

Granulomatosis with polyangiitis presenting with diffuse alveolar hemorrhage requiring extracorporeal membrane oxygenation with rapid multiorgan relapse

A case report

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Abstract

Rationale: Granulomatosis with polyangiitis (GPA) is an antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis affecting small- and medium-sized blood vessels, mostly involving lung and kidney.

Patient concerns: We report the case of a 33-year-old man that presented with acute respiratory distress syndrome caused by alveolar hemorrhage.

Diagnoses: Aggressive GPA presenting with diffuse alveolar hemorrhage and multiorgan involvement.

Interventions: Immunosuppressive therapy, plasma exchange, extracorporeal membrane oxygenation (ECMO).

Outcomes: Relapse occurred very early, despite immunosuppressive treatment, with a rare involvement of genital system (epididymitis) and rapidly progressive glomerulonephritis difficult to treat.

Lessons: GPA is a challenging, multifaceted disease that can require aggressive supportive therapy and is associated with a high rate of relapse that may present with uncommon site of involvement.

Abbreviations: ANCA = antineutrophil cytoplasmic antibodies, DAH = diffuse alveolar hemorrhage, ECMO = extracorporeal membrane oxygenation, GPA = granulomatosis with polyangiitis, PE = plasma exchange.

Keywords: case report, diffuse alveolar hemorrhage, extracorporeal membrane oxygenation, granulomatosis with polyangiitis

1. Introduction

Granulomatosis with polyangiitis (GPA) is a systemic necrotizing vasculitis affecting small- and medium-sized blood vessels, often associated with antineutrophil cytoplasmic antibodies (ANCA).^[1] The disease involves upper and/or lower respiratory tract and kidney. Renal involvement is present in more than 50% patients at presentation and develops in 70% to 80% of them during the course of the disease, with pauci-immune necrotizing crescentic glomerulonephritis.^[2] The lung is the most frequent and sometimes only organ involved (50% to 90%) with alveolar hemorrhage of variable severity and/or parenchymatous nodules,

either single or multiple. Pulmonary-renal syndrome, defined as a combination of diffuse pulmonary hemorrhage and glomerulonephritis, may occur as a rare complication that carries an extremely high mortality rate.^[3]

2. Case report

A 33-year-old Moroccan man with a 5-month history of recurring sinusitis presented with temperature, myalgia, cough, and hemoptysis. Thoracic physical examination revealed reduced vesicular murmur, and chest X-ray showed bilateral diffuse alveolar infiltrates. Laboratory analyses showed elevation of acute-phase proteins (CRP 26 mg/dL) and creatinine (1.2 mg/dL) with nonnephrotic proteinuria and microscopic glomerular hematuria. An antibiotic therapy for community acquired and atypical pneumoniae with levofloxacin 500mg daily iv was established, but on the 3rd day from admission the patient developed respiratory failure unresponsive to noninvasive ventilation and had to be intubated. White lung with consolidations and ground glass areas at computed tomography scan (Fig. 1), diffuse airways bleeding at fiberoptic bronchoscopy, mild normocytic anemia (9 g/dL), and ANCA-PR3 positivity (18.9 U/mL) were consistent with the diagnosis of GPA. Despite maximal ventilatory support, gas exchange did not improve (pH 7.33, PaO₂ 71 mmHg, PaCO₂ 51 mmHg, HCO₃⁻ 25 mmol/L, SaO₂ 94%) requiring extracorporeal membrane oxygenation (ECMO). Treatment with high-dose methylprednisolone (1g daily for 3 days and 1 mg/kg daily thereafter), cyclophosphamide (1.2 g/pulse every 2 weeks for the 1st 3 pulses, followed by infusions every 3 weeks for the next 2 pulses), and plasma

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Figure 1. High resolution CT scans of admission CT with axial, sagittal, and coronal planes including lung and mediastinum showing diffuse “white lung” parenchyma with consolidations, ground glass areas, and ICU devices (ECMO). CT=computed tomography, ECMO=extracorporeal membrane oxygenation, ICU=intensive care unit.

exchange (PE), according to European vasculitis study group recommendations,^[4] was immediately started with respiratory improvement that allowed ECMO and orotracheal tube withdrawal and subsequent discharge from intensive care unit. After 9 days from the beginning of treatment ANCA-PR3 levels normalized (3 U/mL).

