Conflicto de intereses

Los autores declaran no tener ningún conflicto de intereses.

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Diagnostic challenge of recurrent macrophage activation syndrome before and after kidney transplant

Desafío diagnóstico en un síndrome de Activación Macrofágica recurrente, antes y después del transplante renal

Dear Editor,

Hemophagocytic lymphohistiocytosis (HLH) is a rare, life-threatening condition, secondary to an overwhelming inflammatory process. When associated to rheumatic disorders, it can be called as macrophage activation syndrome.[1] The main manifestations are unremitting fever, cytopenias, hepatosplenomegaly and multisystem organ failure. Unfortunately, there is no pathognomonic test, making the diagnosis hard to reach.[2] It can be triggered by infection, malignancy, auto-inflammatory disease and immunosuppression associated with solid organ transplantation. Kidney transplant recipients are, particularly, at risk, and in most cases, infection is the identified trigger.[3]

We present a case of a 42-year-old woman with long standing Systemic lupus erythematosus (SLE) and stage 4 chronic kidney disease (CKD), that following a cholecystitis complicated with cholangitis plus pancreatitis, presented with persistent fever accompanied by refractory anemia, despite laparoscopic cholecystectomy and combined large spectrum antibiotics having been performed. Concomitantly, her renal function declined, requiring hemodialysis initiation. During this period, she was under erythropoietin 30,000 U per week and she received a total of 6 red cell units.

Laboratory investigation showed thrombocytopenia, anemia, with low reticulocyte production index, high lactate dehydrogenase, but normal haptoglobin. Folate and vitamin B12 were normal. Iron kinetics revealed low serum iron, normal transferrin saturation and an extremely high ferritin. Other inflammatory markers as leucocytes, C-reactive protein and procalcitonin were markedly elevated. She evolved with hepatic cytolysis and cholestasis, with normal bilirubin levels, normal lipase and slightly high amylase (104 U/L). Lipid profile showed hypertriglyceridemia. Imaging studies exhibited hepatosplenomegaly and excluded biliary obstruction. No coagulopathy was found.

In the presence of bicytopenia, extremely high ferritin, increased liver enzymes, hypertriglyceridemia and hepatosplenomegaly, MAS was suspected. Bone marrow biopsy was not contributive for the diagnosis, and it was found an increase of serum soluble IL-2 receptor α (sIL-2Rα). After almost two weeks the diagnosis of MAS was made.

As there was strong data indicating a bacterial infectious process ongoing, it was assumed that was the

Table 1 – Evolution of analytical parameters.

Analytical parameters	Ambulatory	1st MAS	Discharge	2nd MAS	Discharge
Leuc/Neut (/μL)	3560/2240	12,690/10,360	4600/3740	4340/2190	7530/4840
Hb (mg/dL)	11.2	7,8	11,2	7.8	14.3
Platelets (/μL)	207,000	61,000	165,000	35,000	162,000
Creatinine/urea (mg/dL)	3.32/140	*Under HD*	*Under HD*	1.82/60	1.52/90
LDH (U/L)	273	784	300	488	220
Sat (%)/ferritin (ng/mL)	34/519	36/10,486	20/226	42/1119	–/938
RPC (mg/L)/PC (ng/mL)	-	354.5/25.1	4.49	81.4/0.296	2.98/-
AST/ALT (U/L)	23/17	393/55	41/70	41/49	23/32
AP/GGT (U/L)	63/12	448/155	212/153	212/217	146/258
CT/TG (mg/dL)	163/143	90/375	160/114	151/413	158/412
C3/C4 (mg/dL)	64.7/15.8	83.3/5.4	71.8/11.9	88.9/7.4	-
Anti-dsDNA (UI/mL)	32	24	61	54	-

Leuc – leucocytes; Neut – neutrophils; Hb – hemoglobin; HD – hemodialysis; LDH – lactate dehydrogenase; Sat – transferrin saturation; RPC – reactive protein C; PC – prolcalcitonine; AST – aspartate aminotransferase; ALT – alanine aminotransferase; AP – alkaline phosphatase; GGT – gamma-glutamyl transpeptidase; CT – cholesterol; TG – triglycerides.

Table 2 – Different types of HLH classification criteria.

