

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

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Abstract

Thoracic air leak syndrome (TALS) is a complication related to chronic pulmonary graft-versus-host disease (pGvHD) and is defined as the occurrence of any form of air leak in the thorax. Four patients, aged 16 to 25 years, underwent surgical procedures for TALS between January 2016 and March 2021. All the patients experienced at least two episodes before surgery. After surgery, patients were temporarily free from air leak symptoms. All the patients eventually died because of respiratory failure. Surgery provides temporary relief to symptoms related to TALS. When TALS develops, pulmonary function progressively worsens toward respiratory failure and death.

INTRODUCTION

Chronic pulmonary graft-versus-host disease (pGvHD) is a complication of allogeneic hematopoietic stem cell transplantation (HSCT) that affects approximately 5.5% recipients and 14% among all long-term survivors who develop chronic graft-versus-host disease (GVHD)¹, with attributable mortality rates of 9% at 3 years, 12% at 5 years, and 18% at 10 years after HSCT in the adult population ².

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 ³, and usually occurs as a late complication of HSCT (i.e., more than 100 days after transplant) ^{4–6}. TALS is reported to affect approximately 0.83-3.08% adult patients after allogeneic HSCT^{7–9}.

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.

RESULTS

Methods

The clinical notes of patients with history of allogeneic HSCT and a diagnosis of pGvHD who underwent surgical procedures for recurrent TALS from January 2016 until March 2021 were retrospectively reviewed.

Case descriptions

Four patients underwent surgical procedures for TALS.

All the patients had history of hematological malignancies diagnosed during adolescence. All the patients received allogenic HSCT; two of them received a second allogenic HSCT for relapsed disease.

All the patients developed pulmonary graft-versus-host disease (pGvHD) as a late complication of allogenic HSCT, and presented with exertional dyspnea and dry cough, radiologic evidence of air trapping, bilateral ground glass lesions and bronchiectasis (Fig 1) and restrictive or mixed restrictive/obstructive pattern at pulmonary function tests.

Pulmonary function tests showed progressive reduction of forced vital capacity (FVC), forced expiratory volume (FEV1) and forced expiratory flow (FEF 25-75%).

All these patients had associated comorbidities, including extra-pulmonary GvHD, malnutrition, defined as age- and sex-adjusted body mass index below 17.0¹⁰, and cardiac dysfunction.

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

Surgery was indicated as an emergency in case of respiratory distress with radiological evidence of tension pneumothorax, or as an elective procedure in case of failure of initial treatment (Fig 2).

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. This patient had contralateral tension 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. This patient was referred for pulmonary transplant but was judged non-eligible due to history of recent hematologic malignancy, previous thoracic surgery, ventricular systolic dysfunction and malnutrition. This patient had right tension hydropneumothorax five months later that required emergency chest drain; general conditions progressively deteriorated and the patient eventually passed away for respiratory failure.

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. 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. Respiratory failure slowly developed; the patient was referred for pulmonary transplant but was judged non-eligible due to history of recent hematologic malignancy, previous thoracic surgery, ventricular systolic dysfunction and malnutrition. The patient ultimately died for respiratory failure two years after surgery.

Surgical procedures and outcomes are summarized in table3 and table 4 in the Supporting Information, respectively.

DISCUSSION

The development of TALS has been attributed to the Macklin effect, which consists in air leak into the pulmonary interstitium with retrograde dissection along the perivascular sheaths^{9, 11}. Air leak is secondary to alveolar rupture caused by high intra-alveolar pressure, related to small airways stenosis and chronic

coughing² associated with alveolar wall weakness caused by pulmonary fibrosis^{9, 12}. The sharp reduction in FEF 25-75% described in this series, which has been associated with small distal airways dysfunction¹³, is consistent with this mechanism.

Risk factors associated with increased incidence of TALS include history of extra-pulmonary chronic GvHD, previous Bronchiolitis Obliterans (BO), male sex, age younger than 38 years and history of repeated allogeneic HSCT^{3, 5, 7}.

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 years⁵ and overall mortality rate among patients between 66.7% and 100%^{8, 9} despite multiple surgical strategies that include simple chest drain, pleurodesis, thoroscopic resection, open thoracic surgery⁴⁻⁷ and even lung transplantation in extreme cases⁶.

In the present case series, all the patients experienced temporary relief from symptoms related to TALS after surgery, but in all cases respiratory function deteriorated, eventually leading to exitus (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 air leak has resolved^{4, 5, 7}; the present data are consistent with this hypothesis.

