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Clinical Research

Pulmonary Arterial Hypertension in Pediatric Patients with Hematopoietic Stem Cell Transplant–Associated Thrombotic Microangiopathy

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A B S T R A C T

Pulmonary arterial hypertension (PAH) is rarely included in the differential diagnosis of cardiorespiratory failure after pediatric hematopoietic stem cell transplant (HSCT) as the clinical presentation is nonspecific and may mimic other etiologies. The pathogenesis of PAH in HSCT is poorly understood and the diagnosis requires a high degree of suspicion. We describe 5 children diagnosed with PAH after allogeneic HSCT. All 5 patients had prolonged clinical signs of transplantation-associated thrombotic microangiopathy (TA-TMA) when they presented with hypoxemic respiratory failure and evidence of PAH. Four of the 5 patients had echocardiographic evidence of PAH, and 1 patient was diagnosed with PAH only on autopsy. PAH was diagnosed a median of 76 days (range, 56-101 days) after a diagnosis of TA-TMA. Despite aggressive medical management, including inhaled nitric oxide, 4 of the 5 patients died. One patient recovered from PAH after 11 months of sildenafil therapy. Three of the 4 deceased patients had an autopsy performed, demonstrating severe pulmonary vascular disease consistent with TA-TMA and severe PAH. We conclude that TA-TMA can be associated with significant pulmonary vascular injury presenting as hypoxemic respiratory failure with PAH after HSCT. Pediatric patients with unexplained hypoxemia after HSCT should be evaluated for both transplantation complications, TA-TMA and PAH, accordingly.

INTRODUCTION

Pulmonary hypertension is rarely considered in the differential diagnosis of cardiorespiratory failure after pediatric hematopoietic stem cell transplant (HSCT). The complication may occur as a primary pulmonary arterial process or secondary to pulmonary venous hypertension, hypoxia, or thromboembolism [1].

Pulmonary arterial hypertension (PAH) is a disorder defined by a progressive increase of pulmonary vascular resistance leading to right ventricular failure and premature death [2]. PAH is defined by a pulmonary arterial pressure over 25 mm Hg at rest and over 30 mm Hg during activity in combination with an increase in pulmonary vascular resistance over 3 Wood's units [3]. Histopathologically, it is characterized by vascular proliferation and remodeling of all 3 levels of the vessel wall with proliferative and obstructive changes including endothelium, smooth muscle cells, and fibroblasts [3-7]. Pulmonary vasoconstriction is a significant early component in PAH [8]. Early in the disease course, PAH may be asymptomatic or present with nonspecific symptoms such as dyspnea on exertion and fatigue. This makes the clinical diagnosis very challenging, especially in complex HSCT recipients with multiple potential causes for respiratory disease [1]. Although transthoracic echocardiography is an excellent noninvasive screening tool to estimate right ventricle (RV) pressure and pulmonary artery (PA) pressure, right heart catheterization with direct pressure measurements remains the gold standard for the diagnosis of PAH [1,9-12]. However, an RV pressure $\geq$50% of the systemic pressure on a screening echocardiogram is highly suggestive of elevated PA pressure in patients with normal cardiac anatomy.

PAH has been reported in almost all forms of inherited and acquired hemolytic anemias [13-15], but its incidence in patients with HSCT-associated thrombotic microangiopathy (TA-TMA) has not been described, with the exception of 2 brief case reports of pulmonary renal disease possibly associated with thrombotic microangiopathy [16,17].

TA-TMA is a severe and multifactorial complication of HSCT and occurs when endothelial injury causes microangiopathic hemolytic anemia and platelet consumption, resulting in thrombosis and fibrin deposition in the microcirculation and end-organ injury. The kidney is the most commonly affected organ, with other organ injury only rarely reported [18]. Herein, we describe a case series of 5 pediatric allogeneic HSCT recipients diagnosed with hypoxemic respiratory failure and PAH with clinical and histologic evidence of pulmonary TA-TMA.

