CASE REPORT

CMV disease complicating induction immunosuppressive treatment for ANCA-associated vasculitis

James Tollitt, Edmond O'Riordan, Dimitrios Poulikakos

Renal Department, Salford
Royal NHS Foundation Trust,
Salford, Salford, UK

Correspondence to
Dr James Tollitt,
jamestol@hotmail.com

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SUMMARY

We present a case of a 71-year-old woman who initially presented with renal-limited antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis. Following standard therapy with cyclophosphamide, steroids and plasma exchange, her renal function began to improve. However, despite appropriate treatment, her renal function subsequently deteriorated and she suffered haemoptysis. Owing to diagnostic uncertainty, bronchoscopy and a repeat renal biopsy were performed. The bronchoscopy washings demonstrated positivity for cytomegalovirus (CMV) DNA, and in combination with a positive serum CMV PCR, immunosuppression was withheld. Treatment with ganciclovir was started. Repeat renal biopsy demonstrated active vasculitis and, following successful treatment of CMV disease, immunosuppression was re-started alongside prophylactic valganciclovir. This resulted in a successful outcome for the patient. Pulmonary CMV disease may mimic pulmonary disease associated with vasculitis, posing a diagnostic challenge to clinicians. We recommend a low threshold when testing for CMV in these patients.

BACKGROUND

In the present case, cytomegalovirus (CMV) disease was confirmed during cyclophosphamide induction treatment by the presence of CMV DNA on bronchial washings. CMV viraemia was confirmed on repeated serological testing.

To the best of our knowledge, this is the first case of successfully treated CMV disease complicating induction treatment for antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) with renal involvement. Furthermore, the combination of haemoptysis and increased transfer factor posed a diagnostic dilemma between resistant vasculitis requiring escalation of immunosuppression and CMV disease requiring temporary cessation of immunosuppression.

CASE PRESENTATION

A 71-year-old woman presented with acute kidney injury stage 3. Besides fatigue, she was asymptomatic. Her medical history included seronegative arthritis and fibromyalgia. She took no regular medications. There was no significant family history. Her vital signs and clinical examination were unremarkable.

INVESTIGATIONS

The patient's blood tests revealed haemoglobin 99 mg/dL, white cell count $8.2 \times 10^9/L$ and C reactive protein 15 mg/L. Creatinine was 298 $\mu\text{mol/L}$ (baseline 67 $\mu\text{mol/L}$ 10 weeks previously). Urinalysis revealed haematoproteinuria. Urine PCR was 0.46 mg/mmol. Renal ultrasound examination was normal. HIV and hepatitis screens were negative. A renal immune screen revealed positive ANCA immunofluorescence. Antiglomerular basement membrane (GBM) antibody was weakly positive 7.8 iU/mL (0.0–7.0 iU/mL) and antimyeloperoxidase antibody was 9.0 iU/mL (0.0–3.5 iU/mL).

Kidney biopsy revealed cellular crescents with focal segmental necrotising lesions in 5 of 20 glomeruli. Immunohistochemistry was negative.

DIFFERENTIAL DIAGNOSIS

- ▶ AAV
- ▶ Anti-GBM disease
- ▶ Systemic lupus erythaematosus
- ▶ Infective endocarditis
- ▶ IgA nephropathy

TREATMENT

The patient was treated with 3 days of intravenous methylprednisolone (15 mg/kg/day) followed by oral prednisolone (1 mg/kg/day). Prompt therapy with 500 mg (7.5 mg/kg) pulsed intravenous cyclophosphamide and eight cycles of 4 L plasma exchange was administered over 16 days. Following two doses of cyclophosphamide separated by 2 weeks and continuation of oral prednisolone, her renal function improved. She required four sessions of temporary haemodialysis.

OUTCOME AND FOLLOW-UP

The patient then suffered one episode of haemoptysis and her renal function deteriorated over subsequent days requiring re-start of renal replacement therapy. Repeat immunology was normal. Full blood count was normal, in particular, lymphocyte count was normal. A contrast CT scan of the thorax was performed (figure 1). Transfer factor was 123.9% predicted.

