Identification of Bacterial Infections and Clinical Manifestation Associated With Cytomegalovirus in Liver Transplantation Patients


ABSTRACT

Introduction. Liver transplantation has become the most effective therapy for the treatment of patients with end-stage liver disease. With new immunosuppressive agents, the incidence of acute rejection has been significantly reduced, but infections have become a serious problem.

Objective. Our objective was to correlate cytomegalovirus (CMV) positivity of antigenemia and polymerase chain reaction (PCR) with clinical manifestations and bacterial infections among patients undergoing liver transplantation.

Methods. This prospective study included patients monitored for 6 months for early detection of CMV infection. Sample collections were performed at the time of surgery and weekly until the second month followed by fortnightly in the third month, and monthly in the fourth to sixth month. CMV infection was defined by positive antigenemia (>3 cells) or 2 positive PCR tests associated or not with clinical symptoms. The methodology for the diagnosis of bacterial infection was through biochemical tests and the automated VITEK/bioMérieux (identification and antibiogram) using samples of urine and blood cultures. Chi-square test was used for dicotomic variables with significant differences when \( P < .05 \).

Results. Sixteen patients (32%) had CMV infections, including 13 (81%) with concomitant infections. Thirty-four patients (68%) did not have CMV infections and 8 of these (24%) had bacterial infection. There was a high correlation with bacterial infections among CMV-positive patients.

Conclusion. Bacterial infections after liver transplantation were associated with CMV infection.
tive for CMV pretransplantation. This study was approved by our Institutional Ethics Committee (CEP no. 430/2003).

To detect CMV, antigenemia was examined by immunofluorescence in peripheral blood, using the methodology described by the manufacturer (Kit CMV Brite Turbo, IQ Products, Netherlands). DNA was obtained according to the method of Schmidt et al\(^5\) with modifications. The PCR reaction to diagnosed the human gene \(\beta\)-globin was performed following the conditions described by De Tommaso et al\(^6\) with modifications. PCR used peripheral blood leukocytes to detect CMV DNA, following the method described by Nogueira et al\(^7\) with some modifications.

Patients were monitored for early detection of CMV infection for 6 months. The sample collections were performed at the time of surgery, weekly until the second month, fortnightly in the third month, and monthly from the fourth to the sixth month.

CMV infection was defined as positive antigenemia (>3 cells) or 2 consecutive positive PCR results within an interval less than or equal to 30 days associated with clinical symptoms. Clinical data were obtained through analysis of medical records and follow-up visits. We considered clinical symptoms associated with CMV infection to be the following: fever, diarrhea, chest pain, flu-like signs, and jaundice. Laboratory results associated with CMV infection were as follows: elevated liver profile (alkaline phosphatase, gamma glutamyl transferase, aspartate aminotransferase, alanine aminotransferase, and total bilirubin), leukopenia, and thrombocytopenia. To prevent infection by herpes virus in patients undergoing liver transplantation, acyclovir was prescribed for 6 weeks, concurrently with the standard immunosuppressive therapy that we have previously described.\(^8\)

The cellular rejection episodes were treated with methylprednisolone and CMV+ subjects received gancyclovir for 21 days with good clinical and laboratory responses.

The methodology for the diagnosis of bacterial infection was biochemical tests and the automated VITEKbioMérieux (identification and antibiogram) using samples of urine and blood cultures.

RESULTS

During this period, 102 patients underwent liver transplantation; 50 patients (49\%) met the inclusion criteria. Thirty-seven patients (74\%) were males and 13 (26\%) females, with ages ranging from 22 to 70 years.

Only 4 patients were followed for less than 6 months due to death 2 at 2 months, 1 at 4 months, and the other 1 at 5 months. Forty-six (92\%) patients were followed for the study period, 40 patients showed good follow up.

Sixteen (32\%) patients experienced CMV infections, with 13 (81\%) showing concomitant bacterial infection. Thirty-four patients (68\%) did not have CMV infection with 8 (24\%) displaying bacterial infections (Fig 1).

In 6 patients, there was high positive antigenemia (>5 cells), which coincided with the histological diagnosis of acute cellular rejection. In 10 patients, the antigenemia was positive with low cellularity (up to 5 cells). None of these patients has clinical symptoms related to active CMV infection, although 4 of them developed acute cellular rejection episodes with symptoms of fever, sickness, myalgia, and jaundice.

Twenty-one patients had bacterial infections confirmed by 23 positive hemocultures and 5 urocultures. In 3 patients the bacterial infection was confirmed by hemoculture and urocultures. Six displayed more than 1 microorganism. The etiologic agents can be observed in Figure 2.

Fig 1. Frequency of CMV infection observed in the period from February 2008 to January 2010 associated or not with bacterial infection \(\chi^2 = 12.61; P = .0004\).

Fig 2. Frequency of etiologic agents found in hemocultures and urocultures according to CMV positivity.

Fig 2. Frequency of etiologic agents found in hemocultures and urocultures according to CMV positivity.

DISCUSSION

CMV infection is a major cause of morbidity and mortality among liver transplant recipients. In this study, CMV infection occurred among 16 (32\%) transplant recipients, consistent with the literature.\(^9\) A previous study in our liver transplantation unit showed a 28\% positivity for CMV antigenemia.\(^8,10\)

Infections developed during the first 3 months, with peak incidence between the third and fourth month.\(^11\) In our study we observed 21 patients with 28 bacterial infections, consistent with the literature.\(^9\)

The common gram-negative bacilli after liver transplantation cause major challenges for clinical treatment.\(^4\) Bacterial infections are the leading cause of death within the first year after liver transplantation. There were 2 recorded cases of death in our study, namely at the second and sixth month after transplantation, respectively.

Approximately 80\% of organ transplant recipients suffer 1 or more infections episode during the first year after transplantation.\(^12\) Our data corroborated the literature, observing 73\% of infections.

An early diagnosis of CMV infection allows for immediate treatment, prevents progression of clinical disease, and
reduces the risk of graft injury. Bacterial infections after liver transplantation were associated with CMV infection.

REFERENCES


