Case Report

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Organizing Pneumonia in A Patient Double-Positive for ANCA and Anti-GBM Antibodies: A Case Report

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ABSTRACT

Both anti-glomerular basement membrane (GBM) disease and the anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) are common causes of pulmonary-renal syndrome. Organizing pneumonia (OP), a special pattern of interstitial lung disease, is extremely rare either in AAV or anti-GBM disease. We report an old woman presented with OP on a background of co-presentation with both ANCA and anti-GBM antibodies.

Key words: organizing pneumonia; double-positive; ANCA-associated vasculitis; anti-GBM antibody

INTRODUCTION

Both anti-glomerular basement membrane (GBM) disease and anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) are common causes of pulmonary-renal syndrome (PRS). Renal involvement usually presents as rapidly progressive glomerulonephritis with dramatically decreasing kidney function. Diffuse alveolar hemorrhage and pulmonary fibrosis are common manifestations of pulmonary involvement[1]. Interstitial lung disease (ILD) is often revealed by computed tomography (CT) in AAV patients and is associated with poor prognosis [2]. However, organizing pneumonia (OP) is extremely rare either in AAV or anti-GBM disease. OP is a special pattern of lung tissue repair after injury characterized histopathologically by polypoid plugs of loose connective tissue in distal air spaces, mostly alveoli and alveolar ducts[3]. To our knowledge, OP in patients with AAV has been reported in literature[4,5], but only one seronegative-case with poor prognosis has been reported in anti-GBM disease[6]. Here we report an old woman presented with OP on a background of co-presentation with both ANCA and anti-GBM antibodies.

CASE DESCRIPTION

A 72-year-old woman was admitted to our hospital with a 5-week history of nausea, vomiting, oliguria, and edema of both lower extremities. She had no known medical history. Laboratory tests performed at a local hospital showed leukocyte count of 10.45 x 10^9/L, hemoglobin level of 49 g/L, serum creatinine of 1261 μmol/L, and serum potassium of 6.98 mmol/L. After receiving immediate treatment with hemodialysis, blood transfusion, antibiotics, and other symptomatic supportive treatment, she was transferred to our hospital. On physical examination, she had a temperature of 36.2°C, pulse of 101 beats per minute, respiratory rate of 18 breaths per minute, and blood pressure of 140/100 mmHg. There were rales in the lungs on auscultation and pitting edema on lower limbs. The other examinations showed normal results.

Laboratory tests showed a leukocyte count of 12.1 x 10^9/L (normal range: 3.5 x 10^9/L – 9.5 x 10^9/L), procalcitonin level of 0.42 ng/mL, serum creatinine of 864.1 μmol/L, and anti-GBM antibody of 116.04 units (normal range: 0 to 20 units). Cytoplasmic anti-neutrophil cytoplasmic antibody (c-ANCA) was positive and

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the anti-myeloperoxidase antibody level was 77.65 units (normal range: 0 to 20 units). Testing for antinuclear antibodies, doublestranded DNA antibodies, and PLA2R antibody were all negative. Chest CT revealed thickening of the interlobular septal walls, ground-glass opacities, and patchy consolidation (**Fig. 1A**).

On the second day after admission, the patient presented with hemoptysis and shortness of breath, without fever or chills. Her symptoms were improved after treatment with sedative drugs and non-invasive ventilation. Because of the concurrence of both ANCA and anti-GBM antibodies, regular plasmapheresis and hemodialysis were initiated. Simultaneously, the patient received intravenous methylprednisolone (120 mg/d for 2 days and 40 mg/d for 16 days) and cyclophosphamide (0.4 g/d for 2 days). Based on the increased leukocyte count and imaging findings of the chest, two sets of blood cultures were obtained. However, five days later, no bacteria or fungi grew. Since alveolar hemorrhage may cause secondary infection, intravenous anti-infective agents were started under the supervision of a senior physician.

The patient did not undergo a renal biopsy or repeated chest CT because of her unstable respiratory condition. After intensive treatment, hemoptysis disappeared and the levels of two autoimmune antibodies significantly decreased (**Table 1**). c-ANCA was negative and her white blood cell count/neutrophil percentage decreased since admission. However, her oxygen saturation was consistently decreasing, which was further complicated by progressive thrombocytopenia (**Table 1**). She was then transferred to the intensive care unit, where tracheal intubation was performed. In addition, chest radiography showed "white lung" on hospital day 14 (**Fig. 1B**). The patient died finally 18 days after admission due to irreversible respiratory failure. Histopathological findings at autopsy unexpectedly revealed OP rather than serious secondary infection after diffuse alveolar hemorrhage (**Fig. 2A**), and crescentic glomerulonephritis was observed in kidney pathology (**Fig. 2B**).

