Cureus
Part of SPRINGER NATURE

Open Access Case Report

Pericardial Effusion Requiring Surgical Window in a Young Woman With Breast Cancer and Prior Immune Checkpoint Inhibitor Exposure

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Review began 07/05/2026
Review ended 08/06/2026
Published 11/10/2026

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DOI: 10.7759/cureus.119446

Abstract

Immune checkpoint inhibitors (ICIs) have emerged over the past decade as a novel treatment strategy in triple-negative breast cancer (TNBC). However, they are associated with immune-related adverse events (irAEs). In rare cases, these may involve the pericardium and cause a pericardial effusion. We report a case of acute fibrinous pericarditis presenting as a significant pericardial effusion requiring surgical pericardial window creation in a patient with prior exposure to the ICI pembrolizumab. This case report illustrates that ICI therapy is not only associated with pericarditis managed medically or with pericardiocentesis but also with pericardial window and pericardiectomy. It underscores how challenging it is to differentiate infectious, malignant, and autoimmune etiologies in complex oncologic patients.

Categories: Cardiology
Keywords: cardiology, immune check-point inhibitor, oncocardiology, pericardial effusion, pericarditis

Introduction

Breast cancer is the most common cancer and the leading cause of cancer deaths in women worldwide [1]. About 15% of all breast cancers are triple-negative breast cancers (TNBC). Due to the absence of molecular markers for estrogen or progesterone receptors and human epidermal growth factor receptor 2 (ERBB2), the treatment options for these types of cancers are limited [2]. Immune checkpoint inhibitors (ICIs) have emerged over the past decade as a novel treatment strategy in TNBC. The only ICI that is currently approved by the Food and Drug Administration (FDA) in the United States is pembrolizumab [3]. The KEYNOTE-522 trial demonstrated that the addition of neoadjuvant pembrolizumab to neoadjuvant chemotherapy improved pathological complete response rates and event-free survival compared to neoadjuvant chemotherapy alone [4].

However, ICIs are associated with immune-related adverse events (irAEs). These can involve various organ systems, including the heart. Myocarditis is known as the most common cardiovascular side effect and has a mortality rate of 25%-50% [5,6]. In rare cases, ICIs may involve the pericardium and cause a pericardial effusion. Pericarditis has been reported in approximately 0.55% and pericardial effusion in approximately 3.98% of patients treated with ICIs [5]. The median time to onset of ICI-associated pericardial disease was 30 days in a prior pharmacovigilance study [7]. According to a systematic review of 20 publications comprising 28 cases of ICI-associated pericardial disease, a surgical pericardial window was rarely required [8]. Cases of delayed ICI-associated pericarditis have been reported but remain uncommon [9]. Cases of isolated pembrolizumab-associated pericarditis or pericardial effusion necessitating a surgical pericardial window have been reported only rarely. We report a case of acute fibrinous pericarditis presenting as a significant pericardial effusion requiring surgical pericardial window creation in a patient with prior exposure to the ICI pembrolizumab. This case highlights the diagnostic and therapeutic challenges of severe pericardial disease associated with ICI therapy.

Case Presentation

A 36-year-old woman presented with a four-day history of chest pain, dyspnea, fever, and malaise. Her past medical history included stage IIA (cT2N0M0) TNBC with breast cancer gene 1 (BRCA1) mutation, adrenal insufficiency, and long QT syndrome with a history of torsades de pointes and cardiac arrest. The patient stated that her chest pain was significantly worse when lying down and improved while sitting up. She had completed neoadjuvant chemotherapy with cyclophosphamide, carboplatin, paclitaxel, and doxorubicin as well as immunotherapy with pembrolizumab within the past year. The last dose of chemotherapy was given ten months prior to presentation and the last dose of pembrolizumab nine months prior to presentation.

She was febrile at 103.1°F, tachycardic at 150 bpm, hypotensive at 92/36 mmHg, tachypneic, and ill-appearing. Laboratory workup results showed leukocytosis and elevated inflammatory markers, including increased C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) values. Serial troponin values, brain natriuretic peptide level, hepatitis C antibody, antinuclear antibodies (ANA), double-stranded DNA

(dsDNA) antibodies, and rheumatoid factor (RF) were normal (Table 1).

Laboratory test	Result	Normal reference range
White blood cell count	19.1 × 10^9/L	4.8-10.8 × 10^9/L
C-reactive protein (CRP)	97.2 mg/L	<5.0 mg/L
Erythrocyte sedimentation rate (ESR)	64 mm/h	0-20 mm/h
Troponin (serial)	6 ng/L on presentation, 8 ng/L at two hours, 14 ng/L at six hours	≤34 ng/L
Brain natriuretic peptide	68 pg/mL	<100 pg/mL
Hepatitis C antibody	Nonreactive	Nonreactive
Antinuclear antibody (ANA) ratio	<0.09 ratio	<0.70 ratio
Double-stranded DNA (dsDNA) antibody	<0.6 IU/mL	0.0-9.9 IU/mL
Rheumatoid factor (RF)	<3.5 IU/mL	<14 IU/mL

TABLE 1: Laboratory findings

Computed tomography (CT) (Figure 1) and echocardiography (Figure 2) showed a new circumferential intermediate-density pericardial effusion measuring up to 1.8 cm.

