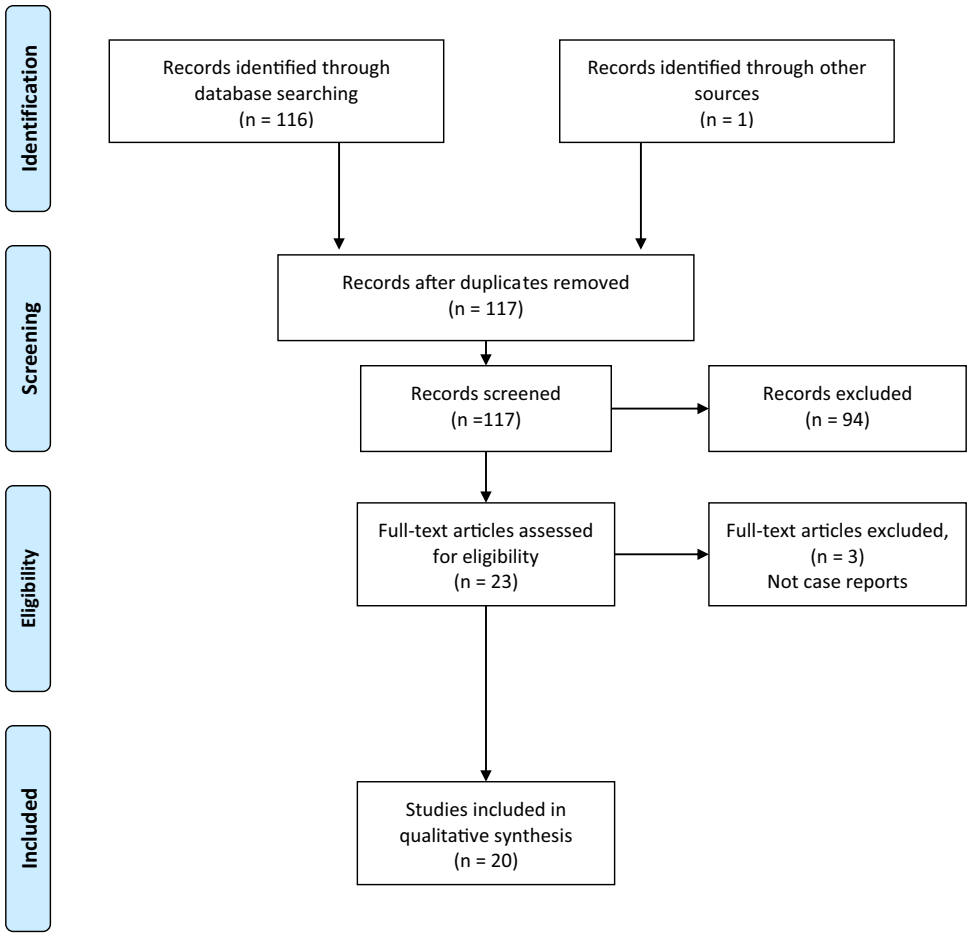

Fig. 1 PRISMA flow diagram

The presence of other irAEs, the absence of malignant cells in pleural effusion or pericardial biopsy, and the administration of corticosteroids were associated with higher rates of recovery or improvement, although these associations were not statistically significant (Table 4).

At the onset of pericardial disease, only 6 patients (21.4%) continued ICIs, whereas 18 patients (64.3%) discontinued ICIs, temporarily (7 patients) or permanently (11 patients). Interestingly, none of the 7 patients who restarted ICIs experienced recurrent pericardial disease.

Discussion

The present systematic review included the largest number of published case reports of pericardial disease in cancer patients treated with ICIs.

