

Case Report

A rare cause of the pulmonary-renal syndrome: a case of atypical haemolytic-uraemic syndrome complicated by pulmonary haemorrhage

Vimal K. Derebail^{1,2}, Palak Parikh³, J. Charles Jennette^{2,4} and Abhijit V. Kshirsagar^{1,2}

¹Division of Nephrology and Hypertension, ²UNC Kidney Centre, ³Department of Medicine and ⁴Department of Pathology and Laboratory Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Abstract

Pulmonary haemorrhage is a potentially life-threatening event that may occur in patients with pulmonary-renal syndromes. These syndromes have typically been thought to occur in small-vessel vasculitides, such as ANCA-mediated disease, Goodpasture's disease and other autoimmune conditions including systemic lupus erythematosus or antiphospholipid antibody syndrome. Here, we present a rare cause for pulmonary haemorrhage with associated renal failure—atypical haemolytic-uraemic syndrome. In this case, renal biopsy was integral to providing a diagnosis and guiding therapy.

Keywords: haemolytic-uraemic syndrome; pulmonary haemorrhage; pulmonary-renal syndrome; thrombotic microangiopathy

Background

Pulmonary haemorrhage is a potentially devastating complication of the pulmonary-renal syndromes. The most well known of these syndromes is that named after Goodpasture who reported a case of haemorrhagic pneumonia accompanied by renal failure. These joint phenomena are now known to occur more commonly with the small-vessel vasculitides, including the ANCA-mediated diseases. They have also been described in other clinicopathologic conditions including systemic lupus erythematosus (SLE), antiphospholipid antibody syndrome and essential mixed cryoglobulinaemia [1,2]. Pulmonary haemorrhage bears high mortality, reaching 10% in ANCA disease [1] and >35% in SLE [3]. These high rates emphasize the importance for early recognition of this life-threatening condition.

Correspondence and offprint requests to: Vimal K. Derebail, Division of Nephrology and Hypertension, UNC Kidney Centre, 7018-A Burnett-Womack, Campus Box 7155, Chapel Hill, NC 27599, USA. Tel: +1-919-966-2561; Fax: +1-919-966-4251; E-mail: Vimal_Derebail@med.unc.edu

Here, we describe a rare case of pulmonary haemorrhage accompanying renal failure in a patient with haemolytic-uraemic syndrome (HUS). A renal biopsy became integral in determining the diagnosis and guiding further treatment.

Case report

A 47-year-old white male with no prior known medical history presented to a community hospital with complaints of scrotal and lower extremity oedema and progressive dyspnoea for several weeks with recent production of blood-tinged sputum. The review of systems was significant for epistaxis, haematochezia and decreased urine output for 2 weeks. Pertinent negatives included: no fevers, chills, rashes, arthralgias, myalgias, haematuria or dysuria. The patient denied use of any new medications or herbal supplements.

At admission to the outside hospital, the patient was found to be thrombocytopenic with platelets of 50 000/ μ L. Serum creatinine was 1.8 mg/dL (159 μ mol/L). Intravenous fluid was administered with no improvement in renal function. Four days following admission, the patient had two episodes of frank haemoptysis. His haemoglobin fell from 10 g/dL (100 g/L) to 7 g/dL (70 g/L) prompting transfusion, and his renal function continued to decline. Due to the constellation of thrombocytopenia, renal failure and haemoptysis, he was transferred to our centre for further management.

Upon arrival, the patient was afebrile, blood pressure was 150/80 mmHg, pulse 80 bpm, respiratory rate 18 and oxygen saturation 98% with 35% oxygen supplementation. Physical examination demonstrated an alert, oriented, malnourished male. Jugular venous distention and bilateral pulmonary rales were present. Cardiac and abdominal examinations were unremarkable. The patient had profound scrotal oedema and 4+ pitting oedema of bilateral lower extremities. Laboratory analysis revealed serum creatinine of 5.8 mg/dL (513 μ mol/L), blood urea nitrogen of 107 mg/dL (38.2 mmol/L) and platelets of 35 000/ μ L. Schistocytes were observed in the peripheral blood smear. Total bilirubin

was elevated to 1.8 mg/dL (31 μ mol/L), LDH was 3333 U/L and haptoglobin was <5 mg/dL (0.05 g/L). Urinalysis at our facility noted 2+ protein, 3+ blood and urine sediment demonstrated numerous muddy brown granular casts with rare acanthocytes.

