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LETTER TO EDITOR

# Acute pericarditis and tamponade from Coxsackie B3 in an adult Hematopoietic-Cell-Allograft recipient: A rare but potentially serious complication

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## Introduction

Allogeneic hematopoietic cell transplant (allo-HCT) represents the only known treatment that can offer a cure for various hematologic malignancies [1,2]. However, morbidity from the procedure remains a significant concern. One major source of morbidity is the development of serious viral infections, such as cytomegalovirus (CMV) and Epstein–Barr virus (EBV), among others [3,4]. Strategies to monitor these infections, namely, preemptive therapy for CMV as well as close surveillance of EBV in the setting of T-cell depletion have reduced the incidence of CMV disease, as well as the development of EBV-related posttransplant lymphoproliferative disorders [3,5]. The occurrence of Coxsackie-virus infection in the setting of allo-HCT, however, is an exceedingly rare complication based on available published literature. Here, we summarize a rare presentation of Coxsackie B3-associated pericardial effusion in the setting of allo-HCT, and highlight this potentially serious and life-threatening complication.

## Case report

We present the case of a 56-year-old man who was diagnosed with peripheral T-cell lymphoma, not otherwise specified. His initial staging workup using positron emission tomography/computed tomography (PET/CT) images showed a mass extending from the base of the tongue and displacing the epiglottis posteriorly, as well as hypermetabolic lymph nodes in the neck region. The bone-marrow (BM) aspirate, biopsy, flow cytometry, and cytogenetic analysis were negative for T-cell lymphoma involvement. He underwent tonsillectomy, septoplasty, and inferior turbinate resection. The pathology disclosed a diffuse proliferation of small- to medium-size lymphocytes, positive for CD3, CD4, and CD5, and negative for CD30 and CD56. The immunohistochemistry showed abnormal T-cells positive for CD3, CD4, CD43, and CD45RO, and negative for CD8 and CD20. The T-cell receptor gene

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rearrangement studies were positive. He was treated with six cycles of dose-dense cyclophosphamide, doxorubicin, vincristine, and prednisone. A repeat PET/CT after three cycles showed complete metabolic response. After completion of the prescribed chemotherapy, he received involved-field radiation therapy with a cumulative dose of 30 Gy. He remained in complete response for approximately 5 years, after which he was found to have bilateral symmetric intense uptake in the nasopharynx and posterior tongue on PET/CT. Biopsy of the nasopharynx revealed an abnormal T-cell population on flow cytometry, positive for CD2, CD3, CD4, CD5, and CD7. Ki-67 index was 40%, consistent with the disease relapse. A repeated BM analysis was again negative for involvement with lymphoma. The patient initially declined therapy. Eight months later, he presented with a progressive disease, notably hypermetabolic lymphadenopathy on both sides of the diaphragm. Flow cytometry of the peripheral blood showed circulating lymphocytes with aberrant phenotype, and a BM biopsy was once again negative for lymphoma. He completed two cycles of salvage chemotherapy with etoposide, methylprednisolone, cytarabine, and cisplatin, along with intrathecal methotrexate and three courses of romidepsin, achieving a partial remission.

