Clinical and imaging characteristics of hematologic disease complicated by air leak syndrome

A STROBE-compliment observational study

Kemin Zhang, MMa, Bing Shi, MBb, Qiang Zhai, MBb, Lihui Jiang, MBa, Xiaoxue Wang, MBa, Shan Jiang, MMb, Hongyan Sun, MDa

Abstract

There are limited systematic studies on hematologic disease complicated by air leak syndrome (ALS). Physicians in radiology departments and hematology departments have a limited awareness of ALS.

The aim of this study was to explore the similarities and differences in clinical data between the clinical group and imaging group in patients with hematologic disease complicated by ALS.

Clinical and CT data for 59 patients with hematologic disease complicated by ALS in our hospital were retrospectively reviewed. Patients were assessed by clinical grouping and image grouping. Data were compared between groups, and \( P < .05 \) was considered statistically significant.

Dyspnea occurred more often in the allo-HSCT (allogeneic hematopoietic stem cell transplantation) group than that in the non–allo-HSCT group (68.8% vs 4.7%, \( P < .001 \)), there were statistically significant differences in inducing factors between groups, and differences in other aspects were not statistically significant. Chest tightness and dyspnea occurred more often in the allo-HSCT with BO/BOOP (bronchiolitis Obliterans/bronchiolitis obliterans organizing pneumonia) group than those in the allo-HSCT without BO/BOOP group (80.0% vs 9.1%, \( P = .013 \)), and differences in other aspects were not statistically significant. Chest pain occurred more often in the HPT (hydropneumothorax) group than that in the other 3 groups (pure pneumothorax [PT], pulmonary interstitial emphysema [PIE], complex ALS) (71.4% vs 11.1%, 0.0%, and 26.5%, \( P = .005 \)); ALS thickness in the HPT group was greater than that in the other 2 groups (PIE and complex ALS) (19.7 cm and 9.5 cm, \( P = .001 \)); catheter drainage occurred more often in the HPT group than that in the other three groups (PT, PIE, complex ALS) (64.3% vs 22.2%, 0.0%, and 2.9%, \( P = .001 \)).

ALS is a high risk in male patients who have a low BMI, have leukemia as a basic disease, and have basic lung diseases (eg, BO/BOOP). CT types are mainly complex ALS, HPT, and pure PT. In addition, clinical symptoms for patients in the HPT group are severe, and there is a high prevalence of catheter drainage.

Abbreviations: allo-HSCT = allogeneic hematopoietic stem cell transplantation, ALS = air leak syndrome, BO/BOOP = bronchiolitis Obliterans/bronchiolitis obliterans organizing pneumonia, CT = computed tomography, DIPI = drug-induced pulmonary injury, GVHD = graft-versus-host disease, HPT = hydropneumothorax, HRCT = high-resolution CT, IPS = interstitial pulmonary syndrome, MPR = multi-planar reconstruction, PIE = pulmonary interstitial emphysema, PM = pneumomediastinum, PT = pneumothorax.

Keywords: air leak syndrome, allogeneic hematopoietic stem cell transplantation, computed tomography, hematopathy
1. Introduction

Air leak syndrome (ALS) is a general term for pulmonary interstitial emphysema (PIE), pneumomediastinum (PM), and pneumothorax (PT). Hematologic disease is a group of diseases that originate or affect the hematopoietic system and blood; it includes leukemia, lymphoma, aplastic anemia, myeloma, thrombocytopenia, among others. Patients with hematologic disease complicated by ALS were first reported in 2007. ALS is rare, in patients with hematopathy after allogeneic hematopoietic stem cell transplantation (allo-HSCT), the incidence is approximately 0.8% to 2.3%. Some cases of patients with allo-HSCT complicated by ALS have been reported worldwide in recent years, and patient overall prognosis is poor. However, there are limited systematic studies on hematologic disease complicated by ALS. Physicians in radiology departments and hematology departments have a limited awareness of ALS. To systematically understand hematologic disease complicated by ALS, data from 59 patients with hematologic diseases complicated by ALS were retrospectively reviewed. These patients were divided in accordance with clinical methods and imaging, and statistical comparisons were performed.

2. Methods

2.1. Study objectives and materials

The inclusion criterion was that hospitalized patients were diagnosed with hematologic disease (leukemia, lymphoma, aplastic anemia, myeloma, thrombocytopenia, hemophilia, pernicious anemia, and myelodysplastic syndrome) complicated by ALS. The exclusion criteria were patients who were diagnosed with primary pulmonary diseases (such as asthma, tuberculosis, and chronic obstructive pulmonary disease) before hematopathy, and mechanical ventilation, trauma, atrogenic trauma, esophageal rupture/perforation, and mediastinal infection caused by acrogenic bacteria before ALS.

