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Original Research Article

CMV: 100 days after Kidney Transplantation

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Abstract: Cytomegalovirus (CMV) infection is frequent after kidney transplantation, typically occurring within the first 100 days post-transplant. This prospective, multicenter study aimed to estimate the frequency of CMV disease beyond 100 days post-transplant and demonstrate the usefulness of virological diagnosis during this period. Of 48 kidney transplant recipients with suspected CMV disease, 17% had positive CMV viremia, and 6% had confirmed CMV disease. The 3 cases of CMV disease presented with high viral loads, viral syndrome associated with tissue-invasive disease. For the 45 patients without confirmed disease, virological diagnosis allowed the identification of other etiologies, mainly infectious or iatrogenic. Although infrequent beyond 100 days, CMV disease can occur and be severe, justifying virological screening in the presence of suggestive signs. Differential diagnosis with other causes remains paramount.

Keywords: Cytomegalovirus, Kidney Transplantation, CMV Disease, Viral Load.

INTRODUCTION

Cytomegalovirus (CMV) infection is the most frequent infection after solid organ transplantation [1, 2]. It generally occurs within the first 100 days post-transplant in the absence of preventive antiviral treatment [3], with an incidence ranging from 8 to 32% in kidney transplantation [4-2]. CMV infection is defined by the detection of viral replication without associated clinical signs in a body fluid or tissue sample [5], while CMV disease is an infection associated with clinical signs attributable to the virus. This disease can manifest as a viral syndrome (e.g., fever, leukopenia, hepatic cytolysis, thrombocytopenia...) [6], or as tissue-invasive involvement [5], (e.g., nephritis, pneumonia, colitis...). CMV can lead to severe direct and indirect consequences. The direct consequences due to viral replication are represented by CMV disease [7], while the indirect effects of CMV infection, which would be related to the pro-inflammatory and immunomodulatory properties of the virus [8,9], can include acute and chronic graft rejection [10, 11], graft-versus-host disease (GvHD), fungal, viral or bacterial superinfections [12], post-transplant lymphoproliferative disorders associated with EBV (PTLD) [13], and death. It should be noted that CMV disease can occur after discontinuation of preventive treatment and is then referred to as late-onset CMV disease.

The objective of our study is, on the one hand, to estimate the frequency of CMV disease in kidney transplant recipients more than 100 days post-transplant and, on the other hand, to demonstrate the usefulness of virological diagnosis in these patients after this delay.

MATERIALS AND METHODS

This is an observational, prospective, multicenter study (3 transplants centers) conducted on kidney transplant recipients from living donors, transplanted for more than 100 days, D+/R+ for CMV, who were not receiving antiviral treatment and in whom CMV disease was suspected by the nephrologist. These patients underwent measurement of CMV viremia (viral load, VL) by quantitative PCR (Roche COBAS Ampliprep/Taqman test) performed on plasma (EDTA tube).

RESULTS

We received samples from 48 patients who had undergone a transplant more than 3 months before the suspicion of disease and the prescription of a CMV viral load. This delay between transplantation and suspicion of CMV disease ranged from 4 months to 20 years. There were 21 women and 27 men (M/F = 1.28), with a mean age of 36.16 years.

We found that the VL was positive in 17% of cases, i.e., 8 transplants recipients. Among them, 6% developed CMV disease, i.e., 3 patients (Fig. 1). 45 patients did not present with CMV disease.

