Increase of acute-phase reactants after kidney transplantation of non-infectious cause

Elevación de reactantes de fase aguda tras el trasplante renal de causa no infecciosa

Dear Editor,

Although an increase in acute phase reactants has been observed in kidney transplant recipients treated with OKT3, there is limited information on whether other immunosuppressive drugs can cause similar abnormalities. The aim of this study was to explore whether Thymoglobulin treatment could induce a non-infectious increase in procalcitonin (PCT) in these patients.

To answer this question, a prospective observational study was conducted, including 33 consecutive patients, recipients of cadaveric donor kidney transplantation (KT). In 14 of these patients, Thymoglobulin was added to the immunosuppression protocol to treat acute rejection (four patients), as rejection prophylaxis in hyperimmunised patients (five patients) or to reduce the dose of calcineurin inhibitors in patients at high risk of graft rejection (five patients). Patients were monitored between days 7 and 30 after KT. Quantitative levels of PCT and C-reactive protein (CRP) were measured before immunosuppressive treatment and at 12 h, 24 h, 72 h and 7 days after it was started. Thymoglobulin treatment was shown to significantly increase PCT levels in these patients (Figs. 1 and 2). It is striking that only one of these patients had a urinary tract infection due to *Enterococcus* spp., while in two patients sepsis was initially suspected due to them having PCT levels >100, but this was ruled out as neither of them had any haemodynamic abnormalities or other signs or symptoms of active infection. The rest of the patients treated with Thymoglobulin had increased PCT levels without infectious symptoms or elevation of other parameters that might indicate infection (for example, leucocytosis, increased erythrocyte sedimentation rate, abnormal clotting). In contrast, PCT levels were normal in the remaining 19 patients who did not receive Thymoglobulin.

PCT is one of the most valuable and commonly tested biomarkers in cases of sepsis of bacterial or fungal origin.[1] During infections, plasma PCT levels can exceed normal values by as much as 1000-fold,[2] such that in sepsis, a correlation has been established between PCT value and sepsis severity.[3]

High-dose immunosuppressive regimens (anti-rejection therapy, induction therapy) and, in particular, the administration of pan-T-cell antibodies (Thymoglobulin) used in transplant patients, are associated with an increased risk of bacterial and fungal infections that are often difficult to diagnose.[4] PCT monitoring has also proven to be of great interest in transplant patients. Similar to the general population, despite immunosuppressive therapy and the potential impact on the natural clearance rate of PCT under abnormal renal function, PCT increases in cases of bacterial or fungal infections in KT recipients.[5]

In our cohort, it appears that the use of Thymoglobulin resulted in a temporary increase in PCT levels, with a peak 24 h after administration. PCT levels do not appear to correlate with the Thymoglobulin dose (even a single 100-mg dose of Thymoglobulin increases PCT). We found that CRP levels also increased in parallel to the PCT levels in these patients, going unnoticed in most cases and secondary to surgery or the inflammatory process of acute rejection. However, CRP levels reached >20 mg/dl in patients with higher PCT levels.

This same increase has also been reported in a patient diagnosed with metastatic melanoma treated with RAF inhibitors and MEK1 and MEK2 kinase inhibitors (dabrafenib and trametinib).[6] Other authors have observed increased PCT and fever in patients with solid organ cancer (without infection), and patients with solid organ cancer with PCT in the normal range and positive cultures.[7–9] While increased PCT is higher and more specific in bacterial and fungal infections, it is also synthesised systemically in other scenarios such as surgery, pancreatitis and severe trauma, possibly by intestinal translocation of lipopolysaccharides or other bacterial products. This mechanism could be the cause of the increased levels observed in patients treated with immunomodulators.[10]

In conclusion, these data support the evidence that increased PCT levels in kidney transplant patients treated with Thymoglobulin may not be the ideal indicator of infection. It would be prudent to confirm this statement by assessing other clinical signs or symptoms before iniciating any treatment.

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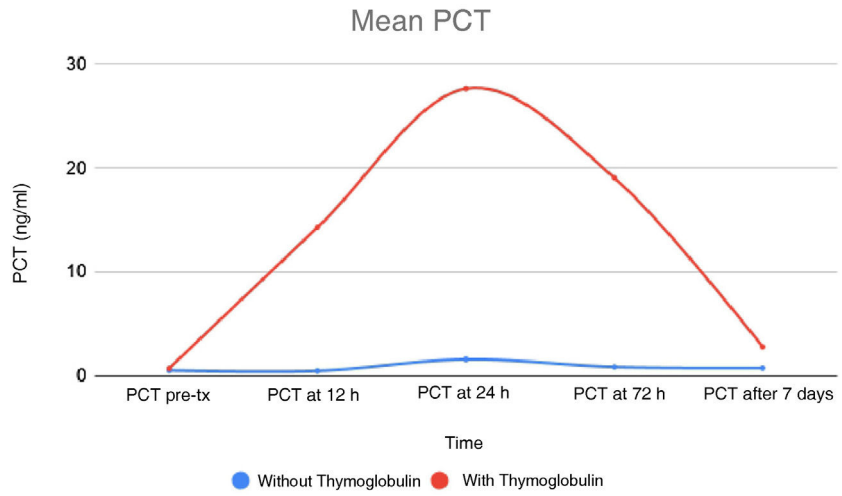

Fig. 1 – Comparative mean time course of procalcitonin (PCT) between the two patient groups: kidney transplant recipients who have received Thymoglobulin and transplant recipients who have not received this treatment. tx: transplantation.

