Diffuse Alveolar Hemorrhage with Predominantly Right-sided Infiltration Resulting from Cardiac Comorbidities

Koji Tamai, Keisuke Tomii, Atsushi Nakagawa, Kojiro Otsuka and Kazuma Nagata

Abstract

Objective  Radiographic findings in patients with diffuse alveolar hemorrhage (DAH) are usually diffuse and bilateral, although they may occasionally be unilateral. The clinical aspects of predominantly unilateral DAH are not well known. Therefore, our objective was to describe the clinical characteristics of predominantly right-sided DAH.

Methods  We retrospectively reviewed data for 460 bronchoalveolar lavage fluid (BALF) samples collected between January 2009 and July 2013. Patients who presented with increasingly hemorrhagic BALF were diagnosed with DAH, and unilateral predominance was determined based on the degree of infiltration on chest radiographs.

Results  The records of 54 patients with DAH were evaluated. The leading etiology was pulmonary congestion due to heart failure (n=15). The radiographs showed right-sided infiltration in 18 patients (33%), left-sided infiltration in six patients (11%) and bilateral infiltration in 30 patients (56%). Predominantly right-sided DAH was often caused by pulmonary congestion resulting from heart failure (10 of 18 patients). A multivariate logistic regression analysis revealed a previous history of cardiovascular disease to be the only significant predictor of right-sided DAH (OR 13.1, 95% CI 2.9-95.4).

Conclusion  Predominantly right-sided DAH is frequently caused by pulmonary congestion resulting from heart failure and is significantly related to comorbidities with cardiovascular disease.

Key words: diffuse alveolar hemorrhage, pulmonary congestion, cardiac comorbidity

(Intern Med 54: 319-324, 2015)
(DOI: 10.2169/internalmedicine.54.3057)
to define connective tissue disease (4). Vasculitis was defined according to the European Medicines Agency algorithm (5). The diagnosis of heart failure was made based on the Framingham criteria (6) (Table 1), and patients who met these criteria and exhibited a clinical course consistent with heart failure, including the response to diuretics, nitroglycerin and non-invasive positive pressure ventilation, were diagnosed with pulmonary congestion due to heart failure. Infection was diagnosed based on positive BALF and blood culture results. Available serological tests, including those of procalcitonin, 1,3-β-D-glucan, Cytomegalovirus antigenemia, anti-Chlamydia pneumoniae antibodies and anti-Mycoplasma pneumoniae antibodies, were also evaluated. Malignant diseases were evaluated according to BALF cytology. The diagnosis of acute exacerbation of interstitial pneumonia was made based on existing criteria (7), and clotting disorders were diagnosed according to a platelet count of <15,000/mL or prothrombin time-international normalized ratio of >1.5, based on a previous report (8). In addition, the diagnosis of drug-induced lung injury was established in cases with a compatible chronology of adverse events following exposure to known pneumotoxic drugs; this diagnosis required the exclusion of other causes. If the etiology could not be determined despite a careful clinical inspection and examination, the case was classified as being of undetermined etiology.

**Materials and Methods**

**Patients**

We conducted this retrospective cohort study in a 700-bed tertiary referral center that plays a central role in treating emergency patients from the surrounding area. A total of 460 consecutive bronchoalveolar lavage (BAL) fluid specimens obtained between January 2009 and July 2013 were reviewed. The diagnosis of DAH was confirmed in cases in which the BAL aliquots became progressively more hemorrhagic (3), and BAL was performed when chest computed tomography (CT) showed wide areas of ground-glass opacity of unknown cause. At our institution, we do not perform BAL in patients obviously diagnosed with heart failure. However, even in patients with cardiac failure, BAL was performed in this study to detect other diseases when atypical signs, such as hemoptysis and decreased hemoglobin were noted or the cardiac failure was resistant to common therapies.

**BAL procedure**

The BAL procedure was performed under oxygen using a nasal cannula or mask. Three doses of 50 mL or five doses of 30 mL of sterile normal saline were instilled in patients with new pulmonary involvement on chest CT and immediately aspirated through the bronchoscope. Non-invasive positive pressure ventilation (NPPV) was used in patients with a poor respiratory status in order to prevent respiratory deterioration during the procedure.

