Thoracic Air Leak Syndrome, Pulmonary Aspergillosis, and COVID-19 Pneumonia After Allogeneic Stem Cell Transplantation in a Child With Myelodysplastic Syndrome

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Summary: Thoracic air leak syndromes (TALS) are very rare among the noninfectious pulmonary complications (PCs). They can either be idiopathic or have several risk factors such as allogeneic hematopoietic stem cell transplantation (allo-HSCT), graft versus host disease and rarely pulmonary aspergillosis. We present a 14-year-old girl with hypoplastic myelodysplastic syndrome who developed graft versus host disease on day 60, TALS on day 150, bronchiolitis obliterans syndrome on day 300, pulmonary aspergillosis on day 400 and COVID-19 pneumonia on day 575 after allo-HSCT. This is the first report of a child who developed these subsequent PCs after allo-HSCT. Therefore, the manifestations of these unfamiliar PCs like TALS and COVID-19 pneumonia, and concomitant pulmonary aspergillosis with management options are discussed.

Key Words: bronchiolitis obliterans, COVID-19, pulmonary aspergillosis, stem cell transplantation, thoracic air leak syndrome

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Thoracic air leak syndromes (TALS) including pneumothorax, pneumomediastinum, and subcutaneous emphysema are very rare among the noninfectious pulmonary complications (PCs) after allogeneic hematopoietic stem cell transplantation (allo-HSCT).[1–8] As they have barely been reported in children undergoing allo-HSCT, most relevant information could have been obtained from adult studies.[9] Cryptogenic organizing pneumonia, bronchiolitis obliterans syndrome (BOS), and total body irradiation (TBI) conditioning regimen have been described as risk factors in patients with TALS.[2–8] However, the combination of TALS and pulmonary aspergillosis after allo-HSCT has only been reported in adults.[9,10] Furthermore, reports on COVID-19 pneumonia in children following allo-HSCT are scarce.[11]

As little is known about the treatment and outcome of TALS in children we report the first pediatric case of complex PCs after allo-HSCT for hypoplastic myelodysplastic syndrome (HMDS) who developed graft versus host disease (GVHD) on day 60, TALS on day 150, BOS on day 300, pulmonary aspergillosis on day 400 and COVID-19 pneumonia on day 575.

CASE REPORT

A 14-year-old girl was diagnosed with HMDS based on bone marrow aspirate and biopsy findings 6 month before allo-HSCT. Her blood counts showed a hemoglobin level of 5.7 g/dL, mean corpuscular volume: 85 fL, absolute neutrophil count 0.24×10^9/L, and platelet count 38×10^9/L. A bone marrow aspirate showed reduced cellularity with moderate dyserythropoiesis and rare micromegakaryocytes. In the bone marrow biopsy, there was 5% to 10% cellularity with islands of few immature cells. Bone marrow karyotype, paroxysmal nocturnal hemoglobinuria panel and diepoxybutane analysis for Fanconi anemia were normal. For the remaining etiology of HMDS as she had no characteristic signs for dyskeratosis congenita (DC) like abnormal skin pigmentation, oral leucoplakia, nail dystrophy or no signs of idiopathic pulmonary fibrosis, telomere length analysis was not done. She required frequent transfusion support with packed red blood cells however platelet suspensions were rarely used. She was hospitalized for neutropenic fever twice.

No pathology was found in the routine pretransplant evaluation including pulmonary function tests (PFTs) (forced expiratory volume in 1 second [FEV_1]/forced vital capacity 85%) and pediatric pulmonology and cardiology consultation. She underwent allo-HSCT because of transfusion dependency from an HLA-matched, ABO incompatible sibling donor. An aplastic anemia oriented reduced intensity conditioning with low dose (300 cGy) TBI and cyclophosphamide was chosen.[12] She received 4×10^6 $CD34^+$ cells collected by harvest. She received GVHD prophylaxis by rabbit antithymocyte globulin (2.5 mg/kg/d; 4 d), cyclosporine-A (Cyc-A) (3 mg/kg with dose adjustment to maintain trough levels between 150 and 200 μg/L) and short course methotrexate (10 mg/m^2). Times to neutrophil and platelet engraftments were 23 and 26 days, respectively. She was 100% chimeric on day 30. The patient was considered to be high risk for cytomegalovirus (CMV) disease because she and her donor were both CMV seropositive before allo-HSCT. She was monitored weekly for CMV by polymerase chain reaction (PCR) and was found to be positive (4235 copy/mL) on day 35 despite prophylactic high dose acyclovir (1500 mg/m^2/d). Ganciclovir was initiated and continued until PCR negativity (14 d).

