Clinical Features and Treatment Strategy of Vasculitis-Associated Diffuse Alveolar Hemorrhage

Ya-Chih Tien¹, Ying-Ming Chiu*¹,², Ming-Hui Hung³, Jin-Lan Shen¹, Chih-Ming Lin*³,⁴,⁵

¹Division of Allergy, Immunology and Rheumatology, Department of Internal Medicine, Changhua Christian Hospital, Changhua City, Taiwan
²Department of Nursing, College of Nursing, HungKuang University, Taichung City, Taiwan.
³Department of Neurology, Changhua Christian Hospital, Changhua City, Taiwan.
⁴Department of Social Work and Child Welfare, Providence University, Taichung, Taiwan.
⁵Department of Medicinal Botanicals and Health Applications, Da-Yeh University, Changhua County, Taiwan

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*Corresponding author: Ying-Ming Chiu, Division of Allergy, Immunology and Rheumatology, Department of Internal Medicine, Nanxiao Street, Changhua City 500-06, Taiwan
Chih- Ming Lin, Department of Neurology, Changhua Christian Hospital, Nanxiao Street, Changhua City 500-06, Taiwan

Abstract

Objectives: To summarize the clinical features and diagnostic approach of patients with vasculitis-associated diffuse alveolar hemorrhage (DAH). To investigate the optimal therapeutic strategy and highlight the effective corticosteroid dose and timing.

Methods: A retrospective chart review of the patients who were admitted to the intensive care unit (ICU) due to vasculitis-associated DAH was performed. Patient characteristics, clinical manifestations, the diagnosis of underlying etiology, treatment, and outcome were collected.

Results: During January 2015 to December 2017, seven vasculitis-associated DAH patients were reviewed. The mean age ± SD was 53.4 ± 18.2 years. Five patients (71%) were female. DAH was the initial presentation in all seven patients (100%). All patients required immediate mechanical ventilation. As first line therapy, methylprednisolone (MTP) pulse therapy combined with cyclophosphamide pulse therapy were administered to all patients. Six patients survived. Four of them received MTP and cyclophosphamide pulse therapy shortly after admission (mean 1.6 days, range: <1-3 days) showed good response to therapy and were extubated successfully within ten days after ICU admission.

Conclusion: Vasculitis-associated DAH is a fatal disorder. Once the diagnosis of DAH is confirmed, intensive administration of MTP and cyclophosphamide pulse therapy initiated within 3 days of admission provide good survival and pulmonary outcome.

Keywords: Alveolar hemorrhage; Corticosteroid; Lung Diseases; Therapeutic; Vasculitis

Abbreviations: DAH: Diffuse Alveolar Hemorrhage; ICU: Intensive Care Unit; MTP: Methylprednisolone; RBCs: Red Blood Cells; ANCA: Antineutrophil Cytoplasmic Antibody; AAV: Associated Vasculitis; BAL: Broncho-Alveolar Lavage; CXR: Chest X-Ray; SD: Standard Deviation; PTU: Propylthiouracil; CRP: C-Reactive Protein; ESR: Erythrocyte Sedimentation Rate; IVIG: Intravenous Immunoglobulin

Introduction

Diffuse alveolar hemorrhage (DAH) is an acute, life-threatening syndrome with clinical manifestations characterized by hemoptysis, dyspnea, reduced hemoglobin, and diffuse radiographic pulmonary infiltrations. The histopathology of DAH involves the accumulation of intra-alveolar red blood cells (RBCs) originating from the alveolar capillaries [1]. A broad spectrum of disorders, including immune-mediated diseases, infections, malignancies, and drugs, are all the possible underlying etiologies of DAH. The most common clinical causes of DAH include small vessel vasculitis, known as antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), followed by Goodpasture syndrome and other collagen vascular diseases [1,2].