**Definitions of the underlying causes of DAH**

The American Rheumatism Association criteria were used.
Figure. (A) Right lung predominant diffuse alveolar hemorrhage (DAH). (B) Left lung predominant DAH. (C) Bilateral infiltration of DAH.

Table 2. Etiology of Diffuse Alveolar Hemorrhage by Laterality on Chest Radiograph

| Diagnosed etiology                                      | Total n=54 | Right lung predominance n=18 | Left lung predominance n=6 | Bilateral n=30 |
|--------------------------------------------------------|------------|------------------------------|----------------------------|----------------|
| Pulmonary congestion due to heart failure              | 15 (28%)   | 10 (56%)                    | 1 (17%)                    | 4 (13%)        |
| Clotting disorder                                       | 10 (19%)   | 4 (22%)                     | 1 (17%)                    | 5 (17%)        |
| Pneumonia                                               | 6 (11%)    | 2 (11%)                     | 0 (0%)                     | 4 (13%)        |
| Acute exacerbation of IP                                | 4 (7%)     | 0 (0%)                      | 1 (17%)                    | 3 (10%)        |
| Hematological malignancy                                | 3 (6%)     | 0 (0%)                      | 0 (0%)                     | 3 (10%)        |
| Vasculitis                                              | 3 (6%)     | 2 (11%)                     | 0 (0%)                     | 1 (3%)         |
| Systemic lupus erythematosus                            | 2 (4%)     | 0 (0%)                      | 0 (0%)                     | 2 (7%)         |
| Drug-induced lung injury                                | 2 (4%)     | 0 (0%)                      | 0 (0%)                     | 2 (7%)         |
| Undetermined                                            | 9 (17%)    | 0 (0%)                      | 3 (50%)                    | 6 (20%)        |

Results

Etiology of DAH and patient characteristics

The records of 54 patients with DAH were evaluated. The major etiology of DAH was pulmonary congestion resulting from heart failure (n=15). In these patients, the number of items that satisfied the Framingham criteria were as follows [expressed as a median (range)]; the major criteria included 4 items (3-8 items), while the minor criteria comprised 2 items (2-4 items) (the major or minor criteria were counted as major criteria). Other etiologies included clotting disorders (n=10), pneumonia (n=6), acute exacerbation of interstitial pneumonia (n=4), hematological malignancy (n=3), vasculitis (n=3), systemic lupus erythematosus (n=2), drug-induced lung injury (n=2) and undetermined (n=9) (Table 2). CXR showed predominantly right-sided infiltration in 18 patients (33%), predominantly left-sided infiltration in six patients (11%) and bilateral infiltration in 30 patients (56%). Ten of 18 patients (56%) with right-sided DAH also had pulmonary congestion resulting from heart failure.

Comparison between the cases of predominantly right-sided DAH and those of bilateral or left-sided DAH

Because only six patients had predominantly left-sided DAH, we compared the differences between those with predominantly right-sided DAH versus bilateral or left-sided DAH, rather than making a three-way comparison (Table 3). There were no differences in the interval from the appearance of symptoms to the CXR evaluation between the two groups. In addition, three of 24 patients with unilateral predominant infiltration on CXR developed bilateral infiltration during the follow-up period. Previous comorbidities with cardiovascular diseases (CVDs, including prior myocardial infarction, post-percutaneous coronary intervention, valvular disorders and prior cardiac surgery), atrial fibrillation and warfarin use were found to be associated with right-sided DAH. In contrast, previous comorbidities with respiratory diseases, including emphysema, interstitial pneumonia, asthma, a history of pulmonary tuberculosis, lung carcinoma and malignant mesothelioma did not correlate with the laterality of DAH. A univariate logistic regression analysis revealed statistically significant differences between the groups in terms of CVD comorbidity, atrial fibrillation and warfarin use. In addition, a multivariate analysis showed a history of
### Table 3. Comparison between Right Lung-predominant DAH and Bilateral or Left Lung-predominant DAH

