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Short communication

Emergence and persistence of multiple antiviral-resistant CMV strains in a highly immunocompromised child

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Abstract

Background: The emergence of human cytomegalovirus (CMV) antiviral resistance plays a significant role in disease progression in immunocompromised patients who have received antiviral therapy.
Objectives: To determine the pattern of antiviral-resistant CMV strains in a highly immunocompromised child.
Study design: Retrospective specimens of blood and urine were analysed using PCR-sequencing to identify antiviral-resistant CMV strains containing UL97 or UL54 mutations.
Results: CMV strains resistant to antiviral agents contributed to disease in a bone marrow transplant recipient with X-linked severe combined immunodeficiency (SCID) treated with ganciclovir (GCV) and foscarnet (FOS). Retrospective analyses detected GCV-resistant CMV (L595S) in a specimen taken after disease progression. This GCV-resistant CMV strain persisted for 1 year, after which time it was no longer detected even though the patient continued to receive GCV. A FOS-resistant strain (T700A) then emerged even though no FOS had been administered in the preceding year.
Conclusion: The detection of antiviral-resistant CMV did not follow the patterns found in other patients tested for antiviral resistance, including emergence of a FOS-resistant strain in the absence of antiviral-selective pressure. These findings indicate the patient's underlying immunosuppressive condition should be considered for diagnosis and management of resistant CMV.
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Keywords: Cytomegalovirus; Antiviral resistance; SCID

1. Introduction

The clinical impact of human cytomegalovirus (CMV) infection in immunocompromised patients has been reduced by prophylaxis and treatment using ganciclovir (GCV), valganciclovir, foscarnet (FOS) or cidofovir (CDV) (Gilbert and Boivin, 2005). However, antiviral-resistant CMV strains can develop in up to 30% of immunocompromised patients receiving long-term antiviral, with an average incidence of approximately 10% for transplant recipients (reviewed in Chou, 1999; Gilbert and Boivin, 2005). Up to 94% of GCV resistant CMV strains contain UL97 protein kinase mutations (Gilbert and Boivin, 2005). However, mutations of UL54 DNA polymerase can confer resistance to GCV, FOS and CDV (Chou, 1999; Gilbert and Boivin, 2005) and new DNA polymerase mutations continue to emerge (Chou et al., 2003; Scott et al., 2007). PCR-sequencing of the UL97 protein kinase and UL54 DNA polymerase genes is a rapid and generally accurate method for detecting antiviral-resistant

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CMV strains (Scott et al., 2004). We report CMV antiviral resistance in a highly immunocompromised patient identified following retrospective analysis. Our findings have implications for the monitoring and management of patient groups at risk of developing antiviral-resistant CMV.

2. Methods

Diagnostic specimens of blood and urine were collected over a 3-year period at the discretion of attending physicians from a child with X-linked severe combined immunodeficiency (SCID) who received a bone marrow transplant at 8 weeks old. Guardian consent was obtained for all specimens and testing conducted following ethical guidelines of the South Eastern Sydney and Illawarra Area Health Service. CMV infection was diagnosis by in-house PCR and culture as described previously (Munro et al., 2005a). CMV load was also intermittently assessed by the Roche COBAS® AMPLICOR™ CMV MONITOR assay at the request of attending physicians. Retrospective analysis of CMV antiviral resistance was carried out on available specimens by sequencing of CMV UL97 and UL54 gene regions associated with antiviral resistance as previously described (Scott et al., 2004), with modification to some primers for increased sensitivity and inclusion of DNA polymerase exonuclease (EXO) I (Chou et al., 2003). UL54 domains EXO I to δ-region C were amplified using primers UL54.iv-cT and UL54.79826B (5′-GCGATGTCTCCGACCTGGTG-3′) in the first round, and UL54.78755T and UL54.79800B (5′-GCGTCGACTTGTGATATCGAG-3′) in the second round. UL54 domains II to V were amplified using outer forward primer UL54.78721B and UL54.77620T (5′-CCGCGTGGCACGCCGTATTTC-3′) in the first round, with second round primers remaining as previously described (Scott et al., 2004). Positive controls consisted of UL97 cloned into pGEM-T Easy vector (Promega, USA), and UL54 cloned into pBluescript (kindly provided by Prof. Sunwen Chou).