This study was conducted at Institute of Hematology and Blood Diseases Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, and it was approved by the ethics committee of this hospital. All the patients in our study had been informed consent. The recorded data of 59 patients in our hospital from January 2014 to December 2018 were retrospectively analyzed, including clinical data (age, sex, height, weight, basic hematologic disease, numbers of basic treatment, symptoms, basic lung disease, inducing factors, history of allo-HSCT, ALS treatment methods, duration, and survival) and CT data (CT images, ALS type, and ALS thickness).

2.2. CT examination and scanning

All patients were scanned with the 64 Slice multidetector CT Scanner (Brilliance, Philips Medical Systems, Germany). Scanning range: the superior thoracic aperture to the adrenal gland. Scanning parameters: 120kV, 180 to 200 mA, 1.5 mm average layer thickness, processing with a layer spacing of 1.5 mm for thin layer reconstruction and multi-planar reconstruction (MPR) image. The ALS thickness was the sum of the thicknesses of PIE, PM and PT. The PT thickness referred to the maximum vertical thickness of the pulmonary hilum to the pleural pneumonia. The PM and PIE thicknesses were both the maximum thickness of pneumonia. The average of all values was used after the double-blind measurement by 2 deputy chief physicians.

2.3. Statistical methods

SPSS22.0 (Chicago, IL) statistical software was used for data analysis. Measurement data were expressed as mean ± SD. Data between groups were compared using t tests. Data between multiple groups were analyzed using variance. The least significant difference test was utilized to compare 2 groups. Data without a normal distribution were expressed by M (IQR). The rank sum test was used for comparison between groups. The count data were expressed by constituent ratios or rates, and the χ² test or Fisher exact test was used for the comparison between groups. The test level P < .05 was regarded as a statistically significant difference.

3. Results

A total of 59 patients with hematologic disease complicated by ALS in our hospital from January 2014 to December 2018 were included. During this time, a total of 54,986 patients were admitted to the hospital, which included a total of 807 patients received allo-HSCT and 28 patients complicated by bronchiolitis obliterans/bronchiolitis obliterans organizing pneumonia (BO/BOOP) with allo-HSCT; therefore, the total incidence of hematologic disease complicated by ALS was 0.011% (59/54986). No deaths occurred in 59 patients with ALS. In addition, ALS disappeared after conservative/catheter drainage therapy for all the 59 patients.

3.1. Baseline data comparison in the allo-HSCT and non-allo-HSCT groups

A total of 59 patients were divided into the allo-HSCT group (n = 16) and the non-allo-HSCT group (n = 43) in accordance with the significant difference in the clinical status between the conventional treatment and allo-HSCT patients. The incidence of ALS in the allo-HSCT group and the non-HSCT group was 2.0% versus 0.1% (P < .001). Baseline data comparison between the 2 groups is shown in Table 1. The number of treatment courses in the allo-HSCT group was greater than that in the non-allo-HSCT group (4 vs. 1, P = .005). The incidence of dyspnea in the allo-HSCT group was higher than that in the non–allo-HSCT group (68.8% vs 47.5%, P < .001). There was no statistically significant difference in chest tightness, chest pain, and without symptom between the 2 groups. The incidence of BO/BOOP in basic lung diseases in the allo-HSCT and non–allo-HSCT groups was 31.3% vs 0.0% (P = .001), respectively; the number of patients without lung diseases in the non–allo-HSCT group was greater than that in the allo-HSCT group (51.2% vs 12.6%, P = .007); there was no statistically significant difference in lung infection and IPS (interstitial pulmonary syndrome) between the 2 groups. There was a statistically significant difference in inducing factors between the 2 groups; cough was the primary cause of ALS in the allo-HSCT group, accounting for nearly 62.5%. Meanwhile, the rate of cough was 27.9% in the non–allo-HSCT group, and there was no distinct cause of ALS in 69.8% of patients. There was no statistically significant difference in other factors between the 2 groups, including age, sex, BMI, basic hematologic diseases, CT type, ALS thickness, treatment methods, and ALS duration.