Two months later, after the 5th bolus of cyclophosphamide and with prednisone 0.3 mg/kg/day, the patient complained arthralgia and testicular pain with edema, cough, and shortness of breath: laboratory data showed worsening of renal function, mild anemia, and hypoxemia (PaO₂ 61 mmHg). Epididymitis was confirmed by ultrasound. Because of rapidly progressive renal failure (estimated glomerular filtration rate 35 mL/min) renal biopsy was performed and showed prominent intracapillary and extracapillary proliferation, with the formation of some fibrocellular crescents and focal capillary necrosis (Fig. 2). Lung computed tomography-scan and fiberoptic bronchoscopy also confirmed alveolar hemorrhage relapse. Treatment with high-dose methylprednisolone (1 g daily for 3 consecutive days) and rituximab (375 mg/m² weekly for 4 weeks) was started with rapid resolution of urologic and pulmonary involvement but delayed and partial improvement of renal function. At a 1-year follow-up, the patient is alive and under treatment with azathioprine (150 mg daily) and prednisone (15 mg daily). Renal function has markedly improved (estimated glomerular filtration rate 94 mL/min) same as gas-exchange (pH 7.42, PaO₂ 86 mmHg, PaCO₂ 36 mmHg, HCO₃⁻ 23 mmol/L, SaO₂ 95%).

The patient signed institutional informed consent form at the time of admission to hospitalization. An approval by ethics committee was not necessary because of the routine health care.

3. Discussion

We report a case of GPA with peculiar aggressiveness, multiorgan involvement, and early relapse; in particular, acute respiratory

distress syndrome caused by severe lung involvement required management with ECMO, and relapse occurred very early, despite immunosuppressive treatment, with a rare involvement of genital system (epididymitis) and rapidly progressive glomerulonephritis difficult to treat.

Although the lung is the target organ most commonly affected in GPA, diffuse alveolar hemorrhage (DAH) is a rare manifestation of the disease, occurring only in 5% to 10% of patients^[5,6] and carries an extremely high mortality rate. It denotes diffuse intraalveolar bleeding from small vessels as a result of severe damage of the lungs’ alveolar-capillary membrane.^[7] Even if the most important predictor of respiratory failure in patients with DAH from ANCA-associated vasculitis seems to be the degree of hypoxemia upon presentation,^[8] our patient developed acute respiratory distress syndrome suddenly despite SaO₂ > 95% in room air and no need of oxygen supplementation at onset. Immunosuppressive therapy combined with PE has dramatically improved survival, but supportive therapies for complications affecting vital organs are often necessary. ECMO can be successfully applied when conventional mechanical ventilation fails in respiratory failure due to pulmonary hemorrhage attributed to various causes, including autoimmune vasculitis. The evidence for the use of ECMO in patients with severe respiratory failure due to alveolar hemorrhage from ANCA associated vasculitis is restricted to a small number of case reports.^[9–11] The aim is to prevent progressive lung damage caused by high airways pressure and oxygen toxicity, allowing immunosuppressive treatment to switch-off the inflammation.^[10] We chose cyclophosphamide instead of rituximab as induction of remission therapy^[12] because we were more familiar with this drug in critically ill patient in intensive care unit setting. A recent paper on DAH secondary to ANCA-associated vasculitis^[8] highlights a higher rate of remission at 6 months achieved with rituximab than with cyclophosphamide, but at the time of this clinical case the study results were not available. Although no