MATERIALS AND METHODS

After institutional review board approval, we reviewed the records of 209 consecutive HSCT recipients who underwent transplantation between March 1, 2009, and April 30, 2011, at Cincinnati Children's Hospital Medical

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Center and identified those with a clinical diagnosis of PAH and/or histologic findings of pulmonary vascular disease. PAH was defined as echocardiographic evidence of right ventricular dysfunction, dilation, and/or elevated pressure (RV pressure ≥50% of the systemic pressure), or histologic evidence of pulmonary vascular disease on lung biopsy or autopsy as evidenced by vascular proliferation and remodeling of all 3 levels of the arteriolar wall with obstructive changes including endothelial, smooth muscle cells, and fibroblasts. All patients with hypoxemic respiratory failure requiring mechanical ventilation who were examined by echocardiogram or had lung tissue available for histologic diagnosis were included in analysis.

Demographic, clinical, and laboratory information of identified patients was abstracted from their medical records. All patients had a baseline pretransplantation electrocardiogram, echocardiogram, and chest computed tomography scan. Baseline pulmonary function assessment was performed by pulse oximetry or formal pulmonary function test, depending on the patient's age and ability to perform pulmonary function test testing within 30 days before undergoing HSCT. These studies were repeated only as clinically indicated during the transplantation course. There were no uniform guidelines for screening for pulmonary hypertension in patients with hypoxemic respiratory failure; therefore, echocardiographic evaluations were performed at the discretion of the treating physician.

TA-TMA diagnosis was made by the treating HSCT physician using uniform published diagnostic criteria: de novo microangiopathic anemia with the presence of schistocytes on peripheral blood smear, de novo thrombocytopenia, elevated lactate dehydrogenase (LDH), low haptoglobin, doubling of serum creatinine, evidence of neurologic symptoms, and/or histologic evidence of microangiopathy on tissue biopsy or autopsy [19]. Because of age-dependent laboratory normal ranges for hemoglobin, LDH, and serum creatinine, these tests were reported as abnormal for each patient based on their values. Elevation in serum creatinine was reported as doubling of serum creatinine from pretransplantation value for each patient. Neurologic symptoms, if any, were defined as a documented change in mental status or seizures coinciding with diagnosis of TA-TMA. Acute graft-versus-host disease (aGVHD) was graded according to the Glucksberg criteria. Viremias were documented by detection of a virus in the blood using quantitative PCR assays defined as a viral load above the lower limit of laboratory detection. Viral illness was defined as PCR detection of a virus in combination with clinical symptoms. All patients had uniform monitoring and prophylactic and supportive care after their transplantation. Patients who underwent HSCT requiring intensive care unit admission were comanaged by the Critical Care and Bone Marrow Transplant Service.

RESULTS

Of the 209 patients undergoing HSCT at our center during this period, 21% (45 patients) developed hypoxemic respiratory failure requiring mechanical ventilation, 87% of them after allogeneic HSCT. Diagnostic echocardiographic studies were performed in 73% (33 of 45 patients); of these, 15% (5 of 33 patients) had clinical and/or histologic diagnosis of PAH after HSCT. Demographic and HSCT treatment characteristics for patients with pulmonary hypertension are described in Table 1. All 5 patients were young children who underwent allogeneic HSCT: 3 for immunodeficiency, 1 for bone marrow failure, and 1 for malignancy. The 3 patients with immunodeficiency received reduced intensity conditioning (RIC) regimen, and the remaining 2 patients received a myeloablative (MA) conditioning regimen. All 5 patients had normal pretransplantation assessment of cardiac and pulmonary function. Only 1 patient developed aGVHD of the skin posttransplantation, whereas 3 of 5 patients had viral infections (Table 1).