3.2. Comparison between allo-HSCT with BO/BOOP and without BO/BOOP

Sixteen patients in the allo-HSCT groups were divided into the allo-HSCT with BO/BOOP group (n = 5) and without BO/BOOP group (n = 11). The incidence of ALS in the allo-HSCT with BO/
BOOP group and without BO/BOOP group was 17.9% versus 1.4% ($P < .001$), respectively. The data comparison results between the 2 groups are shown in Table 2. The clinical symptoms of chest tightness and dyspnea in the allo-HSCT with BO/BOOP group occurred more often than those in the allo-HSCT without BO/BOOP group, with differences of 80.0% versus 9.1% ($P = .013$) and 100.0% vs 54.5% ($P = .019$), respectively. There was no statistically significant difference in chest pain and without symptoms between the 2 groups.

### Table 2

**Comparison between allo-HSCT with BO/BOOP and without BO/BOOP.**

| Symptom                  | With BO/BOOP (n = 11) | Without BO/BOOP (n = 5) | $\chi^2 / z$ | $P$  |
|--------------------------|-----------------------|-------------------------|--------------|------|
| Chest pain               | 2 (18.2)              | 1 (20.0)                | —            | 1.00 |
| Chest distress           | 1 (9.1)               | 4 (80.0)                | —            | .013 |
| Dyspnea                  | 6 (54.5)              | 5 (100.0)               | —            | .019 |
| Without symptoms         | 4 (36.4)              | 0 (0.0)                 | —            | .245 |
| CT types, n (%)          |                       |                         | 1.330        | .416 |
| PT                       | 5 (31.3)              | 18 (41.9)               | —            | .583 |
| PIE                      | 1 (6.3)               | 1 (2.3)                 | —            | .255 |
| Complex ALS              | 10 (62.5)             | 24 (50.8)               | —            | .772 |
| ALS thickness, cm        | 14.9 (7.3, 20.7)      | 12.5 (6.0, 21.0)        | 0.290        | .722 |
| Treatment methods, n (%) |                       |                         | 0.304        | .530 |
| Conservative treatment   | 14 (87.5)             | 33 (76.7)               | —            | .001 |
| Catheter drainage        | 2 (12.5)              | 10 (23.3)               | —            | .019 |
| ALS duration, (days)     | 15 (6.0, 30.5)        | 9 (7.0, 19.0)           | 0.628        | .530 |

| — = no exact value, allo-HSCT = allogeneic hematopoietic stem cell transplantation, ALS = air leak syndrome, BO = bronchiolitis obliterans, BOOP = bronchiolitis obliterans organizing pneumonia, IPS = interstitial pneumonia syndrome, PIE = pulmonary interstitial emphysema, PT = pneumothorax. |
ALS duration between the 2 groups were not statistically significant.

3.3. Comparison between imaging groups

In accordance with the difference in CT manifestation, 59 patients were divided into the PT group (n = 23), the PIE group (n = 2), and the complex ALS group (n = 34); among the PT group, 23 patients were divided into the pure PT group (n = 9) and the hydropneumothorax (HPT) group (n = 14). Patients with PM with/without PIE and PT were included in the complex ALS group. The clinical data comparison results between multiple groups are shown in Table 3, and CT images are shown in Figures 1–6. The incidence of the clinical symptom of chest pain in the HPT group was greater than that in the other 3 groups (71.4% versus 11.1%, 0.0%, and 26.5%, *P* = .005). There was no statistically significant difference in chest tightness, dyspnea, and without symptoms. ALS thickness in the HPT group was greater than that in the other 3 groups, with a median of 19.7 cm. In addition, the difference was statistically significant in the HPT group compared with that in the PIE group and the complex ALS group but was not statistically significant compared with that in the PT group. The use of catheter drainage as a treatment method in the HPT group occurred more often than that in the other 3 groups, with proportions of 64.3% versus 22.2%, 0.0%, and 2.9% (*P* = .001). There was no statistically significant difference in terms of ALS duration in each group.

![Figure 1](image1.png)

**Figure 1.** PIE (interlobular septal type) on CT in an 8-year-old female patient with aplastic anemia, with a history of allo-HSCT, and with a conservative treatment duration of 4 days. PIE—linear air around interlobular septal (black arrow). CT = computed tomography, PIE = pulmonary interstitial emphysema, PT = pneumothorax.

![Figure 2](image2.png)

**Figure 2.** PIE (subpleural type) on CT (MPR-coronal) in a 17-year-old female patient with acute myelogenous leukemia with a history of allo-HSCT, and with a conservative treatment duration of 33 days. PIE—banded air in subpleural in the left upper lobe (black arrow). With cGVHD-related IPS in the upper lobe. CT = computed tomography, PIE = pulmonary interstitial emphysema, cGVHD = chronic graft-versus-host disease, IPS = interstitial pulmonary syndrome.