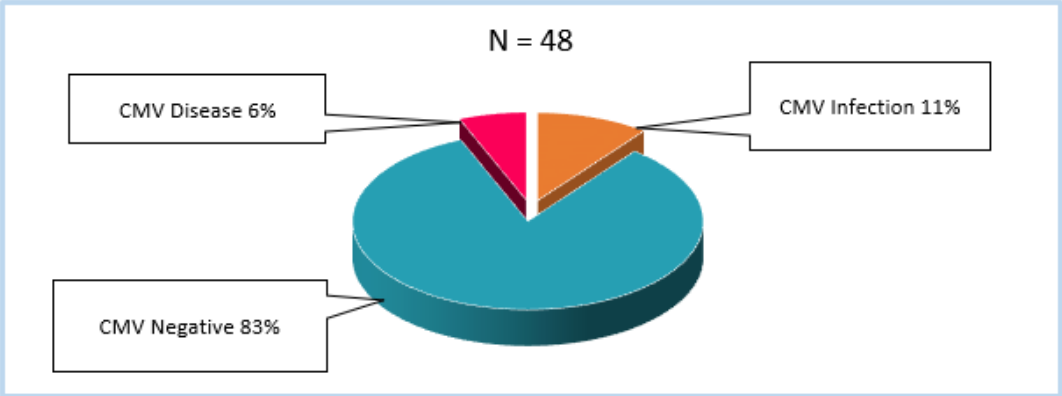

Figure 1: Distribution of patients

In Table 1, we grouped the immunosuppressive treatments, age, clinical and paraclinical signs, CMV VL, and the delay of disease onset after transplantation for the 3 cases of CMV disease. It should be noted that all three patients were receiving MMF and corticosteroids. We observed that the 3 cases were over 50 years old, had received anti-lymphocyte serum, and had presented with a viral syndrome associated with tissue-invasive disease (pneumonia and/or colitis). Their viral loads were high at the time of diagnosis.

Table 1: Characteristics of the three cases of CMV disease

Patient	Induction IS	Maintenance IS	Age (years)	Clinical-Paraclinical Signs	CMV CV (Log IU/ml)	Onset Post-transplant
M1	SAL	Tacrolimus	50	Leukopenia malaise pneumonia colitis renal function impairment	6.09	12 months
M2	SAL	Ciclosporine	54	Fever Leukopenia thrombocytopenia pneumonia	5.88	03 years
M3	SAL	Tacrolimus	59	Leukopenia malaise colitis	4.85	14 months

Regarding patients with a negative CMV VL, they were distributed according to the presence or absence of clinical and paraclinical signs that could be attributed to CMV, as illustrated in Fig. 2.