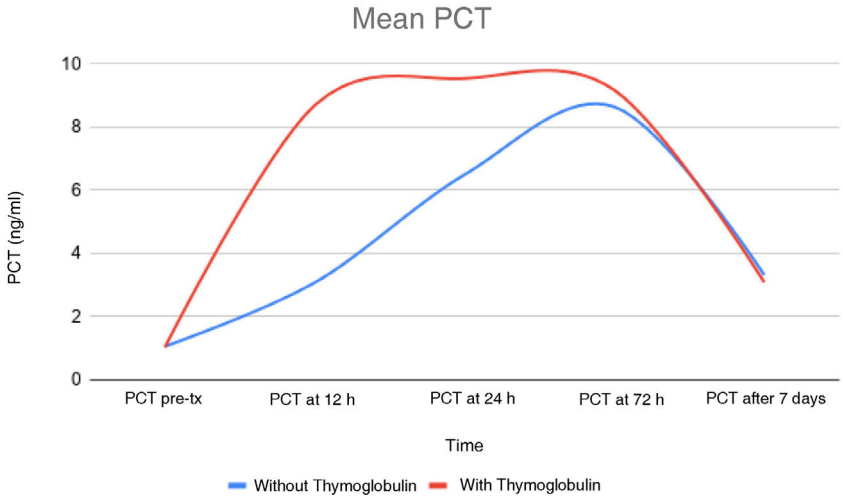

Fig. 2 – Comparative mean time course of C-reactive protein (CRP) between the two patient groups: kidney transplant recipients who have received Thymoglobulin and transplant recipients who have not received this treatment. tx: transplantation.

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Eliminating the concept of unknown chronic kidney disease: 2 cases of autosomal dominant tubulointerstitial nephropathy with pathogenic variant *MUC-1*

Eliminando el concepto de enfermedad renal crónica no filiada: a propósito de 2 casos de nefropatía túbulo-intersticial autosómica dominante con variante patogénica *MUC-1*

Dear Editor,

Confirming a diagnosis for certain renal diseases is only possible with a genetic study. This is the case for autosomal dominant tubulointerstitial kidney disease (ADTKD), as defined by the KDIGO guidelines in 2015.[1]

ADTKDs manifest as progressive loss of renal function, with negative or anodyne proteinuria and usually with normal urinary sediment. On ultrasound, the kidneys are normal or small size, with inconsistent presence of corticomedullary cysts. Renal biopsy is nonspecific, showing only evidence of interstitial fibrosis and tubular atrophy. The five most frequent known causative genes are: *UMOD, MUC-1, REN, HNF1B* and *SEC61A1*, with differential clinical characteristics among them (Table 1).[2–5] Penetrance is close to 100% and there may be intra- and interfamilial variability. They constitute the third most common group of monogenic renal disease, after autosomal dominant polycystic kidney disease and type IV collagen disease.[4]

We present 2 cases diagnosed in our center.

The first case is a 23-year-old female patient, with no relevant medical history, who was consulted for renal function deterioration with creatinine of 1.4 mg/dl, CKDEPI 53 ml/min/1.73 m^2, urine albumin/creatinine ratio of 7.4 mg/g and no alterations in urinary sediment. On ultrasound, the kidneys were of normal size and morphology, although slightly hyperechogenic, with no evidence of renal cysts. There was nothing remarkable in the anamnesis: she had no history of urinary tract infections or nephritic colic, no nephrotoxic intake and no cardiovascular risk factors (she had blood pressure of 120/70 mmHg). Regarding family history (Fig. 1): her maternal great-grandmother died at 35 years of age of "nephropathy," her maternal grandmother started dialysis at 45 years of age, her maternal aunt started dialysis at 55 years of age and her mother started dialysis at 48 years of age. In all 3 cases, chronic kidney disease (CKD) was not affiliated and had been related to vascular profile because she had arterial hypertension at 35–40 years of age. We performed more studies (ANA, anti-DNA, ANCA, ENA, C3/C4, IgA/M/G, proteinogram, HIV/HBV/HCV): all were negative or normal. The patient presented progressive deterioration of renal function with no other potential causes. She refused renal biopsy. Given the familial autosomal dominant profile, clinicians requested a genetic study, which detected a pathogenic variant in the *MUC-1* gene, causing NTIAD. The patient is now 28 years old, with advanced chronic kidney disease (creatinine 5.2 mg/dl CKDEPI 10 ml/min/1.73 m^2), so the progression has been faster than in her other relatives.

The second case is a 29-year-old male, with medical history of arterial hypertension of one year with good control with low-dose antihypertensive drugs; he also had meningitis (2015) and previous appendectomy. He was referred to us because of renal function deterioration (creatinine 2 mg/dl, CKDEPI 38 ml/min/1.73 m^2), with an urine albumin/creatinine

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