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Cytomegalovirus-associated haemophagocytic syndrome in a kidney transplant patient

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To the Editor,

Haemophagocytic syndrome is a rare clinical condition characterised by a generalised, benign proliferation of histiocytes with significant haemophagocytic activity.¹⁻³ The aetiology of these symptoms can be separated into two groups: primary or genetically determined, or secondary: virus, bacteria, fungus, parasites, neoplasia, collagen, immunodeficiency or drugs.¹⁻⁷ Clinical symptoms include fever, hepatosplenomegaly, lymphadenomegaly, neurological symptoms, oedema and rashes.^{1,2,8,9} The most important laboratory findings are: pancytopenia, hypertriglyceridaemia, hypofibrinogenaemia, hyponatraemia, hypoproteinaemia, increased levels of hepatic enzymes, increased amount of LDH and ferritin, pleocytosis in LCR and defective activity of natural killer (NK) cells.¹⁰ The histological analysis found haemophagocytosis in the bone marrow, spleen and lymph nodes. There were no malignant findings and diagnosis was possible with 2% of haemophagocytic cells.¹⁻³ Haemophagocytic syndrome has a poor prognosis despite treatment, with an average survival of 2 weeks after the onset of the clinical symptoms. Survival can reach 60% at 5 years if there is an adequate response to treatment.^{11,12} Agents that interrupt histiocyte function and macrophage activation are therapeutic alternatives, such as etoposide, steroids, high-dose i.v. Ig, cyclosporine A, anti-thymocyte globulin, anti-TNF antibodies, and in some cases, bone marrow transplant.^{13,14}

We present the case of a 53-year-old man, subjected to kidney transplant, who came to the emergency department with fever, temperature

38.5°C over a 24-hour period, with shivers, mild diffuse abdominal pain, asthenia, anorexia, and a decrease in diuresis volume. The physical examination was normal and no important pathology was found from the tests performed at the emergency department: normal X-ray; normal blood and urine tests; negative blood and urine cultures; negative cytomegalovirus (CMV) early-antigen (at that time, CMV polymerase chain reaction (PCR) assays were not available in our hospital). The symptoms worsened, abdominal pain increased, and on the CT scan we observed dilated small bowel loops due possibly to ischaemia or infection. Given the findings and the worsening clinical symptoms, we performed an exploratory laparotomy, without observing anomalies. A coagulase-negative staphylococcus grew in the peritoneal fluid, which was treated with meropenem at 500mg every 12 hours. Following the intervention, the clinical symptoms improved despite having developed a post-operative paralytic ileus, which improved spontaneously. After a few days, the patient presented with fever again, and diarrhoea. There were initially no traces of blood, but he then presented with melaena, associated with neurological deterioration, hepatosplenomegaly and hepatic function alterations, anaemia and thrombocytopenia. New tests were requested: positive CMV early-antigen; CMV PCR assay above 100 000 copies/ml. Eso-Gastro-Duodenoscopy (EGD): infected oesophagus. Analytical tests showed: GOT/GPT: 135/156IU/l; LDH: 558IU/l; sodium: 130mEq/l, fibrinogen:133mg/dl, haemoglobin: 9.2 g/dl; and haematocrit: 26.8%; platelets: 48 000/ μ l with normal leukocytes (normal formula: 5500/ μ l), significant increase in triglycerides (738mg/dl), progressive deterioration of kidney function (creatinine around 4-5mg/dl). Normal haptoglobin, negative indirect Coombs test. Peripheral blood smear: few schistocytes with no reticulocyte. Bone marrow aspiration: compatible with haemophagocytic syndrome (Figure 1).

Given these findings, the patient was diagnosed with CMV-associated haemophagocytic syndrome. The patient visited infection diseases unit and the following therapeutic regimen was started: anti-CMV with ganciclovir 50mg/12h and non-specific i.v. gamma globulin 30g/48h, and methylprednisolone bolus were indicated for haemophagocytic syndrome. The patient continued to take cyclosporine at low doses (around 50ng/ml). Despite being treated, the patient's general and neurological condition worsened and he was finally admitted to the ICU for saturation, where he died 12 hours after admission due to multiple organ failure. The autopsy showed: disseminated CMV infection, mainly affecting the digestive tract and lung (Figure 2) and reactive haemophagocytic syndrome (Figure 1).

The prevalence of haemophagocytic syndrome in kidney transplant patients is 0.4%,¹¹ which makes it a rare complication in this patient group. Furthermore, the most common aetiology for these patients is that secondary to an infection.¹⁴ These patients have poor prognosis meaning that early diagnosis is essential to enable starting therapy early. There is no consensus on treatment strategies, and several treatments have been proposed, such as steroids and cyclosporine,¹⁴ specific immunoglobulin, treating the aetiological agent, etc.

On the other hand, CMV-associated infections in kidney transplant patients is a common complication, although its incidence and repercussion is decreasing due to the prophylaxis employed.¹⁵ In spite of this, it is a diagnosis that we should take into account when a transplant patient's general condition deteriorates, because the complications for this infectious profile are all serious. Early diagnosis and starting correct therapy greatly improves prognosis.

Haemophagocytic syndrome is a rare complication following kidney

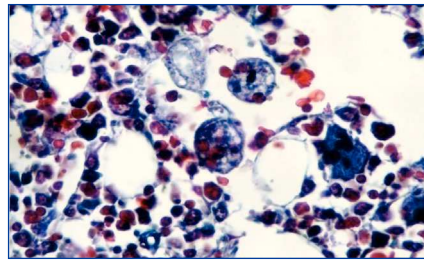


Figure 1. Trichrome staining. Histiocytes with red blood cells indicating haemophagocytic activity in bone marrow.

