

RECURRENT THORACIC AIR LEAK SYNDROME IN PATIENTS AFFECTED BY PULMONARY GRAFT-VERSUS-HOST DISEASE: SURGICAL STRATEGIES AND OUTCOME

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Abstract

Background and aims Thoracic air leak syndrome (TALS) is a complication related to chronic pulmonary graft-versus-host disease (pGvHD) that affects approximately 0.83% to 3.08% patients after allogenic hematopoietic stem cell transplant. Such complication is defined as the occurrence of any form of air leak in the thorax, including spontaneous pneumomediastinum or pneumopericardium, subcutaneous emphysema, interstitial emphysema and pneumothorax and has a negative impact on post-transplant survival. The aim of the present study is to describe a single-center experience in the surgical management of recurrent TALS in adolescents and young adults and its outcome. **Methods** We retrospectively reviewed the clinical notes of patients with previous allogenic hematopoietic stem cell transplant who underwent surgical procedures for recurrent TALS from January 2016 until March 2021. As well we analyzed clinical data, number of episodes of thoracic air leak, surgical procedures and relative outcome. **Results** In the examined period, four patients, aged 16 to 25 years, underwent surgical procedures for TALS, including thoracostomy tube placement, thoroscopic pleurodesis and thoracotomy. All the patients had been diagnosed with pGvHD before the onset of TALS, with a mean time lapse of 276 days (range 42 – 513). These patients experienced on average 4.5 air leak episodes (range 3 – 6). All the patients experienced at least two episodes before surgery. One patient underwent emergency tube thoracostomy only, three patients underwent thoroscopic pleurodesis and two patients underwent thoracotomy. After surgery, patients were free from air leak symptoms for a mean time of 176 days (range 25 – 477). Pulmonary function progressively deteriorated, and all the patients eventually died because of respiratory failure after a mean time of 483 days (range 127 – 1045) after the first episode of air leak. **Conclusions** Surgery provides temporary relief to symptoms related to TALS. When TALS develops, pulmonary function progressively worsens toward respiratory failure and death.

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ABSTRACT

Background and aims

Thoracic air leak syndrome (TALS) is a complication related to chronic pulmonary graft-versus-host disease (pGvHD) that affects approximately 0.83% to 3.08% patients after allogeneic hematopoietic stem cell transplant. Such complication is defined as the occurrence of any form of air leak in the thorax, including spontaneous pneumomediastinum or pneumopericardium, subcutaneous emphysema, interstitial emphysema and pneumothorax and has a negative impact on post-transplant survival.

The aim of the present study is to describe a single-center experience in the surgical management of recurrent TALS in adolescents and young adults and its outcome.

Methods

We retrospectively reviewed the clinical notes of patients with previous allogeneic hematopoietic stem cell transplant who underwent surgical procedures for recurrent TALS from January 2016 until March 2021. As well we analyzed clinical data, number of episodes of thoracic air leak, surgical procedures and relative outcome.

Results

In the examined period, four patients, aged 16 to 25 years, underwent surgical procedures for TALS, including thoracostomy tube placement, thoracoscopic pleurodesis and thoracotomy. All the patients had been diagnosed with pGvHD before the onset of TALS, with a mean time lapse of 276 days (range 42 – 513). These patients experienced on average 4.5 air leak episodes (range 3 – 6). All the patients experienced at least two episodes before surgery.

One patient underwent emergency tube thoracostomy only, three patients underwent thoracoscopic pleurodesis and two patients underwent thoracotomy.

After surgery, patients were free from air leak symptoms for a mean time of 176 days (range 25 – 477). Pulmonary function progressively deteriorated, and all the patients eventually died because of respiratory failure after a mean time of 483 days (range 127 – 1045) after the first episode of air leak.

Conclusions

Surgery provides temporary relief to symptoms related to TALS. When TALS develops, pulmonary function progressively worsens toward respiratory failure and death.

