Clinical case

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Cytomegalovirus colitis in kidney transplant recipients: presentation of two cases

Colitis por cytomegalovirus en trasplante renal: Presentación de 2 casos

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Abstract

Cytomegalovirus infection is a latent risk among immunocompromised kidney transplant recipients and is associated with increased risk of allograft failure and death. CMV infection can manifest as active infection or as CMV disease (divided into CMV syndrome and CMV tissue-invasive disease). We present two cases of tissue invasive CMV disease, presenting within 7 months after kidney transplantation. Both cases were D+/R-, received lymphocyte-depleting agents and mycophenolate, and both received CMV prophylaxis according to General Practice Guidelines. CMV disease criteria included detectable viral replication in blood, classical endoscopic findings and histopathological confirmation. We emphasize the need of categorical identification of CMV infection risk factors among kidney transplantation recipients, specially CMV donor/recipient serostatus and immunosuppressive medication. Although clinical practice guidelines suggest 1 to 3 months of CMV prophylaxis in high-risk cases, extended prophylaxis and immunosuppressive medication adjustment should be considered.

Key words: Kidney transplantation, cytomegalovirus infections.

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Resumen

La infección por citomegalovirus (CMV) es un riesgo latente en pacientes inmunocomprometidos por trasplante renal, asociándose con aumento del riesgo de rechazo del injerto y muerte. La infección por CMV puede manifestarse como infección activa o enfermedad por CMV (dividida en síndrome por CMV y enfermedad tisular invasiva por CMV). Presentamos dos casos de enfermedad tisular invasiva por CMV, la cual se presentó entre los primeros siete meses posteriores al trasplante. Ambos casos eran D+/R-; recibieron agentes depletores de linfocitos y micofenolato y profilaxis para CMV de acuerdo con las guías de práctica clínica. Los criterios para enfermedad por CMV incluyeron replicación viral detectable en sangre, hallazgos endoscópicos clásicos y confirmación histopatológica. Hacemos énfasis en la necesidad de identificar los factores de riesgo para la infección por CMV en pacientes con trasplante renal, especialmente el seroestatus donador/receptor y los medicamentos inmunosupresores. Aun cuando las guías de práctica clínica sugieren de uno a tres meses de profilaxis para CMV en casos de alto riesgo, debería considerarse la profilaxis extendida y el ajuste de los medicamentos inmunosupresores.

Palabras clave: trasplante de riñón, infecciones por citomegalovirus.

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Introduction

Cytomegalovirus infection frequently affects kidney transplant recipients, being associated with an increased risk of rejection and mortality.[1] The infection in kidney transplant recipients occurs as an active infection (evidence of CMV replication in blood regardless compatible signs and symptoms) or as CMV disease, which is divided into CMV syndrome (viral detection in blood with nonspecific signs and symptoms and absence of tissue invasion) and CMV tissue-invasive disease (CMV infection with signs and symptoms of specific organ damage).[2,3]

Gastrointestinal disease is the most common clinical manifestation of the tissue-invasive CMV disease, presenting nausea, vomiting, diarrhea and/or abdominal pain; erythematous erosions, localized ulcers and less frequently plaques, nodules and polyps are found in the endoscopic studies.[4]

We present two cases of CMV tissue-invasive disease, making emphasis on the risk factors associated with the infection and with proposals regarding the duration of prophylaxis and the adjustment of the immunosuppressive treatment.

Presentation of case 1

A 30-year-old male patient with a history of trisomy 21 and G5 chronic kidney disease without requiring replacement therapy before transplant. In January, 2018, he received a living related-donor kidney transplant. Immunosuppression was induced with methylprednisolone 500 mg and thymoglobulin 50 mg, and was maintained with tacrolimus 2 mg every 12 hours, mycophenolic acid 720 mg every 12 hours, and prednisone 30 mg every 24 hours.

The serostatus of the patient for CMV was negative before the transplant (IgG 4.3 AU/ml, IgM 0.08 AU/ml); however, his donor had IgG 135 IU/ml (0-14) and IgM 5 IU/ml (0-22). Prophylaxis was given with valganciclovir 450 mg every 12 hours during one month after the transplant.

