

## Hemolytic Uremic Syndrome Due to Sirolimus in a Heart Transplant Recipient. Case Report

### To the Editor,

Hemolytic uremic syndrome (HUS) is characterized by a triad consisting of microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure. The exact pathophysiology is unknown. A number of theories have been proposed, and it is known that not all HUS cases are identical, with considerable heterogeneity in the clinical, analytical, and microscopic findings, since the mechanisms that produce it are heterogeneous.<sup>1</sup> It appears that the basic alteration is vascular endothelial injury with the release of factors that promote platelet aggregation. For example, the association of *Escherichia coli* with HUS is mediated by the production of a cytotoxin with a well-described mechanism of endothelial damage; this is not the case with drug-related HUS.

The most frequent cause among recipients of a solid organ transplant is cyclosporine. The second is an episode of acute graft rejection; this precedes the onset of HUS in 30%-50% of cases.<sup>2</sup>

We describe a 61-year-old man who had undergone heart transplant 13 years earlier and came to the hospital for overall poor condition and fever (38.5°C) with no etiological focus. As a complication of heart transplantation, he had developed

multiple epidermoid carcinomas of the skin, treated with brachytherapy and surgery. Because of continuous recurrence of the tumors, the immunosuppression was modified: cyclosporine was switched to sirolimus, mycophenolate mofetil dose was reduced, and corticoids were maintained. Fifteen days after the switch, the patient came to the hospital. The examination showed poor overall condition with hematomas on the trunk, and a normal cardiologic examination. Analytical results were as follows: creatinine level 5 mg/dL (previously, 2.5 mg/dL), thrombocytopenia at 71 000/ $\mu$ L, anemia with hemoglobin levels of 6.2 g/dL, schistocytes, and positive hemolytic markers (LDH, 650 mg/dL), normal coagulation, sirolimus concentration 10 ng/dL, and mycophenolic acid 2 ng/mL. The echocardiography, electrocardiogram, and chest x-ray were normal. The analytical findings led us to suspect HUS. Based on the absence of a previous infectious condition and any signs of rejection in the endocardial biopsy that could be triggers, and given the recent introduction of sirolimus, the latter was considered the etiological factor, with blood levels within the therapeutic range. Sirolimus was switched to cyclosporine, and mycophenolate mofetil and corticoids were maintained. Various sessions of plasmapheresis and packed red blood cell transfusions were performed. Progress was favorable and the patient remained afebrile, in good overall condition, and with improved kidney function (creatinine 2.6 mg/dL, hemoglobin 8.3 g/dL with disappearance of hemolysis markers, and platelet count of 250 000/ $\mu$ L).

Renal transplant recipients are at significant risk for recurrent HUS. Likewise, its association with cyclosporine is well-documented, and sirolimus has been used as rescue therapy following cyclosporine-induced HUS.<sup>3</sup> However, in recent years there have been reports of HUS cases in renal transplant recipients in relation to sirolimus alone or, even more frequently, to sirolimus plus cyclosporine.<sup>3,4</sup> There is little experience in cardiac transplant recipients, and the published cases are related to cyclosporine or tacrolimus.<sup>2,5</sup>

The diagnosis of a causal relationship between sirolimus and HUS is made by excluding other causes and by observing a proximity in time. In our patient, sirolimus concentrations were within the therapeutic range, as in the other reviewed cases,<sup>3</sup> and therefore, the damage does not appear attributable to overdose.

Sirolimus, a natural macrolide of *Actinomyces*, is an immunosuppressant with a potent antiproliferative effect that appears to decrease the development of secondary tumors,<sup>6</sup> which is the reason we used it in a patient with recurrent skin cancer.

In several published case studies of renal transplant recipients with sirolimus-related HUS, considerable clinical and analytical improvement is described, although without full recovery of kidney function; this is attributed to late diagnosis and treatment.<sup>5</sup> Our patient's kidney function did improve. However, in light of the experience in patients who have received other organs, we consider that the hemolysis markers should be carefully controlled when modifying the immunosuppression therapy, eg, when switching to sirolimus, in order to facilitate early diagnosis and treatment of HUS.

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