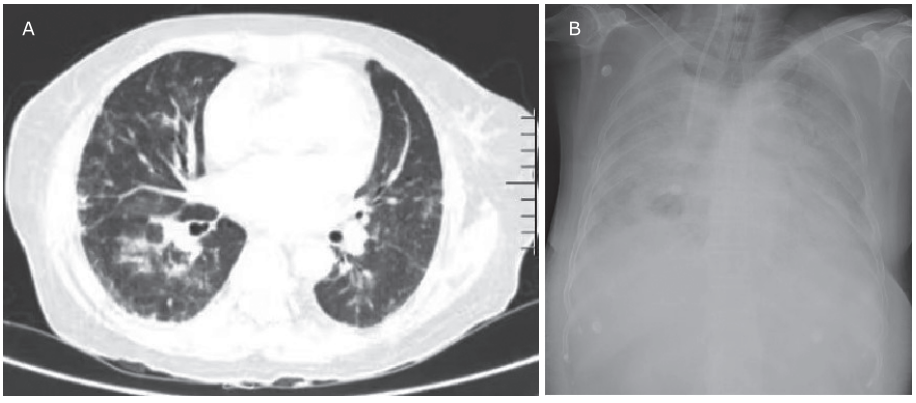

Figure 1. Spectrum of imaging findings of a 72-year-old lady presented with organizing pneumonia.
(A) Chest CT image at admission shows bilateral thickened interlobular septa, perilobular ground-glass opacities and patchy consolidation. (B) Chest radiograph on hospital day 14 shows diffuse pulmonary infiltrates in both lung fields.

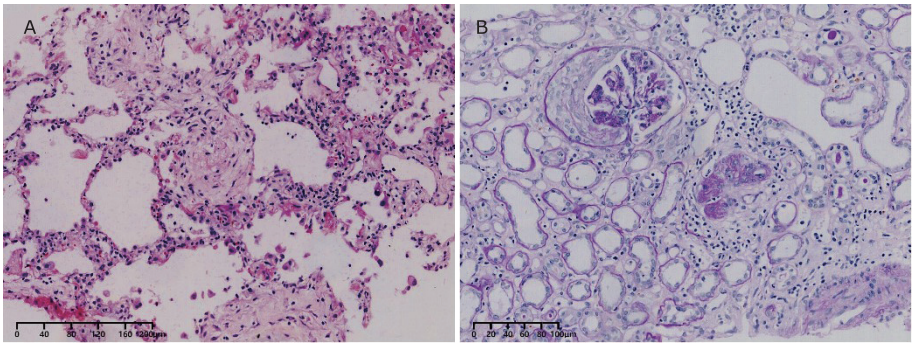

Figure 2. Histopathology of autopsy in a 72-year-old patient revealed organizing pneumonia.
(A) Hematoxylin and eosin-stained section of the lungs shows polypoid granulation tissue in the alveolar space and thickened alveolar septa with inflammatory cells in it, demonstrating organizing pneumonia. (B) Periodic acid-Schiff stained section of the kidney shows crescent formation (12 glomeruli with 12 crescents), indicating crescentic glomerulonephritis.

Table 1 Laboratory test results of platelet count and anti-MPO and anti-GBM antibodies

Item	Day 1 (admission)	Day 5	Day 8	Day 14
Platelet count ($\times 10^9$/L)	189	106	70	49
Anti-MPO antibody (units)	77.65	85.95	-	42.99
Anti-GBM antibody (units)	116.04	110.95	-	35.37

anti-MPO: anti-myeloperoxidase; anti-GBM: anti-glomerular basement membrane

DISCUSSION

Contemporaneous ANCA and anti-GBM antibodies, so-called "double-positive", are relatively rare, with an estimated incidence of less than one case per million population per year[7]. The coexistence of these two antibodies has been well recognized. Up to half of the patients with anti-GBM disease have detectable ANCA, and about 10% of patients with AAV are seropositive for anti-GBM antibodies[8]. However, the mechanism of their association is not clear although evidence has shown that ANCAs precede anti-GBM antibodies[9].

The clinical presentation, treatment, and prognosis of double-positive patients remain to be further clarified. Several retrospective studies reported that double-positive patients shared features of anti-GBM disease, such as high frequency of pulmonary hemorrhage, dialysis requirement at diagnosis, and characteristics of AAV (*e.g.*, multiple organ involvement and older age distribution)[7, 10]. Our present patient was double-seropositive for ANCA and anti-GBM antibodies and exhibited acute kidney failure (requiring dialysis at diagnosis) and pulmonary hemorrhage. Her kidney pathology revealed the 100% involvement of glomeruli by necrotising and crescentic lesions in the same phase, which is similar to anti-GBM patients.

