

CASE REPORT

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Thoracic air leak syndrome as the sole manifestation of chronic lung graft-versus-host disease: a case report

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Abstract

Background: Thoracic air leak syndrome (TALS) is a rare complication associated with chronic lung graft-versus-host disease (GVHD) and bronchiolitis obliterans syndrome (BOS). In the present case, TALS was the sole pulmonary manifestation of GVHD.

Case presentation: A 30-year-old woman presented with dyspnea on exertion and swelling of the neck and face after allogeneic stem cell transplantation for acute myeloid leukemia. She was found to have subcutaneous emphysema, and chest imaging suggested pneumomediastinum, with normal lung parenchyma. Her clinical and radiological findings indicated TALS. There were no other features suggestive of lung GVHD. Her condition improved with conservative management and increased immunosuppression. However, she subsequently had two relapses, developed severe infection and pneumothorax, and died.

Conclusions: The present case report illustrates a unique presentation of TALS, a rare complication of GVHD, in a post-stem cell transplant patient. It highlights the challenges in the diagnosis and management of this condition.

Keywords: Air leak, Leukemia, Graft-versus-host disease, Pneumomediastinum, Stem cell, Transplant, Thoracic air leak syndrome

Background

Thoracic air leak syndrome (TALS) is a rare and fatal complication of hematopoietic stem cell transplantation. It has a cumulative incidence of 0.83–2.1% [1]. The literature on TALS is scarce; hence, many aspects of the syndrome including its presentation remain obscure [2]. This syndrome can include pneumomediastinum, pneumothorax, and/or pneumopericardium. It usually manifests as part of a chronic form of pulmonary graft-versus-host disease (GVHD) with associated bronchiolitis obliterans syndrome (BOS) [3]. Onset usually occurs 1-year

post-transplant but can occur from 60 to 1825 days following transplant; cases as early as 1-month post-transplant have also been reported [4]. This case was unusual because the patient did not have any additional clinical, physiological, or radiological features of lung GVHD other than pneumomediastinum.

Case presentation

We report a case of a 30-year-old woman who underwent allogeneic, matched sibling donor transplant for acute myeloid leukemia in complete remission. She received myeloablative conditioning using a fludarabine–busulfan regimen and a stem cell dose of 10×10^6 cells/kg of CD34+ cells. Tacrolimus and mini methotrexate were used as prophylaxis against graft-versus-host disease (GVHD). Neutrophil and platelet engraftment were

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documented on day +17 and day +11 (05.08.2019), respectively.

Variable number of tandem repeat analysis showed post-transplant chimerism on day +28, and complete donor profile on days +60 and +100. Bone marrow biopsy on day +60 post-transplant showed no evidence of disease, and flow cytometry showed no evidence of even minimal residual disease. Tacrolimus was tapered and discontinued to enhance the graft-versus-leukemia effect.

On follow-up post-transplant day+67, mild transaminitis was noted. By post-transplant day +102, she had developed oral lichen planus, and the liver enzymes were markedly abnormal. She was assessed as having chronic GVHD of mild severity based on the National Institute of Health (NIH) criteria. She was started on budesonide 3 mg thrice daily along with tacrolimus ointment. By post-transplant day+119, the oral lichen planus had worsened, and she also had dry eyes. The GVHD was considered severe based on the NIH criteria. In addition to budesonide, cyclosporine 150 mg twice a day, prednisolone 0.5 mg/kg once daily, and topical agents for the dry eyes were started. Her symptoms improved subsequently.

On post-transplant day+144, she presented with dry cough, but no breathlessness or fever was noted. Clinical examination revealed scattered wheezes bilaterally. High-resolution computed tomography (CT) of the chest showed random small nodules in both lower lobes with minimal surrounding ground glass opacities. There was no evidence of chronic lung GVHD. Multiplex respiratory virus polymerase chain reaction (PCR) was positive for human bocavirus, and serum test for *Aspergillus galactomannan* was negative. Spirometry revealed obstructive ventilatory defect with bronchodilator reversibility. The overall features were suggestive of probable lung GVHD; thus, she was started on metered dose inhalers.