Bronchoscopy was normal. Bronchial washings demonstrated macrophages with no evidence of malignancy, no tuberculosis and no *Aspergillus*. Bronchial washings were positive for CMV DNA. Serum CMV PCR was positive (CMV titre 7391 copies/mL, log 3.87) and intravenous ganciclovir (1.25 mg/kg daily) was started. Cyclophosphamide

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Figure 1 CT of the chest demonstrating small pleural effusions, pericardial effusion and scattered ill-defined clustered lung nodularity predominating in upper lobes.

was withheld. The patient's respiratory symptoms and radiological findings resolved but she remained dialysis dependent. Repeat renal biopsy demonstrated active vasculitis with six cellular crescents. CMV stains were negative. When serum CMV levels became undetectable, cyclophosphamide treatment was resumed alongside oral valganciclovir (450 mg twice weekly). Surveillance of plasma CMV PCR was performed fortnightly. Immunosuppression was continued for a total of 6 months.

At writing, eight months after initial presentation, the patient is independent of dialysis (estimated glomerular filtration rate 16), and has features of neither recurrent CMV disease, nor CMV viraemia, nor active vasculitis.

DISCUSSION

AAV is a common cause of rapidly progressive glomerulonephritis, and standard treatment involves cyclophosphamide, glucocorticoids and plasma exchange.¹ CMV is a persistent β -herpes virus affecting approximately 75% of healthy individuals. Primary infection is rarely symptomatic, but infection can cause major morbidity and mortality in immunocompromised patients.²

In a similar case of AAV complicated by pulmonary CMV disease, immunosuppressive treatment was intensified on respiratory deterioration. Initiation of antiviral treatment when the CMV diagnosis was eventually established was ineffective in controlling the disease.³ This emphasises the importance of a prompt diagnosis of CMV.

CMV pneumonitis associated with pulmonary haemorrhage has been previously reported in HIV patients⁴ and the speculated underlying linking mechanism is CMV-induced vascular injury. A similar mechanism has also been postulated in cases of CMV disease associated with AAV in non-immunocompromised

patients, although it remains conjecture as to whether its role is causative or opportunistic.⁵

In one previously reported case of non-renal AAV, treatment was complicated by CMV-related oesophagitis during induction treatment.⁶ CMV was reactivated on re-initiation of cyclophosphamide after discontinuation of ganciclovir. Our case underscores the potential value of continued antiviral prophylaxis to prevent reactivation during cyclophosphamide treatment.

CMV represents only one infectious complication of AAV. Infection has a major impact on overall mortality and morbidity. Further details are beyond the scope of this article, but Kronbichler *et al*⁷ provide a good overview of this topic.

In this case, anti-GBM antibody was marginally elevated. This case was not in keeping with other described cases of dual positivity⁸ because the renal biopsy did not reveal linear IgG antibody deposition and because of the favourable renal outcome. The diagnosis was more in keeping with ANCA-related disease.

Learning points

- Haemoptysis should be thoroughly investigated at any stage of antineutrophil cytoplasm antibody-associated vasculitis.
- Clinicians should have a low threshold to test for cytomegalovirus in immunocompromised vasculitis patients.
- Strong consideration should be given to continuing prophylactic antiviral treatment when immunosuppression is restarted.

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Contributors DP provided the concept for the article. The article was written by JT, and checked and refined by EO and DP.

Competing interests None declared.

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REFERENCES

- 1 Kidney Disease: Improving Global Outcomes (KDIGO) Glomerulonephritis Work Group. KDIGO clinical practice guideline for glomerulonephritis. *Kidney Int Suppl* 2012;2:139–274.
- 2 Ten Berge IJ, Van Lier RA. The interaction between cytomegalovirus and the human immune system. *Immunol Lett* 2014;162(2PB):141–4.
- 3 Hilal T. Fatal cytomegalovirus disease after combination therapy with corticosteroids and rituximab for granulomatosis with polyangiitis. *Case Rep Rheumatol* 2015;2015:538137.
- 4 Herry I, Cadranet J, Antoine M, *et al*. Cytomegalovirus-induced alveolar haemorrhage in patients with AIDS: a new clinical entity? *Clin Infect Dis* 1996;22:616–20.
- 5 Meyer MF, Hellmich B, Kotterba S, *et al*. Cytomegalovirus infection in systemic necrotizing vasculitis: causative agent or opportunistic infection? *Rheumatol Int* 2000;20:35–8.
- 6 Aries PM, Ullrich S, Gross WL. A case of destructive Wegener's granulomatosis complicated by cytomegalovirus infection. *Nat Clin Pract Rheumatol* 2006;2:511–15.
- 7 Kronbichler A, Jayne DRW, Mayer G. Frequency, risk factors and prophylaxis of infection in ANCA-associated vasculitis. *Eur J Clin Invest* 2015;45:346–68.
- 8 Levy JB, Hammad T, Coulthart A, *et al*. Clinical features and outcome of patients with both ANCA and anti-GBM antibodies. *Kidney Int* 2004;66:1535–40.

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