Multi-Drug Resistant CMV Viremia Secondary to a Rare Viral Mutation in a Transplant Recipient Successfully Treated with Anti-Proliferative Cessation and Immunoglobulins

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Introduction

- Post-transplant viremias are an emerging clinical challenge in paediatric transplant recipients.
- In developed countries, 60 % of children in general population are CMV seronegative at the age of 18 years(1).
- Subclinical CMV viremia is associated with an increased risk of chronic allograft injury(2) and adds to patient morbidity therefore requiring prompt treatment.
- International Transplant Society for CMV Consensus Group advises Ganciclovir, Valganciclovir and Foscarnet as treatment options for CMV viremia(3).
- Viral DNA polymerase resistance mutations are rare but may be associated with cross resistance adding to the challenges when treating such patients.
- We report a rare CMV mutation associated with resistance to all available medications in a CMV seronegative recipient successfully treated with reduction in immunosuppression and intravenous immunoglobulins (IVIG).

Case Report

- A 16 year-old girl with ESRD due to Autosomal Recessive Alport Syndrome.
- She was on renal replacement therapy for three years.
- She received a deceased donor kidney transplant (mismatch 1-2-0, CMV IgG Donor positive / Recipient negative; EBV Donor negative/ Recipient positive).

Immunosuppression:

Induction: Intravenous Basiliximab 20mg on days 0 and 4.
Maintenance: Tacrolimus, Azathioprine and Prednisolone.
CMV Prophylaxis: Valganciclovir for 90 days post transplant (our centre's protocol).

Post transplant course:

Day 44: CMV DNA was first detected with a CMV load of 4964 IU/mL (CMV load log value 3.97). She remained asymptomatic with no evidence of clinical CMV disease.

Day 51: prophylaxis changed to treatment dose oral Valganciclovir (Arrow 1, Graph 1).

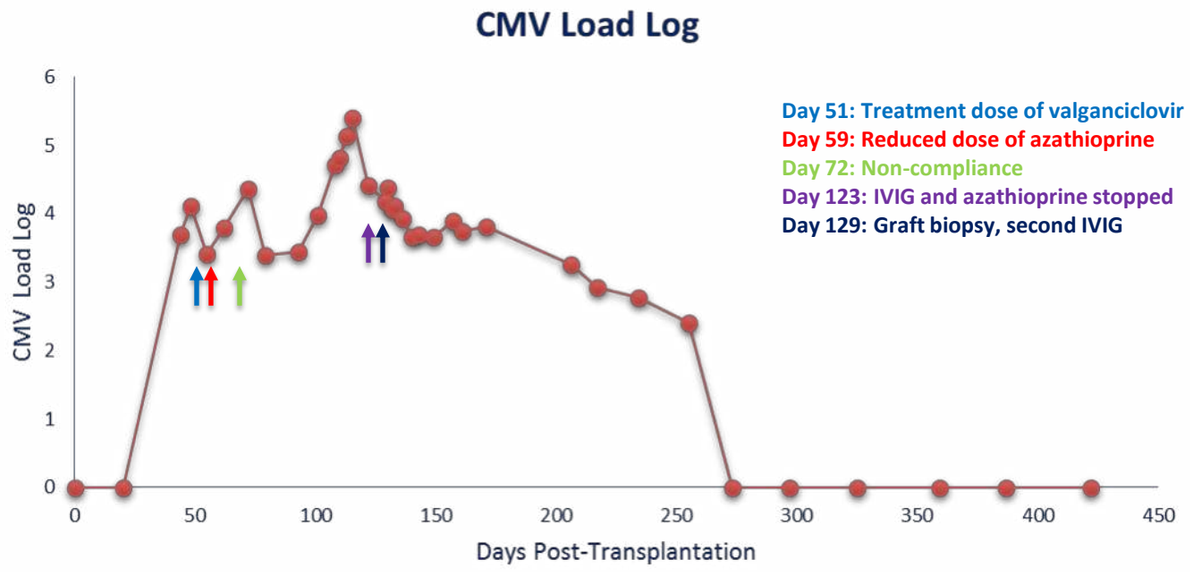
Day 59: reduction in Azathioprine dose (Arrow 2, Graph 1).

Day 72: A 5-day period of non-compliance with antiviral treatment corresponded with further increase in CMV load log (Arrow 3, Graph 1).