The patient was given empiric pulse corticosteroids (7 mg/kg/day for 3 days), and after consultation with Haematology and Transfusion Medicine services, plasmapheresis was initiated within 3 days of transfer for presumed TTP versus small-vessel vasculitis. On hospital day 4, the patient developed a pericardial friction rub and began haemodialysis.

Due to his continuing haemoptysis, a bronchoscopy was performed which demonstrated diffuse alveolar haemorrhage. Further labs revealed positive anti-nuclear antibody (ANA) titre at >1:640, speckled. However, panel for extractable nuclear antigens (ENA) was negative, as were studies for anti-neutrophilic cytoplasmic antibodies (ANCA), anti-glomerular basement membrane (anti-GBM) antibodies, double-stranded DNA, anti-smooth muscle antibodies, anti-phospholipid antibodies and cryoglobulins. Complement levels were low normal with C3 of 75 mg/dL (0.75 g/L) and C4 of 15 mg/dL (0.15 g/L). ADAMTS-13 activity was modestly depressed at 19% and no inhibitor of ADAMTS-13 was detected. Stool cultures and all cultures from the bronchoalveolar lavage produced no growth.

After six plasma exchange treatments, the patient showed no improvement in thrombocytopenia or renal function although the pulmonary haemorrhage abated. A renal biopsy was performed to distinguish whether the underlying process was that of a vasculitis (such as an ANCA-negative, pauci-immune vasculitis or seronegative SLE) or that of a thrombotic microangiopathy (TMA). The plan for treatment was further immunosuppression with cytotoxic agents if a vasculitis was found versus continuation of plasmapheresis for a TMA.

The renal biopsy demonstrated diffuse cortical necrosis, secondary interstitial inflammation, extensive thrombosis and fibrinoid necrosis of arterioles, arteries and some glomeruli consistent with a severe TMA (Figure 1). Immunofluorescence staining was non-specific and electron microscopy demonstrated no immune complex-type electron-dense deposits.

On the basis of the renal biopsy results, the presentation and course were felt to be most consistent with an atypical HUS complicated by pulmonary haemorrhage. After a second series of six plasma exchanges, the patient had an improvement in thrombocytopenia and stabilization of haematocrit. He was eventually discharged home clinically stable to continue haemodialysis as an outpatient.

Discussion

Our report describes a rare cause of pulmonary haemorrhage coexistent with renal failure—the haemolytic-uraemic syndrome (HUS). Extrarenal manifestations of this illness have been described in diarrhoea-associated HUS in organs other than lung including large bowel, cardiac, central nervous system and pancreas [4]. Pulmonary involvement in this syndrome is exceedingly rare. In a review