| Variables                                                | All patients | Right lung dominance | Bilateral or Left lung dominance | p value |
|----------------------------------------------------------|--------------|----------------------|----------------------------------|---------|
| **Characteristics**                                      | n=54         | n=18                 | n=36                             |         |
| Age, yrs                                                 | 69±15        | 73±13                | 67±16                            | 0.04    |
| Gender, male                                             | 39 (72%)     | 15 (83%)             | 24 (67%)                         | 0.3     |
| Duration of hospitalization, days                       | 28±22        | 23±19                | 31±23                            | 0.1     |
| In-hospital mortality                                    | 20 (37%)     | 5 (28%)              | 15 (42%)                         | 0.4     |
| Interval between appearance of symptoms and CXR evaluation, days | 12±9         | 12±9                 | 12±9                             | 0.96    |
| Hemoptysis                                               | 20 (37%)     | 9 (50%)              | 11 (31%)                         | 0.2     |
| Smoking history >20 pack year                           | 22 (41%)     | 8 (44%)              | 14 (39%)                         | 0.8     |
| PaO2/FiO2 on admission                                   | 176±73       | 177±70               | 176±75                           | 0.9     |
| Need for mechanical ventilation on admission             | 8 (15%)      | 2 (11%)              | 6 (17%)                          | 0.7     |
| Need for mechanical ventilation during clinical course    | 28 (52%)     | 5 (28%)              | 23 (64%)                         | 0.01    |
| Positive blood culture                                   | 0 (0%)       | 0 (0%)               | 0 (0%)                           |         |
| **Etiology**                                             |              |                      |                                  |         |
| Pulmonary congestion due to heart failure                | 15 (28%)     | 10 (56%)             | 5 (14%)                          | 0.002   |
| Clotting disorder                                        | 10 (19%)     | 4 (22%)              | 6 (17%)                          | 0.7     |
| Pneumonia                                                | 6 (11%)      | 2 (11%)              | 4 (11%)                          | 1.0     |
| Acute exacerbation of IP                                 | 4 (7%)       | 0 (0%)               | 4 (11%)                          | 0.3     |
| **Underlying conditions**                                |              |                      |                                  |         |
| Hypertension                                             | 27 (50%)     | 9 (50%)              | 18 (50%)                         | 1.0     |
| Diabetes Mellitus                                        | 15 (28%)     | 4 (22%)              | 11 (31%)                         | 0.7     |
| Previous comorbidities with CVD                         | 24 (44%)     | 14 (78%)             | 10 (28%)                         | 0.001   |
| Atrial fibrillation                                      | 12 (22%)     | 8 (44%)              | 4 (11%)                          | 0.01    |
| Chronic kidney disease                                   | 18 (33%)     | 8 (44%)              | 10 (28%)                         | 0.6     |
| Previous comorbidities with respiratory disorders        | 16 (30%)     | 4 (22%)              | 12 (33%)                         | 0.5     |
| Warfarin use                                             | 13 (24%)     | 8 (44%)              | 5 (14%)                          | 0.02    |
| Antiplatelet agent use                                   | 21 (39%)     | 10 (56%)             | 11 (31%)                         | 0.08    |
| **Laboratory data**                                      |              |                      |                                  |         |
| PT-INR                                                   | 1.8±1.5      | 2.1±1.8              | 1.5±1.2                          | 0.3     |
| Platelet counts, ×10⁹/mL                                 | 18.1±12.6    | 21.8±11.8            | 17.5±13.2                        | 0.3     |
| White blood cell counts, /mL                             | 10,700±7,600 | 11,300±7,300         | 10,400±7,800                     | 0.7     |
| Hemoglobin, g/dL                                         | 10.2±2.4     | 10.3±2.1             | 10.2±2.6                         | 0.9     |
| Albumin, g/dL                                            | 2.8±0.6      | 3.0±0.65             | 2.7±0.62                         | 0.06    |
| LDH, IU/L                                                | 425±299      | 345±256              | 466±313                          | 0.07    |
| CRP, mg/dL                                               | 10.6±7.8     | 10.8±6.3             | 10.6±5.5                         | 0.5     |
| BNP, pg/mL                                               | 413±342      | 513±345              | 356±335                          | 0.1     |
| KL-6, U/mL                                               | 450±249      | 470±272              | 407±194                          | 0.2     |
| **Bronchoalveolar fluid**                                |              |                      |                                  |         |
| Cell counts, ×10⁹/mL                                     | 74±72        | 90±60                | 68±76                            | 0.07    |
| Neutrophil, %                                            | 36±29        | 41±25                | 34±30                            | 0.3     |
| Lymphocytes, %                                           | 19±19        | 15±9                 | 21±21                            | 0.9     |
| Macrophage, %                                            | 39±24        | 39±25                | 39±25                            | 1.0     |