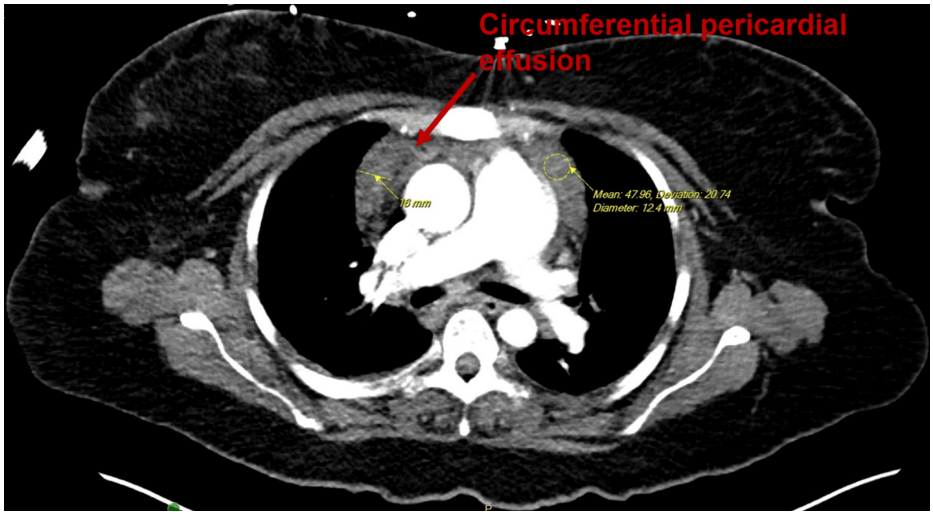


FIGURE 1: Computed tomography angiography demonstrating a circumferential pericardial effusion

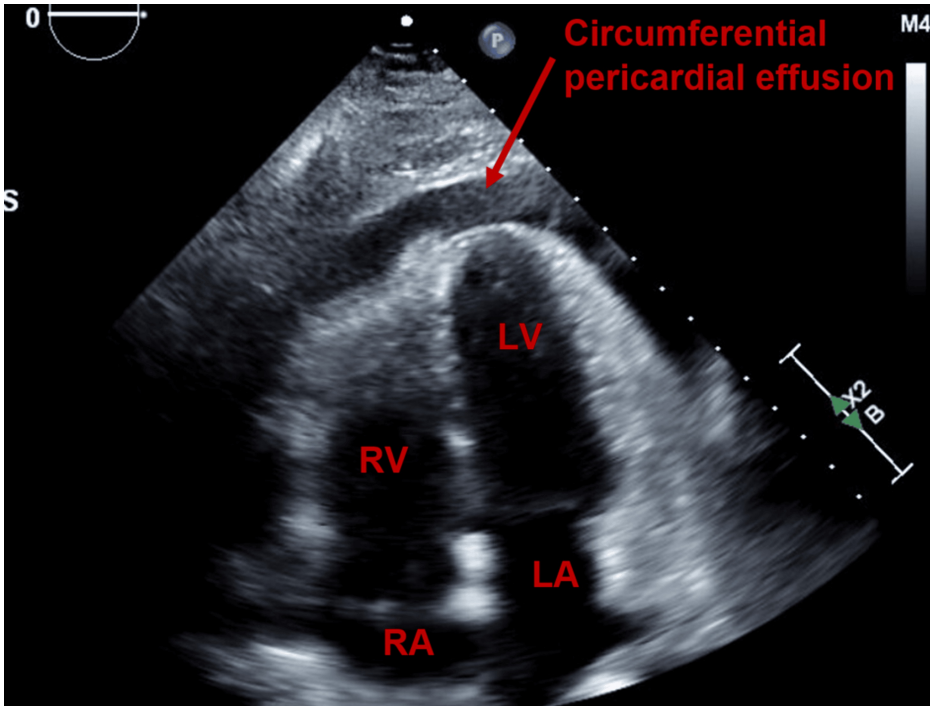


FIGURE 2: Apical four-chamber view on transthoracic echocardiography demonstrating a circumferential pericardial effusion

She was given intravenous fluids for preload maintenance, transferred to the intensive care unit, and underwent urgent surgical management with open subxiphoid pericardial window and partial pericardiectomy. During this procedure, the xiphoid was resected, and a large island of pericardium was removed to create an approximately 4 × 8 cm pericardial window. A 20 French chest tube was placed for continuous drainage of the pericardial space and removed two days later. The patient tolerated this procedure well. She was started on anti-inflammatory therapy with ibuprofen 800 mg three times daily, colchicine 0.6 mg twice daily, and intravenous stress-dose hydrocortisone 200 mg every six hours. The patient experienced significant improvement in symptoms, with complete resolution of dyspnea and improved blood pressure (135/92 mmHg) within three days of initiation of treatment. She was discharged home on ibuprofen, colchicine, and a hydrocortisone taper over five days.

