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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 trasplante 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-2R α). After almost two weeks the diagnosis of MAS was made.

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 – prolactin; 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
<i>Study population</i>	Primary HLH	Secondary HLH in adults	MAS in the setting of sJIA
<i>Diagnostic criteria</i>			
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 Hemophagocytosis in bone marrow, spleen or lymph nodes	(+) (+)	N.A. 0: No; 35: If present in bone marrow	N.A. N.A.

Table 2 (Continued)

	HLH 2004 ⁷	HScore 2014 ⁹	EULAR/ACR/PRINTO 2016 ¹⁰
<i>Fulfillment of criteria</i>	≥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
<i>Patient scores</i>			
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.

As there was strong data indicating a bacterial infectious process ongoing, it was assumed that was the 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 afebrile 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-2R α 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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Acute vision loss on hemodialysis: Mönckeberg arteriosclerosis

Pérdida de visión aguda en hemodiálisis: arterioesclerosis de Mönckeberg

Dear Editor,

Regarding the article published in the journal NEFROLOGÍA ["Acute vision loss in patients with kidney failure",¹ and taking into account the scarcity of cases published in the bibliography, we propose the presentation of the following case of amaurosis in a patient on regular haemodialysis.

We present the case of a 73-year-old woman with a medical history of allergy to iodinated contrast, chronic myeloid leukaemia, insulin-dependent type II diabetes mellitus and chronic kidney disease without histological assessment, on haemodialysis since 2018, with poor tolerance to haemodialysis sessions (hypotension), secondary hyperparathyroidism and glaucoma.

During a haemodialysis session and coinciding with an episode of severe hypotension, the patient had onset of holocranial headache accompanied by acute loss of vision of the left eye. Cranial CT without IV contrast was performed with no findings of interest. She was assessed by Ophthalmology and examination of the eye fundi revealed "bilateral papilloedema with retinal haemorrhagic papillitis as a consequence of left retinal infarction" and she was discharged with a follow-up by the ophthalmology unit.

After three weeks, she presented with the same clinical picture in the right eye, reporting an altitudinal loss with progression to total amaurosis. Assessed by Neurology, a Doppler

ultrasound of the supra-aortic trunks was performed without findings of interest and a temporal artery biopsy was performed, three boluses of 500 mg of methylprednisolone were started due to the suspicion that the patient might be suffering from temporal arteritis.

Laboratory testing

- Acute phase reactants: CRP and ESR in normal range
- Total protein corrected serum calcium (mean): 10.5 mg/dl
- Serum phosphorus (mean): 5–6 (mg/dl)
- i-PTH serum: 850 pg/mL

Temporal artery biopsy

No signs of inflammation. There were calcium deposits in the middle layer of the temporal artery (Figs. 1 and 2).

Given these findings, she was diagnosed with Mönckeberg's arteriopathy, and finally the patient did not regain her vision.

Mönckeberg's arteriosclerosis, or Mönckeberg's medial sclerosis, was described for the first time in 1903 by Johann Georg Mönckeberg, as a calcification of the tunica media of the medium and small muscular arteries of the lower extremities and, less frequently, in the visceral or coronary arteries.^{2,3} It is the calcification that has been commonly associated with kidney disease.

The aetiology of this condition is unknown.⁴

It is mainly related to age, diabetes, time on dialysis, and mineral metabolism. It causes stiffness of the arterial wall and, with it, an increase in systolic blood pressure as well as an increase in pulse pressure and pulse wave velocity. It

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