

Antineutrophil Cytoplasmic Antibody-associated Vasculitis With Alveolar Hemorrhage and Ruptured Renal Aneurysm: a Case Report and Literature Review

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Case report

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Abstract

Background: Antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (AAV) is characterized by necrotizing damage of small -vessel vasculitis and the main violation of the kidney or lung. Manifestation of alveolar hemorrhage and renal aneurysm is extremely rare in Granulomatosis with polyangiitis (GPA).

Case presentation: A 50-year-old Chinese man was admitted due to repeated cough, expectoration, fever and shortness of breath. A chest computed tomography (CT) scan showed bilateral infiltrates in the lower lobe of the lung. GPA was considered based on the pulmonary capillaritis, alveolar hemorrhage, renal insufficiency and cANCA -PR3 positivity. Immunosuppressive therapy combined with plasma exchange (PE) was performed. The patient suffered from a rupture of renal aneurysm. Though selective renal arterial embolization was performed, the patient had a poor outcome.

Conclusions: GPA could be life-threatening, especially large vessel vasculitis involved. The possibility of aneurysmal rupture should be carefully considered and checked frequently in the condition of immunosuppressive therapy.

Background

Antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis is a group of autoimmune disorders that is characterized by necrotizing damage of small -vessel vasculitis and involves the kidney or lung [1]. ANCA-associated vasculitis (AAV) is usually associated with cytoplasmic proteins (proteinase3 and myeloperoxidase) expressed in the cytoplasm of neutrophils without an immune complex, indicating no-use for large vessel vasculitis, according to the Chapel Hill Consensus Conference in 2012[2]. Patients with AAV develop inflammatory necrosis of many organs such as acute respiratory failure (ARF), an uncommon cause that results in a great mortality[3].

Unlike AAV, polyarteritis nodosa (PAN) typically affects medium-vessel arteries without glomerulonephritis or vasculitis in arterioles, capillaries, or venules. Renal aneurysm is frequently encountered in PAN[4]. ANCA is not typically associated with PAN[5].

We report a case of PR3-AAV with alveolar hemorrhage and renal aneurysm as typically found in PAN, suggesting that the AAV may have some relationship with these complication.

Case Presentation

A 50-year-old Chinese man was admitted to a hospital with repeated cough, expectoration, fever and shortness of breath in May 13, 2020. He was received antibiotics treatment in the local hospital. The symptoms of fever and shortness of breath progressively worsened. He was transferred to our hospital for respiratory support treatment on May 29, 2020. His past history was unremarkable.

He had no history of asthma, chronic obstructive pulmonary disease, hypertension and diabetes mellitus.

On admission, the patient was 175 cm in height and weighed 76.8 kg. He got a high fever with body temperature of 38.6°C. He presented the shortness of breath with respiratory rate 32 beats/min, pulse rate 116 beats/min, and blood pressure 138/88 mmHg. Some moist rales could be heard in the basic areas of both lungs. The cardiovascular, abdominal and musculoskeletal examination were normal. Arterial blood gas analysis (FiO₂ 40%) were as follows: PH 7.49, PCO₂ 30mm Hg, PO₂ 79mm Hg, PaO₂/FiO₂ 197mmHg, HCO₃⁻ 22.9 mmol/L, oxygen saturation 89%. Noninvasive ventilation was performed due to hypoxemia for ARF.

Blood routine showed white blood cell count 34.82×10⁹/L (neutrophils 95.6%, lymphocytes 3.1%, eosinophils 0.6%), platelet count 458×10⁹/L, Hemoglobin 107g/L, C-reactive protein > 200mg/L. Erythrocyte sedimentation rate was 80mm/h. Serum creatinine and blood urea nitrogen (BUN) levels were 103umol/L and 9.3mmol/L, respectively. D-Dimer level was 2907ng/ml. pro- B-Type Natriuretic Peptide (BNP) was 6687 pg/ml. Serum procalcitonin (PCT) level was 0.297ng/ml. Serum K, Na and Cl were 4.18mmol/L, 134.8mmol/L and 96.9mmol/L, respectively. Glomerular filtration rate (GFR) and creatinine clearance rate (CCr) were 72.2ml/min and 70.1ml/min, respectively. Urinalysis showed 91 leukocytes per uL (0–25) and 337 erythrocytes per uL (0–25). Urinary sediments were erythrocytes 0.3/HP (0–3), leukocytes 2/HP (0–5) and no casts. Levels of IgG and IgE were normal. Blood culture and serologic tests were found to be negative for human immunodeficiency virus, hepatitis B virus, hepatitis C virus, Epstein-Barr virus, cytomegalovirus, and herpes simplex virus. A chest CT scan showed bilateral infiltrates in the lower lobe of the lung. (Fig. 1A).

