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Large pericardial effusion as a complication in adults undergoing SCT

M Norkin[1,2], **V Ratanatharathorn**[1], **L Ayash**[1], **MH Abidi**[1], **Z Al-Kadhimi**[1], **LG Lum**[1], and **JP Uberti**[1]

[1]Wayne State University School of Medicine, Barbara Ann Karmanos Cancer Institute, Detroit, MI, USA

[2]University of Florida College of Medicine, Gainesville, FL, USA

Abstract

Large pericardial effusion (LPE) leading to cardiac tamponade is a rare complication described in patients undergoing SCT. This complication is considered to be a manifestation of chronic GVHD; however its pathophysiology is poorly understood. Currently, there are no published data systematically describing the incidence, clinical characteristics and outcomes of LPEs in adult stem cell transplant recipients. We retrospectively evaluated 858 adult patients (512 autologous, 148 related and 198 unrelated donor) who underwent hematopoietic stem cell and BM transplants at our institution from 2005 to 2008 for the development of post transplant LPE. Seven patients (0.8%) were found to have LPEs and all these patients had undergone unrelated allografts. The median day of diagnosis post transplant was 229 (range 42–525). None of these patients had active manifestations of GVHD other than serositis at the time of LPE detection. Pericardial window (PW) was successfully placed in all patients who developed cardiac tamponade and most patients with LPE were effectively treated by increasing immunosuppression. We conclude that LPE is a rare late complication after allogeneic transplant in adults and in our study developed only after unrelated transplant. PW can be safely performed in these patients and LPEs can be successfully treated with intensification of systemic immunosupression.

Keywords

stem cell transplant; pericardial effusion; cardiac tamponade; polyserositis; chronic GVHD

Introduction

Compared with other complications seen in SCT, cardiac complications are rare, occurring in 1% of patients.[1] Large pericardial effusion (LPE) is one of these uncommon occurrences, which may contribute to significant post transplant morbidity as it could lead to pericardial tamponade. LPE is recognized as one of the manifestations of polyserositis, which is another complication after allogeneic transplantation. Polyserositis typically presents as excessive edema, ascites and weight gain.[2] Although the pathophysiology of polyserositis is poorly understood, it is generally thought to be a manifestation of chronic GVHD.[3,4]

Correspondence: Dr M Norkin, Division of Hematology/Oncology, University of Florida College of Medicine, 1600 SW Archer Road, PO Box 100278, Gainesville, FL 32610-0278, USA. maxim.norkin@medicine.ufl.edu.

Conflict of interest
The authors declare no conflict of interest.

LPE due to polyserositis was first described in a pediatric patient who received a transplant from his sister for ALL.[5] This patient developed LPE 20 months post transplant as part of a syndrome of severe polyserositis including pleural effusions, ascites and polyarthritis. Subsequently, only a few sporadic cases of LPE due to chronic GVHD in adult patients have been reported.[4,6] To the best of our knowledge, the only published study which systematically addressed the incidence and clinical characteristics of significant pericardial effusions did not include adult stem cell transplant recipients.[7] As little is known of the occurrence, pathogenesis and clinical features of LPE post transplant in adults, we have reviewed and reported the incidence, clinical features and outcomes of sterile non-malignant LPEs at our institution over a 4-year period.

Materials and methods

We evaluated the incidence of LPE for all patients, 18 years and older, who received BM or SCT at Karmanos Cancer Institute from January 1 2005 to December 31 2008. Data were obtained by identifying patients who developed LPE, through a retrospective review of medical records. Wayne State University Institutional Review Board approval was obtained for this retrospective study. Age, diagnosis, type of transplant, HLA match, preparative regimen, GVHD prophylaxis, incidence and severity of post transplant complications were obtained for all patients. LPE was defined as fluid collections that were distributed laterally, apically or anteriorly, and extended further posteromedially or circumferentially within the pericardium.[8] When LPE was detected by computed tomography scan, it was followed by echocardiography to evaluate for cardiac tamponade. Cardiac tamponade was diagnosed based on two-dimensional echocardiography findings of Doppler analysis if right atrial or/ and right ventricular collapse was identified. All patients diagnosed with cardiac tamponade underwent surgery to place a pericardial window (PW) with subsequent evaluation of pericardial fluid and pericardium for the presence of malignant cells, as well as gram stain, bacterial and fungal cultures for identification of pathogens. Retrospective analysis was finalized on March 3rd 2010.

Results

During the 4-year period, 858 (512 autologous, 148 related and 198 unrelated donor) transplants were performed at our institution. Before transplant, cardiac function was assessed by echocardiography in all patients, and none of the patients who subsequently developed LPE had significant abnormalities on the initial cardiac evaluation.