MANUSCRIPT

Background and aims

Pulmonary dysfunction causes significant morbidity and mortality in patients receiving allogeneic hematopoietic stem cell transplantation (HSCT) ¹. In particular, Bronchiolitis Obliterans Syndrome (BOS), that is the main pulmonary manifestation of chronic graft-versus-host disease (GVHD), affects approximately 5.5% allogeneic HSCT recipients and 14% among all long-term survivors who develop chronic GVHD ², with attributable mortality rates of 9% at 3 years, 12% at 5 years, and 18% at 10 years after HSCT in the adult population ³.

Thoracic air leak syndrome (TALS) is a complication related to chronic pulmonary GvHD; such complication is defined as the occurrence of any form of air leak in the thorax, including spontaneous pneumomediastinum or pneumopericardium, subcutaneous emphysema, interstitial emphysema and pneumothorax⁴, and usually occurs as a late complication of HSCT (i.e., more than 100 days after transplant)^{5 – 7}. TALS is reported to

affect approximately 0.83% to 3.08% adult patients after allogenic HSCT⁸, with a mortality rate between 66.7 and 100% in early series^{9–10}.

The aim of the present study is to describe a single-center experience in the surgical management of recurrent TALS in adolescents and young adults and its outcome.

Methods

The clinical notes of patients with history of allogenic HSCT and a diagnosis pulmonary graft-versus-host disease (pGvHD) who underwent surgical procedures for recurrent TALS from January 2016 until March 2021 were retrospectively reviewed. In all the patients, the diagnosis of pGvHD was made according to the National Institutes of Health Criteria¹¹.

Clinical data, radiologic images, pulmonary function tests, number of episodes of thoracic air leak, surgical procedures and outcome were analyzed.

The study was approved for publication by the Internal Review Board (internal protocol n RAP-2023-002).

Results

In the examined period, four patients, all male, aged 16 to 25 years, underwent surgical procedures for TALS.

All the patients had history of hematological malignancies; two patients had acute lymphoblastic leukemia (ALL), one had acute myeloid leukemia (AML) and one had ALK-positive Non-Hodgkin lymphoma (NHL).

All the patients received allogenic HSCT; the two patients affected by ALL received a second allogenic HSCT for relapsed disease. Two patients had Bronchiolitis Obliterans (BO) in the early phase (i.e. earlier than 100 days after HSCT).

All the patients developed pulmonary graft-versus-host disease (pGvHD) as a late complication of allogenic HSCT, i.e. after a mean of 340 days (range 202 – 582) and presented with clinical symptoms (i.e. exertional dyspnea and dry cough in the absence of pulmonary infection), evidence of air trapping, bilateral ground glass lesions and bronchiectasis on high-resolution chest CT scan (Fig 1) and evidence of restrictive or mixed restrictive/obstructive pattern at pulmonary function tests.

In three of the four patients, pulmonary function tests were performed in the 30 days before the diagnosis of TALS; in all these patients forced vital capacity (FVC), forced expiratory volume (FEV1) and forced expiratory flow (FEF 25-75%) were markedly reduced compared to previous tests (see table 2). The remaining patient did not repeat pulmonary function tests due to poor compliance.

All these patients had associated comorbidities; three of these patients had evidence of extra-pulmonary GvHD, three had malnutrition, defined as age- and sex-adjusted body mass index below 17.0¹², and two had cardiac dysfunction.

Clinical characteristics and pulmonary function tests of these patients are summarized in table 1 and table 2, respectively.

All the patients developed TALS with a mean time lapse of 615 days from last HSCT (range 327 – 1094) and a mean of 276 days from the diagnosis of pGvHD (range 42 – 513); these patients experienced on average 4.5 air leak episodes (range 3 – 6). All the patients experienced at least two episodes before surgery.

Surgery was indicated as an emergency in case of acute deterioration of respiratory symptoms (i.e., sudden onset of chest pain, tachypnea and oxygen desaturation) associated with radiological evidence of tension pneumothorax (Fig 2), or as an elective procedure in case of failure to improve after initial observation or emergency treatment (Fig 3).

