Cytomegalovirus Disease with Atypical Presentation in a Renal Transplant Patient: Case Report

Masoud Khosravi,[1] Ali Nobakht,[2] Abdolah R Nikokar[3]

Infection is a major problem after kidney transplantation. Cytomegalovirus (CMV) is the most common viral infection affecting transplant patients. This report presents a rare clinical manifestation of CMV in the form of a hemorrhoid in a 58-year-old woman. One week after undergoing an external hemorrhoidectomy, the patient presented with fever, leukopenia, and thrombocytopenia. Pathological analysis showed CMV in the hemorrhoidal tissue, which was confirmed via a positive PP65 antigenemia assay. Therapy with ganciclovir (250 mg IV b.i.d. for 2 weeks) was started. The patient's response to treatment was good, and she has been doing well since that time. Her plasma creatinine level 2 years later was 79.2 µmol/L (normal range, 53-106 µmol/L). Physicians must always be aware of the hazards of CMV in immunocompromised patients with typical, and even with atypical, presentations. Taking into consideration the statement, "prophylaxis precedes treatment," nephrologists must try to detect CMV in their patients (especially during the first 6 months after transplantation) prior to the appearance of any clinical manifestations. If CMV is detected, preemptive therapy with ganciclovir should be started.

Key words: *Cytomegalovirus infection, Kidney transplantation, Immunosuppression, Endothelial cells*

Infection continues to be a major cause of morbidity and mortality in solid organ transplant recipients, despite overall improvements in surgical techniques, immunosuppressive regimens, and prophylactic regimens. Cytomegalovirus (CMV) is a ubiquitous herpesvirus that persists indefinitely after primary infection, usually in a latent form, in various tissues (eg, kidney, liver, and lung) [1]. CMV disease typically occurs 1 to 4 months (median, 35 days) after solid organ transplantation.

This case report describes a rare case of CMV disease initially diagnosed in an external hemorrhoid in a kidney transplant patient.

Case Report

A 58-year-old woman who had received a living-unrelated kidney transplant in December 2002 was admitted to the Golsar Hospital in Rasht City, Iran, in May 2003, because of a high fever. Both the recipient and the donor had been HIV negative but CMV positive.

The patient's immunosuppression regimen of consisted of cyclosporine microemulsion, USP (150 mg b.i.d.), mycophenolate mofetil (1 g b.i.d.), and prednisolone (10 mg q.d.). Her fever was 39.5°C and was accompanied by chills, malaise, anorexia, nausea, vomiting, and epigastric pain. Results of a clinical examination were unremarkable, except for the high fever. The patient's white blood cell count was 3.2×10^9/L (normal range, 4.5-11.0 $\times$ 10^9/L) with 60% neutrophils, 36% lymphocytes, 1% monocytes, and 3% eosinophils). Other laboratory values included hemoglobin (7.4 µmol/L; normal range, 4.45-9.30 µmol/L), platelet count (95×10^9/L; normal range, 150-450 $\times$ 10^9/L), BUN (6.7 µmol/L; normal range, 2.9-8.9 µmol/L), and plasma creatinine (105.6 µmol/L). Results of the patient's urinalysis were normal. Results of blood and urine cultures were both unremarkable. Results of the patient's chest radiograph were normal. Because of the patient's earlier history of CMV disease and because of her positive clinical and laboratory findings (positive CMV-PP65 antigen) as well as a positive hemorrhoidal tissue pathology report (Figure 1), treatment with ganciclovir (250 mg IV b.i.d. for 2 weeks) was begun.

[1]*Division of Nephrology, Gilan University of Medical Sciences, Gilan, Iran,* [2]*Division of Nephrology, Shaheed Beheshti University of Medical Sciences, Tehran, Iran,* [3]*Division of Pathology, Gilan University of Medical Sciences, Gilan, Iran*

Address reprint requests to: *Masoud Khosravi, Golsar, Street 142, No: 25, Postal Code: 4165763355, Rasht, Iran*

Phone: *00 989 11 131 5796* ***Fax:*** *00 981 31 772 1728* ***E-mail:*** *drmasoudkhosravi@yahoo.com*

Experimental and Clinical Transplantation (2006) 1: 458-461

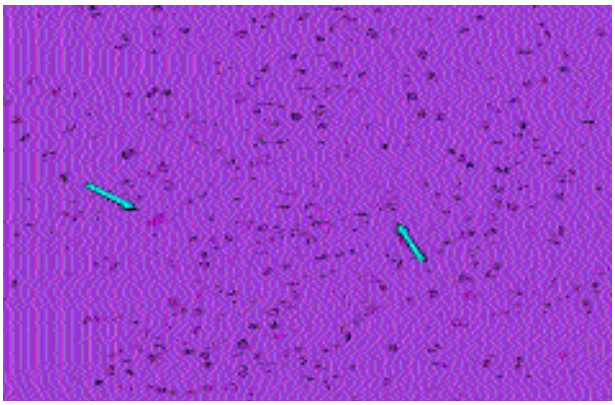

Figure 1. CMV inclusion (owl's eye) in hemorrhoidal tissue (arrows)

However, the cyclosporine dosage was reduced, from 100 mg b.i.d. on admission to 50 mg b.i.d. at 2 weeks' follow-up. Prednisolone at a stress dosage of 40 mg q.d. was continued. Mycophenolate mofetil was discontinued. After about 1 week of treatment, the patient's overall response to the pharmaceutical intervention was good, and her fever subsequently went down. During treatment, the patient's plasma creatinine level was 96.8 μmol/L (normal range, 53-106 μmol/L); in addition, both leukopenia and thrombocytopenia resolved with treatment.

