대한소아신장학회지 제 15 권 제 1 호 2011년
DOI 10.3339/jkspn.2010.15.1.76

□증 례□

Late Cytomegalovirus Disease Causes Ileal Perforation after Kidney trasplantation

Hee Woo Lee, M.D., Hyewon Hahn, M.D. and Young Seo Park, M.D.*

Department of Pediatrics, Eulji University School of Medicine
Department of Pediatrics*, Asan Medical Center,
University of Ulsan College of Medicine

= Abstract =

Cytomegalovirus (CMV) is the single most common infection following kidney transplantation and despite prophylactic strategies and the development of new antiviral agents, it still remains a cause of considerable morbidity and mortality. Current literature suggests that CMV infection may trigger rejection.

We report a case of late CMV disease in a preemptive seropositive recipient who did not receive CMV prophylaxis. Diarrhea and abdominal cramping persisted after the administration of mycophenolate mofetil (MMF) six months after transplantation and resulted in ileal perforation at eight months after transplantation. The boy recovered after six weeks of treatment with ganciclovir. MMF has been mooted as a risk factor for CMV infection since its introduction, and further investigations are required to confirm its role. More attention to infectious complications is necessary and serial monitoring of viral load is recommended when MMF is administered. **(J Korean Soc Pediatr Nephrol 2011;15:76-80)**

Key Words : Cytomegalovirus, Kidney transplantation, Ileal perforation

Introduction

Cytomegalovirus (CMV) is the most common viral infection following kidney transplantation and is associated with an increased incidence of allograft rejection [1-5]. CMV infection is reported in up to two thirds of renal transplant recipients, and the incidence of symptomatic disease is between 5% and 30 %, depending on the immune status of the recipient [2]. CMV disease can occur from infection acquired post-operatively from the transplanted organ or from reactivation of the dormant virus. Gastrointestinal (GI) complications in the renal transplant recipient, both early and late, are generally agreed to be major causes of morbidity and mortality after transplantation [6]. CMV infection of the GI tract can also result in myriads of complications. Mycophenolate mofetil (MMF), introduced in the mid-1990s, has been proposed as a risk factor for CMV infection. A consensus about its role in the incidence and the severity of CMV infection and disease has not been reached. However, infectious complications

접수 : 2010년 10월 26일, 수정 : 2011년 1월 28일
승인 : 2011년 1월 31일
책임저자 : 한혜원, 서울시 노원구 하계동 280-1
을지대학교 의과대학 소아청소년과
Tel : 02)970-8222 Fax : 02)976-5441
E-mail : petercat67@gmail.com

require more attention in this era of newly developed potent immunosuppressive drugs.

This report documents a case of ileal perforation caused by late CMV disease in a CMV seropositive kidney recipient, managed with intravenous ganciclovir.

Case Report

A 10-year-old boy with reflux nephropathy underwent kidney transplantation from a living HLA-fully-mismatched unrelated donor in November 2001. The patient was a CMV-seropositive recipient of a CMV-seropositive transplant, and did not receive CMV prophylaxis. He underwent maintenance therapy with FK506 (Prograf®, Fujisawa, USA), azathioprine, and prednisolone for immune suppression. In May 2002, his serum creatinine rose to 1.3 mg/dL from a baseline of 0.8 mg/dL, and methylprednisolone pulse therapy was undertaken for presumed acute allograft rejection. Graft biopsy revealed mild chronic allograft nephropathy. MMF (Cellcept®, Roche) was substituted for azathioprine; however, the patient complained of diarrhea and abdominal cramping, and so, after only two weeks, azathioprine was reintroduced to replace MMF. In July 2002, the patient admitted to hospital because of elevated serum creatinine (1.7 mg/dL), watery diarrhea that persisted for seven days, abdominal cramping, and fever. He displayed the features of pancytopenia and disseminated intravascular coagulopathy (DIC), but there was no elevation of transaminases. Antibacterial therapy was begun, but treatment with ganciclovir was not used to avoid aggravation of leukopenia. On the sixth day after admission, the patient complained of severe abdominal pain and abrupt abdominal distension was detected. Abdominal radiographs showed free intraperitoneal gas. Exploratory laparotomy identified ileal perforations, and bowel resection and anastomosis were performed. A gross operative specimen showed a necrotic bowel wall with exudates. Histological evaluation revealed intranuclear viral inclusions, and immunohistochemical staining confirmed CMV enteritis (Figs 1 and 2). Treatment with ganciclovir (5 mg/kg) by intravenous infusion every 24 h was begun. The dose was adjusted to accommodate the patient's decreased renal function, and treatment was continued for six weeks. A second exploratory laparotomy in response to bilious vomiting identified ileal adhesion. A third exploratory laparotomy was performed because of bilious drainage from an ileal perforation, and resection was performed. After six weeks of treatment with gancyclovir, a test for CMV pp65 antigen in peripheral blood

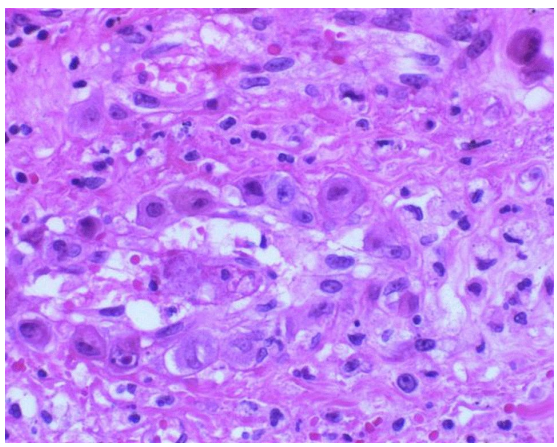

Fig. 1 Ileal resection specimen showing intranuclear and intracytoplasmic viral inclusions (×400, hematoxylin and eosin stain).