The exact incidence of pericardial disease in cancer patients treated with ICIs is still unknown, with reported incidence rates ranging from 0.1% to approximately 7% in different series [7, 8, 31]. This broad range is possibly due to the heterogeneity, both in terms of different grades of severity of the cases included in the studies and in terms of different distribution of potential risk factors for ICI-associated pericardial disease across the studies. Regarding severity of pericardial disease, studies that included only symptomatic patients or pericardial effusions requiring pericardiocentesis reported lower incidence rates [7, 31], whereas higher incidence rates were reported in studies that included asymptomatic patients with incidental findings of pericardial disease [8]. Regarding potential risk factors, male sex, lung cancer and treatment with anti-PD-1/PD-L1 seem to increase the risk of ICI-associated pericardial disease. In fact, in a large retrospective pharmacovigilance study, patients with pericardial disease were more often males (60%), with lung cancer (56%), and treated with anti-PD-1/PD-L1 as single agent (78%) [6]. Consistently with these reports, also the patients included in the present review were mostly male patients receiving anti-PD-1/PD-L1 for NSCLC.

Pericardial disease can be also associated with a number or anticancer agents including anthracyclines, platinum agents, alkylating agents, antimetabolites, microtubule-targeting drugs and tyrosine kinase inhibitors [32], but some retrospective evidence suggests that patients treated with ICIs have higher risk of pericardial disease when compared

Table 2 Cases of pericardial disease in cancer patients treated with ICIs

Author [Ref]	Age, sex	Cancer	ICI	Pericardial event (grading)^	Time to onset	Cardiac imaging	Best response to ICI	Cancer cells in pericardial fluid cytology/tissue biopsy	Additional data on pericardial fluid cytology/tissue biopsy	Associate myocarditis	ICI discontinuation	Treatment	Outcome	ICI rechallenge	Pericardial disease recurrence after rechallenge	Associated irAEs
Altan [12]	73, M	nSqN-SCLC	Anti-CTLA4 + Anti-PD1, NOS	Cardiac tamponade (G4)	78 days	NR	PR	No	Diffuse fibrinous pericarditis with inflammatory infiltrate	Small collections of lymphocytes within myocardium	Yes	Resuscitation	Death (cardiac arrest)	N/A	N/A	None
Altan [12]	65, F	nSqN-SCLC	Anti-PD1/PDL1, NOS	Cardiac tamponade (G4)	131 days	NR	PR	No	Fibrinous pericarditis with mild chronic lymphocytic infiltrate	NR	Yes	Pericardial window Pacemaker (due to arrhythmias)	Death	N/A	N/A	Hypothyroidism
Altan [12]	57, M	nSqN-SCLC	Anti-PD1/PDL1, NOS	Cardiac tamponade (G4)	98 days	NR	SD	No	Fibrosis, hemorrhage, edema, moderate lymphoplasmacytic infiltrate, and fibrinous exudate	NR	Yes	Pericardial window	Recovery	Yes	No	None
Asai [13]	62, M	nSqN-SCLC	Nivolumab	Cardiac tamponade (G4)	1 cycle (7 days)	CT scan	PR	Yes	NR	NR	Yes	Pericardiocentesis	Recurrent effusion (6 weeks after 1st pericardiocentesis); treated with second pericardiocentesis and intrapericardial bleomycin	Yes (after recurrence)	No	None

Table 2 (continued)