The patient was hospitalized five months later due to bloody diarrhea, nausea and vomiting of gastric contents for one week, with a blood pressure of 100/80 mmHg, heart rate 86 bpm, respiratory rate 18 bpm, and temperature 36.4 ºC. biochemical analysis with hemoglobin of 7.4 g/dl, hematocrit 23.48%, platelets 72x10^3/µl, leukocytes 3.03x10^3/µl, glucose 114 mg/dl, urea 58 mg/dl, creatinine 1.5 mg/dl, Na 144 mmol/L, K 4.5 mmol/L, Cl 108 mmol/L, Ca 9.1 mg/dl, Mg 1.5 mg/dl, P 3.9 mg/dl.

A colonoscopy was performed, finding nonspecific colitis with erosions of aphthous "shirt button" appearance (Figures 1 and 2). The histopathological

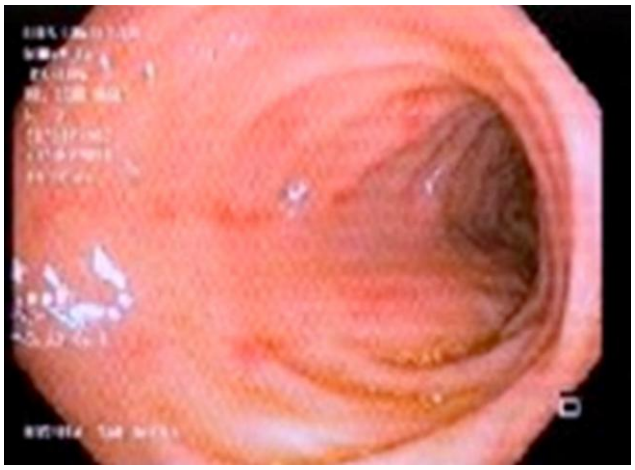

Figure 1. Multiple linear erosions in the left colon

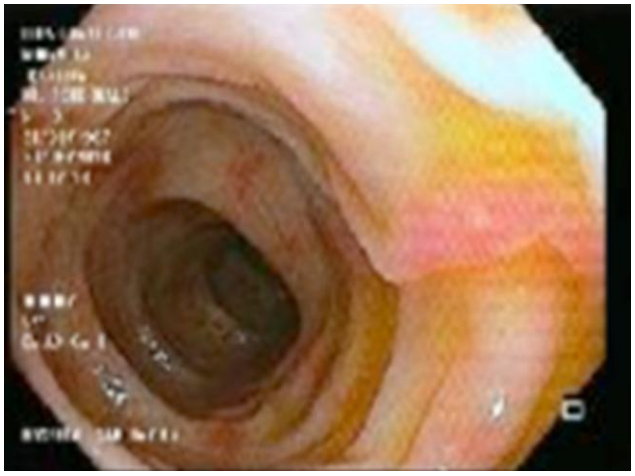

Figure 2. Erosions of aphthous "shirt button" appearance.

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study reported slightly edematous and congestive supporting stroma, mixed inflammatory infiltrate predominantly lymphoid and hemorrhage without involvement of glandular structures and lining mucosa. Mucosal endothelial cells with prominent intranuclear basophilic inclusions, consistent with CMV infection, were identified (Figures 3 and 4). A viral load test was performed in the first weeks after diagnosis, with a result of 1.724 copies/ml (< 200).

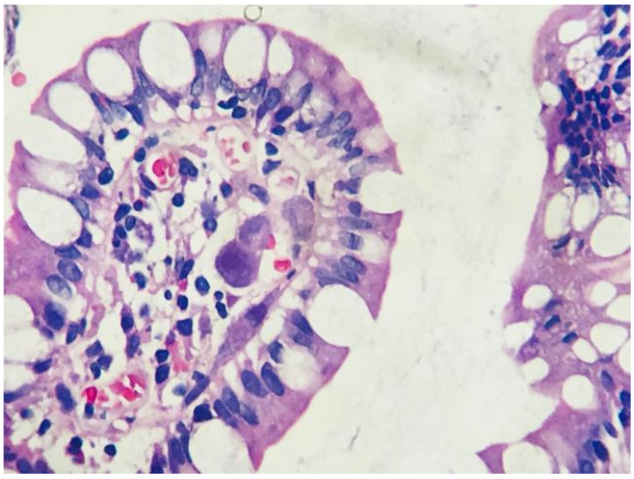

Figure 3. Terminal ileum with mucosal endothelial cells with intranuclear basophilic inclusions.