Vasculitis-associated DAH typically presents with acute/fulminant course and generally demonstrates high morbidity and substantial mortality [3,4]. Therefore, prompt diagnosis and aggressive treatment are required to improve survival. Recognition of vasculitis-associated DAH depends on the awareness of clinicians; once the diagnosis is established, the underlying etiology must be investigated to initiate proper management. Delayed diagnosis and insufficient treatment for the early stages of vasculitis-related...
DAH may lead to irreversible pulmonary and extra-pulmonary organ damage, particularly affecting the kidneys [5]. A combination therapy of corticosteroid, cyclophosphamide, and plasma exchange was recommended in vasculitis patients who present with severe DAH [6,7]. However, the detailed therapeutic strategy (ex. corticosteroid dosing and timing) and associated prognosis have not been reported. The timing and sufficient dose of corticosteroid for appropriate management of vasculitis-associated DAH remain a challenge for clinicians in daily practice.

The aim of this present study was to describe the clinical manifestations and prognosis of seven patients with vasculitis-associated fulminant DAH, highlighting the diagnostic approach and optimal therapeutic strategy.

**Materials and Methods**

We retrospectively reviewed the chart records of patients with vasculitis-associated DAH who were admitted to the intensive care unit (ICU) of Changhua Christian Hospital from January 2015 to December 2017. The diagnosis of DAH was made on the basis of at least three of the following: acute onset pulmonary symptoms (dyspnea, hemoptysis), new infiltrates on chest radiographs, reduced hemoglobin level, or bloody return on broncho-alveolar lavage (BAL) with hemosiderin-laden macrophages in the absence of macroscopic airway lesions [2,8,9]. Data collection included patient characteristics, clinical manifestations (features of DAH, extrapulmonary organ involvement, and laboratory assessment), the diagnosis of underlying etiology, treatment, and outcome (patient survival and pulmonary outcome). The Institutional Review Board of Changhua Christian Hospital reviewed and approved this study.

**Statistical Analysis**

Basic demographic characteristics, clinical manifestations, laboratory test results, chest X-ray (CXR), diagnosis, treatment, and outcomes were reviewed and analyzed. Continuous variables were expressed as mean ± standard deviation (SD) if normally distributed, or as median (range) if skewed.

**Results**

**Characteristics of Patients**

Seven DAH patients were admitted into the ICU from January 2015 to December 2017. Three patients exhibited primary AAV, two exhibited propylthiouracil (PTU)-induced AAV, one exhibited IgA-nephropathy, and the remaining one exhibited Goodpasture syndrome. The mean age ± SD was 53.4 ± 18.2 years. Five patients (71%) were female. DAH was the initial presentation for hospitalization in all seven patients (100%). The details are shown in Table 1.

### Table 1: Clinical characteristics of seven patients with vasculitis-associated DAH.

<table>
<thead>
<tr>
<th>Patient</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age/Sex</td>
<td>27/F</td>
<td>26/M</td>
<td>56/F</td>
<td>56/F</td>
<td>71/F</td>
<td>75/F</td>
<td>63/M</td>
</tr>
<tr>
<td>Diagnosis of underlying etiology</td>
<td>IgA-N</td>
<td>GPS</td>
<td>PTU-AAV</td>
<td>PTU-AAV</td>
<td>Primary AAV</td>
<td>Primary AAV</td>
<td>Primary AAV</td>
</tr>
<tr>
<td>Pulmonary symptoms</td>
<td>Dyspnea/duration (days)</td>
<td>Y/&lt;1</td>
<td>Y/2-3</td>
<td>Y/1</td>
<td>Y/1</td>
<td>Y/1</td>
<td>Y/1</td>
</tr>
<tr>
<td>Hemoptysis/duration (days)</td>
<td>N</td>
<td>Y/2-3</td>
<td>Y/1</td>
<td>N</td>
<td>Y/1</td>
<td>Y/1</td>
<td>N</td>
</tr>
<tr>
<td>Bloody sputum from endotracheal tube</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Others</td>
<td>Anemia on admission/Hb (g/dL)</td>
<td>Y/10</td>
<td>Y/8.6</td>
<td>Y/6.6</td>
<td>Y/6.4</td>
<td>Y/6</td>
<td>Y/6.5</td>
</tr>
<tr>
<td>Reduction in Hb level (g/dL)*</td>
<td>2.8</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>1.3</td>
<td>1.4</td>
<td>NA</td>
</tr>
<tr>
<td>Abnormal chest x-ray</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Bilateral symmetric alveolar opacities</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Extensive asymmetric alveolar opacities involved both upper and lower lung field</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
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<tr>
<td>Broncho-alveolar lavage</td>
<td>NA</td>
<td>Y</td>
<td>NA</td>
<td>Y</td>
<td>NA</td>
<td>NA</td>
<td>Y</td>
</tr>
<tr>
<td>Suggestive of DAH*</td>
<td>NA</td>
<td>Y</td>
<td>NA</td>
<td>Y</td>
<td>NA</td>
<td>NA</td>
<td>Y</td>
</tr>
<tr>
<td>Hemosiderin-laden macrophage</td>
<td>NA</td>
<td>Y</td>
<td>NA</td>
<td>Y</td>
<td>NA</td>
<td>NA</td>
<td>Y</td>
</tr>
<tr>
<td>Renal involvement</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Cr on admission (mg/dL)</td>
<td>0.42</td>
<td>10.42</td>
<td>0.53</td>
<td>2.35</td>
<td>2.13</td>
<td>1.7</td>
<td>11.54</td>
</tr>
<tr>
<td>Acute renal injury requiring dialysis</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Hematuria</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Casturia</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Renal biopsy</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
</tr>
</tbody>
</table>