	HLH 2004[7]	HScore 2014[9]	EULAR/ACR/PRINTO 2016[10]
Study population	Primary HLH	Secondary HLH in adults	MAS in the setting of sJIA
Diagnostic criteria			
Fever (°C)	(+)	0: <38.4; 33: 38.4–39.4; 49: >39.4.	(+)
Hepatosplenomegaly	(+) if splenomegaly	0: None 23: One present 38: Both	N.A.
Immunosuppression drugs and/or HIV	N.A.	0: No 18: Yes	N.A.
Ferritin (ng/mL)	≥500	0: <2000; 35: 2000–6000; 50: >6000.	>684
Cytopenia	(+) if 2 out of 3: Hb <90 g/L; Platelets <100 × 10^9/L Neutrophils <1 × 10^9/L	0: 1 lineage; 24: 2 lineages; 34: 3 lineages. Hb ≤9.2 mg/dL; Platelets ≤110,000/μL Neutrophils ≤5000/μL	(+) if Platelets <181 × 10^9/L
Hypertriglyceridaemia (mg/dL) and/or Hypofibrinogenemia (mg/dL)	(+) either if Triglycerides ≥ 265 Fibrinogen ≤ 150	Triglycerides 0: <132; 44: 132–353; 64: >353. Fibrinogen 0: >250; 30: ≤250.	(+) for each Triglycerides >156 Fibrinogen ≤ 360
AST (U/L)	N.A.	0: <30; 19: ≥30	(+) if >48
Soluble CD25 (U/mL)	(+) if ≥2400	N.A.	N.A.
Low or absent NK cell activity	(+)	N.A.	N.A.
Hemophaocytosis in bone marrow, spleen or lymph nodes	(+)	0: No; 35: If present in bone marrow	N.A.

Table 2 (Continued)

	HLH 2004[7]	HScore 2014[9]	EULAR/ACR/PRINTO 2016[10]
Fulfillment of criteria	≥5 of the 8 clinical and laboratory diagnostic criteria	Score gives the probability of having HLH (best cut-off value: score 169)	Fever + Ferritin >684 ng/mL plus two other diagnostic criteria
Patient scores			
Before kidney transplant	(6) out of (8)	Score of 246	Fever + Hyperferritin + (3)
After kidney transplant	(5) out of (8)	Score of 206	Fever + Hyperferritin + (3)

AST – aspartate aminotransferase; Hb – hemoglobin; HIV – human immunodeficiency virus; HLH – hemophagocytic lymphohistiocytosis; NK – natural killer.

trigger. Immunosuppression was withdrawn and antibiotics were maintained, although no agent was identified. Intravenous human immunoglobulin (IVIg) of 20 g (500 mg/kg) was administered for three days. She became apyretic and almost all analytical parameters improved (Table 1). However, she remained dependent on dialysis at discharge.

During hemodialysis, no significant medical episodes were registered, and patient's hemoglobin levels were within the target, between 10 and 12 g/dL, with an average of 100 U/kg/week of erythropoietin.

Sixteen months after dialysis start, a living-donor kidney transplant from her brother was performed, and five days after, in the setting of a respiratory infection, she developed *de novo* persistent fever, bicytopenia, high ferritin, elevated DHL, hepatic cytolysis, cholestasis, hepatosplenomegaly and hypertriglyceridemia. This time sIL-2Rα was not above the cut-off, but still there were enough criteria for the diagnosis of recurrent MAS. Besides antibiotics and IVIg, corticosteroids dose was increased, tacrolimus maintained, and mycophenolate was withdrawn. Again, no microbiologic agent was identified, after an extended investigation, including bacterial cultures, large panel of virus and mycobacterium tuberculosis. Clinical and analytical improvement was rapidly registered (Table 1).

MAS has been associated to SLE since 1991, when it was first described by Wong et al.[4] The reason why this association occurs is yet to be explained. The challenge is that signs and symptoms as fever, cytopenia and splenomegaly, present in MAS, can easily be part of a SLE flare-up.

Due to HLH diagnostic complexity, different classifications have been proposed. Table 2 summarizes its characteristics. In each episode, our patient met the criteria in all classifications.