Author [Ref]	Age, sex	Cancer	ICI	Pericardial event (grading)^	Time to onset	Cardiac imaging	Best response to ICI	Cancer cells in pericardial fluid cytology/tissue biopsy	Additional data on pericardial fluid cytology/tissue biopsy	Associate myocarditis	ICI discontinuation	Treatment	Outcome	ICI rechallenge	Pericardial disease recurrence after rechallenge	Associated irAEs
Atallah-Yunes [14]	66, F	SqN-SCLC	Pembrolizumab	Pericardial effusion (G3)	1 cycle (10 days)	TTE	Not assessed	No	exudative effusion with lymphocytic predominance	NR	Yes	Pericardiocentesis Steroid (prednisone 60 mg/day)	Recovery (within 5 days after starting steroids)	No	N/A	NR
Chahine [7]	70, M	nSqN-SCLC	Nivolumab	Acute pericarditis/ Pericardial effusion (G2)	13 weeks	TTE	SD	N/A	N/A	NR	Yes	Steroid (prednisone 75 mg/day)	Recovery	Yes	No	None
Chahine [7]	60, F	nSqN-SCLC	Nivolumab + THU-decitabine (clinical trial)	Acute pericarditis /Pericardial effusion (G2)	9 weeks	TTE	NR	N/A	N/A	NR	Yes	Colchicine/Ibuprofen	Recovery	No	N/A	None
Clahine [7]	58,M	NSCLC	Nivolumab	Pericardial effusion (G2)	10 weeks	TTE	NR	N/A	N/A	NR	Yes	Steroid (prednisone 80 mg/day)	Recovery	No	N/A	Pneumonitis
Chu [15]¶	59, M	nSqN-SCLC	Nivolumab	Cardiac tamponade (G4)	3 cycles (6 weeks)	CT scan	PR	No	Granulomatous inflammation and acid-fast bacilli (culture of pericardial effusion positive for M. tuberculosis)	NR	Yes	Pericardiocentesis¶ Prednisone 1 mg/kg Anti-tubercular treatment†	Recovery (within 1 month)	Yes (only 1 cycle skipped)	No	NR
Dasanu [16]	65, F	Melanoma	Ipilimumab	Cardiac tamponade (G4)	4 cycle (9 months, i.e., 6 months after ipilimumab completion)	Chest X-Ray, CT scan, TTE	CR	No	Lymphocytic pericarditis and reactive mesothelial cells	NR	N/A	Pericardiocentesis Steroids (methylprednisolone 60 mg × 4/day)	Recovery (within 2 weeks)	No	N/A	Hyperthyroidism, transaminitis, skin rash, arthritis

Table 2 (continued)

Author [Ref]	Age, sex	Cancer	ICI	Pericardial event (grading)^	Time to onset	Cardiac imaging	Best response to ICI	Cancer cells in pericardial fluid cytology/tissue biopsy	Additional data on pericardial fluid cytology/tissue biopsy	Associate myocarditis	ICI discontinuation	Treatment	Outcome	ICI rechallenge	Pericardial disease recurrence after rechallenge	Associated irAEs
de Almeida [17]	69, M	nSqN-SCLC	Nivolumab	Pericarditis/ Pericardial effusion (G3)	24 cycle (12 months)	CT scan, TTE	PR	No	Nonspecific chronic inflammation with extensive fibrosis and lymphocyte infiltration	NR	Yes	Pericardiocentesis and pericardial window Steroids (prednisone 1 mg/kg/day to prevent constrictive pericarditis)	Recovery with pericardial window (3 days after the onset)	No	N/A	Hypothyroidism
Dhenin [18]	79, F	nSqN-SCLC	Pembrolizumab	Pericardial effusion (G2)	3 cycles (10 weeks)	CT scan, TTE	CR	Not assessed	NR	NR	No	Steroids (methylprednisolone 16 mg/day)	Recovery (within 7 days)	Yes	No (ICI discontinued after 22 weeks due to colitis)	Skin rash, Colitis, myasthenia gravis
Khan [19]	62, M	SqN-SCLC	Pembrolizumab	Cardiac tamponade (G4)	5 cycles (15 weeks)	CT scan, TTE	PR	No	Reactive mesothelial and chronic inflammatory cells	NR	Yes	Pericardiocentesis Steroids (prednisone 1 mg/kg/day)	Improvement (within 6 days)	No	N/A	NR
Kolla [20]	46, M	SCLC	Nivolumab	Cardiac tamponade (G4)	9 weeks	NR	PR	Yes	5% lymphocytes in pericardial fluid analysis	NR	No	Pericardiocentesis	Recovery with pericardiocentesis	N/A	N/A	NR
Kolla [20]	54, F	nSqN-SCLC	Nivolumab	Cardiac tamponade (G4)	7 weeks	NR	PR	Yes	30% lymphocytes in pericardial fluid Analysis	NR	Yes	Pericardiocentesis Steroids (prednisone 20–60 mg/day)	Recurrent effusions	No	N/A	NR
Kushnir [21]	67, M	SqN-SCLC	Nivolumab	Cardiac tamponade (G4)	5 cycles (10 weeks)	CT scan, TTE	PR	No	leukocytes	NR	Yes	Pericardiocentesis Steroids (prednisone 30 mg/day)	Improvement	No	N/A	NR