The patient had undergone an external hemorrhoidectomy about 1 week prior to her admission. She had noticed a painful hemorrhoid about 20 days earlier. Prior to this, she had been healthy, and no hemorrhoid had been present. She did not report any gastrointestinal disturbances including diarrhea. According to the pathology report of the hemorrhoidal tissue, several "inclusion bodies" were reported in the nuclei of the endothelial cells (ECs), confirming CMV involvement (Figure 1).

The patient left the hospital in good condition, and she is presently doing well 2 years after the kidney transplantation. Since her discharge in July 2003, her CMV-PP65 level has remained negative. The patient's BUN and plasma creatinine levels at 1-year follow-up were 5.3 μmol/L and 96.8 μmol/L respectively.

Discussion

Viral infections are a leading cause of posttransplantation morbidity and mortality. The use of more potent immunosuppressive agents is responsible, in part, for the increasing incidence of some viral infections [2].

CMV is the most common opportunistic infection to occur following solid organ transplantation. Symptomatic CMV infection typically occurs during the period of maximal immunosuppression (ie, 1-4 months after transplantation) [3, 4]. Diagnosis of CMV disease requires clinical signs of infection such as fever, leukopenia, or organ involvement [3, 4]. The most common presentation of CMV disease is a mononucleosislike syndrome with fever, malaise, myalgias, and arthralgia, usually associated with leukopenia, a mild atypical lymphocytosis, and, on occasion, thrombocytopenia [3].

There are 2 ways that the clinical syndrome manifests itself in CMV patients [5]. First, there are the direct effects, which are those effects caused directly by infection with lytic virus production. This is apparent on histologic analysis, where it is easy to see the location of the virus, what damage is occurring, and whether it is the immune response to the virus that is causing lytic infection. These are the classic manifestations of CMV [5]. Then, there are the indirect effects, which are those effects caused by cytokines and chemokines produced in response to CMV replication [5]. CMV infection may lead to acute and chronic allograft injury and rejection [1, 5].

Although an association between the gastrointestinal tract and fever in a kidney transplant patient is uncommon [6], it is possible, as was the case in our patient.

Newer techniques for rapidly diagnosing CMV infection include shell vial culture, pp65 antigenemia assay, polymerase chain reaction (PCR), and the hybrid-capture RNA-DNA hybridization assay for qualitative detection of CMV-PCR [7].

Antiviral agents effective against CMV include ganciclovir, valganciclovir, foscarnet, and cidofovir. Leflunomide, a pyrimidine antagonist that inhibits virion assembly, has a potential role in treating infection due to ganciclovir-resistant strains of CMV. Ganciclovir remains the primary agent for preventing and treating established disease. Recent studies suggest that valganciclovir is at least equal to ganciclovir in terms of preventing CMV infection [7]. Owing to the high incidence of CMV in certain subgroups, routine prophylaxis (universal prophylaxis) is often employed during the first 3 months posttransplantation to prevent CMV disease. Valganciclovir is a prodrug of ganciclovir with higher oral bioavailability than that of oral ganciclovir [5, 8].

In the current case, after admitting the patient to the hospital, ganciclovir (250 mg IV b.i.d. for 2 weeks) was begun, and mycophenolate mofetil was temporarily withheld (for 3 months, beginning on hospital admission). The dosage of cyclosporine was

reduced from 100 mg b.i.d. on admission to 50 mg b.i.d. at 2 weeks' follow-up, and prednisolone (at a stress dosage of 40 mg q.d.) was continued and then gradually decreased to 10 mg in the morning.

Our patient's response to ganciclovir infusion was good, as after 5 days of ganciclovir treatment, she became afebrile. She was discharged from the hospital, and her CMV-DNA PCR and PP-65 antigen levels were serially checked (every month for 6 consecutive months); both were repeatedly negative. At the present time, 2 years after CMV infection, the patient is doing well, and her plasma creatinine level remains around 79.2 μmol/L.

The pathogenesis of the hemorrhoid in this case (although not clearly defined) indicated that it could have been due to direct EC injury by human CMV. EC injury is a common feature of viral infection and can alter hemostasis in a direct or indirect manner. Viral infection can alter hemostatic balance resulting in either hemorrhage or coagulation. EC infection may represent a common pathway by which viruses alter hemostasis.