Note: *Reduction in hemoglobin before/after 24-48 hours after the onset of DAH, if data were available for comparison.
DAH is suggested by persistent blood on three sequential lavage aliquots from a single affected area of the lung.

AAV, ANCA-associated vasculitis; Cr, Creatinine; DAH, diffuse alveolar hemorrhage; GPS, Goodpasture syndrome; Hb, hemoglobin; IgA-N, IgA-nephropathy; N, No; NA, not available; PTU, propylthiouracil; Y, Yes.

Clinical Manifestations

Dyspnea was the most common symptom in all seven patients (100%). Other pulmonary symptoms included hemoptysis (in four, 57%) and cough (in one, 14%). All patients required immediate mechanical ventilation, and overt bloody sputum from the endotracheal tube was observed in all patients (100%). Renal involvement with hematuria (in seven, 100%), proteinuria (in six, 86%), and casturia (in one only, 14%) was present in these patients. The mean ± SD serum creatinine level was 4.16 ± 4.37 mg/dL (range: 0.42-11.54 mg/dL). Five patients (71%) suffered from acute renal injury and four (57%) required hemodialysis. Renal biopsy was performed in four patients.

Laboratory Data

Three patients experienced a reduction of hemoglobin within 48 hours after onset of DAH, while the remaining four patients exhibited a low level of hemoglobin (5.9-8.6 g/dL) on admission; however, these four patients lacked previous hemoglobin data for comparison. BAL was performed in three patients (43%); macroscopically hemorrhagic BAL fluid and microscopically hemosiderin-laden macrophages were found in all three patients. Bacterial, Mycobacterium tuberculosis, and fungal cultures, as well as virus analyses, were all negative at the onset of DAH. All patients were checked for C-reactive protein (CRP), procalcitonin, and erythrocyte sedimentation rate (ESR) on admission. The mean ± SD values were as follows: CRP, 12.65 ± 8.96 mg/dL (range 3.24-32.57 mg/dL); procalcitonin, 7.16 ± 11.01 ng/mL (range 0.08-33.15 ng/mL); ESR, 79.71 ± 46.67 mm/h (range 12-140 mm/h).

Chest Radiography

CXRs showed bilateral alveolar opacities in all seven patients. A unique pattern involving extensive, asymmetric, dense alveolar opacities in both upper and lower parts of the lungs was present in six patients (86%); this helped to distinguish alveolar hemorrhage from pulmonary edema, which typically presented as butterfly-like alveolar infiltration at CXR. We have included four patients with different etiologies of DAH as examples; their CXRs on admission are shown in Figure 1.

Figure 1: The chest X-ray (CXR) on admission for four diffuse alveolar hemorrhage (DAH) patients with different underlying causes.

Note: (a) Case 1. IgA-nephropathy. CXR showed extensive and asymmetric alveolar opacities in both upper and lower parts of the lungs. (b) Case 2. Goodpasture syndrome. CXR showed bilateral symmetric peri-hilar alveolar opacities that mimic pulmonary edema. (c) Case 4. Propylthiouracil-induced antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) and (d) Case 7. Primary AAV. For both (c) and (d), CXR revealed extensive, asymmetric, and dense alveolar opacities and consolidation that involved whole portions of the lungs.