Extensive infectious work-up remained negative. This included a viral panel for influenza A, influenza B, respiratory syncytial virus, and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It also encompassed bacterial blood cultures, fungal cultures, aerobic and anaerobic cultures from the pericardial swab, and acid-fast bacilli smear. Final pathology from the pericardial tissue and cytology from the pericardial fluid showed severe inflammation without evidence of malignancy.

Within two weeks of discharge, the patient presented to the emergency department with recurrent chest pain and shortness of breath. Transthoracic echocardiography revealed a small-to-moderate loculated pericardial effusion, primarily surrounding the right ventricle. The echocardiogram demonstrated a preserved left ventricular ejection fraction, normal intracardiac pressures, and no evidence of cardiac tamponade or constrictive physiology. The maximal dimension of the pericardial effusion was less than 1 cm. During hospitalization, she was treated with intravenous ketorolac, resulting in improvement of her chest pain. Given the absence of hemodynamic compromise, the cardiology, critical care, and cardiothoracic surgery teams recommended conservative management with outpatient cardiology follow-up.

Discussion

This case illustrates the challenging diagnostic complexity of pericardial effusions in patients with prior exposure to ICIs. Pericarditis with pericardial effusion may arise from malignancy involving the pericardium [10]. Although a malignant etiology was initially suspected given the patient's underlying breast cancer, the pathologic evaluation showed no evidence of malignancy. Infectious pericarditis from fungal and bacterial etiologies also has a higher prevalence in oncologic patients [10]. However, her fungal and bacterial cultures remained negative as well. This case underscores the importance of obtaining pathologic and culture specimens for determining etiology in this patient population. It demonstrates that clinicians cannot reliably differentiate between malignant, autoimmune, and infectious causes based on symptoms, signs, laboratory blood results, and imaging only.

Even though cyclophosphamide and doxorubicin are associated with pericarditis and pericardial effusion, these adverse events occur within the first month of treatment [11,12]. The patient had received her last dose of chemotherapy ten months prior to presentation. None of her four chemotherapy agents would be expected to cause new-onset pericarditis with pericardial effusion after that many months. Prior exposure to immunotherapy raises concern for a delayed immune-related inflammatory process. Although most irAEs occur while ICI therapy is actively administered, delayed irAEs are possible. According to the American Society of Clinical Oncology (ASCO), late irAEs refer to irAEs occurring six months after discontinuation of ICI therapy [13]. These delayed irAEs are now receiving greater recognition. The time to onset of cardiovascular toxicities after the ICI pembrolizumab can range from two to 54 weeks [13]. This case illustrates that the ICI pembrolizumab is associated with potentially life-threatening pericardial effusion 42 weeks after the last treatment dose. Clinicians should be aware that potentially life-threatening immune-mediated toxicities from ICI can present many months after treatment discontinuation.

The International Cardio-Oncology Society (IC-OS) position statement recommends that three to five days of glucocorticoid treatment should be considered for pericarditis with moderate to severe pericardial effusion from ICI [5]. The administered steroids likely contributed to the improvement of the patient. This is because pericarditis from ICI is thought to be caused by activated T lymphocytes [5].

The case highlights that ICI therapy is not only associated with pericarditis or pericardial effusion managed medically or with pericardiocentesis but, in rare cases, may require surgical intervention beyond it. It demonstrates that ICI therapy may result in a pericardial window and pericardiectomy. The surgical approach was driven by hemodynamic instability, the option to safely place a large-bore drain for therapeutic drainage, and the need for diagnostic tissue sampling. The biopsy findings eventually showed acute fibrinous pericarditis without malignancy. This resulted in a substantial improvement in understanding the patient's disease process.

Although cases of pembrolizumab-associated pericarditis and pericardial effusion have been reported, most have occurred during active treatment or shortly after discontinuation of ICI therapy. Data on delayed cardiovascular irAEs remain limited [7]. Although the temporal association, exclusion of alternative etiologies, histopathologic findings, and clinical response to corticosteroids support an immune-mediated mechanism, a definitive causal relationship between pembrolizumab and the delayed onset of pericarditis cannot be established based on a single case report. Additional studies are needed to better characterize the timing and underlying mechanisms of delayed ICI-associated pericardial disease.

Conclusions

As the use of ICIs continues to expand across oncologic indications, the recognition and management of their cardiovascular toxicities will become increasingly important in clinical practice. This case adds to the growing body of literature demonstrating that pericardial involvement from ICIs can extend beyond cases amenable to medical therapy or simple pericardiocentesis, occasionally necessitating definitive surgical management including pericardial window creation and pericardiectomy. Even when malignancy is strongly suspected, acute fibrinous pericarditis from ICI exposure should be considered. Histopathologic evaluation may be required to guide management by differentiating etiologies in complex cardio-oncology patients. Continued vigilance, early recognition, and individualized treatment strategies are paramount to reducing morbidity and mortality associated with this rare but potentially life-threatening complication.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Jasmin K. Bhullar

Acquisition, analysis, or interpretation of data: Jasmin K. Bhullar, Doris Takwe

Drafting of the manuscript: Jasmin K. Bhullar

Critical review of the manuscript for important intellectual content: Jasmin K. Bhullar, Doris Takwe

Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have

declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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