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Case Report

Refractory anti-viral resistant CMV retinitis in an immunological nonresponder person living with HIV

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ABSTRACT

Cytomegalovirus (CMV) retinitis caused by drug-resistant viruses poses a major challenge in immunocompromised patients. We present the case of a patient living with HIV with persistently low CD4+ T cells count despite effective antiretroviral therapy, who experienced multiple episodes of CMV retinitis associated with iterative acquisition of resistance. The failure of ganciclovir and foscarnet treatments led us to implement a combined therapy of intravenous cidofovir, high-dose ganciclovir, and anti-CMV immunoglobulin as well as intravitreal injections of ganciclovir. This triple therapy was successful but resulted in significant myelotoxicity. Furthermore, the relapse of CMV retinitis and/or CMV viremia with each therapeutic de-escalation reflects the high level of immunodeficiency in our patient, despite sustained control of HIV viremia for several months. This case report highlights the need for a particular management of CMV infection in patients living with HIV who are immunological nonresponders.

Introduction

Cytomegalovirus (CMV) disease, and particularly CMV retinitis, is a frequent and potentially sight-threatening complication in patients living with HIV with CD4+ T lymphocyte count below 100 cells/mm^3. The advent of potent HAART has resulted in rapid immune reconstitution for most patients, making CMV infection or disease less problematic in this population. However, in a subset of patients, suppression of HIV viral replication fails to restore sufficient immune function to control CMV replication, making CMV management challenging. Indeed, the prolonged use of most currently available anti-CMV therapies is limited by significant bone marrow toxicity (ganciclovir or valganciclovir) and nephrotoxicity (foscarnet and cidofovir). In recent years, new drugs have been developed to treat resistant CMV infection (maribavir) or to reduce treatment side effects when used as prophylaxis (letermovir). However, maribavir's use is restricted to solid organ or hematological stem cell transplant recipients, and letermovir's low genetic barrier to resistance limits its use as prophylaxis. This leaves patients living with HIV with limited therapeutic options. Here, we describe the case of a patient living with HIV without immune recovery despite efficient HAART presenting a resistant and persistent CMV infection.

Case report

A 43-year-old woman was diagnosed with HIV infection with a CD4+ T lymphocyte count of 10 cells/mm^3, associated with pneumocystis pneumonia, disseminated Mycobacterium avium infection (affecting the lungs, lymph nodes, urinary system, ileum, and blood), and CMV retinitis (with possible associated colitis and a CMV viral load (VL) of 6.2 log/mL in whole blood). She was treated with cotrimoxazole, clarithromycin, levofloxacin, ethambutol, and ganciclovir. Biktarvy (bictegravir/emtricitabine/tenofovir alafenamide) was later introduced, allowing rapid control of HIV viremia (VL below 200 copies/mL after 5 weeks and below 50 copies/mL after 12 weeks of HAART).

Ganciclovir was administered at a dose of 5 mg/kg every 12 hours for 7 weeks, as retinitis lesions healed slowly, followed by maintenance treatment with valganciclovir (900 mg daily) (Figure 1). Despite prolonged HIV viral suppression, her CD4+ T lymphocyte count did not rise above 100 cells/mm^3. After 7 weeks of maintenance treatment with valganciclovir, CMV VL in the blood

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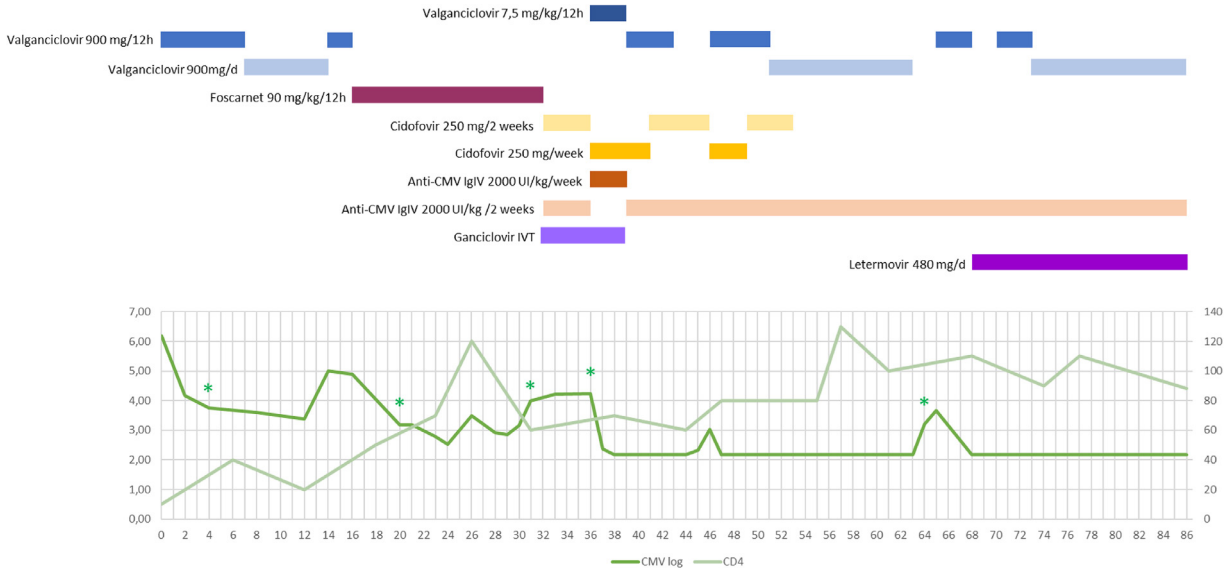