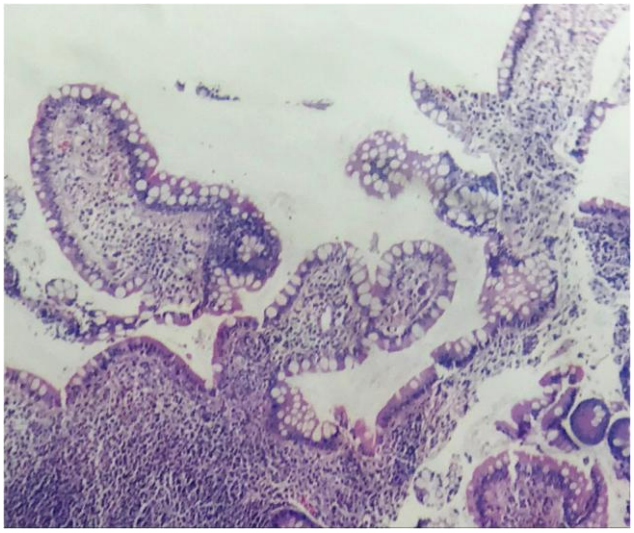

Figure 4. Terminal ileum with edematous and congestive supporting stroma, with inflammatory infiltrate of lymphoid predominance.

CMV tissue-invasive disease was considered as diagnosis. It was treated with intravenous ganciclovir 350 mg every 12 hours for 2 days and subsequently with oral valganciclovir 450 mg every 48 hours for 3 months, with improvement of symptoms. Latest studies: urea 55.9 mg/dl, BUN 26 mg/dl, creatinine 1.2 mg/dl.

Case 2

A 23-year-old male patient with G5 chronic kidney disease of 2 years of evolution, on renal replacement therapy with hemodialysis for 5 months prior to kidney transplantation from a related living donor in October, 2017. The induction of immunosuppression was carried out with methylprednisolone 500 mg and basiliximab 20 mg, and it was maintained with prednisone 40 mg every 24 hours, tacrolimus 3 mg every 12 hours and mycophenolic acid 720 mg every 12 hours.

Before the transplant the CMV serostatus of the patient was negative (IgG < 5 IU/ml, IgM < 5 IU/ml), and his donor was positive, with IgG of 250 AU/ml (0-6) and IgM of 0.270 AU/ml (negative < 0.85). He received prophylaxis with valganciclovir 450 mg every 12 hours for 2 months.

Two months after transplantation, the patient was hospitalized due to data compatible with acute graft rejection, corroborated by biopsy with transient acute ischemia, being managed with six doses of thymoglobulin, 1.25 mg/kg, with remission and normalization of nitrogen compounds.

Seven months after transplantation, he presented abdominal pain, diarrheal stools, asthenia and adynamia of 5 days of evolution. Without alteration in his vital signs (blood pressure of 120/74 mmHg, heart rate of 81 bpm, respiratory rate of 16 rpm, and temperature of 36.2 ºC), but urea of 71 mg/dl, creatinine of 2.99 mg/dl, Na 133 mmol/l, K 3.33 mmol/l, hemoglobin 13.5 g/dl, hematocrit 40,5%, leukocytes 3.7 x 10^3/µl, glucose 115 mg/dl and Cl 104 mmol/l.

