Acute Cardiac Tamponade Following Adult Allogeneic Hematopoietic Transplantation

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Abstract

Large pericardial effusions (LPEs) occur in <1% of adults after allogeneic stem cell transplant (allo-SCT). We present four patients who developed acute, new or worsening dyspnea who were found to have LPEs at <100 days from allo-SCT. Of these, three patients also developed immune thrombocytopenic purpura (ITP) within 100 days of allo-SCT, an association that has not been previously reported. In all patients, ITP developed after LPE (at Days +8,15 and 29). All patients responded well to pericardiocentesis with pericardial drain or pericardial window placement, then steroids and thrombopoietin receptor agonists upon ITP diagnosis. In this case series, we highlight LPE development as a possible severe complication in patients undergoing allo-SCT requiring prompt diagnosis and discuss a common plausible immune cause for ITP and LPEs.

Background

- Allogeneic stem cell transplant (allo-SCT) is commonly utilized for a variety of hematological disorders.
- Frequently reported adverse outcomes include graft-versus-host-disease (GVHD), infections, volume overload, engraftment syndrome, veno-occlusive disease, transplant-associated microangiopathy amongst others.
- LPEs following transplant are uncommon in adults, with reported incidence of <1%.
- From reported cases, early LPEs (within 100 days) are generally not associated with acute GVHD, but rather, with cardiac toxicity from conditioning regimens.
- Concurrent LPEs and ITP is rare.

Methods

- Following approval from the Institutional Review Board (IRB), patient, disease, and transplant characteristics were analyzed.
- LPE was defined by pericardial effusion leading to cardiac tamponade on echocardiogram. Early LPE was defined by development of LPE within 100 days of allo-SCT; those that developed after 100 days were labeled late LPEs.
- Pericardial fluid was analyzed for cell counts, cellular differential, chemistry, LDH, viral infections (CMV, HHV-6, adenovirus and coxsackievirus) and tuberculosis.
- Engraftment was characterized by three consecutive days of absolute neutrophils over 500 and platelets count of over 20,000. Engraftment syndrome was defined by presence of fever, rash and non-cardiogenic pulmonary edema.
- When available laboratory parameters for immunological and or systemic collagen vascular disorders were collected.
- ITP was documented by bone marrow biopsy showing adequate megakaryocytes.

Table 1: Patient, disease, and transplant characteristics

Case	Age	Sex	Disease	Conditioning	Donor	Cell Dose (cells/kg)	GVHD prophylaxis	Engraftment	LPE onset	Total volume removed	Recurrence
1	58	F	AML	TBF	Haploidentical	7.181 x 10^6	Tacro and Mycophenolate sodium	20	19	1.7	yes
2	50	F	ALL	Cy-TBI-Campath	MUD	5.946 x 10^6	Tacro	30	60	1.5	yes
3	19	M	Aplastic Anemia	cyclophosphamide and anti-thymocyte globulin	MSD	3.07x 10^6	Tacro and methotrexate	12	1	>0.3	no
4	43	F	Aplastic Anemia	Cy-TBI-Campath	MUD	7.094 x 10^6	Tacro	21	16	0.15	no
Median	46.5							20.5	17.5		

Patient characteristics

We identified 4 adult patients between August 2008 and November 2021 with early LPEs that led to ACT. Interestingly, 3 of these patients also developed ITP, an association that has not been previously described.

All patients received high-dose cyclophosphamide either as part of conditioning or post-transplant GvHD prevention.