CXR: chest radiograph, PaO₂/FiO₂: partial pressure of arterial oxygen/percentage of inspired oxygen, IP: interstitial pneumonia, CVD: cardiovascular disease, PT-INR: prothrombin time-international normalized ratio, LDH: lactate dehydrogenase, CRP: C reactive protein, BNP: brain natriuretic peptide, KL-6: Krebs von den Lungen-6

Variables were compared using Welch’s t test, Wilcoxon’s test, chi-square test, and Fisher’s exact test, as appropriate.
previous CVD comorbidities to be the only significant predictor of right-sided DAH (Table 4). The in-hospital mortality rate was 37% (20 of 54 patients); there were no statistically significant differences in in-hospital mortality between the patients with and without predominantly right-sided DAH (Table 3).

**Discussion**

To our knowledge, the present study is the first to analyze DAH with lateral dominance. Our results revealed some interesting findings. For example, the major etiology of DAH was bland DAH, especially that caused by heart failure. Moreover, it is especially noteworthy that right lung-predominant DAH was frequently associated with pulmonary congestion resulting from heart failure and significantly associated with CVD comorbidities.

DAH may result from a broad spectrum of diseases with different pathophysiological mechanisms. There are three major etiological categories of DAH: pulmonary capillaritis, bland pulmonary hemorrhage and diffuse alveolar damage (9). Causes of pulmonary capillaritis that may lead to DAH include anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis, Goodpasture syndrome and various collagen diseases. Bland DAH, by contrast, is characterized by hemorrhage into the alveolar space without inflammation or necrosis of alveolar structures (10).

In a previous report, the most common clinical cause of DAH was ANCA-associated vasculitis (11); however, another study found pauci-immune pulmonary capillaritis to be the main cause (12). In a recent study, de Prost et al. reported that the major etiologies of DAH were not immune-related, such as cardiac dysfunction (8). Although vasculitis is considered to be the main etiology of DAH, the pathophysiology of bland DAH, especially that due to cardiac disorders, should be emphasized.

An increased pulmonary capillary pressure induces hydrostatic pulmonary congestion (13), and the pathophysiology of bland DAH resulting from cardiac disorders is thought to involve increased capillary pressure subsequently leading to rupture of the microvasculature (8). Therefore, the pathophysiology of DAH due to heart failure is similar to that of cardiac pulmonary congestion. In this study, the Doppler Ea wave velocity ratio (E/Ea), which correlates with the left atrial pressure, was examined in seven of 15 patients with pulmonary congestion. Six of these subjects were found to have an E/Ea ratio greater than 15, indicating an increased left atrial pressure (14).

The radiographic findings of patients with DAH are usually diffuse and bilateral, although they may occasionally be unilateral. In a study of 116 patients with DAH, 13 subjects (11.2%) exhibited unilateral infiltration on CXR (2). In addition, Witte et al. found that, among 39 patients with DAH, 27 (69.2%) presented with bilateral infiltration, seven (17.9%) presented with right-sided infiltration and three (7.7%) patients presented with left-sided infiltration on initial CXR (15). However, the characteristics of lateralized DAH were not evaluated in these reports, and the diagnosis of laterality was made based on interpretation by experts, without detailed criteria. The present results showed slightly more frequent lateralized DAH, which may be due to the fact that we evaluated predominantly lateralized DAH, not complete unilateral DAH.