Diagnosis

The diagnosis of underlying etiologies for DAH in seven patients was based on the clinical manifestations, laboratory test, and/or histopathology of each patient. Five patients had a diagnosis of AAV; all were diagnosed on the basis of clinical presentation of DAH, positive serum ANCA result, and exclusion of other DAH etiologies. Two of these five patients were diagnosed with PTU-induced AAV on the basis of drug exposure history; the other three were diagnosed with primary AAV due to the lack of associated drug exposure or other risk factors. Notably, in the remaining two patients (one with...
IgA-nephropathy and the other with Goodpasture syndrome), blood
exams including anti-nuclear antibody, ANCA, and anti-glomerular
basement membrane antibody were negative; they were both
diagnosed by evident histopathology results on renal biopsy.

Treatment and Outcome

All patients required mechanical ventilation on admission
for respiratory failure; four patients required hemodialysis for
acute oliguria renal injury. Methylprednisolone (MTP) pulse
therapy (750 mg per day for 3 consecutive days) combined with
cyclophosphamide pulse (0.5-0.75 mg/m², adjusted according to
renal function) therapy were administered to all patients as
first-line therapy. Plasma exchange was performed in six patients
(86%). Intravenous immunoglobulin (IVIG) (0.4 g/kg per day for
5 consecutive days) was prescribed as second-line therapy in two
patients (29%) whose illness was refractory to initial therapy. One
patient with remitting-relapsing DAH received rituximab therapy
(500 mg every week for 4 weeks). All patients received broad
empiric antibiotics and anti-fungal therapy, although there was
initially no positive culture result suggestive of major infection.

Throughout the course of hospitalization, no severe or overt
infection occurred in any of the patients. One patient (case 4) died in
the hospital; thus, the mortality rate was 14%. Initially, this patient
was treated conservatively by giving bolus corticosteroid (MTP 80
mg every eight hours) only. MTP pulse therapy was delayed until
the 8th day after ICU admission; however, the patient died on the
next day after the first dose of MTP due to uncontrolled DAH.

Six patients survived. Four of them (cases 1, 2, 3, and 5) showed
good response to therapy and were extubated successfully within
ten days after ICU admission; all four patients received MTP and
cyclophosphamide pulse therapy shortly after admission. For those
four patients, the duration from admission date to the first dose
of MTP pulse was 1-3 days (mean 1.6 days, range: <1-3 days). The
remaining two surviving patients reported prolonged ventilator
dependency, although they were free from active DAH. One patient
(case 7) began MTP pulse therapy 18 days after admission, followed
by intensive cyclophosphamide pulse and serial sessions of plasma
exchange. However, he experienced four recurrent episodes of
DAH during 2 months of hospitalization. Complete remission of
DAH was eventually reached after rituximab infusion. Due to
prolonged endotracheal intubation, he received tracheostomy
and remained ventilator-dependent. The other patient (case 6)
began a combination of MTP pulse, cyclophosphamide pulse, and
plasma exchange therapy on the day of admission, but her illness
was refractory to those therapies; second-line therapy of IVIG was
delayed until the 7th day after admission. Although DAH resolved
10 days after admission, she remained unconsciousness, likely
due to prolonged hypoxia encephalopathy. Detailed treatment and
prognosis information for the seven patients is summarized in
Table 2.