At the first episode of TALS, all patient presented with mild, progressive worsening of typical symptoms of pGvHD, namely exertional dyspnea and dry cough; no patient had chest pain or desaturation. Therefore, the first episode of TALS was treated conservatively in all the patients.

Patient one had two episodes of TALS that were managed conservatively and underwent emergency right tube thoracostomy at the third episode for acute respiratory distress and evidence of tension pneumothorax; this patient rapidly worsened towards respiratory failure, was admitted to Intensive Care Unit and passed away 25 days after emergency tube thoracostomy.

Patient two underwent emergency left tube thoracostomy for respiratory distress and tension pneumothorax at the second episode of TALS. This patient had persistent pneumothorax after 24 days of negative pressure chest drain and underwent left thoracotomy and wedge resection; pathology demonstrated pleuroparenchymal fibroelastosis. Based on pathological diagnosis and worsening respiratory function, oral nintedanib and chronic oxygen supplementation were started. This patient had ipsilateral relapse three months after surgery, that was managed conservatively, and contralateral pneumothorax that required emergency chest drain insertion and, 30 days later, thoracoscopy and pleural scarification. Pulmonary function progressively worsened with the development of chronic respiratory failure and hypercapnia. This patient was referred for pulmonary transplant but was judged non-eligible due to history of acute myeloid leukemia with a disease-free interval shorter than 5 years, previous thoracic surgery, ventricular systolic dysfunction and malnutrition (body mass index 12). Five months after thoracoscopy, this patient had right tension hydropneumothorax that required emergency chest drain; the episode of TALS resolved but general conditions progressively deteriorated and the patient eventually passed away for respiratory failure five months after the last episode of TALS.

Patient three underwent elective right thoracoscopy and chemical pleurodesis at the second episode of TALS after failure of conservative management. This patient underwent contralateral thoracoscopic bullectomy and chemical pleurodesis one and half months after initial surgery, followed by thoracotomy and wedge resection for persistent left pneumothorax after 10 days; pathology demonstrated pleuroparenchymal fibroelastosis. This patient had left tension pneumothorax 40 days after thoracotomy that required emergency chest drain; respiratory function rapidly deteriorated and the patient died 12 days after the last episode of TALS.

Patient four underwent elective right thoracoscopy and chemical pleurodesis at the third episode of TALS after failure of conservative management. This patient had contralateral pneumothorax 14 months after surgery and two more episodes of TALS, all managed conservatively. Pulmonary function slowly progressed and the patient started chronic oxygen therapy 18 months after surgery. This patient was referred for pulmonary transplant but was judged non-eligible due to history of acute lymphoblastic leukemia with a disease-free interval shorter than 5 years, previous thoracic surgery, ventricular systolic dysfunction and malnutrition (body mass index 14.2). The patient ultimately died for respiratory failure two years after surgery.

Surgical procedures and outcomes are summarized in table 3 and table 4, respectively.

Discussion

Thoracic Air Leak Syndrome (TALS) is a complication of pGvHD that includes all forms of extra-alveolar air leak in the thorax, such as interstitial emphysema, spontaneous pneumomediastinum, and spontaneous pneumothorax^{4, 10}.

The pathophysiologic mechanism underlying TALS has been attributed to the Macklin effect, which consists in air leak into the pulmonary interstitium secondary to alveolar rupture, with retrograde dissection along the perivascular sheaths toward the hilum and into the mediastinum^{10, 13}. In patients affected by pGvHD, alveolar wall rupture is likely to be caused by high intra-alveolar pressure, which is related to small airways stenosis and chronic coughing that occur in Bronchiolitis Obliterans,³ associated with alveolar wall weakness caused by pulmonary fibrosis^{10, 14}. In the subject case series, pulmonary function tests performed before the onset of TALS revealed a sharp reduction in FEF 25-75%, which has been associated with small distal airways dysfunction¹⁵. Such observation is consistent with the proposed pathophysiologic mechanism.