Out of eight patients who were found to have had LPE during this time period, one patient who developed edema, bilateral pleural effusions and LPE during treatment with imatinib for relapsed CML was excluded from the analysis because of the possibility of drug-induced fluid retention. Characteristics of the seven remaining patients with LPE are shown in Table 1. The median age was 47 years (range 36–64). There were three patients with AML, two with non-Hodgkin lymphoma, one with myelodysplastic syndrome and one with ALL. All patients who developed LPE received unrelated stem cell transplants. In contrast, LPE was not detected in 512 autologous and 148 related transplants. The median day of diagnosis of LPE was 229 days (range 42–525) post allograft. Two patients who developed LPE <100 days post transplant had undergone their second allogeneic transplant. Five patients received full intensity preparative regimens; three received BU and fludarabine-containing regimens, one received CVB (CY, etoposide and BCNU) and one received VP16 plus TBI at a dose of 1200 cGy. The remaining two patients had reduced intensity regimens containing fludarabine, dose-reduced BU and TBI dose of 200 cGy.

In six patients (86%), the occurrence of LPE was associated with the presence of concomitant pleural effusions. All seven patients were receiving systemic immunosuppression at the time of development of LPE. Six out of seven patients had a diagnosis of GVHD before the detection of LPE, including skin and gastrointestinal involvement in five and biopsy proven GVHD of the liver in one patient. Four of seven patients were tapering off their immunosuppression before LPE detection and no patient had active manifestations of GVHD other than serositis at the time of LPE detection. One patient developed LPE without any previous history of GVHD, 42 days post transplant.

Six out of seven patients with LPE had evidence of pericardial tamponade by echocardiogram and underwent subsequent PW placement. Four of these six patients were diagnosed by urgent echocardiography performed for an evaluation of clinical symptoms suggestive of cardiac tamponade. The remaining two patients had a computed tomography scan of the chest to evaluate worsening respiratory status, which revealed the presence of LPE and following echocardiogram, demonstrated a cardiac tamponade. All of these patients had a pericardial biopsy and cytologic analysis of the pericardial fluid. None of the patients had evidence of pericardial involvement with a malignant or infectious process on cytology, microbial assessment or biopsy. Biopsy results are shown in Table 1. In addition, all patients were negative for CMV using PCR and were negative for galactomannan assay on their peripheral blood samples within 5 days of LPE detection. One patient was found to have a LPE on the chest computed tomography scan performed for evaluation of respiratory symptoms; however an echocardiogram revealed no evidence of cardiac tamponade. In this case LPE was treated conservatively with aggressive diueresis, β-blockers and spironolactone, with subsequent resolution.

Of the six patients who underwent PW placement, four had their immunosuppression increased and the remaining two had no change in their immunosuppression, one due to concern about early relapse and the second due to rapid deterioration and multi-organ failure.

Three of six patients who had PW placement were alive over a year after the procedure. All had their immunosuppression increased with resolution of pericardial and pleural effusions. Four patients died, none from a consequence of either their pericardial effusion or PW placement. Patient 2 died of progressive GVHD 93 days after PW. Patient 4 died of multi-organ failure 7 days after PW placement. Patient 6 died of disease progression 87 days post PW window placement. Patient 7 died of bronchiolitis obliterans 542 days post LPE detection. Median survival after transplantation in this group of six patients was 243 days, as compared with 218 days in the remaining 192 patients who received unrelated allografts, but did not undergo PW placement.

Discussion

Although the incidence and clinical characteristics of significant pericardial effusions in pediatric SCT have been described in case reports[5,9] and reviews,[7,10] LPE as a complication of allogeneic transplant in adults has not been systematically evaluated. To our knowledge, this is the first comprehensive retrospective review of the LPE in a large group of adult transplant patients.

The first case report of LPE associated with polyserositis in adults was reported by Silberstein *et al.*[4] in a patient who received a transplant from an HLA-identical brother for refractory Hodgkin disease and developed chronic GVHD manifesting with polymyositis, polyserositis with a LPE 1 month after a donor lymphocyte infusion. Cereda *et al.* described another case in which a 29-year-old male who developed heart failure with ventricular wall

thickening and pericardial effusion shortly after allogeneic BMT for CML. All of his abnormalities resolved after successful treatment of GVHD.[6]

The incidence of LPE in patients who received a related or unrelated transplant was 2% (7/346) whereas the incidence in patients who underwent unrelated transplants was 3.5% (7/198). Our overall incidence of 0.8% (7/858) was significantly lower when compared with the pediatric patients wherein the incidence was 4.4%.[7] Furthermore, the pattern of distribution was different as we were only able to identify this complication in patients undergoing unrelated transplantation. No patient who underwent related or autologous transplantation was found to have LPE in our study. In the pediatric group among nine patients with LPE, two underwent autologous BMT, and two had matched related donor transplants.[7] In addition, in pediatric patients LPE occurred at a median of 30 days post transplant, which was much earlier than in our patients wherein LPE was detected at a median of 229 days. The variations in stem cell source and timing of the development of complications may suggest differences in the pathogenetic mechanisms underlying the development of this complication in the adult population. Although no direct evidence exists to prove LPEs were a manifestation of GVHD, the development exclusively in patients undergoing unrelated transplantation lends further evidence to the role of GVHD in the pathophysiology of this complication. Similar to others,[4–7] 6/7 of our patients had received immunosuppressive treatment for acute GVHD before development of LPE; however, in contrast to other reports, development of LPE in our patients was not associated with any other symptoms of GVHD other than pleural effusions. Most of our patients received increased immunosuppression after PW placement for LPE.