The patient was considered a diagnosis of severe pneumonia with ARF and received antibiotic treatment intravenously. On day 3 after admission, His symptoms of shortness of breath with persistent high fever were gradually aggravated. The occurrence of oliguria was appeared. Diffused airways bleeding was found with haemorrhagic bronchoalveolar lavage fluid (BAL) by Fiberoptic bronchoscopy (Fig. 1B) Autoimmune antibody spectrum were as follows: cytoplasmic staining pattern (cANCA) 1:45 (< 1:20), anti- proteinase-3 antibody (PR3-ANCA) 300 RU/ml (0–20), Perinuclear staining pattern (pANCA) < 1:20 (< 1:20), anti-myeloperoxidase antibody (MPO-ANCA) 1.5 RU/ml (0–20), anti-ds-DNA antibody 31.5 IU/ml (0–100), anti-ss-DNA antibody 6.7 IU/ml (0–20), rheumatoid factor 12.06 IU/ml (0–14). Blood routine showed white blood cell count 32.15×10⁹/L (neutrophils 90.2%, lymphocytes 4.3%, eosinophils 0.4%), Hemoglobin 99g/L. Serum creatinine and BUN levels were 301umol/L and 19.08mmol/L, respectively. GFR and CCr were 19.8ml/min and 20.3ml/min, respectively. Serum K, Na and Cl were 4.13mmol/L, 132.1mmol/L and 96mmol/L, respectively. D-Dimer level was 3592 ng/ml. pro- BNP was 7745pg/ml. PCT level was 1.44ng/ml. Increasing lung infiltrates were showed in the chest X-ray (Fig. 1C). Bone marrow biopsy was taken to indicate infection. PR3-AAV with renal insufficiency was considered. The patient received prednisolone (0.6 mg/kg/day) with cyclophosphamide (200 mg biw) intravenously. Hemodialysis and plasma exchange (PE) were immediately started due to the deterioration of renal function and alveolar hemorrhage.

His general condition and inflammatory reaction improved (Fig. 1D). Patients were satisfied with the current treatment. A lung biopsy was performed with the presence of pulmonary capillaritis with extravasation of erythrocytes, fibrosis proliferation and neutrophils infiltration (Fig. 2). On day 10 after admission, the patient had a sharp pain of sudden onset in his left abdominal side. His hemoglobin dropped from 99g/L to 55g/L developed in the subsequent hours, but there were no sign of hemorrhage. A chest CT scan showed increasing bilateral infiltrates in the lower lobe of the lung (Fig. 1E). Abdominal CT scan showed left kidney and left retroperitoneal hematoma (Fig. 1F). Selective arterial angiography showed multiple aneurysms in renal arteries (Fig. 1G). A decrease in hemoglobin and a large hematoma of left kidney and left retroperitoneal were considered the possibility of the ruptured renal aneurysm. Selective renal arterial embolization was performed.

On day 11 after admission, his symptoms of shortness of breath and renal function gradually deteriorated. Serum creatinine and BUN levels were 469 μ mol/L and 39.26mmol/L, respectively. GFR and CCr were 11.5ml/min and 12.2ml/min, respectively. Serum K, Na and Cl were 5.92mmol/L, 138.3mmol/L and 101.1mmol/L, respectively. pro-BNP was 33568 pg/ml. White blood cell count 39.03 \times 10⁹/L (neutrophils 92.8%, lymphocytes 4%, eosinophils 0%), platelet count 307 \times 10⁹/L, Hemoglobin 57g/L, PCT level was 7.13ng/ml. Arterial blood gas analysis indicated hypoxemia with PaO₂/FiO₂ 143mmHg. Titer of cANCA and PR3-ANCA were 1:100 and 264RU/ml, respectively. Increasing lung infiltrates were showed in the chest X-ray (Fig. 1H). Incubation with mechanical ventilation was done immediately. Unfortunately, the patient died of ARF and acute kidney injury (AKI) on June 9, 2020. (Fig. 3).