The prevalence of TALS in patients with a history of allogenic HSCT is reported between 0.83%⁵ and 3.08%⁴. Specific risk factors have been associated with increased incidence of TALS, including history of extra-pulmonary chronic GvHD, previous Bronchiolitis Obliterans (BO), previous invasive pulmonary fungal

infections, male sex, age younger than 38 years and history of repeated allogeneic HSCT^{4, 6, 8}. In the present case series, all the patients were male and younger than 38 years and three of them had at least one other risk factor for TALS, namely repeated allogeneic HSCT, previous BO and extra-pulmonary chronic GvHD (see table 1).

The occurrence of TALS significantly worsens long-term prognosis of patients with a history of allogeneic HSCT, with a survival rate of 44% at 1 year and 15% at 3 years⁶. Early series reported a mortality rate among patients with TALS ranging between 66.7% and 100%⁹⁻¹⁰; the prognosis of these patients has not significantly improved in recent years, with overall mortality ranging from 61%⁶ to 100%⁷.

Patients affected by TALS receive a combination of supportive therapy, increased immunosuppression and surgical treatment, including simple chest drain, chemical pleurodesis, thoroscopic resection, open thoracic surgery⁵⁻⁸ and even lung transplantation in extreme cases⁷, with a mortality rate in patients treated with surgery reported between 64%⁶ and 100%⁷. In these series, the rationale for therapeutic choice between medical and surgical treatment and details about surgical complications and outcome were not specified; such high mortality in patients who have undergone surgery might therefore be related to more severe forms of TALS rather than surgical complications.

In the subject case series all the patients experienced temporary relief from symptoms related to TALS after surgery, but respiratory function deteriorated and air leak relapsed in all cases. In two patients, air leak was eventually controlled but respiratory failure progressively developed, eventually leading to exitus, while two patients had tension pneumothorax as a final complicating event, that led to exitus (see table 4).

It has been proposed that the development of TALS might be interpreted as a sign of severe worsening of pulmonary GvHD, which eventually leads to respiratory failure and death, even in patients in whom resolution of air leak has been obtained^{5, 6, 8}; the present data are consistent with this hypothesis.

Kunou et al have described the successful use of pleural covering technique with oxidized regenerative cellulose mesh in two patients affected by recurrent TALS after HSCT¹⁶. This technique consists in covering the visceral pleura with sheets of bioabsorbable material after resection of bullae^{17, 18}; the bioabsorbable mesh induces thickening of the visceral pleural with minimal or no pleural adhesion¹⁹ and reduces the risk of recurrence after bullectomy in patients affected by primary spontaneous pneumothorax¹⁸. This technique might be a promising surgical option for air leak resolution in patients affected by TALS; however, it cannot address the problems related to progressive pulmonary GvHD and worsening respiratory function.

Referral for lung transplantation could be a surgical option for these patients; however, many of them might be judged as non-eligible, as happened for two of the patients in the subject series, because of history of hematologic malignancy with a disease-free interval shorter than 5 years, previous thoracic surgery, malnutrition or other comorbidities²⁰.

Repeated allogeneic HSCT has become a therapeutic option in pediatric patients with relapsed hematologic malignancies²¹⁻²³; as the number of children and adolescents who receive second allogeneic HSCT increases, a greater number of patients affected by TALS should be anticipated.

In conclusion, surgery provides temporary relief to symptoms related to TALS but has no impact on the progression of pulmonary GvHD. When TALS develops, patients are at very high risk of respiratory failure and death.

Multidisciplinary efforts are mandatory to develop novel strategies for the prevention of TALS, the identification of high-risk patients and the treatment of TALS.