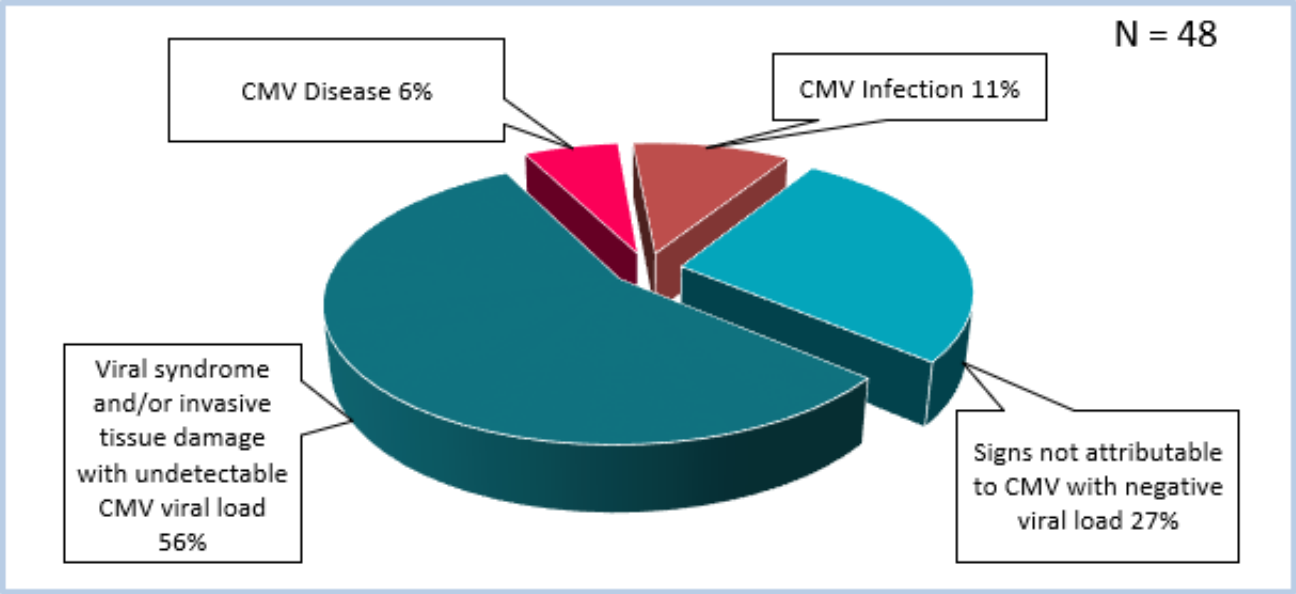

Figure 2: Clinical and paraclinical aspects of patients with a negative VL

The clinical and paraclinical signs that motivated the request for a VL in the 45 transplant recipients without CMV disease are represented in Figure 3. Leukopenia topped the list of signs observed in these transplant recipients. It should also be noted that impaired renal function was a frequent reason for requesting a VL, closely followed by fever and diarrhea. For cases of diarrhea, CMV colitis is possible even with an undetectable VL; however, only a histopathological examination can establish the diagnosis, which is not routinely performed in practice.

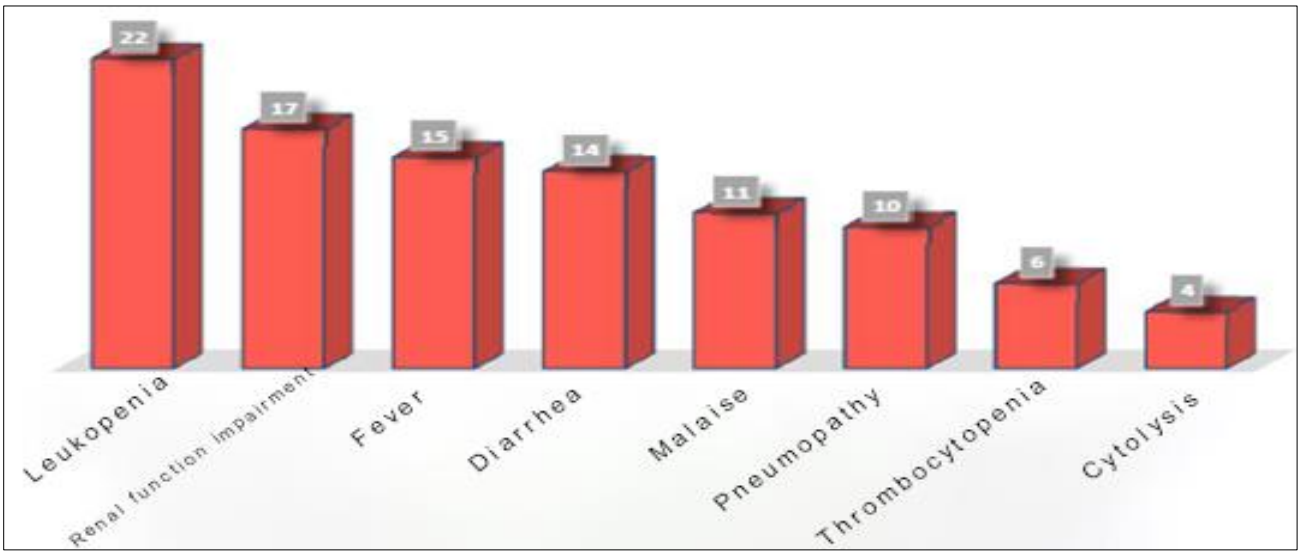

Figure 3: Distribution of different clinical and paraclinical signs in the 45 transplant recipients without CMV disease

Among the various signs mentioned above, some were associated in a way that suggested CMV disease (Fig. 4), but this was excluded because the VL was negative (40 transplants recipients) or low (5 infected patients), but a cause other than CMV was identified (these 5 cases will be detailed later). Signs suggestive of tissue-invasive disease, such as pneumonia and colitis, were the most frequent reason for requesting a CMV VL (45%).