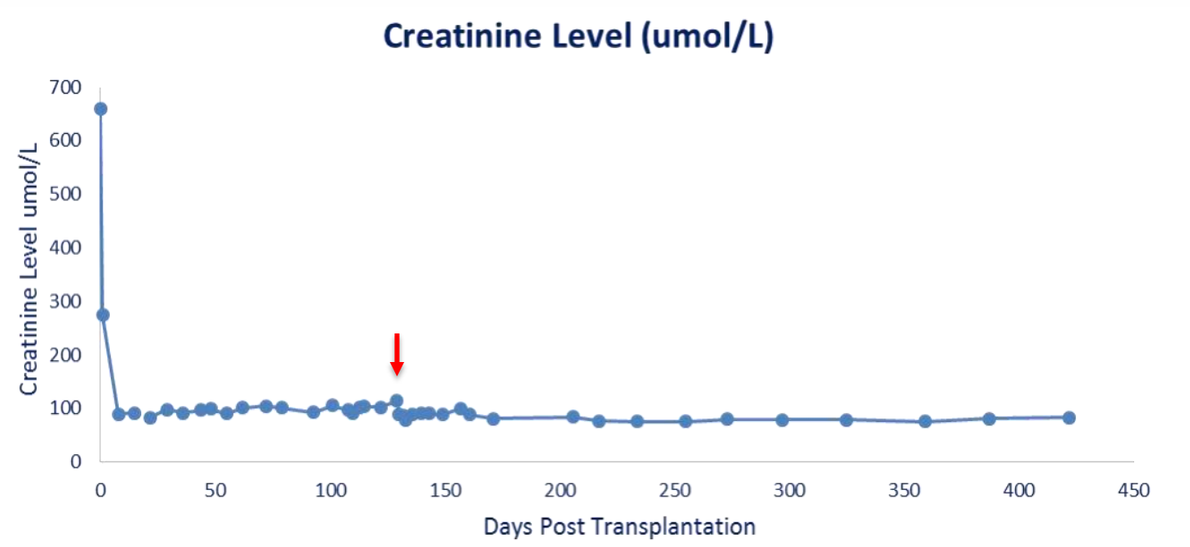
Day 110: a 7-day course of intravenous Ganciclovir given in view of persistently high CMV viral loads. Despite this, the viral load increased to a maximum log value of 5.41.

A rare UL54 deletion mutation (POL gene deletion 981/982) was detected, conferring high level resistance to Ganciclovir and low level resistance to Foscarnet and Cidofovir.

Day 123: IVIG given (dose 1g/kg), Azathioprine stopped (Arrow 4, Graph 1) and Prednisolone changed from alternate days to daily regime. This was associated with a reduction in CMV log count from 4.41 to 4.18.



Graph 1 :CMV Viral Load from transplant until 16 months post transplant



Graph 2: Stable graft function measured by serum creatinine with a rise (Arrow) associated with borderline T cell mediated rejection

Day 129: Rise in creatinine (from a baseline of 85umol/L to 147umol/L) coinciding with a 5-day history of non-adherence with daily Prednisolone (Graph 2).

Graft biopsy confirmed borderline T-cell mediated rejection and CNI toxicity (Banff criteria 3), with no evidence of CMV inclusions and negative immunoperoxidase staining. Treatment included a second dose of IVIG (1g/kg) and two doses of high dose oral Prednisolone (Arrow 5, Graph 1). Creatinine improved.

Serial CMV load levels demonstrated a stable viremia (Graph 1).

Day 273: CMV DNA first undetectable.

Sixteen months: Patient remains well, has a stable graft function (eGFR 69ml/min/1.73m2) and continues on dual immunosuppression with CNI and a low-dose daily Prednisolone only.
CMV DNA remains undetectable.
DSA negative.

Discussion

We present a case of subclinical multi-resistant CMV viremia successfully treated with a reduction in immunosuppression and intravenous immunoglobulins with good patient and graft outcome.

Although rare, viral mutations conferring multi-drug resistance present an emerging therapeutic challenge. The successful outcome in this patient provides a possible treatment framework for other clinicians. This might be particularly useful in countries where access to anti viral medication is difficult.

References

1. Centers for disease control and prevention.
2. Subclinical viremia increases risk for chronic allograft injury in pediatric renal transplantation. Smith JM et al. J Am Soc Nephrol 2010.
3. Updated International Consensus Guidelines on the Management of Cytomegalovirus in Solid-Organ Transplantation. Kotton CN et al. Transplantation 2013.