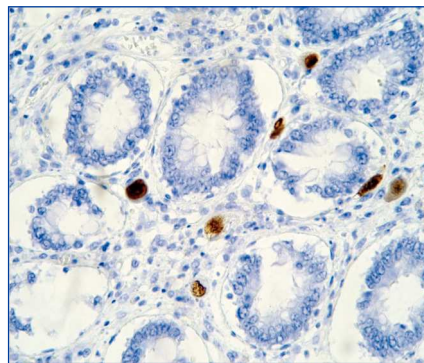


Figure 2. Immunoperoxidase staining. Cells containing CMV in the intestinal tissue.

transplantation. Furthermore, it is a clinical entity that must be considered during the differential diagnosis of these patients, especially if associated with fever, organomegaly and pancytopenia. Bone marrow aspiration allows for a clearer diagnosis, whereas blood test analyses only enable us to make presumptions (pancytopenia, hepatic kidney function alteration, increase in LDH, decreased fibrinogen, increased triglycerides, hyponatraemia, etc). Viral infection is the most common triggering agent for immunosuppressed patients. The problem is that there is still no specific treatment, meaning that transplant patient survival is very low, and if patients were to survive, the kidney graft does not often function correctly.

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al. Virus-associated hemophagocytic syndrome: a benign histiocytic proliferation distinct

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Partial recovery of kidney function for an autologous transplant in a patient with chronic kidney disease and multiple myeloma

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To the Editor,

Multiple myeloma (MM) is a treatable, although incurable disease.¹⁻³ Its prognosis has improved during recent years, with an average survival of 2-3 years, given a therapeutic change with the advent of autologous haematopoietic progenitor cell transplantation (AHPCT) and three new myeloma drugs: thalidomide, lenalidomide and bortezomib,⁴ which have proven to be safe for patients with MM and renal failure.¹

Renal failure is one of the main factors associated with the disease's poor prognosis.² It develops in 25%-30% of cases and 2%-3% of them need dialysis, with an average survival rate of between 4 months to a year.^{3,4} It has a multifactorial origin, although its most frequent cause is the elimination of light chains (Bence-Jones

proteinuria). When it is present in tubules is histologically called "myeloma kidney".¹

We report the case of a 53-year-old patient, diagnosed with MM IgA lambda stage IIB according to the Durie Salmon staging system. He presented with acute renal failure, likely to be secondary to myeloma kidney. He was indicated haemodialysis at diagnosis. He started front line chemotherapy with bortezomib, adriamycin and dexamethasone (PAD combination therapy) prior to AHPCT with melphalan, with excellent clinical tolerance, which allowed him to achieve complete remission (CR). However, he had no kidney response. Eleven months after starting the dialysis programme, the patient presented with an improved glomerular filtration rate (GFR) and was able to stop dialysis treatment definitively 14 months after diagnosis (Table 1).

The degree of renal dysfunction has an impact on MM patients' prognosis, especially in those that need dialysis, reporting lower survival rates, higher short-term mortality (estimated 4 months), greater susceptibility to infections, longer hospital stays and greater compromise to the patient's quality of life. High-dose chemotherapy and AHPCT have traditionally been contraindicated for all of these reasons.⁵ However, the treatment of choice is polychemotherapy in patients under 65 years with a generally good condition. As well as dexamethasone, regimens include vincristine, adriamycin and cyclophosphamide, together with new myelomatosis drugs: thalidomide, lenalidomide and bortezomib, followed by AHPCT,^{5,6} as well as dialysis support when necessary, given that it increases the likelihood of CR for 20%-40% of cases. It has a progression-free survival of 2.5-4 years and a general survival of 4-5 years,⁷⁻⁹ with total or partial GFR recovery in 25%-58%, which entails improved survival.^{4,10}

Tauro et al, and other authors, have reported that patients who receive chemotherapy and AHPCTs can obtain partial kidney function recovery, reducing their dialysis dose and frequency. However, very few patients are able to definitively stop dialysis following treatment. They also describe that the type of paraprotein used (IgA and IgM are associated with a higher risk of progression than IgG), MM evolution time, and renal failure evolution time influence partial kidney function recovery.^{4,10,11}

Badros et al conducted the first prospective study on MM patients undergoing AHPCT. They reported that patients under 70 years old with MM and renal failure including those on dialysis, should be treated with lower chemotherapy doses (melphalan at 140mg instead of 200mg), as it reduces the incidence of adverse effects. They also describe early AHPCT as being a safe treatment, which increases the likelihood of CR, total or partial GFR recovery, and therefore, overall survival. However, results show that 12 months after renal failure, GFR recovery is highly unlikely.⁴

Matsue recently published a study on the possibility of reversing dialysis-dependent renal failure, and its relation to light chains. This study considered high-dose dexamethasone to be the gold standard treatment for patients with MM and renal failure, given its rapid response, and that it should be co-administered with new drugs such as thalidomide and bortezomib, which have proven to be greatly effective at treating MM associated with GFR deterioration. In their study, 67% of patients who had been undergoing dialysis for 2 months stopped dialysis following treatment with dexamethasone and thalidomide. Bortezomib was used successfully as a second-line treatment for 3 dialysis-dependent patients, and did not show any major adverse effects. They also observed a greater survival in those patients who had been undergoing dialysis