Pathogenetic and clinical aspects of ANCA-associated vasculitis

Chen, Min

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Severe pulmonary hemorrhage in patients with end-stage renal disease in antineutrophil cytoplasmic autoantibody-associated vasculitis

Min Chen¹,², Ming-Hui Zhao²

¹Department of Rheumatology and Clinical Immunology, University Medical Center Groningen, the Netherlands, ²Department of Nephrology, Peking University First Hospital, Beijing, China

Abstract

[Background] It has been reported that, after patients with ANCA-associated vasculitis (AAV) progress to end-stage renal disease (ESRD), they are less likely to experience relapse of vasculitis. However, we encountered a few patients with ESRD suffering severe pulmonary hemorrhage due to relapse of AAV. The current study presents our observation on these patients.

[Methods] Of 198 consecutive patients with AAV with follow-up data in our center, 66 progressed to ESRD during follow-up. Clinical and laboratory data were collected and retrospectively analyzed.

[Results] Among the 66 patients with ESRD, 5 experienced severe pulmonary hemorrhage. They had positive serum perinuclear ANCA and myeloperoxidase-ANCA and were diagnosed as microscopic polyangiitis. All 5 patients achieved remission after initial induction therapy. The average duration of follow-up was 47.0 (range 8.0-98.0) months. After progressing to ESRD and starting hemodialysis, these patients experienced severe pulmonary hemorrhage within 9.0 (range 2.0-23.0) months. After immunosuppressive therapy, pulmonary hemorrhage ceased in 4 patients, and the other died of respiratory failure.

[Conclusions] Severe pulmonary hemorrhage can occur in ESRD patients with AAV. Disease activity and relapses of AAV should be monitored even after patients progress to ESRD.
Introduction

Antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (AAV) comprises a group of autoimmune disorders, including Wegener’s granulomatosis, microscopic polyangiitis, Churg-Strauss syndrome and renal-limited vasculitis (ANCA-associated glomerulonephritis), characterized by necrotizing small-vessel vasculitis with autoantibodies directed against neutrophil cytoplasmic constituents, in particular proteinase 3 and myeloperoxidase. It was reported that over 20% of patients with AAV will develop end-stage renal disease (ESRD) during their lifetime [1-4].

The survival of untreated AAV is dismal. The introduction of corticosteroids in combination with cyclophosphamide improved the prognosis of AAV dramatically and converted the disease to a chronic relapsing condition. It was reported that patients with AAV who progressed to ESRD were less likely to experience relapse of vasculitis than before dialysis therapy [5]. Therefore, when patients progressed to ESRD, nephrologists may focus more on renal replacement therapy than on the primary cause of ESRD, i.e. AAV per se. In our clinical practice, we encountered 5 patients with ESRD who suffered from relapses of AAV, manifested as severe pulmonary hemorrhage. The current study presents our observation on these patients.

Patients and methods

We evaluated 198 consecutive patients presenting to the Renal Division, Peking University First Hospital from 1998-2007, with a diagnosis of AAV according to the Chapel Hill Consensus Conference definition [6]. Other diseases causing serum-positive ANCA were excluded clinically, including systemic lupus erythematosus, rheumatoid arthritis, drug-induced vasculitis and Behçet’s disease. During an average follow-up duration of 21.7 (1-180) months, 66 patients progressed to ESRD. Among the 66 patients, those experiencing severe pulmonary hemorrhage during follow-up were recruited for analysis. Other factors causing pulmonary hemorrhage including infection, malignancy, complications of ESRD and overdose of anticoagulant during hemodialysis were excluded. Follow-up visits were
scheduled for every 1 or 2 months. Clinical and laboratory data were collected and analyzed. Relapse was defined as appearance of organ involvement attributable to vasculitis and requiring an increase or re-introduction in immunosuppression [7]. The vasculitic disease activity was measured by the Birmingham Vasculitis Activity Score [8]. This research was in compliance of the Declaration of Helsinki and was approved by the ethic committee of the local hospital. Informed consent was obtained from each patient.