A colonoscopy was performed, observing isolated ulcerations with a fibrinoid base and raised erythema-

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tous halo in the descending colon, of nearly 1 cm in diameter in the transverse colon and more abundant and of larger size in the ascending colon (Figures 5 and 6). The histopathological study reported slightly edematous and congestive supporting stroma, with a moderate amount of mixed inflammatory infiltrate, predominantly lymphoid, and hemorrhage without affecting the glandular structures and the lining mucosa. Mucosal epithelial and endothelial cells with viral cytopathic changes characterized by prominent intranuclear basophilic inclusions, consistent with

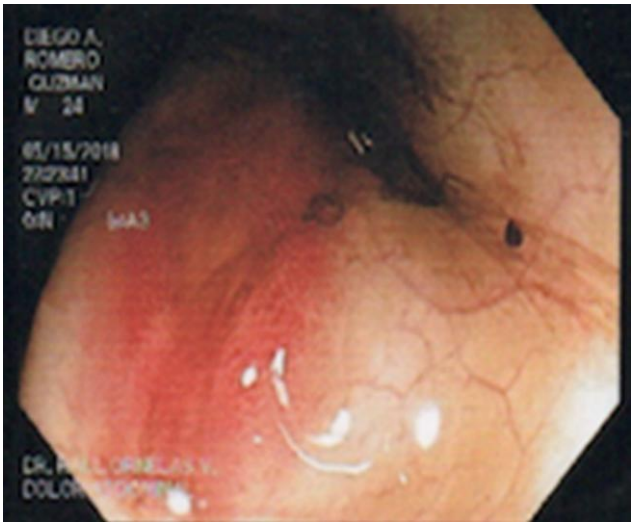

Figure 5. Ulceration with fibrinoid base and erythematous halo.

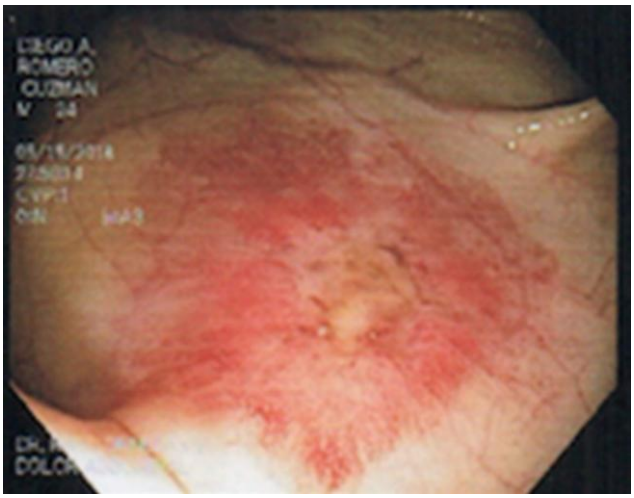

Figure 6. Punched-out lesion with erythematous base.

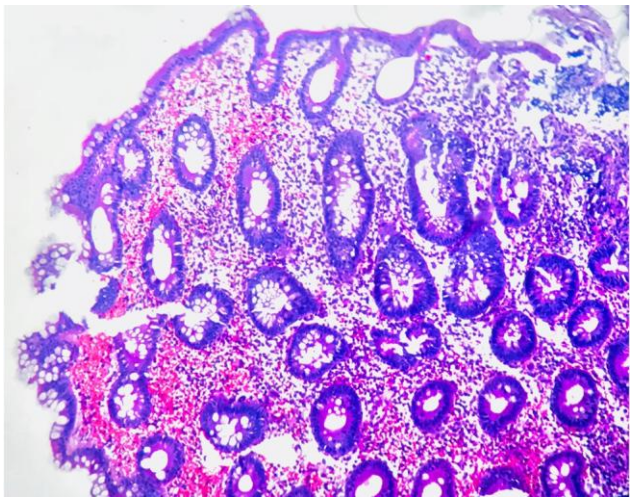

Figure 7. Epithelial mucosa with intranuclear basophilic inclusions.