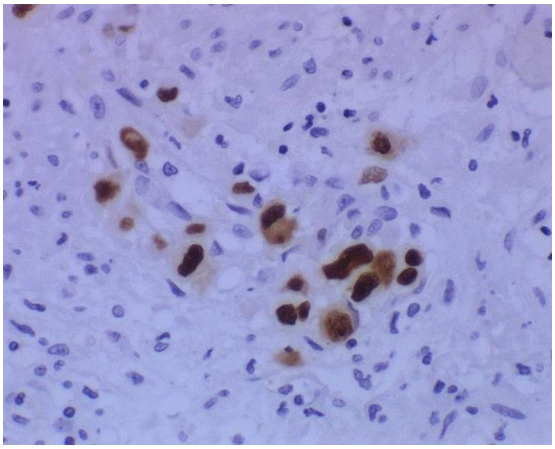

Fig. 2. Immunohistochemical staining for CMV of an ileal resection specimen confirmed CMV enteritis.

neutrophils was negative. Serum creatinine decreased to baseline levels (0.8 mg/dL) and the patient's recovery was uneventful thereafter.

Discussion

Recent success in solid organ transplantation has been achieved in part by advances in immunosuppressive therapy. However, the balance between immunosuppression to prevent allograft rejection and the risk of opportunistic infection is critical. MMF is a potent and selective immunosuppressive agent, and its superiority over azathioprine (AZT) is widely accepted [7]. There are, however, suspicions that MMF increases the incidence of CMV infection, or at least the severity of CMV infections [3, 8, 9, 10]. It is unclear which factors determine whether CMV infections become symptomatic in immunocompromised hosts. MMF inhibits both cellular and humoral immunity, although the mechanism by which MMF increases the severity of CMV disease remains undefined and should be further investigated [8]. In this patient, MMF was administered for only two weeks, but the patient complained of mild abdominal cramping and diarrhea from the commencement of MMF therapy. Considering several cases of an abrupt increase in FK506 blood levels caused by diarrhea [11, 12], an increase in FK506 level during diarrhea might result in over-immunosuppression.

Although a CMV seronegative recipient receiving a CMV seropositive graft is usually considered to be the highest risk [13], the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) data indicate that any pediatric recipient receiving a graft from a seropositive donor, regardless of the CMV immune status of the recipient, is at significant risk of serious CMV infection and deserves special consideration for CMV prophylactic therapy [2, 14]. There are also reports that prophylaxis with enriched anti-CMV immunoglobulin for recipients of CMV seropositive transplants is associated with a decreased risk of hospitalization for CMV infection [2]. Furthermore, prior use of an antiviral agent, such as acyclovir or ganciclovir, is associated with a decreased risk of major organ involvement.

In this case, on preemptive serological screening, a CMV IgG of the recipient was positive and a CMV IgM of the donor was negative, and so CMV prophylaxis was not used. On admission, clinical assessment of the patient suggested CMV disease; however, tests for CMV pp65 antigenemia were negative and conventional diagnostic methods failed to identify CMV disease, despite severe enteritis resulting

in bowel perforation. Only an operative specimen revealed viral inclusions. Therefore, anti-CMV treatment with ganciclovir was delayed because of a concern for the neutropenia caused by ganciclovir.

Although the CMV pp65 antigenemia assay is a rapid and quantitative method with which to monitor CMV infection, it is very laborious. Furthermore, the results may be influenced by several factors, including storage and fixation methods and, as in our patient, leukopenia may mask the presence of CMV. Therefore, CMV-specific real-time quantitative polymerase chain reaction (PCR) might be useful for monitoring CMV infection and anti-viral treatment responses [15, 16]. With combinations of conventional low-risk factors, as observed in our patient for whom CMV prophylaxis was not prescribed, the quantitation of CMV viral load by real-time PCR would ensure safe practice.

Clinical practice guidelines support the selected use of acyclovir, ganciclovir, and CMV hyperimmune globulin for renal transplant recipients who are at high risk [17]. However, reports of late CMV disease six months after transplantation, which is associated with late episodes of rejection [13], and CMV reactivation in seropositive pediatric recipients as in our patient [2], raise concerns about an increase in CMV diseases in this era of newly developed potent immunosuppressants. Therefore, serial monitoring of viral load is recommended.