Results

Table 2: Pericardial fluid characteristics and laboratory findings

Case	Appearance	Viral studies	Nucleated cells	Neutrophils	Rheumatologic profile	CRP at time of LPE
1	Hazy, serous	negative	200	45	ANA screen (-)	15.3
2	Serous	negative	538	31	ANA screen (-)	2.57
3	Serosanguinous, cloudy	negative	78	9	ANA screen (-)	unknown
4	Cloudy, serosanguinous	negative	unknown	unknown	ANA screen (-)	unknown

Development of ACT and Fluid Characteristics

- Engraftment occurred on days +20, +30 (for first transplant), +12, and +21.
- All four patients developed ACT at <100 days from allo-SCT.
- ACT manifested as acute, new, or worsening shortness of breath.
- Three patients developed LPE before engraftment.
- Laboratory analysis did not support bacterial (e.g. tuberculosis) or viral (e.g. CMV, HHV-6, adenovirus and coxsackievirus) infections, and rheumatologic profiles were negative.
- ACT was treated with either pericardiocentesis with pericardial drain or pericardial window.

Biopsy results

- Patient #2 pericardial biopsy showed benign fibroadipose tissue with reactive mesothelial tissue and skeletal muscle.
- Patient #4's pericardial biopsy revealed skeletal muscle fibers and fibroadipose tissue with focal fibrous adhesions.

Outcomes

- Three of the four patients described are alive one or more years after their alloSCT. Two of these had concurrent ITP.
- Patient 1 responded to IVIG and eltrombopag treatment of her ITP, with a most recent platelet count of 50,000/µl and no evidence of GVHD or constrictive pericarditis.
- Patient 2 engrafted for neutrophils only on day +30. On day 60 of transplant, a marrow examination confirmed relapse of ALL. Three months after her first transplant, she received a second transplant ($5.946X10^6$ CD34/kg cells) from the same donor. Her neutrophils did not drop below 500 on her second transplant. ACT occurred on Day +60 from her second transplant. For ITP she received eltrombopag with response. Unfortunately, on day +150 she was hospitalized with mycobacterium avium pneumonia and disseminated Mucormycosis to which she succumbed.
- Patient 3's alloSCT was complicated by HHV-6 viremia on Day +12 which responded to foscarnet. He developed ITP on Day +30 that resolved over the next 11 months on IVIG, romiplostim and rituximab. Unlike patients 1 and 2, he did not receive any systemic steroids. The patient continues to be in good health 14 years post-transplant.
- Patient 4 did not develop ITP or GVHD, and continues to have normal cell counts 5 years post-transplant.

Discussion

- LPE in adult allo-SCT is rare. A single-center retrospective study of 620 adults who received allo-SCTs. Of these, only 2 (0.32%) developed LPE and cardiac tamponade.
- A report of 12 adult patients identified the following risk factors for LPE: Age over 50, multiple allo-SCT, and presence of chronic GvHD.
- Late-onset LPE has been associated with chronic GVHD, while early-onset LPE is associated with conditioning with cyclophosphamide.
- Early LPE in particular is also associated with late neutrophil engraftment and transplant-associated microangiopathy (TA-TMA).
- Cyclophosphamide dose-dependent cardiotoxicity can potentially be augmented with prior myocardial irradiation and/or previous anthracycline exposure.
- Through direct oxidative damage to the myocardium and endothelial cell damage, cyclophosphamide causes capillary microthrombosis and fibrin deposition, potentially leading to heart failure and arrhythmias.
- Prolonged thrombocytopenia after alloSCT with or without associated serositis has been reported in 5-20% of patients, commonly attributed to immune-mediated destruction, impaired cell line differentiation, and/or splenic sequestration.
- Response to steroids, IVIG, and eltrombopag or romiplostim supports possibility immune-mediated post-transplant thrombocytopenia.

Conclusions

- Potential causes of LPE include cyclophosphamide cardiotoxicity, fluid overload, capillary leak syndrome, engraftment syndrome, TA-TMA, and autoimmune phenomenon.
- The specific diagnostic distinctions among EC activation syndromes remains unclear and clinical presentations are known to overlap.
- It is hard to discern whether concurrent prolonged thrombocytopenia and LPE seen in our patients occurred separately or as part of a clinical syndrome.
- Nevertheless, it is important to recognize that LPE can present with cardiac tamponade that is refractory to diuresis and that it can recur.

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Full list of references available by request