On post-transplant day+203, she was admitted due to week-long exertional dyspnea. Clinical examination revealed swelling and crepitus around the neck. High-resolution CT of the thorax showed pneumomediastinum from the neck extending downwards with no other features of chronic pulmonary GVHD; the lung parenchyma was normal (Fig. 1a–d). She was advised to rest and given high-flow oxygen supplementation. Tests for the common respiratory viruses yielded negative results, as did the one for *Pneumocystis jirovecii*. TALS was then considered even if it is rarely a presenting feature of lung GVHD. Though the patient's lung findings showed features of obstructive ventilatory defects, her imaging results were not characteristic of GVHD. At this point, twice weekly injections of etanercept were added to her regimen of steroids and cyclosporine. On reactivation of cytomegalovirus, she was treated with a full course of

ganciclovir. Her symptoms improved, and she was gradually weaned off oxygen support (Fig. 1e–h). However, 1 month later, she was readmitted with similar complaints and with subcutaneous emphysema around the neck. Again, she was placed on high-flow oxygen, and this led to the improvement of her symptoms. Ruxolitinib was then added to the regimen. A third episode 2 weeks later was managed similarly. Serial imaging showed only pneumomediastinum, with no other features of air leak, such as pneumothorax. One month later, she presented again with dyspnea, cough, and fever. She developed type 1 respiratory failure, and repeat imaging revealed bilateral cavitating pneumonia (Fig. 1i–m). She was initiated on broad-spectrum antibiotics, empirical antifungals, mechanical ventilation, and tube thoracostomy for the pneumothorax. Her condition progressively worsened, and she died. Autopsy was not performed owing to deference to religious beliefs.

Discussion and conclusions

First described by Franquet et al. in 2000, TALS is a rare, late-onset pulmonary complication seen in patients who undergo a hematopoietic stem cell transplant. It is defined as the spontaneous leakage of air from the alveoli of the lung to the surrounding structures [5]. The major risk factors for TALS are male sex, age <35 years, GVHD, and tacrolimus-based GVHD prophylaxis. The patient in this case presented with three out of these four known risk factors [6]. TALS is usually a diagnosis of exclusion, after differentials such as aspergillosis, *Pneumocystis jirovecii* pneumonia, and pleuro-parenchymal fibroelastosis, all of which may cause air leak, have been excluded [7]. It is nearly always associated with BOS, which causes distal airway obstruction and air trapping. The proposed mechanism of TALS is the Macklin effect, a three-step sequence of spontaneous alveolar rupture, followed by air dissection along bronchovascular structures to the interstitium, and, finally, air leakage into the mediastinum.

Though the management of TALS depends on the type and severity of air leaks, there is currently no consensus regarding its treatment. Some studies suggest bed rest and high-flow oxygen therapy for patients with pneumomediastinum alone. In the presence of a pneumothorax, tube thoracostomy is considered along with pleural patch closure [8]. Lung transplantation has also been suggested, although with varied success rates [9]. Because TALS is a manifestation of GVHD, supplemental immunosuppression can be attempted. However, immunosuppression increases the risk for infections and can also weaken interalveolar septa and predispose to air leaks. However, without supplemental immunosuppression, the underlying GVHD may worsen [10]. Hence, patients who develop TALS have poor prognoses [11].