Discussion And Conclusions

AAV is characterized by small-vessel vasculitis, particularly involving the glomerular and pulmonary capillaries that lead to rapidly progressive glomerulonephritis (RPGN) and pulmonary hemorrhage (more than 50%) [6]. In this case, white lung with consolidations, alveolar hemorrhage, mild normocytic anemia, and cANCA-PR3 positivity were considered as the diagnosis of GPA. In detail, the patient suffered from multiple organ damage; in particular ARF caused by severe lung involvement and rapidly progressive AKI with a rare involvement of renal aneurysm difficult to treat.

Although the lung is the most commonly affected organ in GPA, alveolar hemorrhage and ARF is a rarely clinical manifestation that carries an extremely high mortality with incidence of only 5–10% in these patients [7–11]. High risk factors including infections, environment or genetic predisposition may trigger an inflammatory response that involves the release of ANCA [12]. ANCA-activated neutrophils secrete proinflammatory cytokines and release reactive oxygen species to amplify vasculitis and disrupt the vascular wall, then migrate into lung compartments through alveolar-capillary membrane, and finally reach alveolar spaces mediated by CXC chemokines [13–14]. Also, severe damage of the alveolar-capillary barrier can cause diffuse intraalveolar hemorrhage from small vessels, an important predictor of ARF in patients with AAV [15–16]. In this case, the patient's respiratory failure was developed progressively due to pulmonary hemorrhage despite the use of noninvasive mechanical ventilation. Immunosuppressive therapy combined with PE was performed according to European vasculitis study group recommendations [17]. The patient's condition was dramatically improved attributed to the supportive therapies for complications affecting vital organs.

Arterial aneurysm formation and rupture is a rare complication of GPA. To the best of our knowledge, Only cases with sufficient clinical data for analysis were identified by a review of the literature. Finally, 6 case reports were included in the present study with renal aneurysm involved (Table 1). All the patients were male with the age of onset ranged from 24 to 50. Three patients had positive ANCA. Moreover, Three patients had a ruptured renal aneurysms, of which one died. In addition, most of these patients were treated with immunosuppressive agents such as steroids and cyclophosphamide. The prognosis of surviving patients was good.

Table 1
Characteristics of patients with renal aneurysm in granulomatosis with polyangiitis

Case /Year	Gender/ Age (y)	Country	Manifestation	Antibodies	Symptoms	Duration of aneurysmal symptoms	Complication with alveolar hemorrhage	Treatment	Rupture	Outcome
Baker /1978	Male/24	American	Renal aneurysms	NS	Abdominal pain	6 weeks	No	PSL 30 mg + CY 150 mg/day	Yes	Good
Moutsopoulos /1983	Male/30	Greece	Renal aneurysms	NS	NS	1 month	No	PSL 1mg/kg/day + CY 2 mg/kg/day	No	Good
Senf /2003	Male/35	Germany	Hepatic, renal, splanchnic aneurysms	C-ANCA positive	Abdominal pain	6 weeks	No	Steroid + PSL + IVCY 750 mg	Yes	Good
Arlet /2008	Male/29	France	Hepatic + renal aneurysm	PR3 ANCA 15 IU/mL	Abdominal pain	NS	No	Coil embolization + steroid + PSL 60 mg + MMF 2.5 g	No	Good
Unlü/2011	Male/43	Netherlands	Renal aneurysms	NS	Abdominal pain and generalized malaise	1 week	No	PSL + surgery	No	Good
Present case	Male/50	China	Renal aneurysms	c-ANCA + PR3 positive	Abdominal pain	3 hours	Yes	Embolization + PSL + CY 200 mg + hemodialysis	Yes	Death