On day 60, she developed grade 2 biopsy proven acute GVHD (aGVHD) both in skin and gut, which was successfully managed by steroids along with Cyc-A for 3 months after allo-HSCT. On day 150 while she was still on Cyc-A with steroids being tapered she presented with dyspnea, nonproductive cough, severe hypoxia (88% oxygen saturation in room-air) and chest pain lasted for 1 week. Physical examination showed diffuse crepitation all over her neck and chest. A chest radiograph showed subcutaneous emphysema and small pneumothorax on the right side. A high-resolution computed tomography (HRCT) scan demonstrated subcutaneous emphysema involving neck and chest wall, diffuse pneumomediastinum, bilateral small pneumothorax, and parenchymal glass

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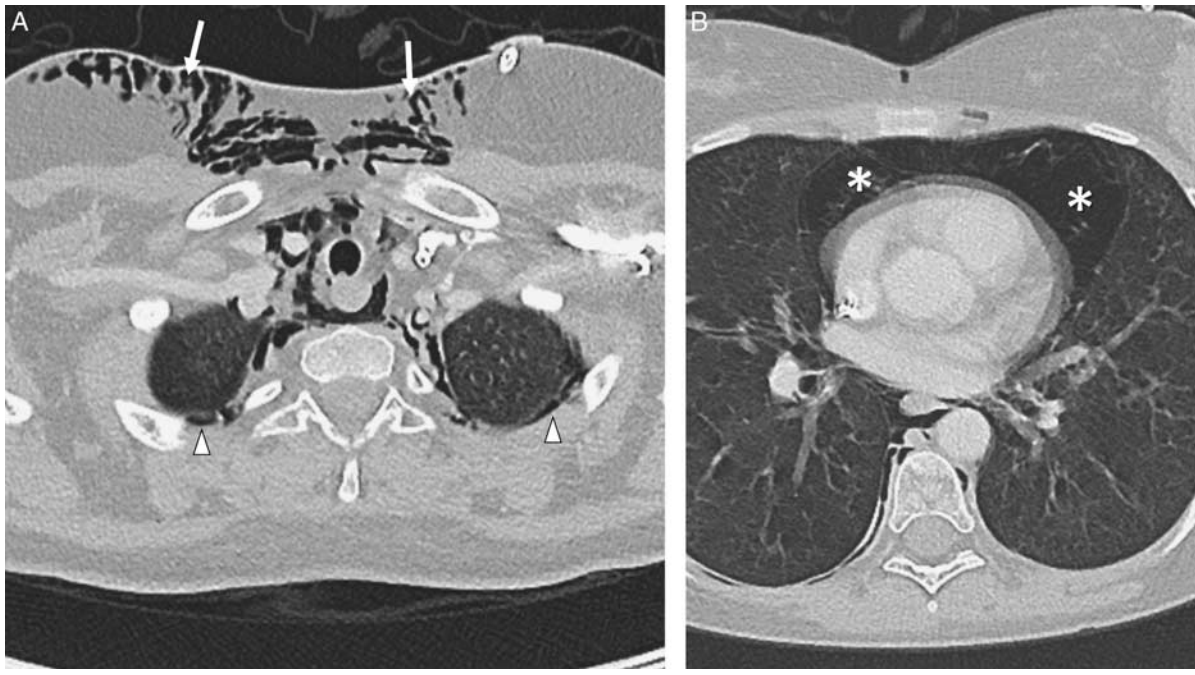


FIGURE 1. High-resolution computed tomography scan of chest shows subcutaneous emphysema (A: White Arrows), pneumomediastinum (B: Asterisks), and limited pneumothorax (A: Arrowheads).

opacities that indicated TALS (Fig. 1). Although ganciclovir was initiated with CMV reactivation suspicion, PCR testing for CMV was found to be negative. Bronchoscopy could not be performed because of sudden deterioration with tachypnea, tachycardia and hypoxia. Besides we and the pediatric pulmonologists decided not to perform the PFTs as it might increase the thoracic air leakage. As she had a GVHD history and pulmonary GVHD could not be ruled out with the existing clinical symptoms and tests she was immediately commenced on broad spectrum antibiotics along with short term methylprednisolone (mPSL) (2 mg/kg/d) while on Cyc-A which initially controlled dyspnea. Two weeks later control HRCT scan depicted that pneumothorax disappeared however pneumomediastinum and subcutaneous emphysema still remain. As a tube insertion for drainage was unsuccessful the treatment continued only with Cyc-A, steroids and oxygen support.