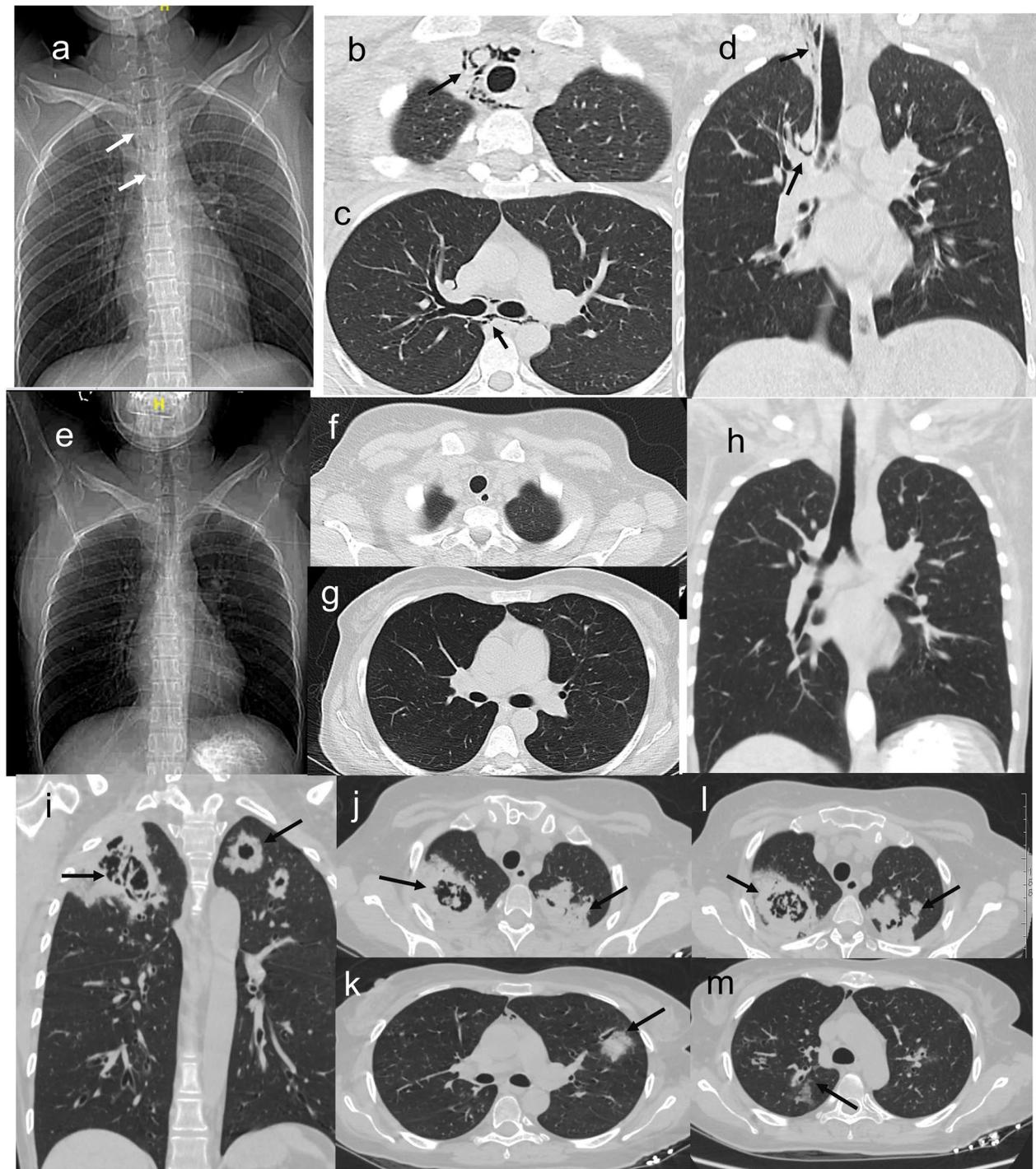


Fig. 1 **a** Chest radiograph shows air out lining the mediastinal contours. **b, c** Axial CT thorax section shows air outlining the mediastinal vessels and tracheobronchial tree. **d** Coronal CT thorax section showing pneumomediastinum. Repeat chest radiograph (**e**), repeat CT thorax, axial CT (**f** and **g**) and coronal CT (**h**) sections reveal resolution of pneumomediastinum. **i-m** CT taken during last admission demonstrates multiple thick-walled cavities with varying amounts of consolidations and nodules. A few of the cavities have nodular soft tissue densities and linear septa within them. CT, computed tomography

TALS, as a manifestation of GVHD, should be studied further due to its association with poor outcomes. Further knowledge about its course may help in formulating timely treatments that may aid in reducing mortality and improving overall outcomes.

The limitations of our case report are that a lung biopsy was not performed due to concerns that such a procedure would worsen her air leak. Furthermore, an autopsy was not performed for social reasons. The absence of histologic examinations of the lung tissue limits our discussion of this case.

This case describes a very rare pulmonary complication, TALS, which should be considered in all patients post stem cell transplant who presents with breathlessness and if diagnosis indicates a very poor prognosis.

Abbreviations

BOS: Bronchiolitis obliterans syndrome; CT: Computed tomography; GVHD: Graft-versus-host disease; TALS: Thoracic air leak syndrome.

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Authors' contributions

AAN: manuscript preparation, editing, coordination of various authors, and final draft. AR: manuscript preparation. AJD: draft editing and critical suggestions. LRV: radiological diagnosis, images, and legends. RG, BT, and VM: supervision and draft revision. The authors have read and approved the final manuscript.

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Consent for publication

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Competing interests

The authors declare that they have no competing interests.

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