PSL: prednisolone; CY: cyclophosphamide; PSL Prednisolone ;mPSL: methylprednisolone; MMF: mycophenolate mofetil; IVCY: intravenous cyclophosphamic

It is difficult to prove the relationship between GPA and renal aneurysm involved due to no pathological evidence found in our patient. We suggest that the incidence of both PR3-AAV and renal aneurysm by chance through their pathologies is very remote. It is more reasonable to consider that the pathology of PR3-AAV is related to the development of renal aneurysm. Aneurysms of the medium-sized arteries are frequently encountered in PAN, whereas their occurrence in smaller arteries is unclear. Damage of the internal and external elastic lamina may contribute to the development of aneurysmal dilation [18]. In addition, the vessel wall is disrupted by inflammation reaction, thrombosis and arterial narrowing resulting in aneurysm formation. Immunosuppressive therapies could lead to thinning of the adventitia that we needed to consider the risk of aneurysmal rupture[19].

In the present case, the patient developed both alveolar hemorrhage and renal aneurysm, a rare manifestation of GPA. PE is recommended in the presence of alveolar hemorrhage and severe renal disease, which is able to remove the ANCAs effectively and yield a good response for prognosis[20].Corticosteroids and cyclophosphamide are reportedly effective for the treatment with arterial aneurysms in GPA. Unfortunately, the patient's condition deteriorated progressively with ARF and AKI. Aneurysmal rupture may result in life-threatening bleeding for poor outcome. ANCA might play a role in ANCA associated large vessel disease in rare cases [21]. Large vessels involvement should be paid attention as an important factor in the development of AAV. Therefore, CT scan be considered to screen for the presence of arterial aneurysm to treat the patient as safely as possible. There are valuable experiences or lessons learned from the case when we encounter rare manifestations of rare diseases in the process of clinical diagnosis.

In conclusion, GPA could be life-threatening, especially large vessel vasculitis involved, which should not be ignored by clinicians. The possibility of aneurysmal rupture should be carefully considered and the condition of the aneurysm should be checked frequently when administering immunosuppressive therapies for GPA with aneurysm.

Abbreviations

AKI: acute kidney injury

ANCA: Antineutrophil cytoplasmic autoantibody

AAV: Antineutrophil cytoplasmic autoantibody -associated vasculitis

ARF: acute respiratory failure

BAL: bronchoalveolar lavage fluid

BNP: B-Type Natriuretic Peptide

BUN: blood urea nitrogen

CT: computed tomography

CCr: creatinine clearance rate

MPO: myeloperoxidase

GFR: Glomerular filtration rate

GPA: Granulomatosis with polyangiitis

PAN: polyarteritis nodosa

PE: plasma exchange

PCT: procalcitonin

PR3: proteinase-3

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the Second Affiliated Hospital of Chongqing Medical University. Written informed consent was obtained from the patient for publication of this case report and any accompanying images. The data used in this study was anonymised before its use

Consent for publication

Written informed consent was obtained from the patient's wife for publication of this case report and any accompanying images.

Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Competing interests

The authors declare that they have no conflicts of interests.

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Authors' contributions

WD, JT and DXW had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. WD, wrote the paper. ZYZ, XL and XQL had acquisition, analysis, or interpretation of the data. JT and DXW contributed to revision of the manuscript for important intellectual content. All authors have read and approved the manuscript.

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References

1. Kallenberg CG, Heeringa P, Stegeman CA. Mechanisms of disease: pathogenesis and treatment of ANCA-associated vasculitides. *Nat Clin Pract Rheumatol.* 2006;2:661-70.
2. Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, et al. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. *Arthritis Rheum.* 2013;65: 1-11.
3. Ware LB, Matthay MA. The acute respiratory distress syndrome. *N Engl J Med.* 2000;342:1334-49.
4. Miyagawa T, Iwata Y, Oshima M, Ogura H, Sato K, Nakagawa S, et al. Polyarteritis nodosa with perirenal hematoma due to the rupture of a renal artery aneurysm. *CEN Case Rep.* 2020 Nov 11. doi: 10.1007/s13730-020-00552-z.
5. Pagnoux C, Seror R, Henegar C, Mahr A, Cohen P, Le Guern V, et al. Clinical features and outcomes in 348 patients with polyarteritis nodosa: a systematic retrospective study of patients diagnosed between 1963 and 2005 and entered into the French Vasculitis Study Group Database. *Arthritis Rheum.* 2010;62:616-26.

