The importance of the histological and immunohistochemical evaluation for diagnosis of serious cytomegalovirus disease without detectable viral load☆

La importancia del estudio histológico e inmunohistoquímico en el diagnóstico de la enfermedad grave por citomegalovirus con carga viral indetectable

Dear Editor,

Gastrointestinal disease by cytomegalovirus (CMV) is increasingly common in transplant patients. To a large extent this is due to the introduction of purine inhibitors in recent years,[1] which may occur at any time during the follow up. Severe invasive CMV disease is not frequent since the instauration of early prevention and specific treatment strategies.[2] Severe invasive CMV disease is defined as the presence of viral syndrome with CMV replication in blood and/or presence of the virus in the affected organ.[3]

In most cases, clinical suspicion of the disease is confirmed by the presence of viral replication in blood that is directly related to the presence of the disease.[4,5] The technique used years ago was the determination of antigenaemia, which is an indirect marker of disseminated infection; now it has been replaced by PCR techniques, which are more sensitive (up to 93%).[5] Those cases in with very low viral load in blood with or without viraemia, and with positive tissue immunohistochemistry, indicates reactivation of the disease in the colon mucosa without systemic translation, so cases of severe CMV disease are not common.[6]

We present the case of a transplant patient treated with mycophenolate mofetil, with severe CMV disease, who had an undetectable viral load by PCR. In this case, the histological and immunohistochemical studies, together with a high clinical suspicion of the disease, led to the diagnosis.

The patient was a 59-year-old man with chronic kidney failure due to IgA nephropathy, with a history of hypertension, hypertensive heart disease, peripheral arteriopathy and posterior/inferior AMI, and with a first cadaveric renal transplant in 2000, with chronic graft nephropathy. He received a second kidney transplant, this time from a living donor, in 2012, requiring boluses of methylprednisolone, thymoglobulin and rituximab for acute antibody-mediated rejection (days +8 and +55 of transplantation), followed by immunosuppressive treatment with prednisone, mycophenolate and tacrolimus. Six months after the transplant, he went to the emergency room for watery diarrhoea during the last 13 days, without blood or mucous, with abdominal pain, fever and severe asthenia. Leukopenia (WBCs 2700/mm^3), thrombocytopenia (platelets 89,000/mm^3), elevated transaminases (AST 653, ALT 494 and GGT 1924 U/l) and impaired kidney function (Cr: 4 mg/dl). Stool culture and toxin were negative. The dose of mycophenolate was reduced with no improvement in symptoms, so PCR for CMV was requested which was negative (serum IgM levels: 0.12; negative). In view of the strong clinical suspicion, an endoscopy was performed, in which infectious colitis was observed in the rectum. Microscopic examination provided a clear diagnosis with the presence of large cells observed with eosinophilic cytoplasm, the presence of intranuclear inclusion bodies, and immunohistochemical staining was positive for CMV. Then, treatment with intravenous ganciclovir was initiated, the symptoms disappeared and the lab test parameters improved, with recovery of basal kidney function.

We believe it is important to maintain a high level of suspicion during post-transplant follow up and to keep in mind that the absence of viral replication in plasma does not rule out the diagnosis of disease.[7] In these cases, it is necessary to perform endoscopy to identify the CMV in tissue by immunohistochemistry that has a high diagnostic yield.

REFERENCES

1. Ter Meulen CG, Wetzels JF, 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.
2. Torres-Madriz G, Boucher HW. Immunocompromised hosts: perspectives in the treatment and prophylaxis of

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cytomegalovirus disease in solid-organ transplant recipients. Clin Infect Dis. 2008;47:702–11.
3. Ljungman P, Griffiths P, Paya C. Definitions of cytomegalovirus infection and disease in transplant recipients. Clin Infect Dis. 2002;34:1094–7.
4. Tong CY, Cuevas LE, Williams H, Bakran A. Prediction and diagnosis of cytomegalovirus disease in renal transplant recipients using qualitative and quantitative polymerase chain reaction. Transplantation. 2000;69:985–91.
5. Franco A, Serrano R, Gimeno A, de Juan J, Merino E, Jiménez del Cerro L, et al. Estudio de carga viral y antigenemia como valores predictivos de recidiva de infección de CMV en el trasplante renal. Nefrologia. 2007;27:202–8.
6. Roncero García-Escribano O, Legaz Huidobro M, Bernardos E, Sánchez Manajavacas N. Reactivación de CMV: ¿dónde está el límite del diagnóstico? Enfermedad inflamatoria intestinal al día. 2012;11:118–24.
7. Franco-Esteve A, Tordera-Fuentes D, Balibrea-Lara N, Merino E, del Pozo C, Olivares J. Enfermedad tardía gastrointestinal por citomegalovirus con carga viral indetectable, un nuevo reto en trasplante renal. NefroPlus. 2013;5:15–8.

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Hidden renal disease in the elderly is no longer buried after 10 years of follow up☆

Enfermedad renal «oculta» en ancianos: ¿deja de ocultarse a los 10 años de seguimiento?

Dear Editor,

Occult renal disease (ORD) is defined as the presence of a glomerular filtration rate <60 ml/min, along with normal serum creatinine levels. Only few studies have been aimed to understand what is the long term outcome of patients diagnosed with ORD. Here we report our 5-year follow-up results, concluding that the serum creatinine levels remained normal with reduced glomerular filtration rate (<60 ml/min/1.73 m^2), with no significant variations as compared with baseline.[1] In this letter we analyse the results of long-term follow-up.

In the study "Elderly People with Chronic Kidney Disease at Hospital General de Segovia", which included 80 elderly patients recruited between January and April 2006. In 38 patients the serum creatinine levels was normal (≤1.1 mg/dl).[2] Those patients diagnosed with ORD were followed during a 10 year period.

Eighteen out of the 80 patients (22.5%), had ORD, they all were women and the mean age was 81.33 ± 6 years. Diabetics were 33.3% and 83.3%had hypertension. Twelve of these 18 patients with ORD died during follow-up. The remaining 6 patients had a mean age of 87.33 ± 6 years at 10 years. They also had no episodes of heart failure or ischaemic heart disease during the course of the study. None of the 18 patients progressed from kidney disease to end-stage kidney disease, so did not require renal replacement therapy.

Baseline and 10-year laboratory test data are shown in Table 1.

We consider that 10-year follow-up period is sufficient for kidney disease to manifest clinical signs; our elderly female patients who are still alive continue to present with the same characteristics as those at baseline, i.e., a glomerular filtration rate <60 ml/min/1.73 m^2, stable, as the *only renal manifestation*,

Table 1 – Data at baseline and after 10 years of follow-up of 6 patients diagnosed with occult renal disease who are still alive.

	Baseline	Ten years	*p* value
Creatinine (mg/dl)	1.01 ± 0.04	1.01 ± 0.23	NS
Glucose (mg/dl)	129.00 ± 34	129.40 ± 52	NS
Potassium (mmol/l)	4.18 ± 0.38	4.86 ± 0.60	0.018
Calcium (mg/dl)	9.56 ± 0.42	9.30 ± 0.77	NS
Haematocrit (%)	40.30 ± 4	39.13 ± 6	NS
MDRD (ml/min/1.73 m^2)	56.01 ± 2	58.12 ± 17	NS

NS: not significant.

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