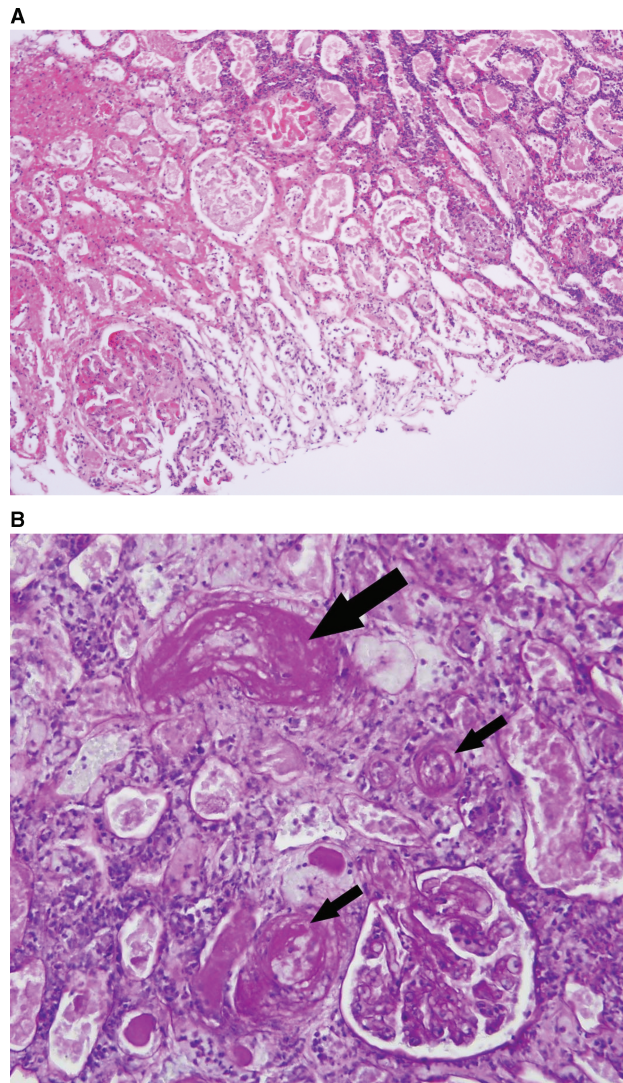


Fig. 1. (A) Kidney biopsy specimen under low magnification demonstrates significant coagulative necrosis. The left side of the field is dominated by interstitial haemorrhage. The right side demonstrates intense neutrophilic infiltration. The glomerular capillaries are engorged and thrombosed. Haematoxylin and eosin stain, 100 \times . (B) Under higher magnification, the thrombotic microangiopathy can be easily appreciated. The interlobular artery (large arrow) has thrombosed and undergone fibrinoid changes. Similar findings are present in the arterioles noted in this field (small arrows). The glomerular capillary lumen and tubular epithelium have been obliterated. Haematoxylin and eosin stain, 200 \times .

of previous accounts, there have been rare reports of pulmonary involvement. Other occurrences have been reported but have been in pediatric patients, in typical diarrhoea-associated HUS or in HUS associated with chemotherapy and neoplasia [5–9].

The aetiology of haemorrhage may occur from direct pulmonary microvascular thrombotic damage. In one autopsy series of three paediatric patients, pulmonary microthrombi were found in all of the patients although none had clinically significant pulmonary haemorrhage [10]. Alternatively or additionally, the bleeding diathesis may result from the haemorrhagic milieu of thrombocytopenia and uraemic platelet dysfunction. Pulmonary oedema due to

volume expansion with airway inflammation would predispose the patient to haemorrhage as well. Regardless of the cause, pulmonary haemorrhage in this syndrome is clearly a life-threatening complication whose true incidence should be better established.

This particular case highlights a rare but important complication associated with HUS. Accurate data on the true incidence of pulmonary involvement in the HUS are still needed and can perhaps be determined by the use of large registries. Distinguishing the underlying atypical HUS from another autoimmune aetiology may only be possible with kidney biopsy, and early recognition would allow for selecting appropriate therapeutic interventions.

Conflict of interest statement. None declared.

References

1. Jara LJ, Vera-Lastra O, Calleja MC. Pulmonary-renal vasculitic disorders: differential diagnosis and management. *Curr Rheumatol Rep* 2003; 5: 107–115
2. Bosch X, Font J. The pulmonary-renal syndrome: a poorly understood clinicopathologic condition. *Lupus* 1999; 8: 258–262
3. Barile L. Pulmonary hemorrhage in systemic lupus erythematosus. *Lupus* 1997; 6: 445–448
4. Gallo EG, Gianantonio CA. Extra-renal involvement in diarrhoea-associated haemolytic-uraemic syndrome. *Pediatric Nephrol* 1995; 9: 117–119
5. Piastra M, Ruggiero A, Langer A *et al.* Pulmonary hemorrhage complicating a typical hemolytic-uraemic syndrome. *Respiration* 2004; 71: 537–541
6. Torra R, Poch E, Torras A *et al.* Pulmonary hemorrhage as a clinical manifestation of hemolytic-uraemic syndrome associated with mitomycin C therapy. *Chemotherapy* 1993; 39: 453–456
7. Au WY, Tang SC, Chan KW *et al.* Pulmonary renal syndrome and thrombotic thrombocytopenic purpura in a patient with giant cavernous hemangioma of the leg. *Arch Intern Med* 2002; 162: 221–222
8. Oakes RS, Siegler RL, McReynolds MA *et al.* Predictors of fatality in postdiarrheal hemolytic uraemic syndrome. *Pediatrics* 2006; 117: 1656–1662
9. Garnacho Montero J, Marmesat Rios I, Leal Noval SR *et al.* The hemolytic-uraemic syndrome: a report of a case which started as a massive pulmonary hemorrhage. *An Med Interna* 1990; 7: 416–418
10. Upadhyaya K, Barwick K, Fishaut M *et al.* The importance of nonrenal involvement in hemolytic-uraemic syndrome. *Pediatrics* 1980; 65: 115–120

Received for publication: 6.8.08

Accepted in revised form: 8.8.08