**Table 2**: Treatment and outcomes of seven patients with vasculitis-associated DAH.

<table>
<thead>
<tr>
<th>Patient</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis of underlying disease</td>
<td>IgA-N</td>
<td>GPS</td>
<td>PTU-AAV</td>
<td>PTU-AAV</td>
<td>Primary AAV</td>
<td>Primary AAV</td>
<td>Primary AAV</td>
</tr>
<tr>
<td>Diagnostic modalities</td>
<td>Renal biopsy</td>
<td>Renal biopsy</td>
<td>Drug exposure Hx ANCA+</td>
<td>Drug exposure Hx ANCA+</td>
<td>Renal biopsy ANCA+</td>
<td>ANCA+</td>
<td>Renal biopsy ANCA+</td>
</tr>
<tr>
<td>Treatment (Tx)</td>
<td>MTP, CY</td>
<td>MTP, CY, PE</td>
<td>MTP, CY, PE</td>
<td>MTP, CY, PE</td>
<td>MTP, CY, PE, IVIG</td>
<td>MTP, CY, PE, IVIG, RTX</td>
<td></td>
</tr>
<tr>
<td>Duration from pulmonary symptom onset to Tx* (days)</td>
<td>2</td>
<td>3-4</td>
<td>&lt;1</td>
<td>~20</td>
<td>3</td>
<td>&lt;1</td>
<td>~21</td>
</tr>
<tr>
<td>Duration from admission date to Tx* (days)</td>
<td>2</td>
<td>1</td>
<td>&lt;1</td>
<td>8</td>
<td>3</td>
<td>&lt;1</td>
<td>~18</td>
</tr>
<tr>
<td>Outcome</td>
<td>Extubated on day 6, CR</td>
<td>Extubated on day 9, ESRD on HD</td>
<td>Extubated on day 10, CR</td>
<td>Death</td>
<td>Extubated on day 7, CKD stage II</td>
<td>Prolonged weaning due to unclear consciousness, ESRD on HD</td>
<td>Relapse DAH s/p tracheostomy, CKD stage III</td>
</tr>
</tbody>
</table>

Note: *The first dose of methylprednisolone 750 mg pulse therapy.

AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibodies; CKD, chronic kidney disease; CR, complete remission; CY, cyclophosphamide; DAH, diffuse alveolar hemorrhage; ESRD, end-stage renal disease; GPS, Goodpasture syndrome; HD, hemodialysis; Hx, history; IgA-N, IgA-nephropathy; IVIG; intravenous immunoglobulin; MTP, methylprednisolone; PE, plasma exchange; PTU, propylthiouracil; RTX, rituximab; Tx, treatment.

Discussion

This report was written to explore early and aggressive
treatment strategy and association with survival and pulmonary
outcome in patients with vasculitis-associated DAH. We found
that corticosteroid pulse plus cyclophosphamide pulse (0.5-0.75 mg/
$m^2$) in a timely manner (initiating administration within 3 days
of admission) provided better survival or pulmonary outcome for
patients with fulminant DAH. The corticosteroid dose should be
as sufficient as MTP 750mg daily for at least 3 consecutive days.
In contrast, delayed treatment after admission resulted in worse
pulmonary outcomes, including mortality.

Although early and aggressive treatment for DAH is important
for survival and prognosis, early recognition of DAH is challenging for


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A combination of high-dose corticosteroid and cyclophosphamide or rituximab has been established as the cornerstone of induction treatment in small vessel vasculitis [6,13]. However, the specific timing of therapy and optimal corticosteroid dose has not been established. In our report, four patients who initiated MTP and cyclophosphamide pulse administration within 3 days of admission exhibited rapid remission from DAH within 1 week; they were extubated successfully within 2 weeks. In contrast, two patients (cases 4 and case 7) underwent delayed therapy due to missed diagnosis of vasculitis and a concern regarding possible infection. In such situations, BAL plays an important role for the purposes of Documentation of alveolar hemorrhage, finding hemosiderin-laden macrophages from cytology analysis, and exclusion of infection [12].

Notably, all of our cases showed a varying degree of renal involvement; hematuria was the most common manifestation, followed by proteinuria. Two cases made the definite underlying etiology of DAH according to the characteristic histopathology of renal biopsy (cases 1 and 2, IgA-nephropathy and Goodpasture syndrome); both cases revealed negative findings in serum immunologic tests. This suggests that biopsy of the damaged organ helps to confirm the underlying etiology of DAH; the kidney may be an optimal organ if active sediment, such as hematuria, is present in urinalysis.

In conclusion, vasculitis-associated DAH is a fatal disorder. The most common presenting symptoms are acute dyspnea, overt bloody sputum from the endotracheal tube with reduced hemoglobin, and extensive alveolar opacities at CXR. Renal involvement is frequent and renal biopsy is helpful for evaluating the underlying etiology. Although infection should play an important role, it should not be viewed as an obstacle. Once the diagnosis of DAH is confirmed, intensive administration of MTP (e.g., 750 mg daily for at least 3 consecutive days) and cyclophosphamide pulse therapy (e.g., 0.5-0.75 mg/m², initiated within 3 days of admission) provide good survival and pulmonary outcome.

**References**


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