All 5 patients required intensive care unit admission for hypoxemic respiratory failure and mechanical ventilation. PAH was diagnosed by echocardiography in 3 of 5 patients within 24 hours of initiating mechanical ventilation. In the remaining 2 patients, 1 was diagnosed with PAH by echocardiogram 20 days after intubation, whereas the other was noted to have evidence of pulmonary vascular disease only on autopsy 33 days from the start of mechanical ventilation. This patient had echocardiography done 1 month before his death, which showed normal biventricular function and RV pressure 28% of systemic, but echocardiography was not repeated after the patient's clinical deterioration. Only 1 patient underwent cardiac catheterization, which demonstrated an elevated mean PA pressure and increased pulmonary vascular resistance. All but 1 patient who was diagnosed with pulmonary vascular disease on autopsy were evaluated by a specialized pulmonary hypertension team.

The clinical presentation was variable for the 5 patients in this series. Two patients (patient 1 and 2) presented with acute respiratory distress. Patient 1 presented to the emergency department with acute hypoxemia 169 days after transplantation. A bronchoalveolar lavage (BAL) was not diagnostic, and his echocardiogram indicated severe pulmonary hypertension with an RV pressure >90% of systemic. Despite aggressive supportive care and therapy with inhaled nitric oxide (iNO), he died within 24 hours. Similarly, patient 2 presented with rapidly progressive hypoxemia 79 days post-HSCT, leading to respiratory failure without any documented infection. Her echocardiogram was notable for an RV pressure 80% of systemic. Her clinical status worsened with progression to shock, despite therapy with iNO and vasopressor support. She underwent emergent cardiac catheterization with balloon atrial septostomy confirming severe PAH with a mean PA pressure of 58 mm Hg and a pulmonary vascular resistance of 7 Wood's units. The septostomy procedure improved her cardiac output, but with progressive hypoxia, her family elected to withdraw support and she died within 24 hours of presentation.

In contrast, the 3 remaining patients (patients 3, 4, and 5) had a more indolent clinical presentation. Patient 3 and 4 developed hypoxemia without any radiologic evidence of parenchymal or alveolar lung disease. In fact, when

Table 1
Patient Demographics and Transplantation Characteristics

Patient	Diagnosis	Age (y)	Gender	Donor Match	HSCT Regimen	Chemotherapy	aGVHD	Infections at PAH Diagnosis
1	XLP	1.8	Male	URD 7/8	RIC	Alemtuzumab, fludarabine, melphalan	None	Blood: negative Nasal secretions: negative
2	FA	5.8	Female	MUD 8/8	MA	Busulfan, fludarabine, cyclophosphamide, ATG	None	Blood: negative BAL: negative
3	HLH	0.6	Male	URD 7/8	RIC	Alemtuzumab, fludarabine, melphalan	Skin	Blood: CMV Nasal secretions: negative
4	XLP	1.8	Male	MSD 8/8	RIC	Alemtuzumab, fludarabine, melphalan	None	Blood: adenovirus Nasal secretions: MPV
5	CML	10.4	Female	MUD 8/8	MA	Busulfan, cyclophosphamide, ATG	None	Blood: BK virus BAL: EBV

HSCT indicates hematopoietic stem cell transplant; aGVHD, acute graft-versus-host disease; PAH, pulmonary arterial hypertension; XLP, X-linked lymphoproliferative syndrome; URD, unrelated donor; RIC, reduced intensity regimen; FA, Fanconi anemia; MUD, matched unrelated donor; MA, myeloablative regimen; ATG, antithymocyte globulin; BAL, bronchoalveolar lavage; HLH, hemophagocytic lymphohistiocytosis; CMV, cytomegalovirus; MSD, matched sibling donor; MPV, metapneumovirus; CML, chronic myelogenous leukemia; EBV, Epstein-Barr virus.