The lung is one of the most commonly affected organ both in AAV and anti-GBM disease. In recent years, many studies have explored the association between AAV and ILD. A recent review of 149 AAV patients with ILD showed that usual interstitial pneumonia (UIP) was the most common CT pattern, followed by non-specific interstitial pneumonia (NSIP)[11]. OP can be an accompanying histological finding in patients with AAV [5]. Takada *et al*. reported a patient with myeloperoxidase-ANCA-associated OP fully recovered after steroid therapy. Tashiro *et al*. reported seven patients diagnosed as anti-GBM disease with pre-existing ILD and six of them died finally due to respiratory failure [12]. However, OP pattern has been rarely reported in anti-GBM disease. Based on the presence or absence of a specifically associated disease, OP can be classified as secondary OP (SOP) and cryptogenic OP (COP). The diagnosis of OP should be based on clinical presentation as well as radiologic and pathologic features [3, 13]. The clinical presentation of OP is nonspecific but can include fatigue, dry cough, exertional dyspnea, and severe shortness of breath[3]. High-resolution CT (HRCT) is recommended for the diagnosis of OP, with the typical pattern on HRCT being multifocal peribronchovascular consolidation[13]. Although OP can be diagnosed in some cases based on the clinical and radiographic features, histopathologic confirmation is still required. Presence of polypoid plugs of loose connective tissue in alveolar spaces and alveolar ducts is the predominant pathologic finding[3]. In our present case, we initially ascribed her irreversible respiratory failure to pulmonary infection since alveolar hemorrhage is prone to secondary infection; however, the final lung pathology reports indicated OP. For the treatment of OP, corticosteroid therapy and immunosuppressive therapy are generally recommended, and a good response is usually seen[3]. However, the treatment response for double-positive patients remains unknown. Bae *et al.*[6] reported a case of seronegative anti-GBM disease with concomitant OP; similarly, the patient also died due to worsened respiratory status. Interestingly, both the case reported by Bae *et al.* and our present patient developed thrombocytopenia during their hospital stay.

The mechanism of the association between OP and ANCA or anti-GBM antibodies is not clear. Recent research has shown that ANCA-activated neutrophils can localize to vulnerable microvascular beds, where they induce injury and release autoantigen for presentation by antigen-presenting cells, allowing antigen recognition by effector T cells, which mediate further injury [14]. Moreover, anti-GBM antibody can bind to the non-collagenous 1 domain of the α3 chain of type 4 collagen in lung membrane basement, further initiating a local inflammatory response, which reduces injury[1]. We assume that OP is associated with injury of alveolar epithelial cells and interalveolar septal capillaries caused by ANCA and anti-GBM antibodies; however, more studies are needed for clarifying the exact mechanism.

In summary, we reported a case of double-positive for ANCA and anti-GBM antibodies with concom-

itant OP. Although rarely seen in clinical practice, OP can be a cause of respiratory failure in double-positive patients. Our report also highlights the importance of lung biopsy for double-positive patients with worsening respiratory status. Moreover, further work is required to clarify the mechanism of the association between OP and ANCA or anti-GBM antibodies and to define optimum treatment strategies for double-positive patients with OP.

Patient consent

Writen consent for publication has been obtained from the patient's son.

Conflict of interests

The authors declare that they have no competing interests.

Authors' contributions

Conception and design: Wang FY and Li XZ; literature search: Wang FY, Li XZ, and Liao ZH; data acquisition: Wang FY, Li XZ, Yin HL, Hu CH, Ning JP, Sun DN, and Feng JT; manuscript preparation: Wang FY, Li XZ, Xu H, and Xiao G; manuscript editing: Wang FY; manuscript review: Li XZ. All authors have read and approved the final version submitted.

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病例报告

ANCA 和抗 GBM 抗体双阳性患者伴机化性肺炎一例

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摘要

抗肾小球基底膜（anti-glomerular basement membrane，GBM）疾病和抗中性粒细胞胞浆抗体（anti-neutrophil cytoplasmic antibody，ANCA）相关性血管炎（ANCA-associated vasculitis，AAV）都是是肺肾综合征的常见原因。机化性肺炎（organizing pneumonia，OP）是一种特殊的间质性肺疾病，在 AAV 和抗 GBM 疾病中都极为罕见。我们报道了一例 ANCA 和抗 GBM 抗体双阳性并伴有机化性肺炎的老年女性病例。

关键词：机化性肺炎；双阳性；病例报告

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