### Table 3

Comparison between image groups.

|                  | PT (n = 23) | HPT (n = 14) | PIE (n = 2) | Complex ALS (n = 34) | χ²/H | P     |
|------------------|-------------|--------------|-------------|----------------------|------|-------|
| Symptoms, n (%)  |             |              |             |                      |      |       |
| Chest pain       | 1 (11.1)    | 10 (71.4)*   | 0 (0.0)†    | 9 (26.5)‡            | 12.749 | .005  |
| Chest distress   | 0 (0.0)     | 4 (28.6)     | 0 (0.0)     | 7 (20.6)             | 3.067  | .369  |
| Dyspnea          | 1 (11.1)    | 1 (7.1)      | 0 (0.0)     | 11 (32.4)            | 4.234  | .196  |
| Without symptoms | 5 (55.6)    | 4 (28.6)     | 2 (100.0)   | 11 (32.4)            | 4.898  | .149  |
| ALS thickness, cm| 12.5 (11.23.9)| 19.7 (12.8, 40.4)| 3.5 (3, 4)‡ | 9.5 (5, 18)§         | 15.687 | .001  |
| Treatment methods, n (%) |    |              |             |                      |      |       |
| Conservative treatment | 7 (37.8) | 5 (35.7)* | 2 (100.0)‡ | 33 (97.1)§         | 25.510 | .001  |
| Catheter drainage | 2 (22.2)   | 9 (64.3)*    | 0 (0.0)†    | 1 (2.9)§            | 1.072  | .300  |
| ALS duration, days | 9 (7, 15) | 19 (7, 53)  | 7.5 (5, 10) | 9 (7, 18)           | 2.617  | .455  |

* The comparison with pure PT, *P* < .05.
† The comparison with HPT, *P* < .05.

ALS = air leak syndrome, HPT = hydropneumothorax, PIE = pulmonary interstitial emphysema, PT = pneumothorax.
4. Discussion

Hematologic disease complicated by ALS was first reported in 2007, and it is the general term used for PIE, PM, and PT. It can be divided into primary and secondary ALS. The pathogenesis of PIE, PM, and partial PT was first introduced by Macklin and Macklin in 1944. PIE is mainly caused by the rupture of alveoli around the bronchial vascular bundle, which is related to the generation of transpulmonary pressure and the toughness of the alveolar wall. The generation of transpulmonary pressure is characterized by excessive alveolar expansion, increased alveolar pressure, and decreased blood volume in the pulmonary vessels. Researchers further described the mechanism of interlobular septal and subpleural PIE and suggested that PIE in this region may indicate the rupture of terminal alveoli in the adjacent region. Part of the primary PT mechanism is still unknown. However, researchers believe that PT is caused by the rupture of the subpleural pulmonary bullae or pneumatocele.

ALS is a rare disease, the incidence of patients with ALS in this group was 0.1% in the non-allo-HSCT group (no literature report), 2.0% in the allo-HSCT group (0.83%–2.3% in the literature), and 17.9% in the group with allo-HSCT and BO/BOOP (20% in the literature), which was substantially higher than that in the average population (<1/44,000). Patients with hematological disease receive multiple drug treatments and have immune reactions. Drug-induced pulmonary injury (DIPI), pulmonary edema, and interstitial pneumonia are easily induced, leading to a more fragile alveolar wall and decreased lung compliance. These patients have a higher incidence of ALS than the general population. However, patients with allo-HSCT require pretreatment before transplantation, and graft-versus-host disease (GVHD) is prone to develop, with further aggravated lung injury, the number of courses of basic treatment in the allo-HSCT group was higher than that in the non-allo-HSCT group (4 vs 1, \( P < .05 \)). Researchers found that chronic graft-versus-host disease...
(cGVHD) is the most relevant risk factor for the incidence of ALS in patients with hematologic disease complicated by allo-HSCT (odds ratio, 13.48). BO/BOOP is a cGVHD-related small airway disease, where the alveolar is more easily ruptured because of terminal alveolar air retention and excessive expansion.