Table 2 (continued)

Author [Ref]	Age, sex	Cancer	ICI	Pericardial event (grading)^	Time to onset	Cardiac imaging	Best response to ICI	Cancer cells in pericardial fluid cytology/tissue biopsy	Additional data on pericardial fluid cytology/tissue biopsy	Associate myocarditis	ICI discontinuation	Treatment	Outcome	ICI rechallenge	Pericardial disease recurrence after rechallenge	Associated irAEs
Nesfeder [22]	64, M	nSqN-SCLC	Nivolumab	Cardiac tamponade (G4)	3 months	TTE	NR	No	Focal mild acute inflammation, mild fibrosis, and scattered atypical cells	NR	NR	Pericardiocentesis Pericardial window	Improvement (10 days)	NR	NR	Hypothyroidism, pneumonia
Oristrell [23]	55, F	Breast cancer	Pembrolizumab (neoadjuvant)	Pericardial effusion (G3)	12 months (6 months after end of ICI treatment)	TTE	N/A	No	Exudate with abundant cellularity and a predominant acute inflammatory component (93% neutrophils)	NR	N/A	Pericardiocentesis Pericardiectomy Noradrenaline (for refractory hypotension) Steroids (drug not stated, 2 mg/kg/day)	Recovery (rapid improvement with steroids)	N/A	N/A	Adrenal insufficiency, hypophysitis, hypothyroidism
Saade [24]	58, F	nSqN-SCLC	Nivolumab	Pericardial effusion (G3)	4 cycles (8 weeks)	Chest X-Ray, CT scan, TTE	PD	No	Hemorrhagic and discretely inflammatory cytology; small reactive T-lymphocytes predominantly CD4 + at pericardial biopsy	NR	Yes	Pericardiocentesis Steroids (dose not reported)*	Improvement (rapidly after pericardiocentesis and steroids)	No	-	NR

Table 2 (continued)

Author [Ref]	Age, sex	Cancer	ICI	Pericardial event (grading)^	Time to onset	Cardiac imaging	Best response to ICI	Cancer cells in pericardial fluid cytology/tissue biopsy	Additional data on pericardial fluid cytology/tissue biopsy	Associate myocarditis	ICI discontinuation	Treatment	Outcome	ICI rechallenge	Pericardial disease recurrence after rechallenge	Associated irAEs
Saade [24]	65, M	nSqN-SCLC	Nivolumab	Pericardial effusion (G4)	35 cycles (71 weeks)	Chest X-Ray, TTE	PR	No	hemorrhagic and inflammatory cytology; pericardial hyperplasia with T-lymphocyte infiltrate, mostly CD4 +	NR	Yes	Surgical drainage Steroids (dose not reported)*	Improvement	Yes (16 months after onset)	No	Colitis
Saade [24]	55, F	nSqN-SCLC	Nivolumab	Pericardial effusion (G2)	3 cycles (6 weeks)	CT scan, TTE	PD	Not assessed	Not assessed	NR	Yes	None*	Improvement (after ICI discontinuation)	No	N/A	Colitis
Shaheen [25]	70, F	nSqN-SCLC	Nivolumab	Pericardial effusion (G3)	1 cycle (4 days)	TTE	NR	Not assessed	Not assessed	NR	No	Colchicine Steroids (prednisone 1 mg/kg/day)	Resolution (in 5 weeks). Recurrence (1 week after steroids were stopped): nivolumab was discontinued, and steroids restarted (prednisone 1 mg/kg/day), with resolution of recurrent pericardial effusion (in 3 weeks)	Yes (with low-dose steroids)	No	NR
Tachihara [26]	70, M	nSqN-SCLC	Pembrolizumab	Cardiac tamponade (G4)	3 cycles (9 weeks)	Chest X-ray, CT scan, TTE	PR	Yes	NR	NR	No	Pericardiocentesis	Recovery with pericardiocentesis	N/A	N/A	NR

Table 2 (continued)