한 글 요 약

신 이식 후 소장 파열을 초래한 후기 cytomegalovirus 질환

을지대학교 의과대학 소아청소년과
*울산대학교 의과대학 서울아산병원 소아청소년과**

이희우 · 한혜원 · 박영서*

Cytomegalovirus (CMV)는 신 이식 후 발생하는 감염의 가장 흔한 원인으로, 예방요법과 새로운 항 바이러스 제제의 도입에도 불구하고 심각한 결과를 초래하며, 거부반응을 촉진한다는 의견도 제시되고 있다.

저자들은 이식 전 CMV 양성이었던 환아에서 후기 CMV 질환이 발병한 증례를 보고하고자 한다. 이식 6개월 후 mycophenolate mofetil ((MMF)을 투여한 후로 설사와 복통을 호소하던 환아는 이식 후 8개월에 소장이 파열되었다. 환아는 6주간의 치료 후에 호전되었다. CMV감염의 위험 인자로 MMF의 역할에 대해서는 더 논의가 필요하나, MMF 투여 시 이식 후 바이러스 감염에 대한 주의와 주기적인 추적 관찰이 필요하다.

References

1) Pouteil-Noble C, Ecochard R, Landrivon G, Donia-Maged A, Tardy JC, Bosshard S, et al. Cytomegalovirus infection—an etiological factor for rejection? A prospective study in 242 renal transplant patients. Transplantation 1993;55:851-7.
2) Bock GH, Sullivan EK, Miller D, Gimon D, Alexander S, Eloois E, et al. Cytomegalovirus infections following renal transplantation—effects of antiviral prophylaxis: A report of the North American Pediatric Renal Transplant Cooperative Study. Pediatric Nephrol 1997;11:665-71.
3) Robinson LG, Hilinski J, Graham F, Hymes

L, Beck-Sague CM, Hsia J, et al. Predictors of cytomegalovirus disease among pediatric transplant recipients within one year of renal transplantation. Pediatr Transplant 2002;6:111-8.
4) Wolf DG, Spector SA. Early diagnosis of human cytomegalovirus disease in transplant recipient by DNA amplification in plasma. Transplantation 1993;56:330-4.
5) Fisher L, Rautenberg P, Bienengrabe H, Leimenstoll G. Antigenemia, immunoblotting, and enzyme immunoassay for early diagnosis of cytomegalovirus infection in renal transplant patients. Transpl Int 1993;6:201-5.
6) Komorowski RA, Cohen EB, Kauffman HM, Adams MB. Gastrointestinal complications in renal transplant recipients. Am J Clin Pathol 1986;86:161-7.
7) Mathew TH. A blinded, long-term, randomized multicenter study of mycophenolate mofetil in cadavaric renal transplantation: results at three years. Tricontinental Mycophenolate Mofetil Renal Transplantation Study Group. Transplantation 1998;65:1450-4.
8) Sarmiento JM, Dockrell DH, Schwab TR, Munn SR, Paya CV. Mycophenolate mofetil increases cytomegalovirus invasive organ disease in renal transplant patients. Clin Transplant 2000;14:136-8.
9) ter Meulen CG, Wetzels JFM, Hilbrands LB. The influence of mycophenolate mofetil on the incidence and severity of primary cytomegalovirus infections and disease after renal transplantation. Nephrol Dial Transplant 2000;15:711-4.
10) Abbott KC, Hypolite IO, Viola R, Poropatich RK, Hshieh P, Cruess D, et al. Hospitalization for cytomegalovirus disease after renal transplantation in the United States. Ann Epidemiol 2002;12:402-9.
11) Zylber-Katz E, Granot E. Abrupt increase of Tacrolimus blood levels during an episode of Shigella infection in a child after liver transplantation. Ther Drug Monit 2001;23:647-9.
12) Hochleitner BW, Bosmuller C, Nehoda H, Fruhwirt M, Simma B, Ellemunter H, et al. Increased tacrolimus levels during diarrhea. Transpl Int 2001;14:230-3.
13) Slifkin M, Tempesti P, Poutsiaka DD, Snydman DR. Late and atypical cytomegalovirus disease in solid-organ transplant recipients. Clin Infect Dis 2001;33:E62-8.
14) Snydman DR, Werner BG, Heinze-Lacey B, Veradi VP, Tilner NL. Use of cytomegalovirus immune globulin to prevent cytomegalovirus disease in renal transplant recipients. N Engl J Med 1987;317:1049-54.
15) Tanaka Y, Kanda Y, Kami M, Mori S, Amaki T, Kusumi E, et al. Monitoring cytomegalovirus infection by antigenemia assay and two distinct plasma real-time PCR methods after hematopoietic stem cell transplantation. Bone Marrow Transplant 2002;30:315-9.
16) Griscelli F, Barrois M, Chauvin S, Lastere S, Bellet D, Bourhis JH. Quantitation of human cytomegalovirus DNA in bone marrow transplant recipient by real-time PCR. J Clin Microbiol 2001;39:4362-9.
17) Jassal SV, Roscoe JM, Zaltzman JS, Mazzulli T, Krajden M, Gadawski M. Clinical practice guidelines: prevention of cytomegalovirus disease after renal transplantation. J Am Soc Nephrol 1998;9:1697-708.