The incidence of ALS is high in young males with a low BMI\(^{12}\)(easy to generate trans-pulmonary pressure in respiration dynamics\(^{14}\)). Patients in the allo-HSCT group and the non–allo-HSCT group had an average age of 33.8 and 22.6, with a mean BMI of 19.4 and 19.5 and a male ratio of 68.8% and 62.8%, respectively. The difference between the groups was not statistically significant, and the difference was relatively the same as that reported in the literature\(^{13,15}\). Of a total of 59 patients, 44 patients had leukemia as the basic disease, especially in patients with BO/BOOP, and there were no deaths in these 59 patients during the duration of ALS. This result may be related to physicians’ awareness of the improvement of ALS. Researchers\(^{9}\) reported that there were 6 deaths in 18 patients with ALS complicated by BO/BOOP, and there were no deaths in these 59 patients during the duration of ALS. This result may be related to physicians’ awareness of the improvement of ALS. Researchers\(^{9}\) found that the 1-year and 3-year overall survival rates of patients with hematologic diseases complicated by ALS with allo-HSCT were much lower than those of patients without ALS. Many researchers\(^{11,16}\) suggest that the incidence of ALS is an early warning signal for greater lung injury in patients.

In summary, hematologic disease complicated by ALS is prone to occur in young males with a low BMI and patients with leukemia as the basic disease, especially in patients with BO/BOOP complicated by allo-HSCT. Chest tightness, chest pain, and dyspnea are common symptoms, and cough is the most common inducing factor of ALS. CT is the criterion standard for the diagnosis of ALS\(^{11,16}\). In particular, the application of thin-layer high-resolution CT and MPR has improved the detection rate of PIE. Furthermore, PIE is the basis of pleural pathogenesis, which can be divided into 3 types according to CT imaging: interlobular septal type (Fig. 1), subpleural type (Fig. 2), and bronchial vascular bundle type (Fig. 3). After the occurrence of PIE, free air is generated along the bronchial vascular bundle (mainly around the pulmonary vein) to the hilum region under the pressure gradient and with respiratory movement (i.e., Macklin effect\(^{110}\)), and it enters the mediastinal space to form PM (Fig. 4); free air can enter the neck subcutaneously upward and/or downhill into the pleitoneum. If the pericardium is ruptured, a pneumopericardium is formed; if the pleura is damaged, PT is generated (Fig. 4). HPT is generated under the condition of PT with pleural effusion/hemorrhage (Figs. 5 and 6). In this study, complex ALS was most common (34/59), followed by HPT (14/59) and PT (9/59). ALS thickness in the HPT and PT group was higher than in the other groups, the average thickness was 12.5 cm and 19.7 cm, respectively; this result may be related to the lack of passage in the pleural cavity.

Conservative treatment (staying in bed, oxygen uptake, and antibiotics) is commonly used in the treatment of hematologic disease complicated by ALS\(^{1,8,9}\). Among the 59 patients in this study, 47 patients received conservative treatment, and 12 patients needed catheter drainage. Of these, catheter drainage for patients with HPT had the highest rate (9/12). Patients with hematologic disease are prone to low blood pressure, bleeding, and low immunity; therefore, these serious traumatic treatment methods such as puncture or catheter drainage should be used more carefully. The median duration of ALS in the allo-HSCT and non-allo-HSCT groups was 15 days (slightly less than the 16.3 days reported in the literature\(^{19}\) and 9 days, respectively. The longest duration was 30 days in the allo-HSCT and BO/BOOP groups, and the shortest duration was 7.5 days in the PIE group.

The overall prognosis of hematologic disease complicated by ALS is poor, especially in patients with ALS complicated by BO/BOOP. Researchers\(^{9}\) reported that there were 6 deaths in 18 patients with ALS complicated by BO/BOOP, and there were no deaths in these 59 patients during the duration of ALS. This result may be related to physicians’ awareness of the improvement of ALS. Researchers\(^{9}\) found that the 1-year and 3-year overall survival rates of patients with hematologic diseases complicated by ALS with allo-HSCT were much lower than those of patients without ALS. Many researchers\(^{11,16}\) suggest that the incidence of ALS is an early warning signal for greater lung injury in patients.

In summary, hematologic disease complicated by ALS is prone to occur in young males with a low BMI and patients with leukemia as the basic disease, especially in patients with BO/BOOP complicated by allo-HSCT. Chest tightness, chest pain, and dyspnea are common symptoms, and cough is the most common inducing factor of ALS. The CT types that are mainly present are complex ALS, HPT, and PT. Moreover, the overall clinical symptoms of patients with HPT are severe, and the proportion of catheter drainage is high.

5. Limitations

The number of patients in this study is still not large, and further multicenter studies are needed. The influence of other variables...
was not excluded. Multivariate logistic regression analysis for independent risk factors is still required.

