Quantitative cytomegalovirus (CMV) antigenaemia during antiviral treatment of AIDS-related CMV disease

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In order to assess the value of quantitative measurement of cytomegalovirus (CMV) antigenaemia as a marker for the guidance of antiviral chemotherapy in the AIDS setting, 33 patients with CMV complications and showing at least 20 pp65-positive polymorphonuclear leucocytes per $2 \times 10^5$ cells, received either ganciclovir or foscarnet as induction and maintenance therapy. Antigenaemia was assessed every 1–4 weeks. During acute-phase antiviral therapy, a significant decrease of CMV antigenaemia (>50% of pretreatment levels) paralleled clinical improvement in 2–7 weeks in 32 of 33 subjects. In ten of 24 evaluable patients followed up during a further 4–12 months, disease relapses occurred concurrently with an increase of CMV antigenaemia in seven cases, while three cases of relapsing retinitis did not show a significant increase in antigenaemia. All patients with recurrent disease had a favourable response to further treatment, including halted clinical progression and significant decrease in antigenaemia. In HIV-related CMV disease, periodic monitoring of quantitative CMV antigenaemia proves useful in evaluating response to antivirals, in guiding therapeutic management and in predicting disease relapses.

Introduction

The direct detection of cytomegalovirus (CMV) pp65 antigen in polymorphonuclear leucocytes (PMNL), i.e. antigenaemia, is a reliable, highly sensitive and specific laboratory technique in both the diagnosis and the monitoring of symptomatic CMV infection in the immunocompromised host, as well as in the setting of HIV disease. The aim of our study was to evaluate quantitative CMV antigenaemia as a marker for the guidance of antiviral treatment in HIV-infected patients suffering from CMV-related complications.

Materials and methods

In 1994, an indirect immunofluorescence assay for the quantitative detection of the lower matrix protein of CMV encoded by UL83 (pp65) in PMNL, was introduced in the diagnostic workup of all our patients with advanced HIV disease and < 100 CD4+ T-lymphocytes per microlitre, suffering from fever without signs of localization, or showing a clinical picture characteristic of a CMV-related complication (i.e. retinitis, cholestatic hepatitis, oesophageal ulcerations, erosive gastritis, colitis–proctitis). The CMV antigen assay was performed as originally described, and modified by Revello et al. Only elevated CMV antigen levels were considered as significant in our study, in order to rule out cases with a very low CMV burden, probably unrelated to present clinical disease: a level of at least 20 pp65-positive cells per $2 \times 10^5$ PMNL was selected as the cut-off value. All patients with suspected CMV disease underwent appropriate clinical, laboratory, instrumental and histopathologic examinations needed for its confirmation, concurrently or immediately after CMV antigen assay. All subjects suffering from a confirmed or a strongly suspected CMV-related complication received acute-phase antiviral treatment for at least 21 days with either iv ganciclovir (10 mg/kg/day) or iv foscarnet (180 mg/kg/day), and subsequently a maintenance treatment with half-dose iv ganciclovir and/or foscarnet. Periodic CMV antigen determinations were repeated at a 1–4 week interval during both acute-phase and suppressive treatment, in
order to assess treatment response and eventual disease relapses: a drop in antigenaemia to a level below 50% of the pretreatment values was considered as a favourable laboratory response to antiviral therapy.

**Results**

Until October 1996, 189 consecutive HIV-infected patients at risk for CMV-related complications (as assessed by the above-mentioned definition) were evaluated, and 33/189 (17.5%) tested positive by CMV antigen assay. All these patients (25 males and eight females, aged 29–54 years; 15 ex-intravenous drug users, 12 homosexual/bisexual males, and six heterosexuals), showed a severe HIV-related immunodeficiency, with a mean CD4+ cell count of 21.2 ± 19.6/µL (range 2–60 cells/µL); 22 out of 33 had a previous history of systemic disease (mean 230.7 ± 126.5 pp65-positive PMNL/2×10⁵ cells), as opposed to the 13 subjects suffering from CMV-related complications (mean 138.1 ± 126.5 pp65-positive PMNL/2×10⁵ cells; P = 0.04, Student’s t-test). A ll patients had systemic and/or visceral CMV disease: cholestatic hepatitis in four cases, colitis-proctitis in four, and oesophagitis and erosive gastritis in three (all confirmed by endoscopy and histopathological studies), while a clinical picture including hyperpyrexia, wasting syndrome, and peripheral neuropathy was recognized in the remaining nine patients as strongly suggestive of CMV disease, since other HIV-related complications and other aetiologies were carefully excluded after a thorough clinical examination. In this last group of patients, suspicion of CMV disease was confirmed later, on the grounds of the favourable clinical and laboratory response obtained after administration of the specific antiviral therapy.