Detection of ANCA

ANCA was detected by an indirect immunofluorescence assay and antigen-specific ELISAs. Standard indirect immunofluorescence assay were performed according to the manufacturer (EUROIMMUN, Lübeck, Germany). In antigen-specific ELISAs, 2 highly purified known ANCA antigens, proteinase 3 and myeloperoxidase, purified as previously reported [9], were used as solid phase ligands. The results of ELISA were expressed as percentage of a known positive control.

Results

Among the 66 patients progressing to ESRD, 5 experienced severe pulmonary hemorrhage during follow-up.

Demographic features and ANCA specificities

Among the 5 patients, 3 were male and 2 were female, with an average of 60.0 (range 17-78) years at diagnosis. All the 5 patients had positive perinuclear ANCA and myeloperoxidase-ANCA and were diagnosed as microscopic polyangiitis. The mean interval between onset of the disease and diagnosis was 4.8 (range 1.0-10) months.

Clinical manifestations at presentation

The clinical and pathological manifestations of the 5 patients at presentation are listed in Table 1.

Initial Treatment and pre-dialysis follow-up

All 5 patients received corticosteroids together with cyclophosphamide. Three patients received additional intravenous methylprednisolone pulse therapy (7-15 mg/kg/day) (Table 1). After induction therapy, all 5 patients achieved remission within a mean duration
of 4 months. During maintenance therapy, intravenous cyclophosphamide every 3 months or daily oral azathioprine was administrated.

Data of pre-dialysis follow-up of the patients are listed in Table 2.

### Table 1. Clinical and pathological details of the five ESRD patients with severe pulmonary hemorrhage

<table>
<thead>
<tr>
<th>Patient</th>
<th>Clinical spectrum and renal function</th>
<th>Urinary sediment after IT</th>
<th>ESR and CRP after IT</th>
<th>ANCA level after IT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>After IT, Scr decreased from 189 to 150 μmol/L. Thereafter, the renal function deteriorated slowly and progressed to ESRD 82 months later.</td>
<td>Remained negative.</td>
<td>Remained normal.</td>
<td>Dropped.</td>
</tr>
<tr>
<td>2</td>
<td>After IT, Scr decreased from 300 to 230 μmol/L. 15 months later, a relapse brought her into ESRD though reinstitution of IT relieved extra-renal manifestations.</td>
<td>Remained negative except for the relapse.</td>
<td>Remained normal except for the relapse.</td>
<td>Did not drop.</td>
</tr>
<tr>
<td>3</td>
<td>After IT, Scr decreased from 645 to 220 μmol/L. Thereafter, the renal function deteriorated slowly and progressed to ESRD 36 months later.</td>
<td>Remained negative.</td>
<td>Remained normal except for the relapse.</td>
<td>Dropped.</td>
</tr>
<tr>
<td>4</td>
<td>Manifested as ESRD at presentation. IT relieved extra-renal involvement and he began chronic hemodialysis 1 month after diagnosis.</td>
<td>Remained negative.</td>
<td>Remained normal.</td>
<td>Turned negative.</td>
</tr>
<tr>
<td>5</td>
<td>After IT, Scr decreased from 597 to 400 μmol/L. Thereafter, the renal function deteriorated slowly and progressed to ESRD 43 months later.</td>
<td>Remained negative.</td>
<td>Remained normal.</td>
<td>Dropped.</td>
</tr>
</tbody>
</table>

**Table 2. Data of the patients during pre-dialysis follow-up**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Clinical spectrum and renal function</th>
<th>Urinary sediment after IT</th>
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<td>After IT, Scr decreased from 300 to 230 μmol/L.</td>
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<td>After IT, Scr decreased from 645 to 220 μmol/L.</td>
<td>Remained negative.</td>
<td>Remained normal except for the relapse.</td>
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<td>Manifested as ESRD at presentation. IT relieved extra-renal involvement and he began chronic hemodialysis 1 month after diagnosis.</td>
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<td>After IT, Scr decreased from 597 to 400 μmol/L.</td>
<td>Remained negative.</td>
<td>Remained normal.</td>
<td>Dropped.</td>
</tr>
</tbody>
</table>

**Abbreviations:** IT: induction therapy; ANCA: antineutrophil cytoplasmic antibody; Scr: serum creatinine.
Chapter 8

Pulmonary hemorrhage and outcomes

The average duration of follow-up for the 5 patients was 47.0 (range 8.0-98.0) months. The average duration of progressing to ESRD was 35.4 (range 1.0-82.0) months after diagnosis. After receiving chronic hemodialysis, these patients experienced severe pulmonary hemorrhage within 9.0 (range 2.0-23.0) months (Figure 1). ANCA levels were elevated in 4 patients (No. 1, 2, 4 and 5). Arterial oxygen tension decreased in 4 of 5 patients, and 2 of them developed respiratory failure.