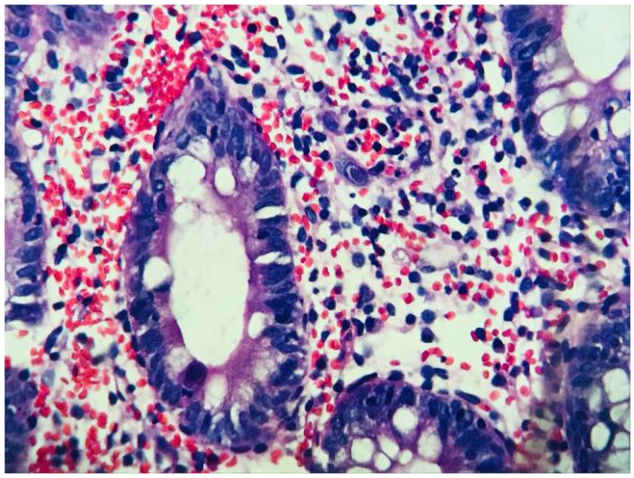

Figure 8. Edema and congestion of supporting stroma.

CMV infection, were identified (Figures 7 and 8). A viral load test was performed with a result of 38.386 copies/ml (< 200).

The patient was treated with ganciclovir 350 mg intravenously every 12 hours for 4 days and subsequently with valganciclovir 450 mg orally every 12 hours until completing 21 days of treatment, with remission of the clinical picture and biochemical improvement (urea 39.2 mg/dl, BUN 18.3 mg/dl, creatinine 2.3 mg/dl). The viral load in the control two months after the onset of the clinical picture was lower than 200 IU/ml.

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Discussion

Cytomegalovirus infection is a latent risk in immunosuppressed kidney transplant patients, with an incidence of CMV disease of 24% in the first 100 days, with a general frequency of infection of 50-80% and of CMV disease of 20-60%.[5-7] It occurs in three forms: primary infection (seronegative recipient and seropositive donor, D+/R-), reactivation of latent CMV (consequence of immunosuppression, even when both the recipient and the donor are seronegative), and reinfection (previously seropositive recipient who becomes infected with another serotype of the virus).[8]

Coinciding with the international reports and other documented cases, both cases presented with gastrointestinal disease, the most common clinical manifestation of invasive CMV disease, characterized by nausea, vomiting, diarrhea and/or abdominal pain, with endoscopic findings of erythematous erosions, localized ulcers and less frequently, plaques, nodules and polyps.[8-11] Other less frequent manifestations are pneumonitis, nephritis, retinitis, pancreatitis and hepatitis.[2]

The main risk factors for the development of the infection are the following:

- The donor/recipient serostatus:
  - Positive donor/negative recipient (D+/R-): the highest risk, without prophylaxis 69% can develop infection and 56%, CMV disease.
  - Positive recipient (R+): lower risk of CMV disease without prophylaxis (20%), but up to 67% risk of reinfection.
  - Negative donor/recipient (D-/R-): low risk, less than 5% develop infection without prophylaxis.
- Induction of immunosuppression with lymphocyte depleting agents such as thymoglobulin.
- Maintenance of immunosuppression with mycophenolate.
- Use of lymp hocyte depleting agents or high doses of glucocorticoids to treat an acute rejection.[1,3,7]

As it can be seen, the two cases presented shared all the risk factors mentioned. Both were D+/R- and the immunosuppression with mycophenolate was maintained. In case 1, immunosuppression was induced with a lymphocyte depleting agent and in case 2 a lymphocyte depleting agent was used as a treatment for the acute rejection that occurred; therefore, they are considered high risk.

For 20 years, there has been a grade A recommendation for the prophylaxis of CMV in seronegative recipients with a seropositive donor and immunosuppression with a lymphocyte depleting agent, as well as in seropositive recipients who use immunosuppression with a lymphocyte depleting agent regardless of the donor's serostatus.

In cases of a seronegative recipient with a seropositive donor and immunosuppression without lymphocyte depletion, the recommendation is grade B. In the seropositive recipient with immunosuppression without lymphocyte depleting agent, regardless of the donor's serostatus, the recommendation is grade C, and when both donor and recipient have negative serostatus, regardless of the immunosuppression regimen, prophylaxis is not recommended.[12,13] Even so, the serostatus prior to transplantation, the identification of high- or low-risk recipients, and the standardized use of prophylaxis against CMV in high-risk cases are not generally reported in other publications.[9]

Even though a grade C recommendation is considered, in the experience of a center with D+/R+ serostatus in all cases, the universal use of prophylaxis for CMV reduced the incidence of CMV disease by 14.2%.[7]