At the time of diagnosis, the quantitative CMV antigen assay showed significantly greater levels in the 20 patients with systemic disease (mean 230.7 ± 113.2 pp65-positive PMNL/2 × 10⁵ cells), as opposed to the 13 subjects suffering from retinitis (mean 138.1 ± 126.5 pp65-positive PMNL/2 × 10⁵ cells; P = 0.4, Student’s t-test). A ll patients suffering from CMV-related complications received acute-phase antiviral treatment for at least 21 days with either iv ganciclovir or foscarnet. Twenty-four of them (11 with retinitis, and 13 with systemic/visceral disease) had a subsequent follow-up time of at least 4 months (range 4–11 months). The remaining nine subjects were unevaluable because they had a follow-up period shorter than 4 months (four patients, one of whom died), or did not have regular CMV antigen measurements (three patients), or were lost at follow-up (two patients). During induction antiviral treatment, a significant decrease of CMV antigenaemia (to values <50% of the pretreatment levels) paralleled clinical improvement in a period ranging from 2 to 7 weeks (mean 3.6 ± 0.9 weeks) in 32 out of 33 evaluable patients, with 27 subjects attaining zero or very low CMV antigen levels (fewer than 10 cells/2 × 10⁵ PMNL) within 4 weeks of treatment. Only one subject with concurrent Kaposi’s sarcoma and advanced immunodeficiency (2 CD4+ lymphocytes/µL) failed to respond to antiviral therapy, on both clinical and laboratory grounds, and died after 5 weeks.

During the follow-up period, clinical relapses of CMV disease occurred despite maintenance antiviral therapy in ten out of 24 evaluable patients (13 episodes altogether), and were preceded by a significant increase in CMV antigenaemia (with values at least twice as high as those attained after the induction phase) in seven cases (eight episodes altogether). On the other hand, three patients with a relapse of retinitis (five episodes altogether) did not show a significant rise in their CMV antigenaemia, compared with values observed after induction therapy. Nine of the 13 episodes of disease relapse were initially predicted by elevated antigenaemia requiring a switch of antiviral treatment (ganciclovir to foscarnet, or vice versa), and the further persistence of elevated antigen levels led to a combined antiviral therapy (with both ganciclovir and foscarnet) in two cases. In all these patients with recurrent disease a favourable response was obtained, characterized by resolution of signs and symptoms or at least halted clinical progression, and by a significant decrease in CMV antigenaemia (always to <50% of values observed at the time of disease relapse).

The profile of quantitative CMV antigenaemia evaluated in one patient suffering from CMV hepatitis associated with hyperpyrexia and followed over 12 months is presented in the Figure. An increase in CMV antigenaemia was observed concomitantly with the first episode of disease and the subsequent recurrence, while anti-CMV chemotherapy resulted in disease remission together with normalization of CMV antigen levels.

**Discussion**

The use of CMV antigenaemia as a screening technique enables an early identification of CMV disease, and makes it easier to diagnose eventual episodes of disease relapse in patients with severe HIV-related immunodeficiency. Moreover, the quantitative technique is remarkably useful in diagnosing CMV-related complications associated with HIV disease, particularly when this viral aetiology is strongly suspected but difficult to confirm.

In HIV-infected patients suffering from organ-specific or systemic CMV-related complications, periodic monitoring of quantitative CMV antigenaemia during the course of the disease may prove useful in evaluating the response to antiviral treatment and in predicting eventual disease relapses occurring during maintenance antiviral therapy. Even though some preliminary evidence of the usefulness of CMV antigenaemia as a valuable laboratory tool in the monitoring of anti-CMV chemotherapy has been obtained among transplant recipients, experience is still lacking in the setting of AIDS. Until now no studies specifically focusing on longitudinal monitoring of quantitative CMV antigenaemia and its relationship with acute-phase and maintenance anti-CMV treatment have been reported.
CMV antigen assay represents a more rapid, less expensive, and easy-to-perform assay, when compared with quantification of viraemia, which has proven useful for monitoring CMV infection and its treatment in patients with AIDS.\(^1\)

In our series, a clear relationship was found between the number of pp65 antigen-positive cells, the localization and the clinical course of CMV disease, and the response to antiviral treatment, with CMV antigen levels falling proportionally to clinical improvement, and rising again during most disease relapses. The apparently reduced sensitivity of the CMV antigen assay during recurrences of CMV retinitis is probably due to the combined effects of antiviral maintenance therapy, and the usually lower antigen levels associated with this CMV localization, compared with systemic disease.\(^5,8\)

Further studies are needed to assess the usefulness of quantitative CMV antigenaemia in the monitoring of response to antiviral treatment, and in the identification of cases of reduced efficacy or potential resistance to anti-CMV compounds, in the setting of HIV disease and AIDS.

**References**


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