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Interstitial Pneumonitis caused by Everolimus

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Dear Editor,

mTOR inhibitors are immunosuppressors that block proliferation signal and have a lower nephrotoxic potential. However, a series of adverse reactions have been described, especially with sirolimus,

among which the most outstanding is pneumonitis.

We present the case of a 70 year old man, suffering from hypertension and dyslipidaemia, who received his first kidney transplant from a deceased donor in March 2009, due to chronic kidney disease secondary to chronic pyelonephritis. Immunosuppressive treatment consisted of basiliximab, mycophenolate, everolimus and steroids. The patient presented good evolution, with creatinine on discharge at 1.7 mg/dl.

The patient is admitted 4 months after transplant surgery with a fever over 10 days, cough and dyspnoea. On physical examination poor general condition is noted with chills, tachycardia, bilateral crepitation and oxygen saturation of 93% (arterial blood gas: pH 7.50, pCO₂ 26.8, pO₂ 60, HCO₃ 20.9 mmol/l). The patient also presented non-pruriginous erythematous exanthema on the back and chest, with lip herpes.

Laboratory findings were 3,980 WBC/ μ l (eosinophils 29.3%), haemoglobin 12.1 g/dl, platelets 276,000, creatinine 1.79 mg/dl, plasma sodium 138 mEq/l, plasma potassium 3.9 mE/l, and plasma levels of everolimus of 14 ng/ml. On the chest X-ray a bilateral interstitial pattern was seen and the chest CT showed pulmonary nodules and infiltrates with thickening of the bilateral interstitium (Figures 1 and 2). Antigen studies and cultures of cytomegalovirus (CMV) were negative, as also pneumococcal and *Legionella* antigen studies. A bronchoscopy was performed and signs of chronic bronchopathy were seen with negative BAL and BAS. Empiric treatment with wide spectrum antibiotics and antivirals was begun, without any clinical improvement and with radiological worsening. Therefore, suspecting pneumonitis due to everolimus, we decided to discontinue this drug and introduce tacrolimus. On the day after discontinuing everolimus the

patient presented clinical and radiological improvement with resolution of the condition.

To summarise, knowing that pneumonitis may appear with all mTOR inhibitors can lead to rapid discontinuation of the drug, preventing unnecessary diagnostic and therapeutic action in kidney transplant patients.

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Figure 1. Chest X-ray .

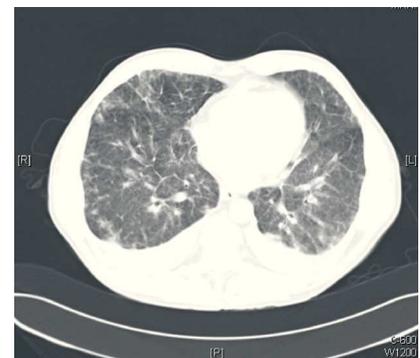


Figure 2. Chest CT

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Mixed Cryoglobulinaemia in a Patient after Kidney Transplant

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Dear Editor,

Hepatitis C virus infection (HCV) is associated with cryoglobulinaemia¹, mainly mixed type II, associated or not with membrane-proliferative glomerulonephritis. The prevalence of cases with clinical symptoms is 1:1,000,000, but 40-60% of the patients with HCV have elevated cryoglobulins. In transplant patients, who were previously HCV positive,^{2,4} this is an important cause of *de novo* glomerulonephritis. In these patients the prevalence of cryoglobulinaemia after transplant is 2.7-45%.

We present a case of a 63 year old patient with renal failure due to postpartum cortical necrosis, on haemodialysis since 1980. She was HCV positive. In a liver biopsy performed in 1986 slight chronic portal and lobular inflammation without any signs of activity were seen, since then there has been ALT elevation 2-3fold.

The patient underwent her first transplant in 1992, and lost graft function due to glomerulopathy of the transplant in 1996. The second transplant was performed in 2001. The patient received

immunosuppression with mofetil mycophenolate, tacrolimus and steroids. The patient had a maximum panel reactive antibody (PRA) prior to transplant of 52%, which decreased to 0% during the months prior to transplant surgery. Plasma creatinine was stable (1.5-1.7 mg/dl), proteinuria positive and less than 500 mg/24 hours. In January 2007 prednisone was discontinued, with a subsequent increase of proteinuria that reached nephrotic proportions in January 2009. The HCV viral load was persistently positive.

The patient is admitted in February 2009 to Pneumology due to non-condensing respiratory infection and stable renal function. Clinical symptoms improve on antibiotic therapy. One week later the patient presents arthromyalgia, fever, oedemas and petechial lesions in lower limbs (Figure 1). The patient presents progressive deterioration with dyspnoea, leukocytosis, anaemia and creatinine rise (4 mg/dl), requiring therefore haemodialysis due to oligoanuria.

We ruled out haemolytic-uremic syndrome (peripheral blood smear with no schistocytes, normal platelet count, and absence of severe hypertension). ANCA and anti-GBM were negative, ruling out these causes of secondary rapidly progressive renal failure. The



Figure 1. Vasculitis Skin lesions

patient was positive to plasma cryoglobulins (30%), complements (C4 <2; C3 111) and rheumatoid factor (positive; 408 U/l). The HCV viral load was 31,263,906 copies/ml, genotype 1. Renal biopsy showed changes compatible with cryoglobulinaemic membrane-proliferative glomerulonephritis, glomeruli with a proliferative membrane pattern, cell proliferation and hyaline thrombi. With a diagnosis of membrane proliferative glomerulonephritis associated with HCV, treatment with plasmapheresis was begun, causing reversion of skin and lung lesions, but the patient remained dialysis-dependent. Given the advanced renal failure, treatment with pegylated interferon and ribavirin was begun, and haemoglobin was closely monitored. Four months later the viral load was undetectable.

HCV treatment was chosen, with pegylated interferon and ribavirin,^{1,3,5} but in patients with renal failure, creatinine clearance must be monitored. According to the levels of creatinine clearance, ribavirin and/or pegylated interferon may not be advisable or it may be necessary to monitor haemoglobin levels. In cases in which this occurs plasmapheresis may be used or drugs such as rituximab³ used for (renal, neurological or skin) exacerbations. Once overcome, antiviral drugs will be administered. Furthermore, pegylated interferon is contraindicated in patients that have undergone transplant,³ but in our case the patient had already returned to dialysis.

In our patient we blamed the persistent proteinuria on possible chronic changes, although it may have been related to cryoglobulinaemia. We would like to highlight the importance of keeping this possibility in mind, since this condition is quite frequent with a subclinical presentation and can lead to kidney transplant failure.²

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