Author [Ref]	Age, sex	Cancer	ICI	Pericardial event (grading)^	Time to onset	Cardiac imaging	Best response to ICI	Cancer cells in pericardial fluid cytology/tissue biopsy	Additional data on pericardial fluid cytology/tissue biopsy	Associate myocarditis	ICI discontinuation	Treatment	Outcome	ICI rechallenge	Pericardial disease recurrence after rechallenge	Associated irAEs
Vittorio [27]	71, M	nSqN-SCLC	Nivolumab	Pericardial effusion (G2)	3 cycles (5 weeks)	TTE	PR	Yes	NR	NR	No	Pericardiocentesis, pericardial window	Recurrent effusion after 6 weeks (nivolumab permanently interrupted after recurrence)	N/A	N/A	NR
Yamasaki [28]	65, M	nSqN-SCLC	Nivolumab	Cardiac tamponade (G4)	4 cycles (8 weeks)	Chest X-ray, TTE	PR	Yes	WBC: 3025/µL, 84% lymphocytes	No	No (discontinued after 5 more cycles due do PD)	Pericardiocentesis	Improvement (with pericardiocentesis)	N/A	N/A	None
Yamasaki [28]	71, M	nSqN-SCLC	Nivolumab	Cardiac tamponade (G4)	2 cycles (4 weeks)	Chest X-ray, CT scan, TTE	PD	Yes	WBC: 756/µL, 3% lymphocytes	No	Yes	Pericardiocentesis	Recurrent effusion after 1 month	No	N/A	None
Yun [29]	59, M	Melanoma	Ipilimumab	Pericardial effusion (G3)	4 cycles (6 months, i.e., 3 months after ipilimumab completion)	CT scan, TTE	NR	No	fibrinous pericarditis	NR	N/A	Pericardiocentesis Indomethacin Steroids (methylprednisolone 125 mg/day)	Recovery	N/A	N/A	Skin rash, hypothyroidism, adrenal insufficiency, diarrhea
Zarogoulidis [30]	60, M	nSqN-SCLC	Nivolumab	Pericarditis (unknown)	4 months		NR	No	NR	NR	Yes	Pericardiocentesis Steroids (methylprednisolone 16 mg×2/day)	Recovery	No	-	Bowel perforation

CR, complete response; N/A, not applicable; NR, not reported; nSqNSCLC, non-squamous non-small cell lung cancer; PR, partial response; PD, progressive disease; SCLC, small cell lung cancer; SqNSCLC, squamous non-small cell lung cancer; TTE, trans-thoracic echocardiogram; WBC, white blood cells count

^Grading was defined according to NCI-CTCAE v 5.0; when the authors did not explicitly state the grade of severity, it was inferred on the basis of case description [11]

¶Pericardiocentesis was not explicitly reported by the authors but since pericardial effusion culture and pericardial biopsy were performed, in all probability pericardiocentesis or other forms of pericardial drainage/aspiration were done;

†*Mycobacterium tuberculosis* was found in the pericardial effusion, the case was interpreted as tubercular reactivation during therapy with immune checkpoint inhibitors, and the patient received antitubercular therapy in addition to steroids

*One of these 3 patients also received colchicine (but authors did not state who)