6. Geetha D, Kallenberg C, Stone JH, Salama AD, Appel GB, Duna G, et al. Current therapy of granulomatosis with polyangiitis and microscopic polyangiitis: the role of rituximab. *J Nephrol* 2015;28:17-27.
7. Hermon MM, Golej J, Emminger W, Puig S, Szepfalusi Z, Trittenwein G. Acute hemorrhagic respiratory failure caused by Wegener's granulomatosis successfully treated by bronchoalveolar lavage with diluted surfactant. *Wien Klin Wochenschr*. 2003;115:793-6.
8. Esposito S, Corona F, Defilippi A, Petaccia A, Chidini G, Dell'Era L, et al. Wegener's granulomatosis presenting with life-threatening lung hemorrhage in a 7-year-old child. *Rheumatol Int*. 2010;30:1665-8.
9. Joseph M, Charles AG. Early extracorporeal life support as rescue for Wegener granulomatosis with diffuse alveolar hemorrhage and acute respiratory distress syndrome: a case report and literature review. *Pediatr Emerg Care*. 2011;27:1163-6.
10. Vanoli J, Riva M, Vergnano B, D'Andrea G, L'Imperio V, Pozzi MR, et al. Granulomatosis with polyangiitis presenting with diffuse alveolar hemorrhage requiring extracorporeal membrane oxygenation with rapid multiorgan relapse: A case report. *Medicine (Baltimore)*. 2017;96:e6024.
11. Kaya H, Yilmaz S, Sezgi C, Abakay O, Taylan M, Sen H, et al. Two cases of extrapulmonary onset granulomatosis with polyangiitis which caused diffuse alveolar haemorrhage. *Respir Med Case Rep*. 2014;13:32–6.
12. Scott DG, Watts RA. Systemic vasculitis: epidemiology, classification and environmental factors. *Ann Rheum Dis*. 2000;59:161–3.
13. Bosch X, Guilabert A, Espinosa G, Mirapeix E. Treatment of antineutrophil cytoplasmic antibody associated vasculitis: a systematic review. *JAMA*. 2007;298:655-69.
14. Reutershan J, Ley K. Bench to bedside review: acute respiratory distress syndrome – how neutrophils migrate into the lung. *Crit Care*. 2004; 8: 453-61.
15. Mahajan V, Whig J, Kashyap A, Gupta S. Diffuse alveolar hemorrhage in Wegener's granulomatosis. *Lung India Off Organ Indian Chest Soc*. 2011;28:52–5.
16. Cartin-Ceba R, Diaz-Caballero L, Al-Qadi MO, Tryfon S, Fervenza FC, Ytterberg SR, et al. Diffuse alveolar hemorrhage secondary to antineutrophil cytoplasmic antibody-associated vasculitis: predictors of respiratory failure and clinical outcomes. *Arthritis Rheumatol Hoboken NJ* 2016;68:1467–76.
17. Yates M, Watts RA, Bajema IM, Cid MC, Crestani B, Hauser T, et al. EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis. *Ann Rheum Dis* 2016;75:1583–94.
18. Ng WF, Chow LT, Lam PW. Localized polyarteritis nodosa of breast: Report of two cases and a review of the literature. *Histopathology* .1993;23: 535-539.
19. Niimi N, Miyashita T, Tanji K, Hirai T, Watanabe K, Ikeda K, et al. Aortic Aneurysm as a Complication of Granulomatosis with Polyangiitis Successfully Treated with Prednisolone and Cyclophosphamide: A Case Report and Review of the Literature. *Case Rep Rheumatol*. 2018;2018:9682801.
20. Klemmer PJ, Chalermkulrat W, Reif MS, Hogan SL, Henke DC, Falk RJ. Plasmapheresis therapy for diffuse alveolar hemorrhage in patients with small vessel vasculitis. *Am J Kidney Dis*. 2003;42:1149-53.
21. Chirinos JA, Tamariz LJ, Lopes G, Del Carpio F, Zhang X, Milikowski C, et al. Large vessel involvement in ANCA-associated vasculitides: report of a case and review of the literature. *Clin Rheumatol*. 2004; 23: 152–9.