The mechanism by which predominantly right-sided DAH occurs in conjunction with heart failure is somewhat speculative. For example, it has been reported that right lung pulmonary congestion due to heart failure is significantly related to severe mitral regurgitation, and the pathogenesis of this condition is believed to involve the velocity vector of the regurgitant blood flow directed toward the right pulmonary veins (16). However, right-sided pulmonary congestion may also be present in patients with acute cardiac decompensation without mitral regurgitation (17). Since both pulmonary congestion and bland DAH associated with cardiac disorders result from increased capillary pressure, both may occur on the right side predominantly. The current findings suggest that CVD comorbidities, including ischemic heart disease and mitral regurgitation, predisposes patients to cardiac decompensation, ultimately leading to right-sided DAH. In addition, left-sided cardiac enlargement resulting from heart failure has the potential to physically impede the blood flow in the left pulmonary artery, thus inducing right-sided pulmonary congestion in such patients (18). Another mechanism is poor lymphatic drainage in the right lung due to the presence of a small-caliber right bronchomediastinal trunk in comparison with that of the left lung with a large-caliber thoracic duct (19). Moreover, various right pulmonary venous drainage patterns are associated with right-sided pul-

**Table 4. Univariate and Multivariate Analysis for Predictors of Right Lung-predominant Diffuse Alveolar Hemorrhage**

| Variables                                  | Univariate analysis | Multivariate analysis |
|--------------------------------------------|---------------------|-----------------------|
|                                           | OR (95% CI)         | p value               |
| OR (95% CI)                                | p value             | OR (95% CI)           | p value               |
| Age, yrs                                   | 0.96 (0.91-1.01)    | 0.1                   | 1.07 (1.01-1.13)      | 0.065                 |
| Previous comorbidities with CVD            | 9.1 (2.6-38.7)      | 0.0004                | 13.1 (2.9-95.4)       | 0.0005                |
| Atrial fibrillation                        | 6.4 (1.7-28.5)      | 0.007                 | 1.7 (0.3-12.3)        | 0.6                   |
| Warfarin use                               | 5.0 (1.4-20.0)      | 0.02                  | 6.8 (0.9-69.2)        | 0.07                  |
| CVD: cardiovascular disease                |                     |                       |                       |                       |
| Variables were evaluated using the univariate and multivariate logistic regression model.
monary congestion (20). As in the setting of heart failure, increased capillary pressure and poor venous drainage may be associated with the onset of right-sided DAH, although this remains largely speculative.

In the present study, BAL procedures were safely performed in all cases. In patients with a poor respiratory status, NPPV was safely used as needed during the procedure. In patients with cardiac failure with atypical signs, such as hemoptyis and decreased hemoglobin, or disease that is resistant to common therapies, BAL should be considered based on the potential complication of DAH. Evaluating the presence of DAH is advisable for determining whether to continue or discontinue anti-coagulants and anti-platelet agents in patients with cardiac disorders.

In the present study, infection was diagnosed based on positive BALF and blood cultures. Sepsis is an important etiology of secondary acute respiratory distress syndrome (ARDS), which may cause DAH. Blood cultures were performed in all patients; however, no subjects displayed positive results. Moreover, no patients were diagnosed with Pneumocystis pneumonia, atypical pneumonia or Cytomegalovirus infection on the BALF or serological tests.

The major limitation of this study is the method used to determine DAH laterality based on the degree of infiltration on CXR. Although chest CT is more precise for evaluating the area of infiltration, it is difficult to identify the dominant side on chest CT images. Determining laterality on CXR, in contrast, is easy and practical in the clinical setting. In previous reports, the laterality of pulmonary congestion due to heart failure was evaluated based on the interpretation of CXR images (16). Therefore, the area of infiltration on CXR was used as a criterion in the present study.

In conclusion, the major etiology of DAH in this study was bland DAH, especially that due to heart failure. Moreover, predominantly right-sided DAH was found to be associated with pulmonary congestion resulting from heart failure and significantly associated with CVD comorbidities.