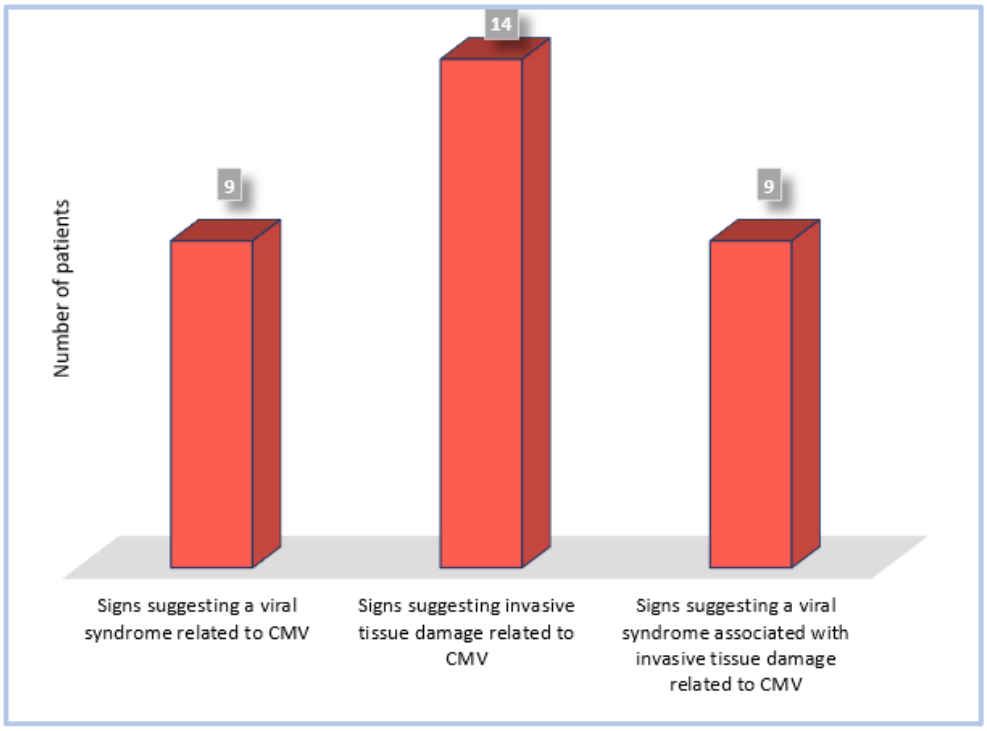

Figure 4: Differents symptomatologies observed that could suggest CMV disease

The signs presented by cases of infection with a positive CMV VL (n = 5) corresponded to signs that could support a diagnosis of probable CMV disease, but the VL was low, and other causes could explain the symptomatology. In fact, all of them showed a good clinical course under treatment for these other causes, except for Patient 1 (deceased). Table 2 lists the clinical and paraclinical signs that motivated the request for a CMV PCR, as well as the diagnosis retained for the 5 transplant recipients infected with CMV.

Table 2: Clinical and paraclinical signs, VLs, and diagnoses retained for cases of CMV infection (n = 5)

Infected Patient	Post-Transplant Time	Clinical-Paraclinical Signs	CV CMV (Log UI/ml)	Diagnosis retained
1	5 years	Leukopenia, Thrombocytopenia Diarrhea ARF (Acute Renal Failure)	2.29	Septicemia due to Pseudomonas aeruginosa (deceased)
2	10 months	Fever Pneumonia ARF	2.38	Pulmonary Tuberculosis
3	7 years	Pneumonia ARF	2.15	Pneumocystis jirovecii Pneumonia
4	6 years	Diarrhea ARF	2.13	Urinary Tract Infection due to bacteria
5	13 months	Malaise Cytolysis ARF	2.49	BK Virus Infection

In Table 3, we summarize the causes retained for the clinical and paraclinical signs observed in the 45 transplant recipients without CMV disease. These patients represent 94% of the studied population.