Figures

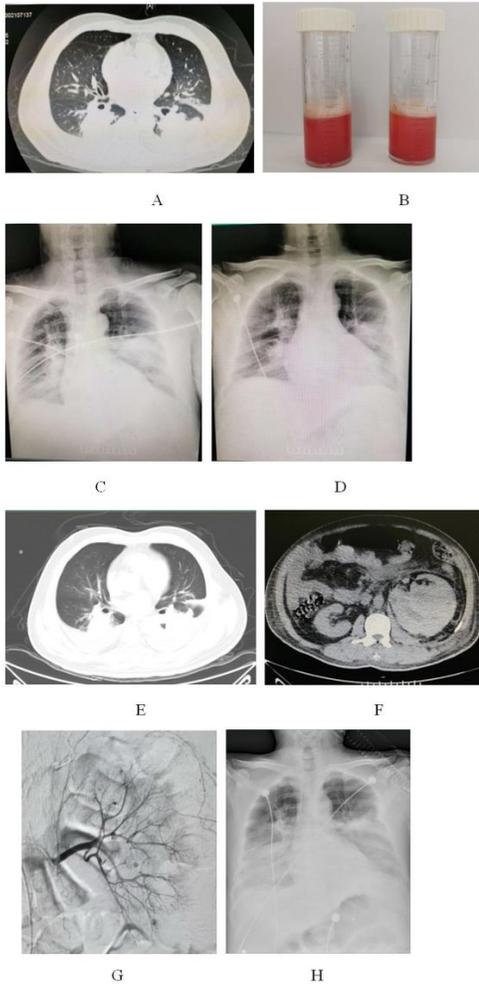


Figure 1

A: On the day of admission, chest X-ray showed bilateral infiltrate in the lower lobe of the lung. B: Haemorrhagic bronchoalveolar lavage fluid by Fiberoptic bronchoscopy. C: On day 3 of admission, increasing lung infiltrates were showed in the chest X-ray. D: On day 6 of admission, bilateral infiltrates in the the lung were improved. E: On day 10 of admission, increasing bilateral infiltrates in the lower lobe of the lung were shown in the chest CT scan. F: Abdominal CT scan showed left kidney and left retroperitoneal hematoma. G: Selective arterial angiography showed multiple aneurysms in renal arteries.