Kunou et al have described the successful use of pleural covering technique in two adults affected by recurrent TALS after HSCT¹⁴. This technique consists in covering the visceral pleura with sheets of bioabsorbable material^{15, 16}, which induces thickening of the visceral pleural with minimal or no pleural adhesion¹⁷ and reduces the risk of recurrence of TALS¹⁶. This technique might be a promising surgical option for air leak resolution; however, it cannot address the problems related to 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 because of history of hematologic malignancy with a disease-free interval shorter than 5 years, previous thoracic surgery, malnutrition or other comorbidities¹⁸.

Repeated allogeneic HSCT has become a therapeutic option in pediatric patients with relapsed hematologic malignancies¹⁹⁻²¹; as the number of children and adolescents who receive second allogeneic HSCT increases, a higher incidence of 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 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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Data Availability Statement: The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

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LEGENDS

FIGURE 1 : CT appearance of pulmonary GvHD

FIGURE 2 : persistent pneumothorax in patient with TALS after tube thoracostomy (red arrow)

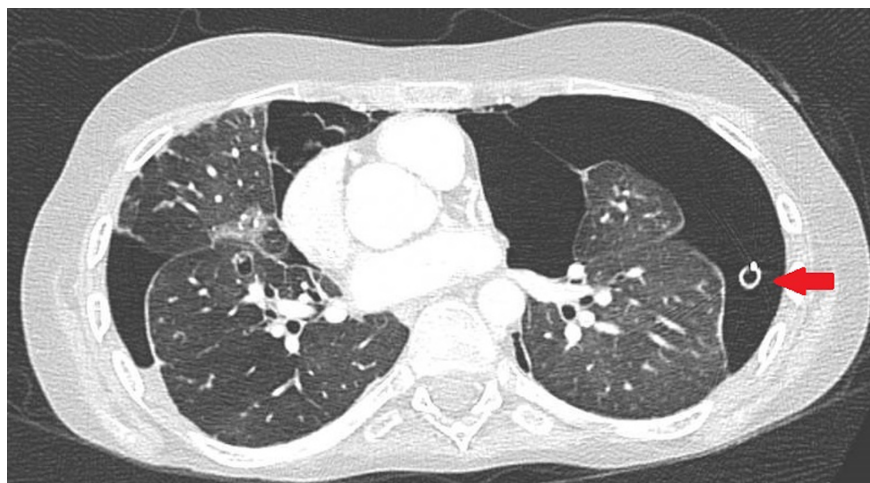
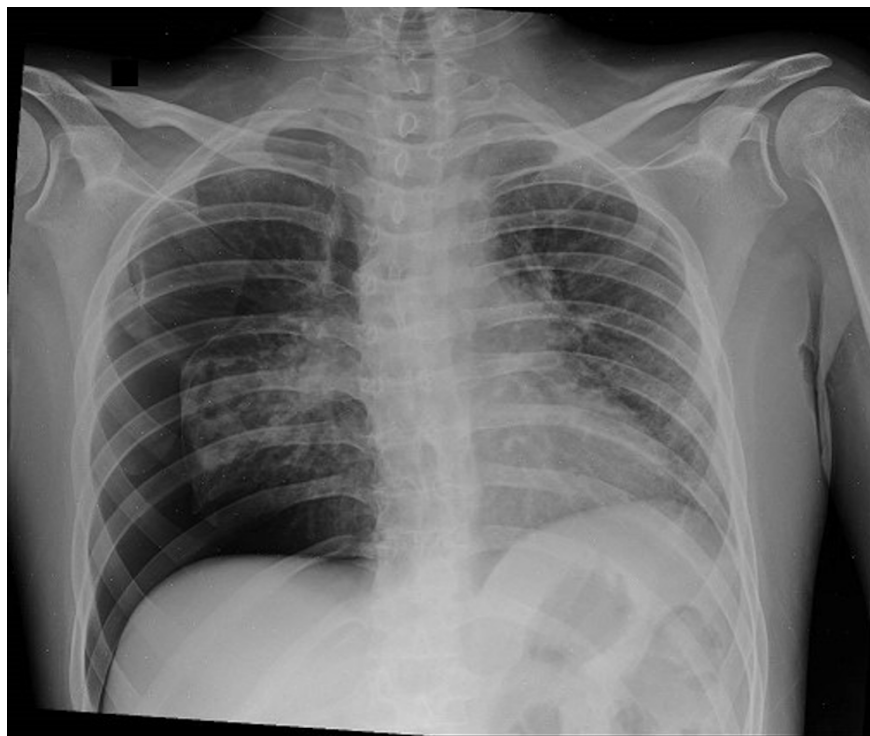
TABLE 1: Clinical characteristics of the analyzed population

TABLE 2: Pulmonary Function Tests of the analyzed population

TABLE 3: Surgical characteristics of the analyzed population

TABLE 4: Outcome of the analyzed population





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