Figure 1. Evolution of CMV viral load, CD4 T cell count under CMV treatments. *: Blood genotypic resistance test. IVT, intravitreal injections.

Table 1
Viral load and genotypic testing in blood samples.

Date	Viral load (UI/mL)	Viral load (log UI/mL)	Mutation in UL97	Mutation in UL54	Results
4 weeks after ganciclovir initiation	3752	3.57	None	None	No antiviral drug resistance[a]
Under valganciclovir 900 mg/j	2827	3.45	L595[W,L][b]	None	Ganciclovir resistance
After 5 weeks of foscarnet	6573	3.82	None	A809[A,V][c]	Ganciclovir and foscarnet resistance
Under cidofovir + anti-CMV IgIV	9567	3.98	None	P522[P,S][d]	Ganciclovir and cidofovir resistance
Under anti-CMV Ig prophylaxis	5721	3.76	None	None	No antiviral drug resistance[a]

[a] Antiviral drugs evaluated: ganciclovir, maribavir, foscarnet et cidofovir. Reference for the technique used in (9).
[b] L595W mutation detected as a mixed population W/L; mutation conferring a high level of resistance to ganciclovir (resistance index [RI] ≥5).
[c] A809V mutation detected as a mixed population A/V; mutation conferring a low level of resistance to ganciclovir (RI < 5) and a high level of resistance to foscarnet (IR ≥ 5).
[d] P522S mutation detected as a mixed population P/S; mutation conferring a low level of resistance to ganciclovir (RI < 5) and to cidofovir (RI < 5).

increased again. Valganciclovir dosing was increased to 900 mg twice daily, but it was ineffective, suggesting possible CMV resistance. Valganciclovir therefore was discontinued, and foscarnet (90 mg/kg every 12 hours) was started. Genotypic resistance testing confirmed ganciclovir resistance (mutation L595W in the UL97 phosphotransferase) (Table 1).

The VL slowly decreased with foscarnet, and regular ophthalmologic examinations showed no sign of active retinitis. Fourteen weeks later, CMV VL increased again, and ophthalmologic examination showed recurrence of active retinitis. Genotypic resistance testing confirmed the acquisition of a new mutation conferring resistance to both foscarnet and ganciclovir (mutation A809V in the UL54 DNA polymerase). Foscarnet was stopped, and a treatment regimen including cidofovir (2 injections a week apart, followed by one injection every 2 weeks), CMV-specific immunoglobulins (400 UI/kg on days 1, 4, and 8, then 200 UI/kg every 2 weeks alternating with cidofovir injections), and intravitreal injections of ganciclovir were started.

Despite this, the VL continued to increase, and new retinitis lesions appeared in the contralateral eye. A new genotypic resistance blood test revealed resistance to ganciclovir and cidofovir but not to foscarnet (mutation P522S in the UL54 DNA polymerase). A genotypic resistance test was also performed in vitreous humor, but the VL was too low to produce interpretable results. Assuming the patient might be infected with multiple CMV subpopulations carrying different resistance mutations and potential compartmentalization of these subpopulations, the treatment was intensified with high doses of ganciclovir (7.5 mg/kg every 12 hours), and the frequency of cidofovir injections as well as anti-CMV IgIV was increased to once a week. Renal function was carefully monitored and remained within acceptable limits (eGFR between 60 and 90 mL/min). One week later, the CMV VL decreased, and retinitis lesions began to heal, although a QuantiFERON-CMV assay showed no detectable CMV-specific cell-mediated immune response.