Table 3 Characteristics of patients with pericardial disease under ICI treatment

N = 28	
Gender	*n* (%)
Male	18 (64.3)
Female	10 (35.7)
Primary cancer	***n* (%)**
NSCLC	24 (85.7)
SCLC	1 (3.6)
Melanoma	2 (7.1)
Breast cancer	1 (3.6)
ICI	*n* (%)
Nivolumab	18 (64.3)
Pembrolizumab	5 (17.9)
Ipilimumab	2 (7.1)
Anti-PD1/PDL1, NOS	2 (7.1)
Anti-PD1 + Anti-CTLA4, NOS	1 (3.6)
Median time of onset, day (min–max) [IQR}	70 (4–497) [44–116]
Best response to ICI	*n* (%)
CR	2 (7.1)
PR	13 (46.4)
SD	2 (7.1)
PD	3 (10.7)
Not reported/not applicable	8 (28.6)
Other irAEs	*n* (%)
No	17 (60.7)
Yes	11 (39.3)
Type of irAEs	
Dysthyroidism (hyper/hypo)	6 (21.4)
Colitis/diarrhea/bowel perforation	5 (17.9)
Skin rash	3 (10.7)
Adrenal insufficiency	2 (7.1)
Pneumonitis	2 (7.1)
Arthritis	1 (3.6)
Hypophysitis	1 (3.6)
Myasthenia gravis	1 (3.6)
Transaminitis	1 (3.6)
Grading of pericardial disease at presentation	*n* (%)
G4	15 (53.6)
G3	6 (21.4)
G2	6 (21.4)
G1	–
Unknown	1 (3.6)
Malignant cells in pericardial effusion/tissue	*n* (%)
Yes	7 (25.0)
No	15 (53.6)
Unknown	6 (21.4)
Treatment	*n* (%)
Pericardiocentesis/drainage	19 (67.8)
Pericardial window	5 (17.9)
Steroids	16 (57.1)
Other*	6 (21.4)
No treatment	1 (3.6)
Outcome	*n* (%)
Death	2 (7.1)
Recovery/improvement	21 (75.0)
Recurrence	5 (17.9)
Management of ICI	*n* (%)
Treatment already completed at the onset	3 (10.7)
Continued	6 (21.4)
Temporarily discontinued, then restarted	7 (25.0)
Permanently discontinued	11 (39.3)
Not reported	1 (3.6)

CR, complete response; NOS, not otherwise specified; PD, progressive disease; PR, partial response; SD, stable disease

*Other treatments included: colchicine in 2 patients; colchicine plus ibuprofen in 1 patient; indomethacin in 1 patient; intrapericardial bleomycin in 1 patient; anti-tubercular therapy in 1 patient

Table 4 Association between characteristics of patients and pericardial disease outcome

Characteristics	Outcome	P
Grade at the onset	Improvement rate*, % (*n*/*N*)	
G4 (*n* = 16)	68.8% (11/16)	1.000
≤G3 (*n* = 11)	72.2% (8/ 11)	
Best response to ICI	Improvement rate, % (*n*/*N*)	
CR/PR (*n* = 15)	66.7% (10/15)	1.000
SD/PD (*n* = 5)	80.0% (4/ 5)	
Other irAEs	Improvement rate, % (*n*/*N*)	
Yes (*n* = 11)	90.9% (10/11)	0.191
No (*n* = 17)	64.7% (11/17)	
Malignant effusion	Improvement rate, % (*n*/*N*)	
Yes (*n* = 7)	42.8% (3/ 7)	0.053
No (*n* = 15)	86.7% (13/15)	
Pericardiocentesis/drainage/window	Improvement rate, % (*n*/*N*)	
Yes (*n* = 21)	76.2% (16/21)	1.000
No (*n* = 7)	71.4% (5/ 7)	
Steroid therapy	Improvement rate, % (*n*/*N*)	
Yes (*n* = 15)	86.7% (13/15)	0.197
No (*n* = 13)	61.5% (8/13)	
Discontinuation of ICI	Improvement rate, % (*n*/*N*)	
Yes (*n* = 18)	72.2% (13/18)	1.000
No (*n* = 6)	66.7% (4/ 6)	
Rechallenge of ICI	Recurrence rate, % (*n*/*N*)	
Yes (*n* = 7)	0% (0/ 7)	0.521
No (*n* = 11)	18% (2/ 11)	

*Improvement rate defined as rate of patients with full or partial recovery of pericardial disease, with no evidence of recurrence; recurrence rate defined as rate of patients with initial resolution/improvement of pericardial disease, followed by recurrent/worsening pericardial disease