The authors state that they have no Conflict of Interest (COI).

References

1. Zamora MR, Warner ML, Tudor R, et al. Diffuse alveolar hemorrhage and systemic lupus erythematosus. Clinical presentation, histology, survival, and outcome. Medicine (Baltimore) 76: 192-202, 1997.
2. de Prost N, Parrot A, Cuquenelle E, et al. Diffuse alveolar hemorrhage in immunocompetent patients: etiologies and prognosis revisited. Respir Med 106: 1021-1032, 2012.
3. Robbins RA, Linder J, Stahl MG, et al. Diffuse alveolar hemorrhage in autologous bone marrow transplant recipients. Am J Med 87: 511-518, 1989.
4. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 40: 1725, 1997.
5. Watts R, Lane S, Hanslik T, et al. Development and validation of a consensus methodology for the classification of the ANCA-associated vasculitides and polyarteritis nodosa for epidemiological studies. Ann Rheum Dis 66: 222-227, 2007.
6. McKee PA, Castelli WP, McNamara PM, et al. The natural history of congestive heart failure: the Framingham study. N Engl J Med 285: 1441-1446, 1971.
7. Collard HR, Moore BB, Flaherty KR, et al. Acute exacerbations of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 176: 636-643, 2007.
8. de Prost N, Parrot A, Picard C, et al. Diffuse alveolar haemorrhage: factors associated with in-hospital and long-term mortality. Eur Respir J 35: 1303-1311, 2010.
9. Lara AR, Schwarz MI. Diffuse alveolar hemorrhage. Chest 137: 1164-1171, 2010.
10. Ichimescu OC, Stoller JK. Diffuse alveolar hemorrhage: diagnosing it and finding the cause. Cleve Clin J Med 75: 258, 260, 264-265 passim, 2008.
11. Travis WD, Colby TV, Lombard C, et al. A clinicopathologic study of 34 cases of diffuse pulmonary hemorrhage with lung biopsy confirmation. Am J Surg Pathol 14: 1112-1125, 1990.
12. Afessa B, Tefferi A, Litzow MR, et al. Diffuse alveolar hemorrhage in hematopoietic stem cell transplant recipients. Am J Respir Crit Care Med 166: 641-645, 2002.
13. Mebazaa A, Gheorghiade M, Piña IL, et al. Practical recommendations for prehospital and early in-hospital management of patients presenting with acute heart failure syndromes. Crit Care Med 36: S129-S139, 2008.
14. Mullens W, Borowski AG, Curtin RJ, et al. Tissue Doppler imaging in the estimation of intracardiac filling pressure in decompensated patients with advanced systolic heart failure. Circulation 119: 62-70, 2009.
15. Witte RJ, Gurney JW, Robbins RA, et al. Diffuse pulmonary alveolar hemorrhage after bone marrow transplantation: radiographic findings in 39 patients. AJR Am J Roentgenol 157: 461-464, 1991.
16. Attias D, Mansencal N, Auvert B, et al. Prevalence, characteristics, and outcomes of patients presenting with cardiogenic unilateral pulmonary edema. Circulation 122: 1109-1115, 2010.
17. Shin JH, Kim SH, Park J, et al. Unilateral pulmonary edema: a rare initial presentation of cardiogenic shock due to acute myocardial infarction. J Korean Med Sci 27: 211-214, 2012.
18. Schnyder PA, Sarraj AM, Duvoisin BE, et al. Pulmonary edema associated with mitral regurgitation: prevalence of predominant involvement of the right upper lobe. AJR Am J Roentgenol 161: 33-36, 1993.
19. Akiyama K, Suetsugu F, Hidai T, et al. Left-sided unilateral pulmonary edema in postinfarction ventricular septal rupture. Chest 105: 1264-1265, 1994.
20. Marom EM, Herndon JE, Kim YH, et al. Variations in pulmonary venous drainage to the left atrium: implications for radiofrequency ablation. Radiology 230: 824-829, 2004.