Table 2
Characteristics of PAH and Lung Pathology

Patient	RV Pressure (%) of Systemic*	Days from HSCT to dx of TMA	Days from HSCT to dx of PAH	Days from dx of TMA to PAH	Days from Intubation to dx of PAH	Days from Intubation to Death	PAH Therapy	Status	Lung Autopsy (A) or Lung Biopsy (B)
1	92	+91	+169	78	1	1	iNO	Dead	A: Severe TMA and PAH
2	80	+17	+79	62	1	1	iNO Septostomy	Dead	Autopsy was not done
3	54	+132	+208	76	20	49	iNO	Dead	A: Severe TMA and PAH In situ + CMV
4	Not done	+15	+71	56	33	33	iNO	Dead	A: Severe TMA and PAH In situ + adenovirus
5	60	+149	+250	101	1	N/A	Sildenafil	Alive	B: Constrictive bronchiolitis Mild vasculopathy

PAH indicates pulmonary arterial hypertension; RV, right ventricle; HSCT, hematopoietic stem cell transplant; dx, diagnosis; TMA, transplant-associated thrombotic microangiopathy; +, days posttransplantation; iNO, inhaled nitric oxide; CMV, cytomegalovirus; N/A, not applicable.
* By echocardiogram for hypoxemia evaluation.

respiratory failure developed in these 2 patients, it was initially attributed to prolonged cytomegalovirus (CMV) and adenoviral infections, respectively. Because of difficulty oxygenating while on ventilator support, they were empirically treated with iNO. Patient 3 had an echocardiogram performed 20 days after intubation that was highly suggestive of PAH (ventricular septal flattening with RV pressure 54% of systemic), whereas patient 4 was diagnosed with PAH only on autopsy. Patient 5 had prolonged BK viremia and intermittent oxygen requirements. She underwent diagnostic BAL, after which she remained on mechanical ventilation for hypoxemia. Her echocardiogram showed an RV pressure 60% of systemic. Diagnostic lung biopsy showed constrictive bronchiolitis and mild vasculopathy. The patient was treated with sildenafil for 11 months and is currently doing well off oxygen more than 2 years after transplantation (Table 2). None of the patients had any radiologic lung abnormalities when they presented with hypoxemia.

TA-TMA occurred in 13% of patients (28 of 209) undergoing HSCT during this period. Notably, in the subset that developed hypoxemic respiratory failure and underwent echocardiography evaluation, the occurrence of TA-TMA was 60% (20 of 33 patients). All 5 patients diagnosed with pulmonary hypertension had clinical evidence of active TA-TMA for a median of 76 days (range, 56-101 days) before developing hypoxemic respiratory failure. Acute kidney injury attributed to TA-TMA with refractory hypertension and severe proteinuria was present in all 5 patients, with 2 of them requiring renal replacement therapy (Table 3). Because there is no uniform therapeutic approach to TA-TMA therapy, calcineurin inhibitor cyclosporine was discontinued in 3 of 5 patients 12 to 26 days after TA-TMA diagnosis, based on the primary transplantation physician's decision. Rituximab and therapeutic plasma exchange were attempted for patient 3 very late in the disease course without obvious clinical benefit because of advanced organ injury. Patient 5 received 3 weekly doses of rituximab for Epstein–Barr virus infection during active TA-TMA (Table 3).

Three of the 4 deceased patients underwent autopsies, which demonstrated severe pulmonary vascular disease. In all cases, lung histology was consistent with acute and subacute TA-TMA, with endothelial separation noted in the pulmonary arterioles, extravasation of fragmented RBC into surrounding tissue, and formation of fibrin thrombi. These findings were associated with marked thickening of all 3 layers of the vascular wall, with up to 95% occlusion of the arteriolar lumens in all lung pathology samples (Figure 1). Some areas had intra-arteriolar fibrin microthrombi with focal areas of organization and recanalization suggestive of chronic and progressive endothelial injury. Patients 3 and 4 had evidence of TA-TMA in other organs including the kidneys. CMV and adenovirus were detected in the lung

