Complex regional pain syndrome associated with erythropoietin therapy☆

Síndrome de dolor regional complejo asociado a terapia con eritropoyetina

Dear Editor,

We present the case of a 28-year-old Caucasian male diagnosed at the age of 4 months with chronic pyelonephritis secondary to vesicoureteral reflux that required treatment with haemodialysis. He had undergone transplantation from cadaveric donor 15 years earlier; induction therapy included corticosteroids, mycophenolate mofetil, tacrolimus and basiliximab and the later was discontinued for maintenance immunosuppressive therapy. Graft function immediately after transplantation was satisfactory, and no proteinuria was detected. One month after the transplant, he developed diabetes mellitus, requiring insulin. Immunosuppression was switched from tacrolimus to cyclosporin A.

Seven years later, the patient developed normochromic, normocytic anaemia with haemoglobin levels of 9.2 mg/dL and haematocrit 28%. Treatment with subcutaneous epoetin beta was initiated, 10,000 IU per week. Three months later, he came to the clinic for severe bilateral, asymmetric pain in ankles and knees, with difficulty to walk. No history of trauma was identified. Clinical examination revealed inflammatory signs in periarticular soft tissues in the lower extremities. Electromyography did no show signs of peripheral neuropathy that could have been explained by the diabetes. Results from blood and urine laboratory test results were: creatinine: 1.5 mg/dL, urea: 72 mg/dL, 24 h urinary protein: 854 mg, total calcium: 9.5 mg/dL (reference values [RV]: 8.5–10.5), phosphate: 4.5 mg/dL (RV: 2.3–4.3), PTH: 95 pg/mL (RV: 15–65), alkaline phosphatase: 127 U/L (RV: 90–290), C reactive protein: 0.1 mg (RV: <0.8 mg/dL), uric acid: 7.8 mg/dL (RV: 1.9–7.4 mg/dL), serum HbA_{1c} 6.6% (RV: 3.4–5.5%) and cyclosporin A: 111 ng/mL. Bone scintigraphy revealed generalised increased uptake by bone structures suggestive of a metabolic pattern related to his hyperparathyroidism. Also notable was evident bilateral symmetrical increased uptake in the osteoarticular structures of the hips, knees, ankles and feet, consistent with complex regional pain syndrome (CRPS), which confirmed the clinical suspicion (Fig. 1A).

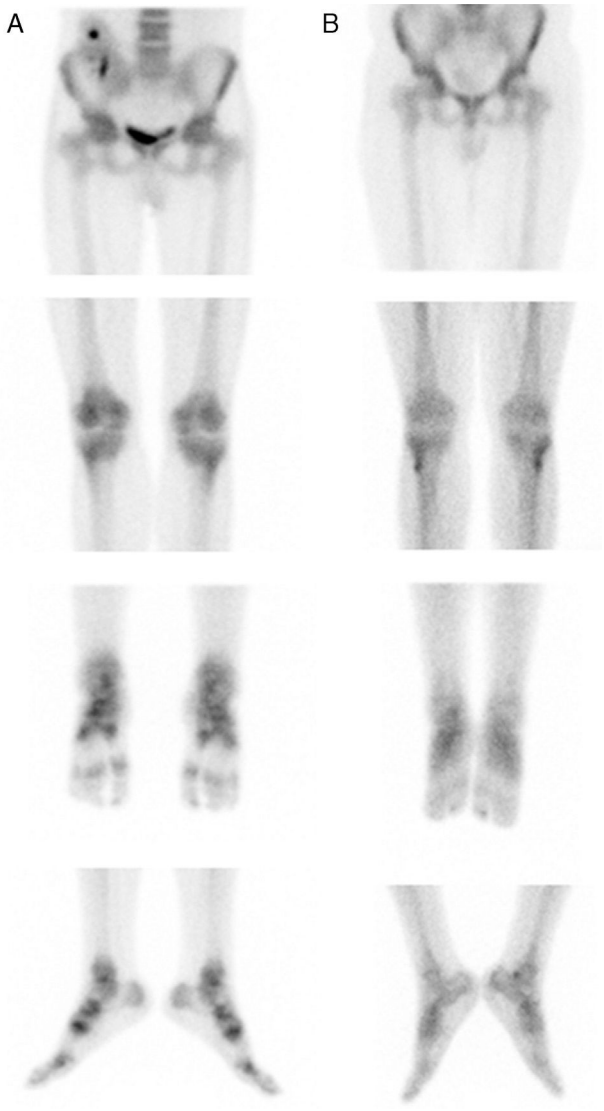

Fig. 1 – Bone scintigraphy consistent with CRPS (A) with resolution of the process in the post-treatment follow-up (B).

DOI of original article:
http://dx.doi.org/10.1016/j.nefro.2017.01.002.

☆ Please cite this article as: Coloma A, Sánchez N, Fuster D, Ruiz C, Xipell M, Orozco J, et al. Síndrome de dolor regional complejo asociado a terapia con eritropoyetina. Nefrología. 2018;38:99–101.