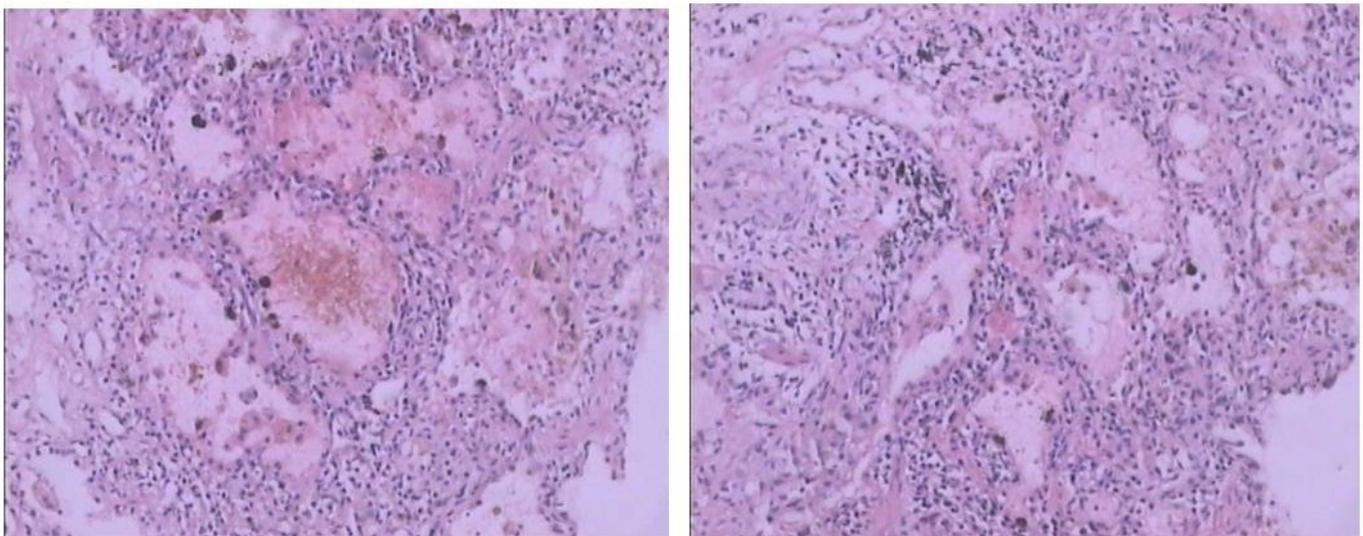


Figure 2

A lung biopsy showed pulmonary capillaritis with extravasation of erythrocytes, fibrosis proliferation and neutrophils infiltration

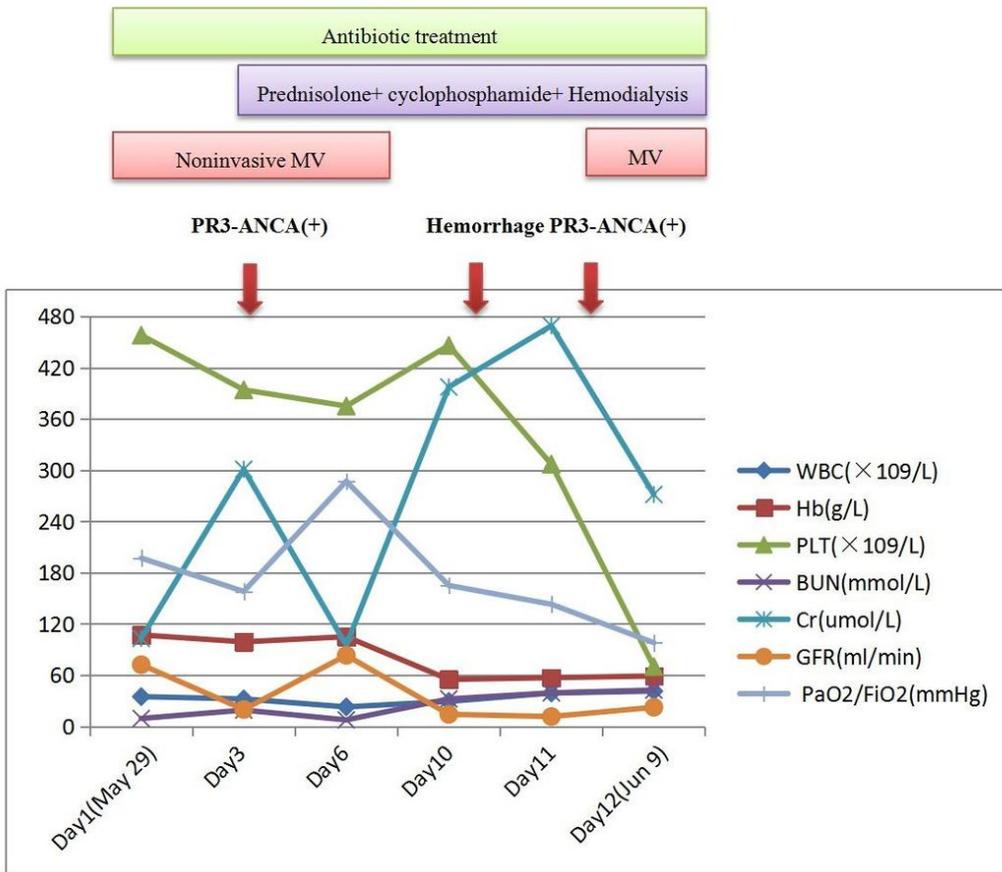


Figure 3

Clinical course of this patient