Upon pulmonary hemorrhage, 4 patients were treated with intravenous methylprednisolone pulse therapy (7-15 mg/kg/day) and the other received oral prednisone (60 mg/day); 2 patients received additional plasma exchange therapy; 2 patients received mechanical ventilation. After the above treatment, pulmonary hemorrhage was controlled in 4 patients and the other 1 died of respiratory failure due to late referral. One patient died of secondary infection though the pulmonary hemorrhage was controlled (Table 1).

The rate of pulmonary hemorrhage in AAV patients on dialysis tended to be lower than that in AAV patients not on dialysis [0.045 (CI, 0.037 to 0.053) vs. 0.083 (CI, 0.081 to 0.085) events/patient-year, P=0.17].
Discussion

ANCA-associated vasculitis is a group of multi-system autoimmune diseases. Kidney and lung are the 2 most vulnerable organs. Pulmonary hemorrhage is one of the most common and fatal manifestations of patients with AAV. Although the introduction of corticosteroids and cyclophosphamide has dramatically improved the outcome of patients with AAV and most patients could achieve remission, relapses are still challenges to physicians. It was found by Hogan et al. that relapses are associated with subsequent progression to ESRD [10]. However, it was reported that, after patients had progressed to ESRD, the relapse rate is relatively low [5, 11], though this remains controversial [12]. In the current study, we reported 5 patients who, though on chronic hemodialysis therapy, experienced life-threatening pulmonary hemorrhage due to relapses of AAV.

Among the 5 patients with pulmonary hemorrhage, other factors causing pulmonary hemorrhage including infection, malignancy, complications of ESRD and overdose of anticoagulant during hemodialysis were excluded clinically. Except for one patient who died of respiratory failure due to late referral, pulmonary hemorrhage responded to immunosuppressive therapy, indicating that the pulmonary hemorrhage was truly caused by relapse of AAV.

The percentage of pulmonary hemorrhage in AAV patients with ESRD was only 7.6% (5/66) in the current study. In contrast our previous studies suggested that, among the 137 patients achieving remission and dialysis independence after induction therapy [13, 14], the percentage of relapse manifesting as pulmonary hemorrhage was 12.4% (17/137). In the current study, the rate of pulmonary hemorrhage in AAV patients on dialysis also tended to be lower than that in AAV patients not on dialysis. This indicates that, after patients had progressed to ESRD, relapses including pulmonary hemorrhage were less likely to occur. The impairment of immune response, especially cell-mediated response, in patients with ESRD might contribute to the decreased relapse rate of AAV [5].

Our study raises 2 clinical issues. Firstly, relapses of AAV can happen even in those who already progressed to ESRD; some relapses could be fatal though not very common. On the other hand, when chronic dialysis commences, physicians especially nephrologists sometimes tend to focus on the management of dialysis therapy including adequacy of dialysis,
hemoglobin level and calcium-phosphate product, and neglect the primary cause of ESRD, i.e. AAV per se. Therefore, disease activity and relapses of AAV should be monitored rigorously, even after patients progress to ESRD. Integrating laboratory and clinical profiles, including erythrocyte sedimentation rate, C-reactive protein, and change of ANCA levels as well as manifestations of organ involvement [14], is helpful for the diagnosis of relapses. Secondly, whether patients with AAV during hemodialysis benefit from immunosuppressive therapy to reduce the risk of relapse remains a controversial issue. It was suggested that a therapeutic strategy to maintain long-term remission was needed in patients with ESRD due to AAV [12]. However, since patients with AAV and ESRD had a high rate of infections [5], how to safely and effectively adjust treatment needs further investigation.

In conclusion, though not very common, severe pulmonary hemorrhage caused by relapses of AAV in patients with ESRD can occur. Disease activity and relapses of AAV should be monitored rigorously, even after patients progress to ESRD.

Acknowledgements

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[References]


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