Infections and immunosuppression are frequent reported triggers.[3] Both conditions can be present in the context of a solid organ transplantation, as the kidney. To date, HLH has been reported in less than a hundred kidney transplant patients, representing a rare complication.[2]

Most cases reported were triggered by all-kind infections, viral in its majority.[2] More rarely, it can occur in the setting of neoplasms, and there are also some reports associated to allograft rejection.[5]

Although the best protocol is yet to be established, treatment of HLH should be oriented to the underlying disease and associated trigger. In order to diminish the hyperinflammatory process, high dose of steroids are usually indicated.[6] In the setting of kidney transplant, besides steroids, and given the role of cyclosporine described in HLH-2004,[7] calcineurin inhibitors should be maintained, and the antimetabolite suspended.[2,5] The use of IVIg can be also beneficial and should be considered, especially if rejection is suspected.[6,8]

In conclusion, HLH is a rare condition and kidney transplants are at risk due to the immunosuppression regimens and susceptibility to infections. A high level of suspicion leads to early recognition and prompt treatment, which can be decisive for patient's prognosis. Due to its rarity, no strong evidence is available to guide therapy and for that reason we should consider each case individually.

Conflicts of interest

The authors have no conflicts of interest to declare.

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Pérdida de visión aguda en hemodiálisis: arterioesclerosis de Mönckeberg

Acute vision loss on hemodialysis: Mönckeberg arteriosclerosis

Sr. Director:

A propósito del artículo publicado en la revista de Nefrología «Pérdida aguda de visión en pacientes con insuficiencia renal»[1], y teniendo en cuenta la escasez de casos publicados en la bibliografía, proponemos la presentación del siguiente caso de amaurosis en paciente en programa de hemodiálisis.

Presentamos el caso de una mujer de 73 años con antecedentes personales de alergia al contraste yodado, leucemia mieloide crónica, diabetes mellitus tipo II insulinodependiente, enfermedad renal crónica sin control histológico en programa de hemodiálisis desde 2018, con mala tolerancia a dichas sesiones (hipotensión), hiperparatiroidismo secundario a ERC y glaucoma.

Durante una sesión de hemodiálisis y coincidiendo con episodio de hipotensión severa la paciente comienza un cuadro cefalea holocraneal que se acompaña de pérdida de visión aguda en el ojo izquierdo. Se realizó TAC craneal sin contraste IV, en el que no se apreciaron hallazgos de interés. Fue valorada por oftalmología observando en el fondo de ojo «edema de papila bilateral con papilitis hemorrágica retiniana como consecuencia de infarto de retina izquierda» fue dada de alta con revisión en consulta de oftalmología.

Tras 3 semanas presenta mismo cuadro en el ojo derecho refiriendo un déficit altitudinal con progresión hasta amaurosis total. Valorada por neurología, se realizó una ecografía-doppler de troncos supraaórticos sin hallazgos de interés y realización de biopsia de arteria temporal, se iniciaron 3 bolos de 500 mg de metilprednisolona ante la sospecha de poder estar sufriendo una arteritis de la temporal.

Analítica

- Reactantes de fase aguda: PCR y VSG en rango de normalidad
- Calcio sérico corregido con proteínas totales (media): 10,5 mg/dl
- Fósforo sérico (media): 5-6 mg/dl
- PTH i sérica: 850 pg/ml

Biopsia arterial temporal

No se aprecian signos inflamatorios, depósitos de calcio en la lámina media de la arteria temporal (figs. 1 y 2).

Ante estos hallazgos fue diagnosticada de arteriopatía de Mönckeberg, finalmente la paciente no recuperó la visión.

La arterioesclerosis de Mönckeberg o esclerosis de la media de Mönckeberg, fue descrita por primera vez en 1903 por Johann Georg Mönckeberg, como una calcificación de la túnica media de las arterias musculares medianas y pequeñas de las extremidades inferiores y con menor frecuencia, en las arterias viscerales o coronarias[2,3]. Es la calcificación que se ha asociado de forma habitual con la enfermedad renal.

Etiopatogénicamente es una entidad de origen desconocido[4].

Está relacionada principalmente con la edad, la diabetes, el tiempo en diálisis y el metabolismo mineral. Provoca rigidez de la pared arterial y, con ello, aumento de la presión arterial sistólica y aumento de la presión del pulso y de la velocidad de la onda de pulso. Contribuye al desarrollo de hipertrofia ventricular izquierda, fibrosis, disfunción ventricular, disminución del riego coronario durante la diástole e insuficiencia cardiaca.