Table 3
TA-TMA Features and Management

Clinical Features/Management	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
De novo anemia and thrombocytopenia	Yes	Yes	Yes	Yes	Yes
LDH*	×2.0	×2.0	×3.3	×4.4	×3.6
Haptoglobin (normal 16-200 mg/dL)	<7	<7	<7	<7	<7
Schistocytes†	1+	1+	1+	1+	1+
Creatinine‡	×2.5	×2.8	×9.0	×3.5	×6.8
GFR (mL/min)§	75	48	25	40	24
Proteinuria‖	4	0.5	9.9	3.5	4.4
Antihypertensive medications¶	6	4	8	4	4
Cyclosporine discontinued (d)#	Yes (20)	No	No	Yes (26)	Yes (12)
Rituximab use	No	No	Yes	No	Yes
Renal replacement therapy	No	No	Yes	No	Yes
Therapeutic plasma exchange	No	No	Yes	No	No

TA-TMA indicates transplant-associated thrombotic microangiopathy.
* LDH (lactate dehydrogenase) elevation × (times) above upper normal level for age.
† 1+ is indicative of 1% to 5% of schistocytes on the grading scale using 100 × objective with ~100 RBCs per field.
‡ Serum creatinine elevation × (times) from pretransplantation baseline.
§ GFR (glomerular filtration rate, mL/min) based on cystatin C.
‖ Proteinuria by random urine protein/creatinine ratio with a ratio >2 being nephrotic range proteinuria.
¶ Number of antihypertensive medications that the patient was receiving.
# Number of days (d) that cyclosporine was discontinued after TA-TMA diagnosis.

