The role played by immunoregulatory abnormalities in the development of a malignant plasma cell disorder still remains unclear. In fact, it is difficult to establish whether the immune dysregulation which characterizes multiple myeloma (MM) is a phenomenon that precedes or follows the malignant disease. In the literature, however, a few cases are reported regarding HIV-associated MM. These support the existence of a relationship between HIV-related immunosuppression and the occurrence of MM.1-3 In this connection some recent observations showing that abnormalities in immunoregulation may precede the development of MM are also of interest.4

For this reason we think the description of a case of MM arising in a renal transplant subject after long-term drug related immunosuppression could be informative.

Case report

A 58-year-old man who had suffered since his youth from chronic renal failure due to glomerulonephritis recently came to our attention. His recent medical history revealed that, at age 53, because of progression of chronic renal failure (hypertension, serum creatinine levels > 3 mg/dL) the patient was compelled to undergo hemodialysis. At age 56, because of further worsening of renal function, he received a cadaveric kidney transplant.

Shortly after this therapeutic procedure a combination of immunosuppressive drugs, including oral cyclosporin A (CyA)(14 mg/kg/day), azathioprine (2 mg/kg/day) and prednisone (2 mg/kg/day), was started.

One month after transplant renal function recovered (serum creatinine 1.3 mg/dL) and the CyA dosage was tapered (10 mg/kg/day). Two months later the patient was taken ill with cytomegalovirus interstitial pneumonitis, which lasted several weeks and was cured with appropriate treatment (gancyclovir). At five months post transplant, he developed a gastric ulcer that was treated with conventional drugs. Five months later a persistent asymptomatic increase of serum transaminase levels with normal serum bilirubin concentration was observed.

Since this laboratory finding was not associated with serological detection of anti-HBV or anti-HCV antibodies, it was thought to be related to drug toxicity. For this reason azathioprine administration was stopped, while CyA (10 mg/kg/day) and prednisone (0.2 mg/kg/day) were continued.

Twenty-nine months after transplant the patient began to complain of diffuse bone pain, mainly located in the lumbar spinal column.

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His physicians diagnosed arthritis, but two months later, namely thirty-one months from transplant, the patient was hospitalized because of the persistence of bone pain and the appearance of both pharyngeal and rectal candidosis. On that occasion, a diagnosis of IgG-k multiple myeloma with skeletal localization was formulated on the basis of the results of laboratory, clinical and instrumental investigations, and a first cycle of melphalan (10 mg/day × 4 days) and prednisone (100 mg/day × 4 days) was started.

When the patient was first referred to our outpatient service he showed anemia (Hb = 11 g/dL) and still complained of bone pain. The most significant alterations in blood chemistry parameters were increases in transaminases (ALT = 230 IU/mL, AST = 550 IU/mL), creatinine (2.29 mg/dL) and urea (0.88 g/dL) with normal serum calcium levels; however, immunologic markers for hepatitis were negative. Serum paraprotein evaluation with immunofixation confirmed the IgG-K monoclonal component, while free K-chains were detectable in the urine. A marrow aspirate specimen demonstrated about 46% plasma cells. Interleukin-6 serum concentration (ELISA) was increased (600 pg/mL). Cytogenetic investigations did not show any significant alterations. Phenotypic evaluation of peripheral lymphoid cells showed unremarkable changes in the CD4+ cell count, while an absolute increase of the suppressor T-cells (CD8⁺ = 1.28×10⁹/L) and an inverted CD4⁺/CD8⁺ ratio (0.78) were observed.

Serum IgG-IgM antibodies against Epstein Barr virus (anti-EBV) and cytomegalovirus (anti-CMV) were positive. We were not able to research the EBV-genoma. Because of the rejection risk, no discontinuation of immunosuppressive drugs was decided.

Discussion
This case in our opinion is speculative with regard to a possible relationship between kidney transplantation and the development of myeloma. To our knowledge no instance of true myeloma has been described so far among the several cases of B-lymphoproliferative disorders arising in organ transplant recipients. Only poorly-defined monoclonal or oligoclonal gammapathies have been reported in HBsAg-positive renal transplant patients.²

In the mechanism responsible for development of lymphoproliferative disorders occurring in organ-transplant recipients (mainly of the B lineage), a crucial pathogenic role seems to be played by drug-induced chronic immunosuppression.⁶,⁷,¹⁰ This latter is thought to facilitate Epstein-Barr virus activation or reactivation which, in turn, could lead to uncontrolled lymphoid proliferation,⁶-¹¹ as is also indicated by clinical and experimental studies of plasmacytoma genesis.²,⁵,¹²-¹³ Nevertheless, the increase of some cytokines, such as IL-6 and IL-10, notoriously implicated in the development of B lymphoproliferative disorders, has to be considered as well in the mechanism of the uncontrolled immunosuppression-mediated lymphoproliferation that occurs in certain organ transplant subjects.¹⁴

For this reason some laboratory findings observed in our patient, such as serological positivity for anti-EBV antibodies in association with abnormal IL-6 serum levels, could be of interest. Although to date there has been no evidence that CyA has the capacity to induce an increase in IL-6 serum levels, as instead immunosuppressive agents (OKT3)¹⁴ have a relationship between an immune effect of CyA¹⁵-¹⁷ and increased cellular release of IL-6 could be hypothesized.

In this context the immunological finding observed in our patient of abnormal expansion of suppressor T cells with consequent inversion of the CD4/CD8 ratio (which was greater than expected in primary MM) could be significant.¹⁸,¹⁹

Finally, even though we do not have any information about the immunological laboratory features of this patient prior to kidney transplant, the record of both viral and fungal infections in his medical history after transplant represents clinical confirmation of drug-mediated immunosuppression during that period. In this regard some clinical and experimental data¹-⁴,²⁰ which show the role played by immune dysregulation, however induced, in the development of MM, are of interest.

Thus, it is possible to suppose that a relationship between drug related immune suppression and MM might exist in the patient described here.

Since we decided to continue administration
of immunosuppressive drugs because of the risk of organ rejection, unfortunately we were not able to verify further the relationship between long-term drug-mediated immunosuppression and MM. We believe, however, that reports of additional comparable cases are warranted in order to gain a more precise understanding of what influence, if any, may be exerted by drug-induced chronic immunosuppression in the development of MM in organ-transplant recipients.

References