The etiologies underlying the different clinical pictures were mainly infectious (other than CMV) and iatrogenic, accounting for 40% and 29% of cases, respectively. We note that 35 patients received appropriate treatment for the disease corresponding to the retained diagnosis and showed a good clinical course.

Table 3: Differents causes retained for the 45 patients in the population

Retained Causes	Number of Patients with Negative CV	Number of Patients with Positive CV (Infected)	Total (%)
Infection: Bacterial Parasitic Viral	 11 2 0	 3 1 1	18 (40%)
Iatrogenic	13	/	13 (29%)
Graft Rejection	4	/	4 (09%)
Cancer/Endometriosis	2	/	2 (04%)
Poor treatment adherence	1	/	1 (02%)
Undetermined	7	/	7 (16%)
Total	40	5	45 (100%)

DISCUSSION

The occurrence of CMV disease after 100 days post-transplant was 6% (3 cases of disease out of 48), clearly showing that the risk of disease onset is primarily within the first 3 months post-transplantation. This was also found in a study involving 556 cases of CMV infection/disease in kidney transplant recipients, where 6.1% developed the disease after 6 months post-transplant [14]. A Colombian study conducted on 1620 kidney transplant recipients estimated the frequency of the disease after 6 months to be 2.7% [15]. However, even though the frequency of the disease is lower, this risk is not zero, and one case of CMV disease was observed in our study three years after transplantation, highlighting the need to remain vigilant even after 6 months post-transplant.

Our three cases of CMV disease were over 50 years old, which seems to be explained by the age-related senescence of the immune system, making these subjects more at risk of developing the disease [16, 17].

The fact that all cases of CMV disease had a high viral load (mean of 5.6 log IU/mL) and presented with a viral syndrome associated with tissue-invasive disease (pneumonia and/or colitis) is evidence of the tendency of CMV to cause more severe late-onset diseases than those observed within the first 3 months post-transplant. This has also been demonstrated in the literature, where tissue-invasive involvement was more frequent in transplant recipients after 6 months (60.5% vs. 21.6%) [14]. Our hypothesis would be that the lack of awareness among patients about this virus leads to a delay in consultation and, consequently, an aggravation of the clinical and paraclinical picture of the disease.

It is important to note that thanks to the implementation of virological diagnosis for CMV, 94% of patients who presented with clinical and paraclinical signs, some of which were suggestive of a viral syndrome associated or not with tissue-invasive disease (pneumonia or colitis), were attributed to a cause other than CMV due to a negative or low VL, thus allowing the nephrologist to investigate other etiologies. However, as mentioned above, colitis remains a diagnostic challenge in routine practice for us and elsewhere. For cases of diarrhea, CMV colitis could exist with an undetectable VL, and only a histopathological examination could establish the diagnosis, which is not commonly performed in practice. Nevertheless, these patients showed a good clinical course.

We observed that leukopenia, fever, and malaise were frequent reasons for suspecting CMV

disease in this population, although the virological diagnosis refuted this suspicion. Furthermore, 32 patients, including 5 infected with CMV, presented with a viral syndrome and/or tissue-invasive disease, which could have been treated excessively with Ganciclovir if the VL had not guided the diagnosis toward an etiology other than CMV. In this study, 94% of patients did not suffer from probable CMV disease, but the etiology was found to be predominantly infectious (40%) in most cases, which was also found in other studies where infectious causes were the most frequent [18, 19].

CONCLUSION

In light of our results, it is important to remain vigilant and continue to raise awareness among transplant recipients about CMV even after 100 days post-transplant, so that they seek medical attention promptly in case of suggestive signs and do not develop tissue-invasive disease. However, since the risk of developing the disease remains low after this period, other infectious or iatrogenic causes should be prioritized.

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