He underwent an allogeneic peripheral-blood stem-cell transplant from a matched-related donor (8/8, human leukocyte antigen A,B,C and DRB1), following a preparative regimen of fludarabine plus pharmacokinetically targeted intravenous busulfan (area under the curve: 3500 μmol/min/L per dose × 4 doses) and acute graft-versus-host disease (GVHD) prophylaxis consisting of tacrolimus and mycophenolate mofetil. On Day +44 from allo-HCT, he presented with dyspnea and severe chest pain radiating to the left arm without signs of apparent hemodynamic compromise. The electrocardiogram showed unspecific repolarization changes, and serial cardiac enzymes were within normal levels. A small pericardial effusion was evident on transthoracic echocardiogram, supporting the diagnosis of pericarditis. The peripheral blood was tested for Coxsackie B1—B6, and quantitative serology results were positive for Coxsackie B3 (1:80). The results of other B-serotypes of Coxsackie were as follows: B1 < 1:10, B2 1:10, B4 1:40, B5 < 1:10, and B6 < 1:10. The C-reactive protein was elevated. He was started on colchicine. Two weeks later, he presented with a large left pleural effusion (Fig. 1). A repeat echocardiogram confirmed worsening pericardial effusion with evidence of early diastolic right-atrium collapse (not shown). He underwent a subxiphoid pericardial catheter insertion, and placement of a left-sided chest tube and a pericardial window. The pathology from the pericardium and the cytology from the drained pleural and pericardial fluids were all negative for lymphoma. The pericardial fluid tested negative for Gram stain, bacterial cultures, fungal cultures, and acid-fast bacilli. His postoperative course was uneventful, and he was discharged from the hospital 5 days later on colchicine for a total of 4 weeks. His symptoms resolved and he remains asymptomatic at the most recent follow-up on day +152 postallografting.

## Discussion

This case highlights a unique presentation of pleuropericarditis with cardiac tamponade from Coxsackie B3 in an adult patient following an allo-HCT. The serologic titers were unremarkable for other Coxsackie B serotypes, suggesting that Coxsackie B3 was the most likely pathogen. A possible limitation of our findings is the absence of polymerase chain reaction as an additional confirmatory test. However, one might argue that the potential advantage of a polymerase-chain-reaction testing would be mainly attributable to increasing sensitivity of detection. Three large studies have shown that in 78—86% of cases the causative agent of acute pericarditis remained idiopathic [6—8]. It is presumed that a large majority of these cases were due to undiagnosed viral etiologies.

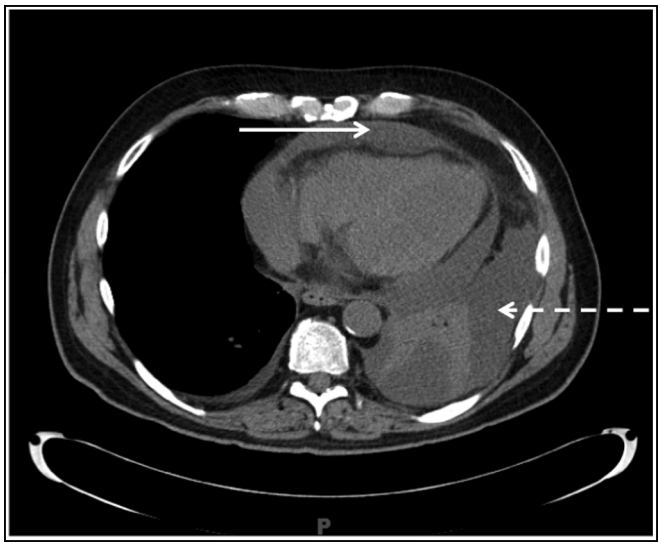

**Fig. 1** Computerized tomography of the chest. The solid arrow indicates pericardial effusion. The dotted arrow indicates pleural effusion.

**Table 1** Outcomes of patients described in the medical literature who developed pericardial disease in the setting of allo-HCT.

| Authors | *N* | Age (years) | Diagnosis | Transplant type | Days from transplantation | Pericardial-fluid analysis | Surgical intervention | GVHD | Outcome |
|---|---|---|---|---|---|---|---|---|---|
| Murdych and Weisdorf [13] | 4 | 22—38 | Various | 1 Auto-HCT; 3 allo-HCT | +1 to +70 | No organisms | Majority pericardiocentesis | None | Two deaths; two alive |
| Norkin et al. [11] | 7 | 36—64 | Various | Allo-HCT | +42 to >+500 | No organisms | Majority pericardial window | Skin, GI, liver | Alive |
| Liu et al. [15] | 6 | 36—55 | Various | Allo-HCT | +9 to +369 | No organisms | Majority pericardiocentesis | Eyes, skin, GI, oral cavity, lung | Alive |
| Ferreira et al. [10] | 1 | 39 | AML | Allo-HCT | >+500 | No organisms | Pericardiocentesis; pericardiostomy | Skin, oral cavity, liver | Alive |
| Neier et al. [18] | 1 | 20 | ALL | Allo-HCT | +28 | No organisms | None | Liver | Death |
| Holbro et al. [17] | 1 | 28 | MDS | Allo-HCT | +19; +35 | HHV-6 | Pericardiocentesis × 2 | None | Alive |