3. Results

A child with X-linked SCID was born on the 21 January 2002. CMV was first detected in the blood of this child at 25 days of age by CMV PCR, coincident with the development of a mild respiratory illness and culture detection of CMV in the bronchial wash, at which point intravenous (IV) GCV treatment (5 mg/kg/day) was initiated (Fig. 1). Subsequent retrospective testing of a dried blood spot taken 2 days after birth indicated the CMV infection had been acquired congenitally (Alford et al., 1990; Munro et al., 2005b; Revello and Gerna, 2002). The child remained CMV PCR-positive and intermittently urine culture-positive despite GCV treatment, but antiviral resistance testing requested after 20 days of treatment (at 6 weeks of age) did not detect any antiviral-resistant CMV (Fig. 1). A haploid T-cell depleted bone marrow transplant donated by the father was given to the child at 8 weeks of age, with IV GCV continued during and following transplantation. CMV continued to be intermittently detected by PCR and culture, and 1 week post-transplant the CMV load was at 1300 copies per ml of blood and CMV was again detected in bronchial wash. Two weeks post-transplant the child developed diarrhoea and was switched to IV FOS for 6 weeks. The child remained CMV PCR-positive on FOS and was switched back to GCV at 8 weeks post-transplant. After a further 2 months of GCV treatment the viral load had increased to 39,990 copies/ml. At this time the GCV was

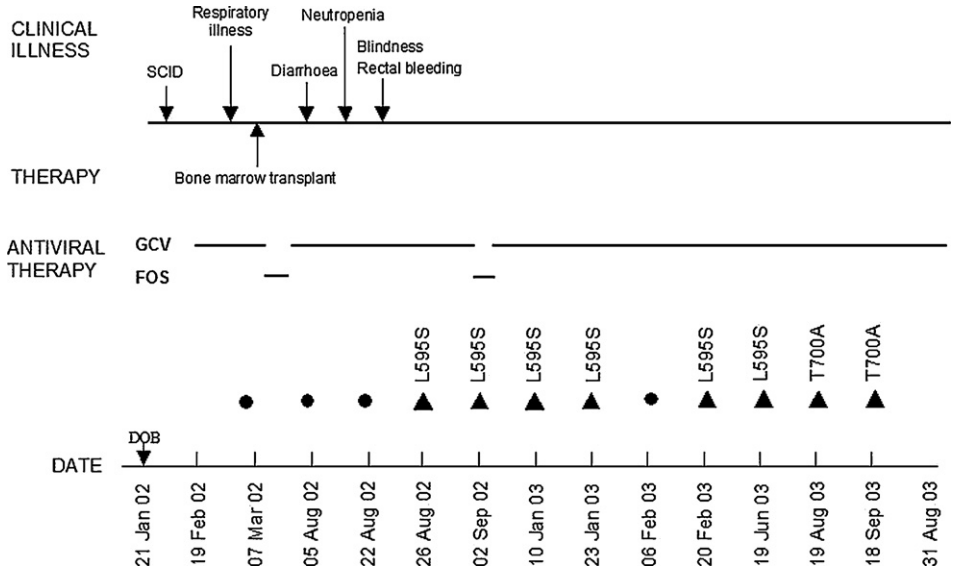

Fig. 1. Emergence of CMV antiviral resistance due to UL97 protein kinase and UL54. DNA polymerase mutations detected by PCR-sequencing: (●) represent sensitive CMV sequences; (▲) are antiviral-resistant CMV sequences. Not to scale.

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