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Multicentric Castleman's disease in kidney transplant: A case report and literature review

Enfermedad de castleman multicéntrica en el trasplante renal: reporte de un caso y revisión de la literatura

Dear Editor,

A 58-year-old man with end-stage renal disease (ESRD) secondary to an IgA nephropathy received his first deceased-donor kidney transplant in 2005 and a second one in 2009. Induction immunosuppression consisted of thymoglobulin, mycophenolate, tacrolimus, and corticosteroid. Maintenance immunosuppression consisted of tacrolimus, mycophenolate, and prednisone, with a late switch from mycophenolate to everolimus due to viral infections.

In September 2018, he attended the Emergency Department presenting fever and hypotension, physical examination was normal with no evidence of lymphadenopathy. The serum creatinine was 1.9 mg/dl (baseline 1.4 mg/dl). The hemogram revealed a high white blood cell count of $10.7 \times 10^3/\mu\text{l}$, with $1.97 \times 10^3/\mu\text{l}$ lymphocytes, and hemoglobin of 13.9 g/dl.

Due to the suspicion of urinary sepsis, cultures (urine and blood) were taken, and he was treated with antibiotics. Despite the use of an appropriate antibiotic, the patient persisted with fever, therefore we decided to request a FDG-PET/CT and polymerase chain reaction (PCR) for various viruses. PCR for CMV, BK, HSV-1, HSV-2, and HV-6 were negatives, while PCR for herpes virus-8 (HV-8) was positive. The result of FDG-PET/CT was the presence of multiple hypermetabolic lymph nodes at both sides of the diaphragm. With the suspicion of a lymphoproliferative syndrome, we reduced immunosuppressive

therapy to prednisone and 2 monthly doses of intravenous (IV) immunoglobulins. The histological examination of a lymph node (Figs. 1 and 2) revealed the presence of multicentric Castleman disease (CD) with positivity for HV-8 and after that, the patient was evaluated by the Hematology team. They decided to treat according to the following regimen: valganci-

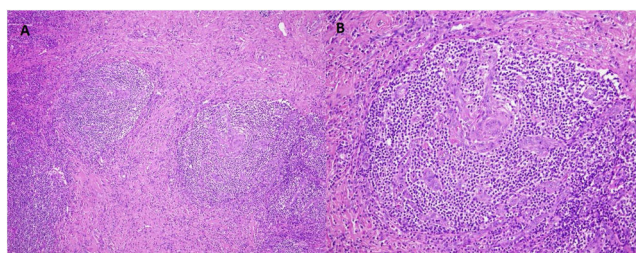


Fig. 1 – (A) Multicentric Castleman's disease. Follicles with lymphocytes arranged in concentric layers ("onion-skinning"). H/E 10 \times . (B) Atretic follicular centers with sclerotic blood vessels that radially penetrate the germinal centers, forming hyaline vascular lesions ("lollipop lesions"). H/E 20 \times .

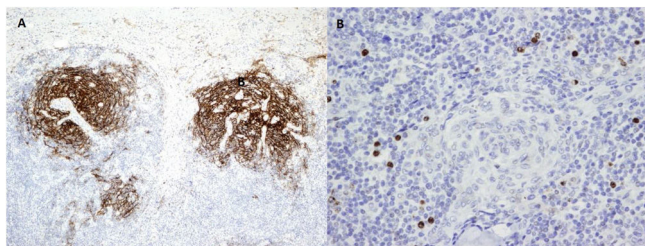


Fig. 2 – (A) Expanded concentric meshworks of follicular dendritic cells. CD21 immunostaining, 10x. (B) Immunostaining for herpesvirus 8, 40x.

clovir for 3 months and four doses of rituximab (4 doses for a month, with a total accumulated dose of 2.8 g).

At present, the patient has no signs of Hematological activity, and renal function keeps stable (mean serum creatinine 1.5 mg/dl) without proteinuria. Because of the reduction of immunosuppressive therapy, he developed transient de novo class I donor-specific antibodies. However, he did not exhibit other signs of rejection. Current immunosuppression consists of everolimus, prednisone, and monthly IV immunoglobulins (20 g).

Discussion

CD is an uncommon lymphoproliferative disorder that is divided into unicentric or multicentric. It is a condition related to states of immunosuppression, mainly HIV and other viruses such as HV-8.

Although the pathophysiology is not completely understood, one possible explanation involves the proliferation of B lymphocytes that are influenced by levels of interleukin 6 (IL-6) and other molecules. In CD IL-6 increases in a great amount with the consequent proliferation of B-lymphocytes and secretion of immunoglobulin G. In the same way, VEGF (vascular endothelial growth factor) could be secreted in response to IL-6¹, and in turn, VEGF would contribute to the production of IL-6 by endothelial cells².

In the literature, only ten cases of CD related to solid organ transplantation (SOT) have been reported until now. Six of them were related to kidney transplantation³. In our center, from 1950 to 2020 we have had 24 cases, and only one (the present case) related to a kidney transplant.