Twenty days after TALS diagnosis on day 170 after allo-HSCT while on steroid taper oxygen need increased, her respiratory status worsened with abnormal blood gas levels and she was intubated. The results of blood, catheter, urine and throat cultures were all negative. There were also no signs of *Pneumocystis jirovecii* pneumonia or aspergillus infection in repeat HRCT scan. Deterioration of the respiratory status while reducing steroids strengthened the suspicion of steroid-dependent pulmonary GVHD and pulse dose mPSL was commenced on at a dose of 10 mg/kg/d for 3 days, simultaneously Cyc-A was switched to tacrolimus (FK). On day 173, with normal arterial blood gas levels she was extubated and recovered within 1 month.

At 4 months follow-up after discharge, on day 300 after allo-HSCT, control HRCT (Fig. 2) showed complete resolution of TALS and new occurrences of small airway thickening and bronchiectasis in both lungs as well as obstructive pattern in PFTs with FEV_1/FVC ratio 61% of predicted value, FEV_1 73% of predicted value. These findings were thought to be consistent with BOS.[13] As she was steroid dependent for GVHD and PCs the fluticasone azithromycin and montelukast (FAM) regimen (fluticasone propionate 440 mcg/d, azithromycin 250 mg 3 times a week, montelukast 10 mg/d) suggested by European transplant committee[14] was initiated with systemic steroids which was promptly tapered later.

On day 400, while on FAM treatment and steroid taper besides prophylactic fluconazole and acyclovir the patient developed exertional dyspnea with productive cough and fever. Thorax HRCT (Fig. 3) showed peribronchial nodules surrounded by ground glass attenuation, bronchial wall thickening and cylindrical bronchiectasis in both lungs consistent with pulmonary aspergillosis with no evidence of TALS. Treatment continued with broad spectrum antibiotics and caspofungin monotherapy in addition to mPSL and FK. Her respiratory status continued to deteriorate despite oxygen treatment and she was intubated again. Bronchoalveolar lavage PCR test was positive for aspergillus whereas negative for *P. jirovecii* and CMV. *Aspergillus terreus* was identified from bronchoalveolar lavage culture. Voriconazole was added to caspofungin treatment for salvage therapy. She was extubated after 2 weeks of mechanical ventilation support while receiving combined



FIGURE 2. Control high-resolution computed tomography scan 4 months after thoracic air leak syndrome shows complete resolution and new occurrences of small airway thickening and bronchiectasis in both lungs (white arrows).

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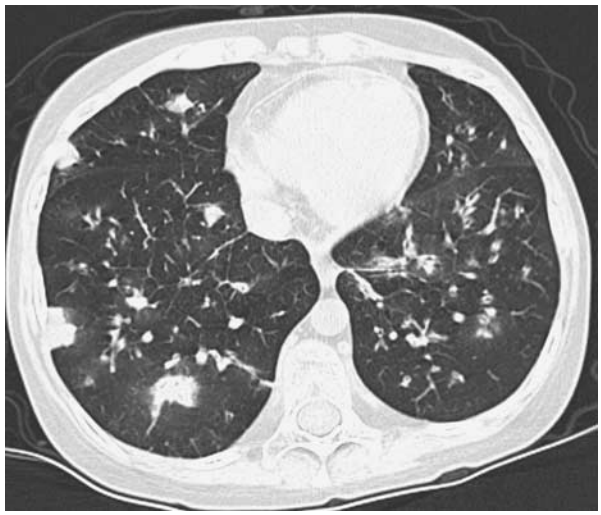


FIGURE 3. High-resolution computed tomography scan shows peribronchial nodules surrounded by ground glass attenuation consistent with pulmonary aspergillosis.

antifungal treatment, and discharged after 45 days. From this date until day 575 she has been well with infrequent oxygen support at home with monthly follow-ups.

