

Late cytomegalovirus infection after hematopoietic stem cell transplantation: case reports

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Cytomegalovirus is related to high rates of morbidity and mortality after hematopoietic stem cell transplantation. This report highlights the importance of adequate monitoring and management of this infection. We report on two cases of patients with late subclinical cytomegalovirus infection. These patients were monitored for antigenemia by indirect immunofluorescence assay. Active cytomegalovirus infection is most common in the first three months after transplantation however the cases reported herein show the importance of monitoring for active infection after Day +100 post-transplantation. Early detection of active infection enables quick preemptive therapy. In conclusion, we emphasize that patients with risk factors for developing severe or late cytomegalovirus disease should be monitored for more than 100 post-transplant days as late active infection is a reality.

Keywords: Hematopoietic stem cell transplantation; Cytomegalovirus infections/diagnosis; Cytomegalovirus infections/therapy; Fluorescent antibody technique; Humans; Adult; Case reports

Introduction

Hematopoietic Stem Cell Transplantation (HSCT) is a procedure that aims to restore bone marrow function. It is used to treat hematologic disorders, inborn metabolism errors, immune deficiencies and other diseases^(1,2). During the post-HSCT period, due to reduced immune surveillance, there is an increase in the possibility of infectious complications^(1,3).

Cytomegalovirus (CMV) is a common infectious agent during the post-HSCT period with seroprevalence ranging from 30-90%^(1,3). Active CMV infection is an important cause of morbidity and mortality in transplant patients, which highlights the importance of monitoring this infection^(1,3). CMV monitoring is carried out using the antigenemia assay by indirect immunofluorescence to detect the pp65 protein and by the 'DNAemia assay' with amplification of the genomic regions of CMV by real-time polymerase chain reaction (RT-PCR). Both techniques are recognized as satisfactory by international guidelines however they have advantages and limitations that must be considered before making any choice^(4,5).

Early detection of active CMV infection allows the adoption of preemptive treatment to replace empiric therapy or universal prophylaxis⁽⁶⁾. International guidelines suggest that the monitoring of CMV should be performed until Day (D)+100 for allogeneic transplantations and until D+60 for autologous transplantations however reactivation of this infection has been observed after this period⁽⁵⁾.

This report aims to highlight the importance of monitoring for late active CMV infections. It describes two patients who presented CMV reactivation more than 100 days after HSCT.

Case 1

A 34 year-old male patient underwent related allogeneic HSCT eight months after the diagnosis of B-cell acute lymphoblastic leukemia (ALL). The pre-transplant serostatus for CMV indicated D⁺R⁺. Fludarabine, Ara-C, etoposide and melphalan were used in the conditioning regimen. Prophylaxis for graft-versus-host disease (GVHD) was carried out using cyclosporine and methotrexate initiated at D+4. The patient had some fever peaks on D+6 (38.5°C), D+7 (38.4 and 38.7°C) and D+12 (38.1°C), however none were related to CMV. On D+21 the patient had no complaints and on D+24 he was discharged. The patient received acyclovir (200 mg/day) as post-transplant prophylaxis for 47 days (D+28 to D+75). On D+56 he showed the first signs of chronic GVHD with elevated liver enzymes, labial mucosa with areas of hyperpigmentation and whitish inner mouth mucosa, palmar and plantar hyperemia, nausea, itching of the back and oropharynx sensitivity. On D+63 the patient presented abdominal pain. Due to signs of skin, gastrointestinal (GIT), mouth, and liver GVHD, the cyclosporin was changed to alternating 100 mg and 200 mg doses and prednisone (60 mg/day) was associated. On D+94, the patient reported asthenia, mild fever, epigastric pain, pain in the mouth and a sore throat, all related to GVHD. A smear and CMV antigenemia during this period

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were both negative. On D+101, the patient still had epigastric pain and pain in the oral cavity attributed to GVHD however the CMV antigenemia revealed 30 positive cells/200,000 leukocytes (Figure 1). Immediately, even with subclinical infection, treatment was initiated with intravenous ganciclovir (5 mg/kg/dose b.i.d) for ten days, continuing with ambulatory ganciclovir for 15 days. The total leukocyte counts at D+100 and D+101 were $2.73 \times 10^9/L$ and $3.0 \times 10^9/L$, respectively. The antigenemia became negative by D+118 and at D+148 remained negative. On D+248, the patient still showed signs of liver, ocular, oral mucosa and skin GVHD.

Case 2

A 50-year-old female patient underwent unrelated allogeneic HSCT after diagnosis of myelodysplastic syndrome (refractory anemia with excess blasts II). The pre-transplant serostatus for CMV indicated D*R+. Fludarabine, busulfan and anti-thymocyte globulin (ATGAM) were used in the conditioning regimen. On D+79, cutaneous and gastrointestinal tract GVHD was diagnosed and confirmed by duodenal biopsy. At this time, tacrolimus and methylprednisolone were introduced. The patient had fever and CMV antigenemia as shown by 29 positive cells/200,000 leukocytes only on D+180 (Figure 1). Therapy with intravenous ganciclovir (5 mg/kg/dose) for 14 days was introduced immediately and ambulatory treatment continued for seven days with ganciclovir (200 mg/day). The antigenemia became negative on D+201. At D+229, the patient developed mild fever and the CMV antigenemia was two positive cells/200,000 leukocytes (Figure 1). Due to the low value of antigenemia and spontaneous resolution of the fever, antiviral therapy was not initiated. On D+236, the CMV antigenemia was negative and remained so until D+257. On D+995, the patient had liver, gastrointestinal and ocular GVHD.