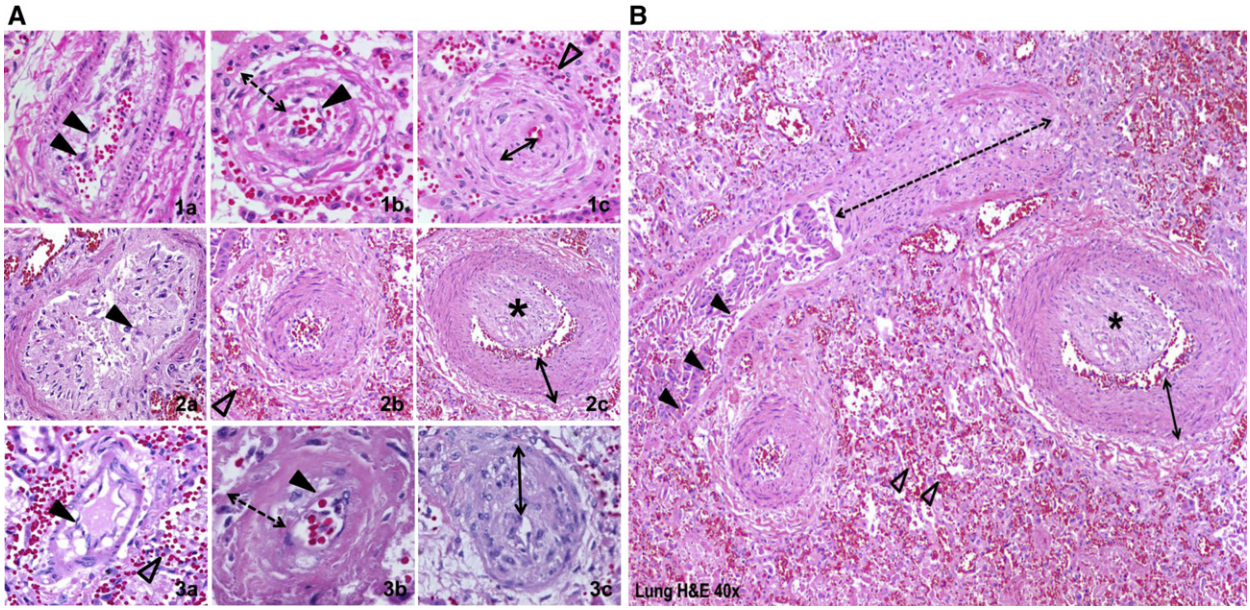

Figure 1. Lung histology from autopsy specimens showing histopathologic changes of transplantation-associated thrombotic microangiopathy (TA-TMA) and pulmonary arterial hypertension (PAH). (A), Lung histology from patient 1 (1a, b, c), patient 3 (2a, b, c), and patient 4 (3a, b, c) demonstrated severe vascular disease involving pulmonary arterioles. All 3 autopsies demonstrated different stages of severe vascular injury present in the same sample ranging from acute microangiopathic vascular injury (1a, 2a, 3a) to subacute (1b, 2b, 3b), and finally severe obliterative changes consistent with histological evidence of PAH (1c, 2c, 3c) (H&E, ×40). Black arrowheads show acute and subacute signs of TMA with endothelial cells "floating" in the vascular lumen after complete separation from the basement membrane. Transparent arrowheads indicate red cell fragments extravagated into surrounding tissues. Other vessels show thickening of all 3 layers of the vascular wall, with up to 95% occlusion of the arteriolar lumens in all lung pathology samples (solid double headed arrows, 1c, 2c, 3c). Some areas have intra-arteriolar fibrin microthrombi (star) with focal areas of organization suggestive of chronic and progressive endothelial injury. 1b, 2b, and 3b depict subacute vascular injury with separated endothelium (black arrowheads) and initial stages of proliferation of vascular wall (dotted double arrows). (B), Lung histology from patient 3 (H&E, ×40) illustrating different stages of vascular injury ranging from acute vascular lesions with separation of the endothelium (black arrowheads), lumen occluding fibrin and cell debris (dotted double headed arrow) with severe red cell fragmentation and extravasation into surrounding tissues (transparent arrowhead), to advanced proliferation of vascular wall (solid double headed arrow) with fibrin microthrombi with focal evidence of organization and near obliteration of vascular lumen (star).

tissue by in situ testing, respectively, for those 2 patients. Autopsy in patient 1 was limited to the lungs. PAH because of TA-TMA was the primary cause of death reported in all 3 patients' autopsies.

DISCUSSION

We describe 5 cases of PAH in pediatric patients who underwent HSCT after a prolonged course of untreated TA-TMA. PAH was severe and a significant contributor to the death in 4 of 5 patients in our cohort. The diagnosis of PAH became apparent only after these patients clinically worsened, and in 1 patient, only at autopsy. At the time, we did not have uniform screening guidelines for patients who underwent HSCT with hypoxemic respiratory failure. Only 73% of patients with respiratory failure underwent echocardiographic evaluation, hence, we cannot comment on exact prevalence of PAH in our pediatric HSCT population. However, based on available data from patients who were evaluated, pulmonary hypertension occurred in 15% (5 of 33 patients) of posttransplantation patients with respiratory failure. It is very likely that the nonspecific presentation of PAH and the high index of suspicion required for diagnosis makes this complication underdiagnosed in the pediatric HSCT population [20-22].

All 5 patients diagnosed with PAH in our study had a prolonged history of TA-TMA. It is important to note that TA-TMA occurred in a much higher proportion in patients who presented with hypoxemic respiratory failure. TA-TMA is an increasingly recognized complication after HSCT with high associated morbidity and mortality [23]. TA-TMA typically affects renal vasculature. However, as evidenced by our cases, TA-TMA may be associated with significant pulmonary vascular injury, leading to hypoxemic respiratory failure after HSCT. It seems plausible that the persistent endothelial injury damaging the small blood vessels of the kidney in TA-TMA could also affect the pulmonary vasculature. Specifically, pulmonary arteriolar narrowing could be caused by microthombi formation, fibrin deposition, and damage from RBC and platelet fragments. Persistent inflammation and vasoconstriction would then promote vascular wall proliferation, leading to the increased vascular resistance seen in PAH [24-26]. An acute stressor, such as active hemolysis, could promote vascular spasm contributing to a rapid elevation in PA resistance, fulminant right heart failure, and hemodynamic collapse.

It is also possible that pulmonary vascular endothelial trauma may significantly interrupt normal nitric oxide production and metabolism, and alter the response of endothelin receptor function [8]. Both these pathologic mechanisms may have implications for treatment options [27,28].