In the absence of prophylaxis, viral replication appears between the first and the sixth month after transplantation, coinciding with the period of maximum immunosuppression.[8] However, since the publication of the clinical practice guidelines for the prevention of CMV disease 20 years ago, until now,

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the duration of the prophylaxis for CMV has not been standardized (its administration for 1 to 3 months is recommended in some bibliography,[12-14] while in another is already recommended for up to 6 months, especially in high-risk patients).[1,15] In our cases presented, the patients received prophylaxis with valganciclovir 450 mg every 12 hours, one during one month and the other during two months, despite both are considered of high risk. The cause for suspension was the presence of adverse events (leukopenia).

It has been found that the risk of CMV disease persists even after the completion of the prophylaxis. The IMPACT study, conducted with 326 high-risk patients, compared the time of prophylaxis with valganciclovir for 100 vs. for 200 days, finding a decrease in the rate of late disease in the group of 200 days (16 vs. 37%, respectively).[16] In addition, a systematic review that analyzed the benefits and risks of antiviral drugs found that prophylaxis for CMV reduces the risk of herpes simplex disease, herpes zoster, pneumocystosis and bacterial infection, acute rejection and loss of the graft.[8] It is considered that prolonged prophylaxis is a measure to reduce the infection rate.[16] Therefore, extended prophylaxis in high-risk patients, with an emphasis on risk-benefit and cost-benefit, is a topic of high impact to be included in clinical trials and clinical practice guidelines. Despite being very common the report of adverse events, most of them are mild and without major repercussion (91%), especially gastrointestinal (diarrhea). Regarding the hematological effects (mainly leukopenia), although they occurred more frequently in patients receiving extended prophylaxis (38 vs. 26%), the average leukocyte count, the incidence of febrile neutropenia, agranulocytosis, anemia , thrombocytopenia and pancytopenia were similar in standard (100 days) and extended (200 days) prophylaxis, as well as the requirement of granulocyte colony stimulating factor (14 vs. 13% respectively).[16]

The adjustment of the dosage of valganciclovir is recommended depending on the renal function (estimated with the Cockroft-Gault or MDRD formulas), as it follows: eGFR >60ml/min = 900 mg/day, 40-59 ml/min = 450 mg/day, 25-39 ml/min = 450 mg every 48 hours, 10-24ml/min = 450 mg twice a week, its use is not recommended in case of eGFR <10ml/min.[15]

Another controversial aspect lies in the adjustment of immunosuppression once the CMV has been documented. In addition to the specific treatment with intravenous ganciclovir or oral valganciclovir, some authors recommend reducing or discontinuing the antimetabolite (mycophenolate or azathioprine), under the concept that the infection is a manifestation of excessive immunosuppression (recommendation grade 2D).[13] However, there is another theory that proposes an increase in the dose of immunosuppressants in patients with CMV disease, since the infectious process is related to an increased risk of graft rejection.[2] In the cases presented, the dose of mycophenolate of case 1 was decreased and that of case 2 was increased. Both cases had a favorable evolution; however, more evidence is required to issue a strong recommendation on the adjustment of the immunosuppression.

Conclusion

CMV infection is a latent risk in kidney transplant recipients. We emphasize the need to identify the risk factors for CMV infection in kidney transplant recipients, especially the donor/recipient serostatus and the immunosuppressive drugs. It is proposed that future clinical trials include extended prophylaxis in high-risk cases, as well as immunosuppression adjustment once the CMV infection is detected.

Conflict of interest

There is no conflict of interest on the part of the authors.

Ethical responsibilities

Protection of people and animals

The authors declare that no experiments were performed on human beings or animals for this research.

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Right of privacy and informed consent

The authors declare that patient data do not appear in this article.

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Contribution of the authors

Claudia Alejandra Aceves Quintero: Collection of data from files, search for articles and writing of the work.

Juan Carlos Corona Meléndez: Search for articles and writing of the work.

Gonzalo Agustín García y Otero: Search for articles and writing of the work

Marco Antonio Amaya Carreño: Collection of data from files and endoscopic and histopathological images.

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