After 1 month, and two measurements of VL below detection, the treatment was eased: ganciclovir was stopped, valganciclovir (900 mg every 12 hours) was introduced, cidofovir and anti-CMV IgIV injections were spaced to every 2 weeks (alternating). The VL remained undetectable, and no new retinitis lesions were observed during monthly ophthalmological examinations. Unfortunately, the patient developed prolonged treatment-induced pancytopenia. Valganciclovir was suspended to limit myelotoxicity. However, 2 weeks later, CMV VL rose again, prompting the resumption of valganciclovir at 900 mg every 12 hours and an increase in the frequency of cidofovir infusions. This approach rapidly brought the CMV VL under control. The treatment was gradually tapered every 2 weeks under close monitoring of the CMV VL, which remained negative throughout first, the cidofovir infusions were spaced out to every 2 weeks, followed by a reduction of valganciclovir to a maintenance dose (900 mg per day), and finally, cidofovir was discontinued. CMV VL remained negative for 10 weeks.

Valganciclovir was then discontinued again, but 1 week later, CMV VL increased once more. A new genotypic resistance test revealed no resistance mutations, so valganciclovir was reintroduced at 900 mg every 12 hours for 3 weeks, successfully bringing the CMV VL under control. Due to persistent pancytopenia and only a brief increase in the CD4+ T lymphocyte count above 100 cells/mm³, letermovir was introduced as maintenance therapy. Two

weeks later, a routine ophthalmologic examination revealed a relapse of retinitis, even though CMV VL remained negative in the blood. After 3 weeks of valganciclovir at 900 mg every 12 hours and resolution of the retinitis lesions, valganciclovir was added at a maintenance dose alongside letermovir and anti-CMV IVIg. The CMV VL remained below detection under this triple therapy.

Discussion

Managing ganciclovir-resistant CMV retinitis is challenging. Maribavir does not penetrate well into the central nervous system, making it unsuitable for treating retinitis [1]. In our case, the iterative acquisition of resistance led us to use combination therapies, which increased toxicity. The necessity for combination therapy in such refractory infections is likely due to heterogeneous intratissue virus populations with mixed antiviral sensitivities. Adding anti-CMV-specific IgIV might be beneficial in such complex situations, although ocular penetration of Ig is uncertain [2]. Similarly, intravitreal injections are based on pharmacokinetic considerations, but their clinical benefit is still debated.

The iterative acquisition of resistance in our case is particularly notable. The European guidelines for managing CMV retinitis in patients living with HIV recommend 21 days of valganciclovir 900 mg bid, followed by maintenance therapy with valganciclovir 900 mg/d for 3 months if CD4+ T lymphocyte count is >100 cells/mm³, without mentioning CMV viremia monitoring (2019 EACS guidelines). In contrast, for solid organ transplant (SOT) recipients, international guidelines recommend guiding therapy duration with weekly monitoring of CMV VL and continuing treatment doses of (val)ganciclovir until CMV DNAemia is eradicated below a specific threshold (depending on the assay used) and all clinical signs of CMV disease are resolved [3]. In SOT recipients, failure to eradicate plasma DNAemia at the end of treatment is a major predictor of virologic recurrence, and reducing antiviral dosing in the setting of persistent CMV DNAemia has been associated with a significant risk of ganciclovir resistance [4,5].

Patients living with HIV differ from SOT recipients because, once on HAART, they usually achieve good immunological recovery, sufficient to suppress CMV DNAemia, even without CMV antiviral treatment [6]. A subset of patients living with HIV, however, fails to achieve normalization of CD4+ T-cell counts despite persistent virological suppression (referred to as “immunological nonresponders”), putting them at increased risk for opportunistic complications, though to a lesser extent than those who are both immunologic and virologic nonresponders [7,8]. The mechanisms underlying incomplete immune reconstitution are not fully understood. It has been associated with CD4+ T lymphocyte count nadir, duration of infection, baseline VL, history of opportunistic infection, comorbidities, and age [9].

In conclusion, our case report suggests that patients living with HIV who are immunological nonresponders with CD4+ T lymphocyte counts <100/mm³ should be managed like SOT recipients, with prolonged anti-CMV treatment at adequate dosages if CMV DNAemia is not controlled. As exemplified by our experience, reducing antiviral dosing after the recommended 21 days of therapy and control of retinitis could lead to iterative acquisitions of resistance.

Declarations of competing interest

There is nothing to declare.

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