Herpesviruses (including CMV) induce a prothrombotic phenotype by inhibiting the normal anticoagulant and antithrombotic properties of the endothelium [9]. CMV infects ECs (both in vivo and in vitro), smooth muscle cells, and macrophages—all of which are important to the pathogenesis of vascular diseases—and it alters expression of cell adhesion molecules. In patients with CMV disease, circulating infected ECs may help to disseminate the virus. Certain viral infections, including CMV infection, increase the risk of thrombosis. Mesenteric arterial or venous thrombosis can occur in patients with acute-phase CMV infections, and the virus may be associated with vasculitis in these patients. Hypothetical mechanisms for the increased risk of thrombogenic events include the loss of anticoagulant factors (eg, thrombomodulin, prostacyclin, and tissue plasminogen activator), increased levels of procoagulation factors (eg, von Willebrand factor), vasculopathy, endotheliitis, and anticardiolipin syndrome. CMV may directly damage intact vascular endothelium, possibly by altering its thromboresistant surface. CMV-infected ECs are thrombogenic. CMV infection increases intracellular and cell surface expression of von Willebrand factor.

The EC is a key cell type in the pathogenesis of CMV infection. ECs, particularly those from the microvasculature in the brain, lungs, heart, gastrointestinal tract, and placenta, are frequently infected, and circulating infected ECs has been identified in CMV-infected patients. The ability of CMV to replicate in ECs is also considered important in enabling the virus to maintain a lifelong infection in the host. Increasing evidence suggests that CMV infection can induce vascular damage that may be directly associated with thrombosis and life-threatening complications. However, vasculopathy with thrombosis is a rare presentation of CMV infection; it is primarily reported in transplant patients receiving high-dosage immunosuppressive therapy and in patients infected with human immunodeficiency virus. Furthermore, in several case reports, extensive vascular involvement and thrombosis were noted in nonimmunocompromised hosts with acute-phase CMV infections [10].

Conclusions

The importance of this atypical presentation is that physicians must continually be aware of CMV infection hazards in their immunocompromised patients with or without fever and even with an unusual presentation, for example, allograft dysfunction occurring many years after transplantation, enterocolitis without fever and leukopenia [11], or as a nasal polyp after renal transplantation [12].

CMV is a ubiquitous herpesvirus that persists indefinitely after primary infection, usually in a latent form in various tissues (eg, kidney, liver, and lung) [1]. The development and availability of rapid diagnostic assays for detecting CMV have paved the way for a new prophylactic approach to treatment, that is, preemptive therapy. Theoretically, therefore, if one were able to serially monitor patients with these assays and detect CMV at a point early enough in the replicative cycle, or when replication was just beginning, and one added antiviral therapy (eg, valganciclovir), that hopefully one would be able to prevent progression to clinical disease (via pre-emptive therapy) [1, 6, 13]

References

1. Pescovitz MD. Prevention and treatment of cytomegalovirus disease in solid organ transplant recipients: the clinical and economic impact of evolving strategies. Introduction. Am J Health Syst Pharm 2003; 60: S3-S4
2. Hwang EA, Kang MJ, Han SY, Park SB, Kim HC. Viral infection following kidney transplantation: long-term follow-up in a single center. Transplant Proc 2004; 36: 2118-2119
3. Fishman JA, Rubin RH. Infection in organ-transplant recipients. N Engl J Med 1998; 338: 1741-1751
4. Rubin RH, Colvin RB. Impact of cytomegalovirus infection on renal transplantation. In: Racusen LC, Solez K, Burdick JF, eds. Kidney transplant rejection. New York, Marcel Dekker; 1998, pp 605-626

5. Rubin RH, Alexander BD, MD, Tapper ML. New therapeutic options in CMV infection. Available at: http://www.medscape.com Accessed December 30, 2002
6. Pizzo PA. Fever in immunocompromised patients. N Engl J Med 1999; 341: 893-900
7. Renal Week 2002: American Society of Nephrology 35th annual meeting advances in clinical nephrology and renal transplantation. Available at: http://www.medscape.com Accessed December 10, 2002
8. American Transplant Congress. 2003 The Fourth Joint American Transplant Meeting immunosuppression and infection: opposing challenges in solid organ transplantation. Available at: http://www.medscape.com Accessed July 16, 2003
9. Nicholson AC, Hajjar DP. Herpesvirus in atherosclerosis and thrombosis: etiologic agents or ubiquitous bystanders? Arterioscler Thromb Vasc Biol 1998; 18: 339-348
10. Rahbar A, Soderberg-Naucler C. Human cytomegalovirus infection of endothelial cells triggers platelet adhesion and aggregation. J Virol 2005; 79: 2211-2220
11. Boobes Y, Al Hakim M, Dastoor H, Bernieh B, Abdulkhalik S. Late cytomegalovirus disease with atypical presentation in renal transplant patients: case reports. Transplant Proc 2004; 36: 1841-1843.
12. Kulkarni AA, Badve SV, Tapiawala SN, Deshpande RB, Shah BV. Cytomegalovirus nasal polyp after renal transplant. J Assoc Physicians India 2003; 51: 614-615
13. Lake KD. New prophylactic treatment strategy for cytomegalovirus disease. Am J Health Syst Pharm 2003; 60: S13-S16