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Conflict of interest statement

No author has any conflict of interest to disclose

Legend of tables

Table 1: clinical characteristics of patients

Table 2: pulmonary function test

Table 3: surgical procedures

Table 4: outcome

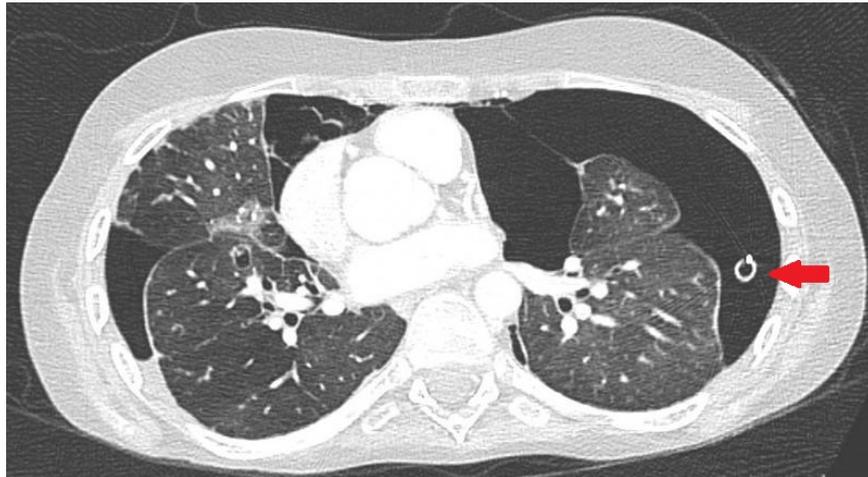
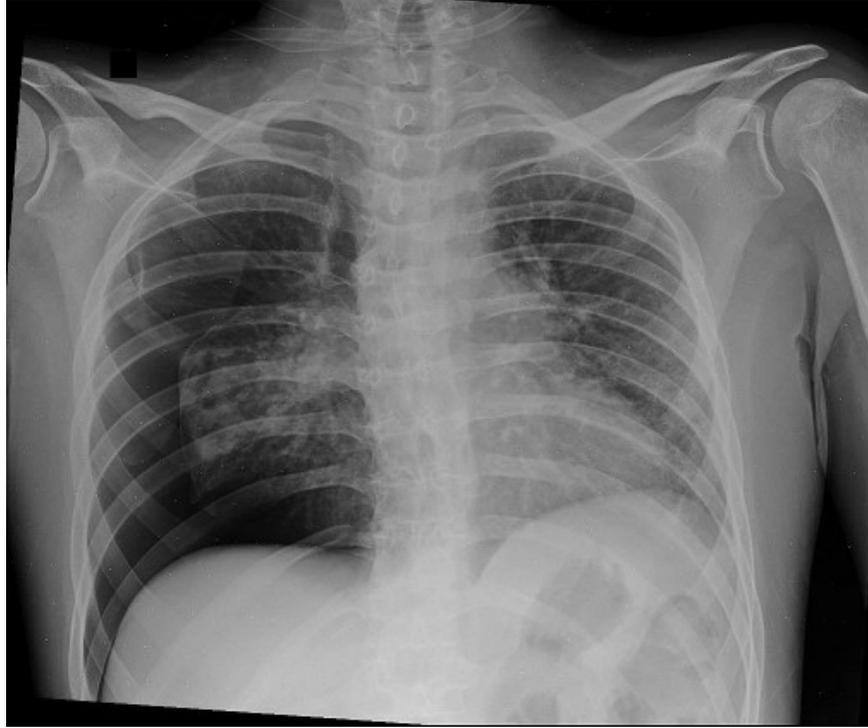
Legend of figures

Figure 1: CT appearance of pulmonary GvHD

Figure 2: pneumothorax as clinical manifestation of TALS

Figure 3: persistent pneumothorax in patient with TALS after tube thoracostomy (arrow)





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Table 1 - clinical characteristics.xlsx available at <https://authorea.com/users/601581/articles/634496-recurrent-thoracic-air-leak-syndrome-in-patients-affected-by-pulmonary-graft-versus-host-disease-surgical-strategies-and-outcome>

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