ALL = acute lymphoblastic leukemia; Allo = allogeneic; AML = acute myeloid leukemia; Auto = autologous; GI = gastrointestinal; GVHD = graft-versus-host disease; HCT = hematopoietic cell transplant; HHV-6 = human herpesvirus type 6; MDS = myelodysplastic syndrome.

Although similar cardiac events have been described in the literature as manifestations of transplant-associated toxicities or less commonly GVHD, to the best of our knowledge this is the first case that identifies Coxsackie B3 as the causative agent. The occurrence of Coxsackie-virus infection in the setting of allo-HCT is not a commonly known complication based on available published literature. Coxsackie B3 virus is a cytolytic enterovirus that can cause severe cardiac injury in the setting of myocarditis and pericarditis. Estrin and Huber [9] investigated the inflammatory pathophysiology of cardiac damage in myocarditis to explain why immunosuppressive drugs fail to prevent myocarditis. The authors concluded that Coxsackie B3 virus induces immunosuppressant-resistant cytokine production by helper T-cells. The development of pericardial effusion in the setting of allo-HCT has been described in association with GVHD [10]. Norkin et al. [11] described a series of seven cases of large pericardial effusion out of 858 adult patients who underwent a hematopoietic cell transplant (HCT) (autologous = 512, allogeneic = 346) from a single institution. All but one required a pericardial window, and nonspecific inflammatory changes were described in six patients who underwent a pericardial biopsy. Six of them had a preceding GVHD [11]. Although following allo-HCT, cardiac complications in the setting of GVHD occur in less than 1% of patients [11], pericardial effusions and cardiac tamponade are rare, yet life-threatening manifestations of GVHD [12]. Table 1 summarizes previously described cases of patients who developed pericardial effusions following HCT.

Several risk factors are implicated in the development of pericardial effusions, which are not immune mediated [11]. Chemotherapy regimens consisting of anthracycline, etoposide, or cyclophosphamide have been associated with pericardial damage when used in the conditioning phase before HCT [13], mainly via generating cardiotoxic reactive oxygen species [14]. Infective pericarditis with viral, bacterial, or fungal organisms is also consequently a risk factor for pericardial effusion and cardiac tamponade [15]. It is important to keep in mind that, in the setting of immunosuppression, infective pericarditis may progress in the absence of fever [16]. Additionally, radiation therapy involving the mediastinum may contribute to cardiac toxicity [11].

Holbro et al. [17] described the case of a young patient who developed pericardial effusion, which progressed to cardiac tamponade between Day +19 and Day +28 following allo-HCT, and her symptoms recurred on Day +35. Despite pericardial fluid positivity for human herpesvirus 6, the authors attributed her complications to sirolimus, with an unclear pathophysiology. Other described causes include fluid overload posttransplant, iron overload from blood transfusions, disease relapse, or no clear etiology in some cases [15,18].

## Conclusion

Our report aims to increase awareness of the occurrence of Coxsackie-associated life-threatening pericarditis, as well as cardiac tamponade in adult patients undergoing allo-HCT. This certainly remains a rare complication, yet a life-threatening one that must be recognized early on to allow for timely intervention. Given the numerous complications that occur following allo-HCT, it is at times

challenging to determine the specific etiology, and at the same time identify which of these pose the greatest risk to the development of a complicated pericardial effusion. While many characteristics of pericarditis in the setting of allo-HCT would suggest an association with GHVD [15], it is imperative to rule out infectious etiologies, such as Coxsackie B virus, as in our case.

## Conflicts of interest

The authors declare no relevant conflicts of interest in relation to this manuscript.

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