Author contributions
Conceptualization: Kemin Zhang, Bing Shi, Qiang Zhai.
Data curation: Kemin Zhang, Lihui Jiang, Hongyan Sun.
Formal analysis: Bing Shi, Qiang Zhai, Shan Jiang.
Investigation: Kemin Zhang, Lihui Jiang, Xiaoxue Wang, Shan Jiang.
Methodology: Kemin Zhang, Bing Shi, Qiang Zhai.
Project administration: Lihui Jiang.
Software: Bing Shi, Qiang Zhai.
Supervision: Kemin Zhang, Hongyan Sun.
Writing – original draft: Kemin Zhang.
Writing – review & editing: Kemin Zhang, Bing Shi, Qiang Zhai.
Kemin Zhang orcid: 0000-0002-0691-9427.

References
[1] Franquet T, Rodríguez S, Hernández JM, et al. Air-leak syndromes in hematopoietic stem cell transplant recipients with Chronic GVHD: high-resolution CT findings. J Thorac Imaging 2007;22:335–40.
[2] Park SJ, Park JY, Jung J, et al. Clinical manifestations of spontaneous pneumomediastinum. Korean J Thorac Cardiovasc Surg 2016;49:287–91.
[3] Colin GC, Ghaye B, Coche E. Tension pneumomediastinum secondary to thoracic air-leak syndrome in chronic graft versus host disease. Diagn Interv Imaging 2014;95:317–9.
[4] Gorospe L, Cabañero-Sánchez A, Muñoz-Molina GM, et al. Bilateral pneumomorax secondary to air leak syndrome 22 years after allogeneic bone marrow transplantation. Arch Bronconeumol 2017;53:459–60.
[5] Ishii T, Bandoh S, Kanaji N, et al. Air-leak syndrome by pleuroparenchymal fibroelastosis after bone marrow trans-plantation. Intern Med 2016;55:105–11.
[6] Meira Dias O, Cavalcanti Coelho DL, Ribeiro de Carvalho CR. Interstitial Emphysema leading to pneumomediastinum in a bone marrow transplant patient. Am J Respir Crit Care Med 2013;188:e4.
[7] Sotooude H, Daneshbod Y, Mirfarzaelian H. Photocutnic. Thoracic air- leak syndrome. Arch Iran Med 2014;17:729–30.
[8] Sakai R, Kanamori H, Nakaseko C, et al. Air leak syndrome following allo-SCT in adult patients: report from the Kanto Study Group for Cell Therapy in Japan. Bone Marrow Transplant 2011;46: 379–84.
[9] Moon MH, Sa YJ, Cho KD, et al. Thoracic air-leak Syndromes in hematopoetic stem cell transplant recipients with graft-versus-host disease: a possible sign for poor response to treatment and poor prognosis. J Korean Med Sci 2010;25:658–62.
[10] Macklin MT, Macklin CC. Malignant interstitial emphysema of the lungs and mediastinum as an important occult complication in many respiratory diseases and other conditions: interpretation of the clinical literature in the light of laboratory experiment. Medicine 1944;23:281–358.
[11] Kim HR, Yoo SM, Lee HY, et al. Presence of subpleural pulmonary interstitial emphysema as an indication of single or multiplealveolar ruptures on CT in patients with spontaneous pneumomediastinum. Acta Radiol 2016;57:1483–9.
[12] Lyra Rde M. Etiology of primary spontaneous pneumothorax. J Bras Pneumol 2016;42:222–6.
[13] Sahni S, Verma S, Grullon J, et al. Spontaneous pneumomediastinum: time for consensus. N Am J Med Sci 2013;3:460–4.
[14] Miller MR. Structural and physiological age-associated changes in aging lungs. Semin Respir Crit Care Med 2010;31:521–7.
[15] Dajer-Fadel WL, Argüero-Sánchez R, Ibarrate-Pérez C, et al. Systematic review of spontaneous pneumomediastinum: a survey of 22 years’ data. Asian Cardiovasc Thorac Ann 2014;22:997–1002.
[16] Barcia SM, Kukreja J, Jones KD. Pulmonary interstitial emphysema in adults: a clinicopathologic study of 53 lung explants. Am J Surg Pathol 2014;38:339–45.
[17] Bergeron A. Late-onset noninfectious pulmonary complications after allogeneic hematopoietic stem cell trans-plantation. Clin Chest Med 2017;249–62.
[18] Kasargod V, Awad NT. Clinical profile, etiology, and management of Hydropneumothorax: An Indian experience. Lung India 2016;33: 278–80.