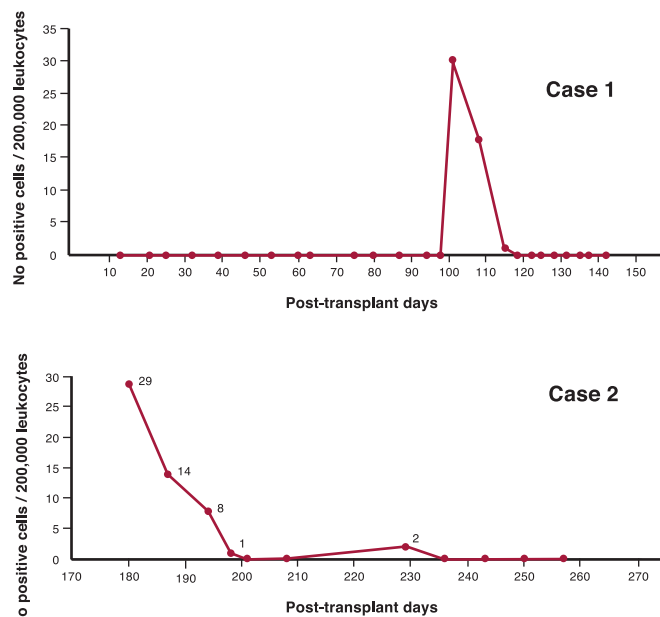


Figure 1 - Evolution of cytomegalovirus antigenemia in Cases 1 and 2

Discussion

The post-transplant period requires care to prevent complications and the associated risk factors. The monitoring and early diagnosis of infections improve the quality of life of transplant patients⁽²⁾.

Active CMV infections occur due to primary infection, reactivation of latent virus or reinfection. The highest incidence occurs between D+28 and D+100 after HSCT, most commonly in patients submitted to allogeneic transplants and less frequent in patients submitted to autologous transplantations^(1,2). Even so, international guidelines recommend monitoring for CMV infection until D+100 after allogeneic and until D+60 after autologous transplantations⁽⁵⁾. On the other hand, late infections can occur; this highlights the need for continued monitoring. The cases reported herein ratify this affirmation, with emphasis on Case 2, whose reactivation occurred six months after transplantation (Figure 1).

Some subgroups of transplant recipients are considered high risk for developing severe disease and late CMV. The risk factors for severe CMV disease include: unrelated graft, CMV disease within the first three post-transplantation months, chronic GVHD, undetectable T-cell immunity against CMV, T-cell depletion of the graft or use of anti-T cell therapy (fludarabine, alemtuzumab, 2-clorodeoxiadenosina), steroid use, low CD4⁺ cell counts (< $50 \times 10^9/L$) and pre-transplant serostatus D*R⁻⁽⁵⁻¹⁰⁾. For transplant recipients with these risk factors, the routine monitoring of CMV infection is indicated during the period of substantial immunosuppression⁽⁵⁾. Both these patients had chronic GVHD, used depleting T-cell therapy (fludarabine) and, in Case 2, the donor was unrelated.

GVHD is a major cause of mortality after HSCT. GVHD occurs in 40 to 50% of allogeneic transplant recipients, accounting for 15 to 40% of transplant-related mortality⁽⁷⁾. HSCT recipients use GVHD prophylaxis consisting of drug combinations that cause intense immunosuppression and predisposes them to serious infectious complications, including increased likelihood of the reactivation of CMV⁽⁷⁾.

Active monitoring of CMV reduces the need for universal prophylaxis and the use of empirical antiviral therapy^(9,10). Symptomatology suggestive of CMV, which would be treated with antiviral agents, can be secondary to the other infections and not just CMV. Therefore, by monitoring, it is possible to reduce the unnecessary exposure of patients to the toxic effects of drugs, the development of drug resistance, and the costs of prolonged therapy and longer hospital stays⁽⁹⁾.

Even with long universal prophylaxis, active CMV infections have been observed. According to Schroeder et al.⁽⁹⁾, universal prophylaxis may delay CMV reactivation, which would be a problem, as it creates the possibility that reactivation occurs in a period in which the patient is not being closely monitored by the clinical team. In addition, prolonged prophylaxis can lead to the development of drug resistance⁽⁹⁾.

Increasingly sensitive techniques are necessary to monitor CMV infection in an attempt to identify more individuals with early viral replication. Thus, the antiviral treatment can be started quickly, reducing the severity of CMV infection. The challenge

we face today is to choose the most suitable among the various diagnostic tools for each clinical situation. It is also important to note that one must take into consideration the cost of these diagnostic tests, the cost of medications and the side effects resulting from their use.

The patients reported in Cases 1 and 2 were monitored by CMV antigenemia once per week until D+120, and after this period when they showed any sign, symptom or favorable clinical context. The beginning of the antigenemia procedure occurred within six hours after collecting the biological samples and the results were sent to the clinical team by e-mail within 24 hours of collection. In the reported cases, the patients were called to start antiviral therapy shortly after detecting the active infection. We found that the implementation of early diagnosis of active CMV infections is very feasible and contributes significantly to the quality of treatment provided to transplant patients.

In conclusion, we emphasize that patients with risk factors for developing severe disease or late CMV should be monitored beyond 100 days after transplant as the late occurrence of active infection is a reality.

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