Development of LPE might be triggered by non-immune mechanisms not directly associated with GVHD. For example, patients undergoing transplantation for thalassemia have an unusually high incidence of cardiac tamponade within a month after transplant. The lack of myocardial injury and complete resolution of these effusions after simple pericardiocentesis suggested that damage to the pericardium may be caused by drug toxicity during conditioning. This was thought to be related to the conditioning regimens, which usually contain CY, and the associated iron overload often seen in patients with thalassemia. Pericardial effusion with cardiac tamponade was shown to develop acutely after conditioning with CY_{11} or BCNU.[12] LPEs with cardiac tamponade have also been reported post transplant as a consequence of infective pericarditis due to *Streptococcus pneumoniae*,[13] Aspergillus, [14] CMV[15] or EBV[16] reactivation in an immunocompromised host.

In the current study, we consider it is unlikely that infection, drug toxicity or relapsed disease had a role in the development of LPE. None of the patients in our study had evidence of acute or localized infections of the pericardium, which could have led to the development of infectious pericarditis. In addition, none of our patients had evidence of relapse in the pericardium contributing to the LPE. In the majority of our patients, effusions developed many months after the preparative regimens were administered making it unlikely that drug toxicity related to pretransplant chemotherapy contributed to the development of LPE. Two patients who developed LPEs within 100 days of transplant, were both on their second transplant and neither received CY nor BCNU. Anecdotal evidence of pericardits and pericardial effusions caused by TBI is described in the literature.[11,17] In our study three patients who subsequently develop LPE received a TBI-containing preparative regimen; however the median time to post-transplant LPE development in this group was 217 days. Thus, radiation-induced pericardial damage was unlikely to be a significant contributing factor in these patients. The elimination of these other causes further supports the hypothesis that the inflammatory process involving the pericardium was caused by immune-mediated mechanisms most likely associated with GVHD.

Surprisingly, in our patients the serosa was the only site of GVHD exacerbation without involvement of other organs. Resolution of subsequent pleural effusions with high dose steroids in some patients and persistence in others resembles the response to steroids in the treatment of GVHD. We were able to place PWs successfully in all our patients with cardiac tamponade and no deaths occurred related to the procedure. Three patients with PWs were alive and clinically well over a year after the procedure was performed.

We conclude that LPE is an uncommon late complication post transplant that may be treated safely with PW placement, with resolution of tamponade. Although the exact pathophysiology of LPE is unclear, its association with patients undergoing unrelated transplantation who have a history of GVHD suggests that it is likely to be one of the manifestations of GVHD.

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Table 1

Patient characteristics

Patient #	Age	Diagnosis	Donor	HLA match	Cytoreduction	GVHD site	Post transplant day when LPE detected	Concomitant PE	Pericardial window	Pericardial biopsy	Immunosuppression of the LPE detection
1	36	ALL	MUD	10/10	VP16-TBI	Skin, GI (not active)	217	Yes	Yes	Chronic inflammation and fibrin exudates on the surface, consistent with fibrinous pericarditis	Tacrolimus
2	41	AML	MUD	10/10	Bu-Flu	Skin (not active)	51	No	Yes	Portion of fibroconnective tissue with reactive mesothelial lining consistent with pericardium	Tacrolimus
3	58	AML	MUD	10/10	Bu-Flu	Skin, GI, liver (not active)	290	Yes	Yes	Mild chronic inflammation and organizing granulation tissue	Tacrolimus+ methylprednisolone
4	64	MDS	MUD	10/10	Bu-Flu-TBI	None	42	Yes	Yes	Mesothelium-lined fibroadipose tissue with no significant pathological findings	Tacrolimus
5	41	AML	MUD	10/10	Bu-Flu	Skin, GI (not active)	525	Yes	Yes	Markedly thickened portion of pericardium showing acute fibrinous and organizing pericarditis with focal hemorrhage	Tacrolimus+ methylprednisolone+ rituximab
6	47	NHL	MUD	9/10	Bu-Flu-TBI	GI (not active)	230	Yes	Yes	Mild acute and chronic inflammation and benign reactive mesothelial hyperplasia	Tacrolimus
7	47	NHL	MUD	8/10	CVB	Skin, GI (not active)	250	Yes	No	Not done	CYA

Abbreviations: CVB=CY, etoposide and BCNU; CYA=cyclosporine; Flu=fludarabine; GI=gastrointestinal tract; LPE=large pericardial effusion; MDS=myelodysplastic syndromes; MUD=matched unrelated donor; NHL=non-Hodgkin lymphoma; PE=pleural effusion.