Treatment strategies in CD include dose adjustments of immunosuppressive agents. Moreover, higher doses of corticosteroids could reduce lymphocyte proliferation, while a switch from calcineurin inhibitors to sirolimus may promote remissions⁴, this could be related to lower levels of VEGF and to a lesser viral replication of HV-8⁵. Secondly, patients with an active HV-8 infection should be treated with antivirals⁶. Additionally, HIV patients should receive antiretroviral treatment. Thirdly, rituximab is the treatment of choice in MCD associated with HV-8 infection. Since the introduction of this drug, survival has dramatically improved from 42% to 94% at two years⁷. Anti-interleukin-6 receptor monoclonal blockade with tocilizumab could be another option, it is especially

interesting because of its potential role in preventing graft rejection⁸.

In our case, we stopped tacrolimus and we maintained everolimus. As a part of our protocol of reduced IS we also used intravenous pulses of immunoglobulins every month because of its demonstrated antiviral effect on some herpesvirus⁹ while the patient was treated by the Hematology Department.

We think that the development of de novo DSA could be related to the decrease in IS, and their subsequent decrease could be explained in part by the addition of Rituximab. Comparatively, with the 6 previously reported cases of CD in kidney transplantation, 3 patients died, 1 lost the graft, and 2 survived. Only one of the survivors received chemotherapy (cyclophosphamide, vincristine, doxorubicin, and prednisone), and the other survivor was treated with radiotherapy and a regimen of less intense IS. The other four patients did not receive any special treatment or just a decrease in IS³.

In conclusion, CD is a very uncommon disease, especially in kidney transplant patients. We report the first case of kidney transplant with CD treated with Rituximab, which has proved to be a safe and effective therapy for CD and graft survival.

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Síndrome de encefalopatía posterior reversible en el transcurso de fuga pleuroperitoneal masiva en una paciente en diálisis peritoneal

Reversible posterior encephalopathy syndrome in the course of massive pleuroperitoneal leakage in a patient on peritoneal dialysis

Sr. Director:

La fuga pleuroperitoneal (FP) es una complicación infrecuente en diálisis peritoneal (DP), con una incidencia estimada menor del 2%¹⁻³, siendo causa de una alta tasa de abandono de la técnica³.

Hay múltiples factores predisponentes incluyendo la hipotonía muscular diafragmática, defectos diafragmáticos congénitos, gradientes de presión pleuroperitoneal aumentados como puede ocurrir en la enfermedad poliquística renal y alteraciones del drenaje linfático^{1,4}.

Clínicamente la FP se manifiesta como disnea de aparición más o menos súbita, pérdida de ultrafiltración y derrame pleural³, pero no hay casos descritos previamente cuyo motivo de consulta haya sido un episodio convulsivo por síndrome de encefalopatía posterior reversible (SEPR) al realizarse la técnica de DP y existir FP masiva.

Presentamos el caso clínico de una mujer de 24 años con insuficiencia renal crónica por nefropatía mesangial IgA en diálisis peritoneal ambulatoria continua desde hacía un mes, que es trasladada a urgencias debido a cefalea intensa y visión borrosa con posterior pérdida de conocimiento y movimientos tónico-clónicos generalizados mientras estaba realizando un recambio de DP. Como otros antecedentes existía una obesidad con IMC de 32 e hipertensión arterial controlada con enalapril y furosemida. Posteriormente sufre 2 episodios convulsivos más y se constatan cifras de tensión arterial (TA) de 260/112 mmHg y saturación de O₂ del 87%. La anamnesis con la familia reportó la existencia de una disminución de los balances de drenaje peritoneal y dolor costal derecho desde hacía unos 2-3 días, constatando ya un peor control de la TA con cifras de 165/100 mmHg. Se le administra inicial-

mente oxigenoterapia, labetalol, clonazepam y levetiracetam endovenosos con disminución progresiva de las cifras tensionales. Las pruebas complementarias muestran una radiografía de tórax con derrame pleural derecho masivo (fig. 1), análisis con iones correctos, TC craneal normal, punción lumbar sin evidencia de infección y fondo de ojo con mácula preservada en ambos ojos sin exudados ni hemorragias sugestivas de retinopatía hipertensiva. El estudio de líquido pleural es compatible con un trasudado con cifras de glucosa superiores a la glucemia plasmática. Con la orientación diagnóstica de fuga pleuroperitoneal masiva derecha y ante la gravedad de la clínica, se coloca un catéter yugular derecho y se inicia hemodiálisis con ultrafiltración progresiva, observando recu-

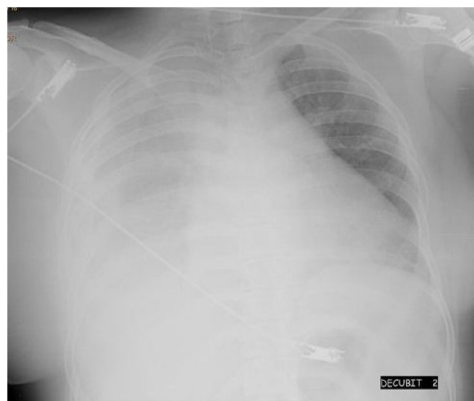


Figura 1 – Derrame pleural derecho masivo.