with patients receiving other therapies [6, 7, 31]. Particularly, in their pharmacovigilance study, Salem et al. showed a 3.8-fold increased risk of reporting pericardial disease for patients treated with ICI as compared with the full database (0.30% vs 0.08%) [6]. In a small retrospective study on NSCLC patients, the incidence of pericardial effusion among patients treated with ICIs ($n=60$) was higher (6.7%) when compared with a control group of patients ($n=60$) with NSCLC receiving other anticancer agents (3.3%), even when patients with contemporary pleural effusion were excluded (adjusted incidence: 3.3% vs 1.6%) [7]. Similarly, a retrospective study on 3,966 patients treated with ICIs and 82,517 patients treated with anticancer agents other than ICIs at the MD Anderson from 2015 to 2017, showed that the prevalence of hemodynamically significant pericardial effusion among patients treated with ICIs was higher than that observed among patients not receiving ICIs (0.38% vs 0.11%) [31]. Therefore, although relatively rare, pericardial disease is more frequently associated with ICIs than with other anticancer agents, and this finding may represent a relevant aspect due to the expanding role of ICIs across a number of different tumor types and, consequently, the ever-growing number of cancer patients treated with these drugs.

ICI-associated pericardial disease represents a clinically relevant problem also because it may be potentially fatal, with mortality rates ranging from approximately 7%, as reported in the present analysis, up to more than 20%, as reported in the pharmacovigilance study [6]. In our review, however, pericardial disease was reversible in the majority of cases, with an improvement rate of 75%.

ICI-associated pericardial disease is often a diagnosis of exclusion. Differential diagnosis mainly includes progression or pseudo-progression of the underlying cancer, and infectious disease [13, 15, 19]. Although the differential diagnosis between immune-related toxicity and progression/pseudoprogression of cancer is often challenging, some clinical and pathological elements may be helpful for a proper assessment. Particularly, the presence of other irAEs, the absence of malignant cells in pericardial effusion or pericardial biopsy, and/or objective response or stable disease of the other tumor sites are more suggestive for an immune-related toxicity rather than cancer progression. Interestingly, we observed that patients with other irAEs and/or without malignant effusion (i.e., those with highly suspected immune-related pericardial disease) had higher improvement rates as compared to patients without other irAEs and those with malignant effusion, respectively. When progressive cancer in patients with malignant pericardial effusion is suspected, intrapericardial injection of chemotherapy such as bleomycin could represent an option, although it was used only in 1 out of the 28 case reports included in this review [13]. Also, other possible etiologies such as infectious disease should be ruled out. Particularly, Chu et al. reported a case of pericardial tamponade caused by a hypersensitivity response to tuberculosis reactivation after ICIs. In such case, antitubercular treatment was given in addition to corticosteroids, achieving pericardial disease recovery [15].

In the present review, clinical presentation of pericardial disease was severe or life-threatening in most patients, consistently with data reported in the pharmacovigilance study, where 81% of pericardial disease were severe events [6]. However, given the retrospective nature of these evidence, it could not be excluded that asymptomatic, mild cases were under-detected or under-reported, thus leading to an overestimation of severe cases.

In most patients, pericardial disease was characterized by effusion with tamponade physiology, often requiring invasive interventions such as pericardiocentesis, surgical drainage or pericardial window. As reported above, the MD Anderson study on hemodynamically significant pericardial effusion among patients treated with ICIs revealed a low incidence rate (0.38%), but the relative risk of pericardiocentesis was significantly increased (3.1) for patients receiving ICIs when compared with those not receiving ICIs [31]. These data suggest that patients on ICIs are more likely to need pericardiocentesis, but the reason remains unclear. In our review, 21 out of 28 patients (75%) with any grade pericardial disease and 19 out of 21 patients (90%) with G3–G4 pericardial disease needed an invasive management (i.e., pericardiocentesis, surgical drainage or pericardial window) of pericardial effusion. Only 5 patients were successfully treated with a conservative approach, and all of them had a low-grade (G2) pericardial disease [7, 18, 24].

Regarding medical treatment, corticosteroids represent the cornerstone of management for most irAEs [3]. Although in the present review only slightly more than half patients (57.1%) received corticosteroids, they achieved a better improvement rate as compared to those who did not receive steroids, thus suggesting that corticosteroids have a role for the treatment of ICI-associated pericardial disease.