Given our observation that 60% of patients (20 of 33) with hypoxemic respiratory failure had evidence of TA-TMA, and of these, 25% (5 of 20) had pulmonary hypertension, we recommend that any pediatric patient with hypoxemic respiratory failure after HSCT should be evaluated for TA-TMA and PAH. This is especially important in critically ill HSCT recipients with respiratory failure and/or shock of unclear etiology. TA-TMA should be assessed by monitoring for microangiopathic hemolysis with twice-weekly LDH, weekly haptoglobin, and reviewing the daily peripheral blood smear for schistocytes. Close attention should be given to blood pressure and renal function, including proteinuria. If

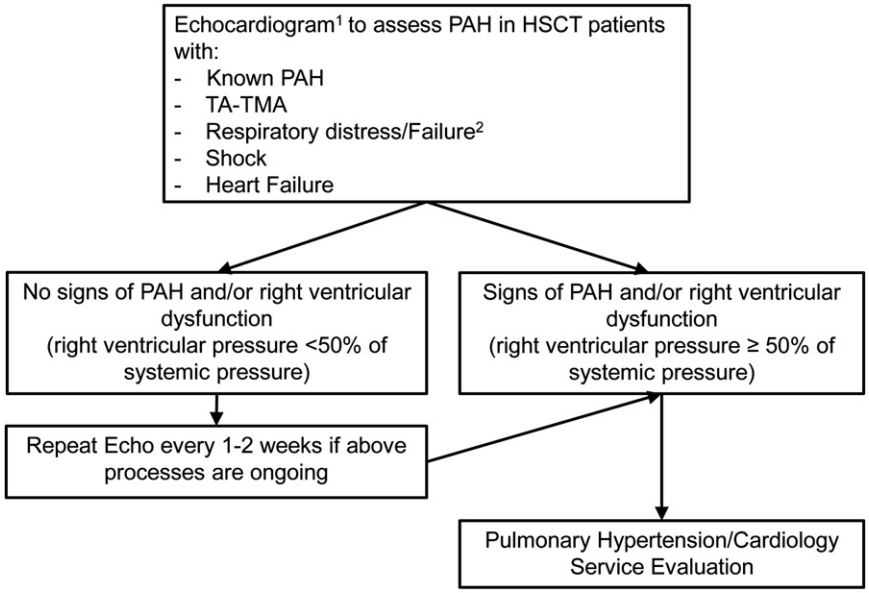

Figure 2. Screening and follow-up algorithm for pulmonary arterial hypertension (PAH) in pediatric patients who underwent hematopoietic stem cell transplant (HSCT). TA-TMA indicates transplantation-associated thrombotic microangiopathy.

clinically feasible, calcineurin inhibitors should be discontinued in patients with a diagnosis of TA-TMA, and alternative immunosuppressive agents such as mycophenolate mofetil and/or steroids should be considered for GVHD prophylaxis. Rituximab and therapeutic plasma exchange had been used in patients who undergo HSCT with successful reversal of microangiopathy reported in small cohorts of patients, although without clear understanding of the mechanism of action in the HSCT population, and might be beneficial in such a patient cohort if introduced promptly [18].

Bedside transthoracic echocardiography is an easy to perform and noninvasive screening test to rapidly assess RV pressure and function. This should be compared to the pretransplantation cardiopulmonary assessments. If the screening echocardiogram is normal and respiratory failure persists, the echocardiogram should be repeated every 1 to 2 weeks. RV pressures 35% to 49% of systemic require very close monitoring. Patients with symptoms of pulmonary hypertension and/or RV dysfunction (RV pressure $\geq$50% systemic) should be immediately evaluated by the cardiology/pulmonary hypertension team (Figure 2). When indicated (inconclusive echocardiographic or clinical evaluation), right heart catheterization should be strongly considered to confirm the diagnosis and test responsiveness to pulmonary vasodilators to improve the otherwise poor outcome of PAH. Best therapeutic options should be guided by the cardiology/pulmonary hypertension team, because selection of appropriate therapies for PAH is complex and there are no standardized pulmonary vasodilator regimens for PAH therapy in children [29,30].

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