On day 575 after allo-HSCT, in the transplant outpatient setting the physician observed sudden onset of respiratory distress while on immunosuppressive treatment and voriconazole prophylaxis. She was hospitalized and oxygen support together with broad spectrum antibiotics and intravenous voriconazole were started immediately. She developed respiratory acidosis and severe hypercapnia (pH: 7.26; $PaCO_2$: 98 mm Hg) and transferred to intensive care unit within 2 hours after admission. Her respiratory status continued to deteriorate despite oxygen treatment and she was intubated again. Her chest radiograph showed no apparent bacterial pneumonia. Bilateral peripheral ground glass and consolidative pulmonary opacities were detected in HRCT. COVID-19 PCR test was found to be positive in both nasopharyngeal swab and endotracheal aspirate. She had had no typical COVID-19 infection symptoms (fever, cough, etc.), and no history of contact to anyone with COVID-19. She was started favipiravir with a diagnosis of COVID-19 pneumonia. However, she passed away on day 60 while on mechanical ventilation.

DISCUSSION

Noninfectious PCs are relatively rare, but serious complications of allo-HSCT in children. TALSs including pneumothorax, pneumomediastinum, and subcutaneous emphysema following allo-HSCT are among the life-threatening noninfectious PCs with an incidence of 0.8% to 2.3% as reported by retrospective case series.[2–4] Several causes like pulmonary aspergillosis, BOS, cryptogenic organizing pneumonia, and TBI conditioning regimens have been reported as major contributing risk factors for TALS after allo-HSCT.[9] TALS can also be observed during the course of GVHD. This is the first report of consecutive occurrences of TALS, BOS, pulmonary aspergillosis, and COVID-19 pneumonia following allo-HSCT in a 14-year-old girl with HMDS.

The literature contains only 8 cases of children with TALS who have undergone allo-HSCT for thalassemia major (n: 1), leukemia (n: 4), MDS (n: 2), and severe aplastic anemia (n: 1) (Table 1).[2–8] The median age of these cases with TALS was 16 years (7 to 18 y). Of them, 7 were adolescent boys (88%) in contrast to our adolescent girl. Except one, all reported cases with TALS had previous pulmonary GVHD. The other patient had acute skin, liver, and gut GVHD before TALS.[7] Similarly in adult series there are TALS cases without preceding pulmonary GVHD.[9] Although there are reported adult dyskeratosis DC cases who had suffered from TALS after allo-HSCT for HMDS our patient had none of the clinical signs of the classic DC.[15,16]

Our patient who underwent allo-HSCT for HMDS developed skin and gut GVHD on day 60 without any signs of pulmonary GVHD. We were clearly surprised to diagnose grade 2 GVHD in this patient who have undergone a MSD allograft with an intensively and precisely applied sufficient prophylaxis. As she was both very smart and compliant with the therapy, occurrence of GVHD is remained to be explained. Alessandrino et al[17] reported that pretransplant transfusion-dependency is associated with an increased occurrence of aGVHD in MDS patients due to the presence of parenchymal iron overload and iron radical-mediated injury of organs. Our patient was also transfusion-dependent and had been transfused with packed red blood cells every 2 weeks before allo-HSCT. In the other hand, Logan et al[18] described an increased risk of aGVHD in the recipients of ABO minor mismatch bone marrow grafts. It is possible that both the transfusion-dependency and ABO mismatch transplantation with bone marrow graft increased the risk of aGVHD in our patient.

Proven pulmonary GVHD as BOS by PFT and imaging was diagnosed at day 300 barely after the recovery of TALS. Our patient received reduced intensity conditioning with low dose TBI, cyclophosphamide, and short course methotrexate, Cyc-A for GVHD prophylaxis. Both TBI and MTX are risk factors for BOS, which is a manifestation of pulmonary GVHD. Four of the reported pediatric patients with TALS in Table 1 received 12 cGy TBI and 2 of them developed BOS.[2,6] The other 2 patients who received 12 cGy TBI had interstitial pneumonia consistent with chronic pulmonary GVHD rather than BOS.[3] The remaining 3 patients with pulmonary GVHD have also BOS however further information about their conditioning and GVHD prophylaxis regimen was unavailable.

Although the noninfectious PCs are reported to increase the risk of TALS in allo-HSCT patients, infectious PCs like pulmonary aspergillosis is a further risk factor for development of TALS which is only reported in adult cases.[2,10] However, TALS and pulmonary aspergillosis after allo-HSCT has not been reported previously in pediatric series. The clinical course of pulmonary aspergillosis in our case was also different and interesting as she presented with severe respiratory findings of TALS on day 150 before pulmonary aspergillosis on day 400. It is likely that the time point and the nature of the previous lung damage (caused by CMV, TALS, BOS) with the addition of aspergillosis contributed to the dismal outcome in our case.