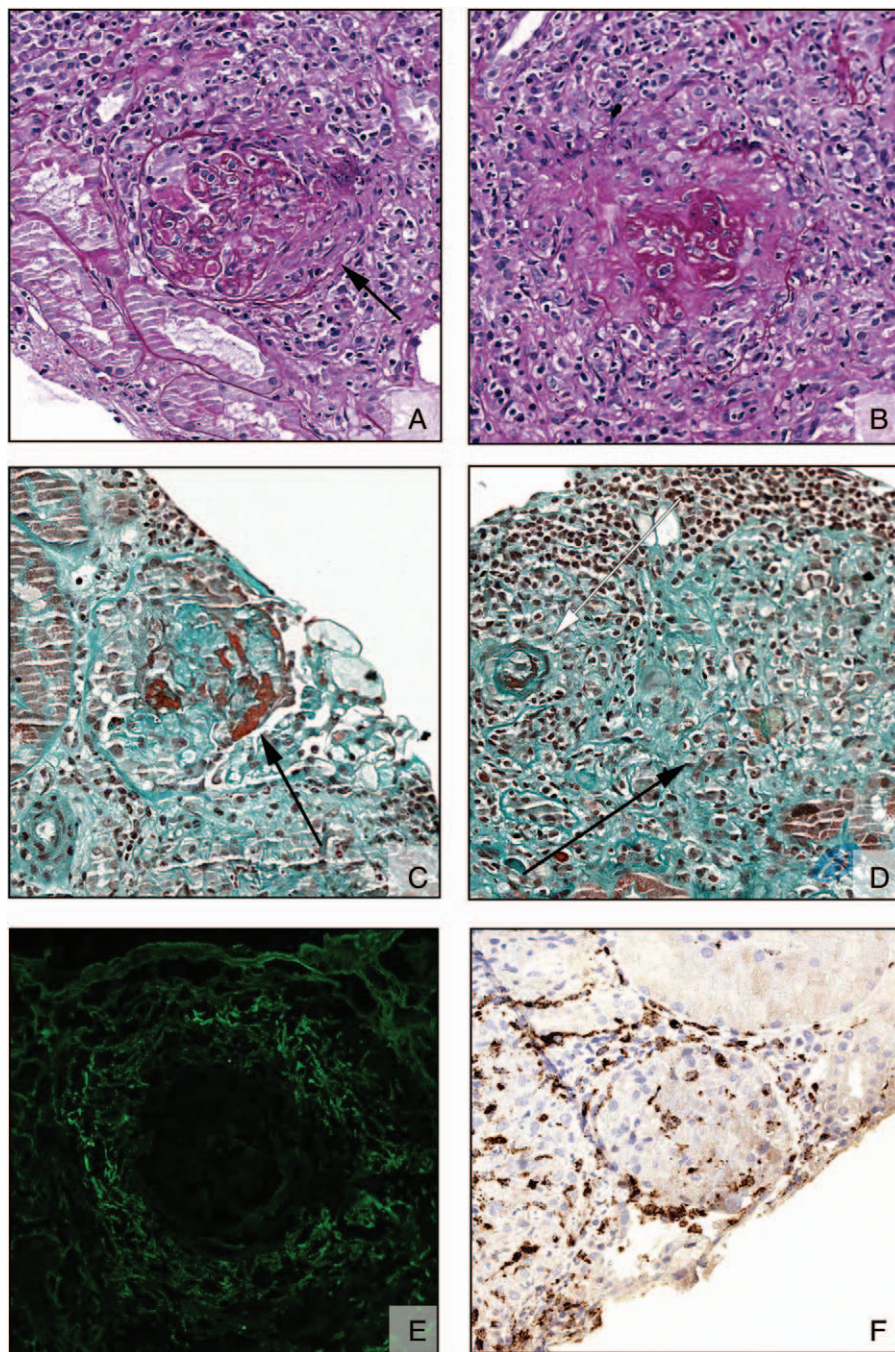


Figure 2. Histopathological features of GPA. The renal biopsy of this patient showed a prominent intracapillary and extracapillary proliferation, with formation of some fibrocellular crescents (A, black arrow, $\times 20$, PAS). Moreover, glomerular tufts were affected by a massive pericapsular granulomatous reaction (B, $\times 20$, PAS) and focal capillary necrosis (C, black arrow, $\times 20$, Masson). The massive interstitial infiltrate composed by mononuclear cells completely destroyed glomerular structures (white arrow), involving vessels with a peculiar granulomatous arteritis pattern (black arrow, D, $\times 20$, Masson). Finally, in immunofluorescence can be noted the typical periglomerular deposition of fibrinogen (E) and the presence of CD68-PGM1+ macrophages around glomerular tuft in immunohistochemistry (F). GPA=granulomatosis with polyangiitis, PAS=periodic acid-Schiff.

definitive data about the role of PE as add-on therapy for severe alveolar hemorrhage are available, we treated our patient with PE even though only mild renal involvement was manifest at onset.

Relapse during GPA occurs frequently: over half of patients relapse within 5 years and 1 quarter within 2 years.^[1] In our patient, the relapse of DAH together with the onset of rapidly progressive renal failure and epididymitis after only 2 months and despite aggressive induction therapy raises the question about

uncontrolled disease instead of early relapse. The patient was treated with rituximab plus methylprednisolone pulses for early treatment failure as rescue therapy.

Although all body organs can be virtually affected during GPA, urogenital involvement is rare and reported in less than 1% of patients.^[13] In particular epididymitis was described in only 3 case reports, always as the initial manifestation of the disease. In the present clinical case rituximab therapy allowed complete

remission of epididymis and lung involvement, whereas only partial improvement of renal function was achieved. Although rituximab retreatment has been shown superior to azathioprine as maintenance therapy,^[14] we chose to introduce azathioprine considering the still elevated dose of prednisone and the persistence of proteinuria despite the aggressive treatment.

In conclusion, GPA is a challenging, multifaceted disease that seldom requires aggressive supportive therapy including ECMO. Proper follow-up during treatment is needed due to the high rate of relapse that may present with uncommon site of involvement.

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