Guidelines of the European Society of Cardiology for the management of pericardial disease recommend the use of colchicine and aspirin or non-steroidal antiinflammatory drugs (NSAIDs) for the treatment of acute pericarditis and recurrent pericarditis, and also for the treatment of pericardial effusion when associated with systemic inflammation [33]. In the present review, however, only 5 patients received colchicine and/or NSAIDs with or without corticosteroids, achieving complete recovery in 4 cases, and initial improvement followed by effusion recurrence in 1 case. Due to the paucity of data, definitive conclusion on the role of colchicine and NSAIDs for ICIs-associated pericardial disease cannot be drawn, but they may possibly have a role for the management of mild–moderate cases.

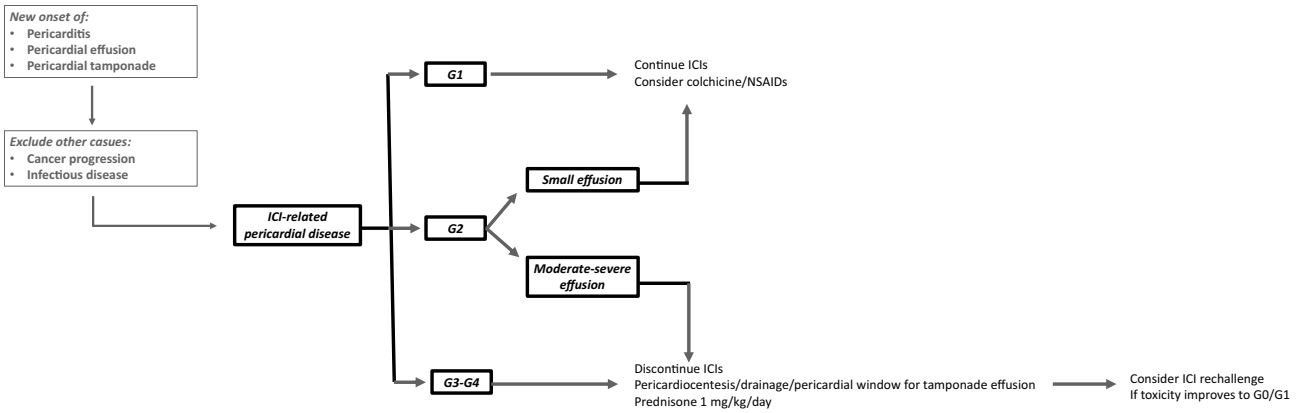

Fig. 2 Proposed approach for the management of ICI-associated pericardial disease

Among the 28 case reports included in our review, the majority of patients discontinued ICIs. After recovery, treatment was then restarted in 7 patients with no recurrence or worsening of the pericardial disease. This finding suggests that a rechallenge of ICIs after recovery of pericardial disease may be a feasible strategy.

The present study has several limitations, mainly due to its nature of retrospective review of case reports: (1) some details on risk factors, diagnostic work-up or management of cardiac symptoms could be missing; (2) a potential publication bias cannot be excluded, and mild cases or cases with fatal outcome could have been under-reported; particularly, no cases of G1 pericardial disease have been reported; (3) sample size is limited, and the observed associations between patients' characteristics and outcome were not statistically significant, and thus, our conclusions are merely speculative; (4) patients selected for rechallenge were probably those in better clinical conditions, and in the daily clinical practice the choice of the rechallenge should be considered carefully on an individual basis.

Our systematic review shows that, although potentially fatal, this condition may be reversible in the majority of cases. Based on this review, a reasonable approach to manage ICI-associated pericardial disease could be as it follows: for severe cases (G3–G4), perform pericardiocentesis or other invasive interventions to treat pericardial effusions with tamponade physiology, discontinue ICIs, administer high-dose corticosteroids (prednisone 1 mg/kg/day); for moderate cases (G2 pericardial disease), in selected patients with small effusions consider to continue ICIs and administer colchicine ± NSAIDs, whereas in patients with moderate–severe effusions discontinue ICIs and administer high-dose corticosteroids (prednisone 1 mg/kg/day); for mild cases (G1 pericardial disease), continue ICIs and consider colchicine ± NSAIDs. Once full recovery or meaningful clinical improvement has been achieved and steroids tapered to low-dose (prednisone < 10 mg/day) or stopped, a rechallenge of ICIs seems to be feasible (Fig. 2).

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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