Inhaled corticosteroids are reported to be associated with increased risk of aspergillosis.[19] The development of invasive pulmonary aspergillosis (IPA) under fluconazole prophylaxis in our patient suggested that previous noninfectious PCs, low dose systemic and inhaled corticosteroids use in FAM regimen and prolonged immunosuppressive treatment might have contributed to the development of IPA. This was the cost of the GVHD treatment which she satisfactorily responded.

The management of cases with TALS after allo-HSCT is controversial. Although several treatment regimens like immunosuppressive drug changes, pulse dose steroid administration and invasive procedures are recommended, the optimal therapeutic approach remains unclear. Our case responded to FK switch and pulse dose steroid. The eventual however a bit

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TABLE 1. Pediatric Patient Characteristics With Thoracic Air Leak Syndrome

References	Age/Sex	Underlying Disease	Donor	HLA Matching	Conditioning	GVHD Prophylaxis	GVHD	Lung Complications	IPA	CMV	Type of ALS	Treatment of ALS	Outcome
Vogel et al[2]	14 y/male	SAA	Not reported	Identical	TBI (12 Gy)	Cyc-A	Yes	BOS	–	–	PM, PT	Not reported	Alive
Toubai et al[3]	16 y/male	MDS	MUD	Identical	TBI (12 Gy), BU, CY	Cyc-A, sMTX	Yes	IP	–	–	PM, PT	Pleural adhesion, mPSL	Died
Toubai et al[3]	16 y/male	ALL	MUD	Identical	TBI (12 Gy), VP-16, CY	Cyc-A, sMTX	Yes	IP	–	–	PM, PT	mPSL	Died
Moon et al[4]	18 y/female	AML	MUD	1 Ag mismatch	Not reported	Not reported	Yes	BOS	–	–	PM, PT, SE	Drainage	Died
Sotoude et al[5]	11 y/male	TM	Not reported	Not reported	Not reported	Not reported	Yes	BOS	–	–	PM, PP, PT, SE	Not reported	Died
Suzuki et al[6]	16 y/male	MDS	MSD	Identical	TBI (12 Gy), CY	Cyc-A	Yes	BOS	–	–	PT	Drainage	Alive
Ebihara et al[7]	17 y/male	ALL	MUD	1 Ag mismatch	Not reported	mPSL, FK	Yes	—	–	+	PT	Drainage	Alive
Masetti et al[8]	7 y/male	ALL	MUD	1 Ag mismatch	Not reported	Not reported	Yes	BOS	–	–	PM, PT, SE	Drainage, mPSL, FK, MMF, imatinib	Alive
This case	14 y/female	MDS	MSD	Identical	TBI (300 cGy)	Cyc-A, sMTX	Yes	BOS	+	+	PM, PT, SE	mPSL, FK	Alive

– indicates not exist; +, exist; ALS, air-leak syndrome; BOS, bronchiolitis obliterans syndrome; BU, busulfan; CMV, cytomegalovirus; Cyc-A, cyclosporin-A; CY, cyclophosphamide; FK, tacrolimus; IP, interstitial pneumonia; IPA, invasive pulmonary aspergillosis; MMF, mycophenolate mofetil; mPSL, methylprednisolon; MSD, matched sibling donor; MUD, matched unrelated donor; PM, pneumomediastinum; PP, pneumopericardium; PT, pneumothorax; SE, s.c. emphysema; TBI, total body irradiation; VP-16, etoposide.

delayed switch of immunosuppressive drugs was because the radiologic images are not specific and could easily be mixed with viral and fungal infections namely CMV and aspergillus.

Prognosis is poor and treatment is difficult when TALS is complicated with pulmonary aspergillosis after allo-HSCT.[1,20] The mortality of TALS is between 67% and 100% after allo-HSCT.[2,3] Of the 8 reported pediatric cases, 4 (50%) survived (no information is available about their survival periods) whereas 4 died within a median of 6 months after diagnosis.[2–8] Our case had been alive after 3 different life-threatening PCs. However, she developed a sudden onset respiratory distress on day 575 due to COVID-19 infection and required immediate mechanical ventilation support. She succumbed to death on day 60 on mechanical ventilation (on day 635 after HSCT) because of COVID-19 pneumonia. This is the first report of a child with 4 consequent life-threatening PCs after allo-HSCT. Unfortunately, COVID-19 pneumonia had been the final straw leading to death in the damaged lungs caused by TALS, BOS, IPA.

In conclusion, appropriate diagnosis and identification of PCs, particularly TALS after allo-HSCT are of great clinical importance. Early detection and treatment of these PCs after allo-HSCT are substantial for survival.

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