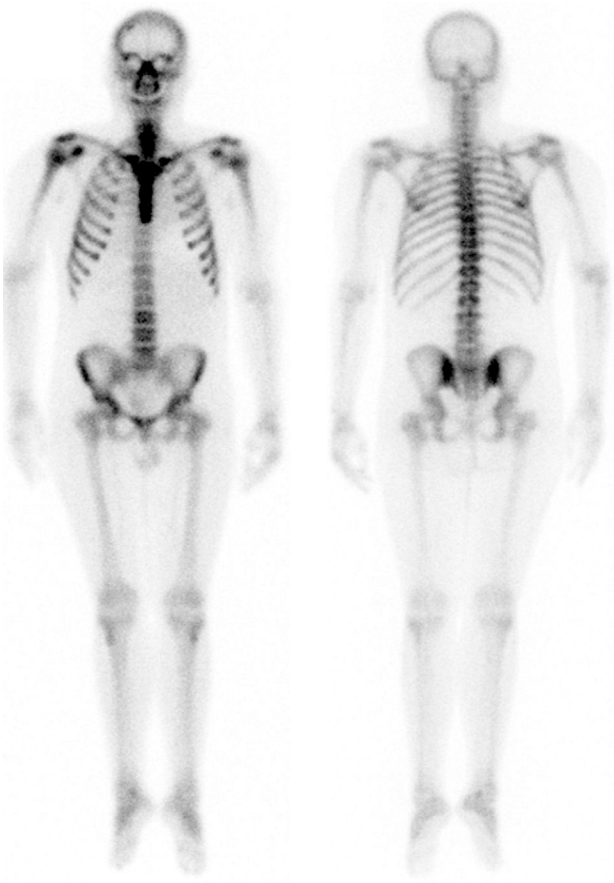

Fig. 2 – Bone scan showing a metabolic pattern related to the patient's hyperparathyroidism.

The symptoms gradually resolved after discontinuing the epoetin, until complete improvement. Follow-up bone scintigraphy showed normalisation of the previously observed abnormalities in the lower extremities (Fig. 1B). The whole body scan continued to show an uptake pattern typical of patients with hyperparathyroidism, as in this case (Fig. 2).

CRPS is characterised by the presence of pain that is disproportionate in time or degree with respect to any known trauma or lesion, together with warmth and inflammation, combined with sensory, autonomic, trophic, sudomotor and vasomotor abnormalities. In order to make the correct diagnosis, there must be an initiating noxious event or a cause of immobilisation.[1] In this patient, the initial event was the subcutaneous injection of erythropoietin (EPO). Bone scintigraphy was consistent with CRPS, with these findings key for the diagnostic confirmation. Finally, the patient's significant clinical improvement after withdrawal of the EPO with no other therapeutic intervention suggests that this was a case of CRPS associated with EPO treatment.

EPO is a glycoprotein produced mainly by the interstitial fibroblasts in the peritubular renal cortex. Patients with advanced chronic kidney disease (CKD) eventually develop normochromic, normocytic anaemia due to reduced endogenous synthesis of EPO. Moreover, anaemia in patients with diabetic nephropathy usually appears very early. EPO and its derivatives have been widely used for the treatment of the anaemia of CKD, and its cardioprotective and neuroprotective effects are well known.[2,3] It has also been reported that the administration of EPO may protect against the development of the sensory and autonomic peripheral nerve dysfunction that results from diabetes.[4] In this case, the patient was diabetic with no known polyneuropathy, and developed CRPS after subcutaneous EPO administration.

At present, the onset of CRPS has been described in association with drugs, such as calcineurin inhibitors and sirolimus in transplant recipients, isoniazid and phenytoin or phenobarbital.[5–7] Nevertheless, the development of CRPS associated with EPO therapy has not been described to date. In this case, the patient had been under cyclosporin treatment for years, and while there is no temporal relationship between the start of cyclosporin administration and the onset of CRPS to explain the symptoms, it could be a predisposing factor for the development of this syndrome.

In conclusion, this case shows the possible relationship between the administration of EPO and the onset of CRPS, since the withdrawal of EPO resulted in complete clinical resolution in the patient. This case is the first description of CRPS secondary to the administration of EPO, although further studies are recommended to support this association.

REFERENCES

1. Harden RN, Oaklander AL, Burton AW, Perez RSGM, Richardson K, Swan M, et al., Reflex Sympathetic Dystrophy Syndrome Association. Complex regional pain syndrome: practical diagnostic and treatment guidelines, 4th edition. Pain Med. 2013;14:180–229.
2. Arcasoy MO. The non-haematopoietic biological effects of erythropoietin. Br J Haematol. 2008;141:14–31.
3. Hosseini-Zare MS, Dashti-Khavidaki S, Mahdavi-Mazdeh M, Ahmadi F, Akrami S. Peripheral neuropathy response to erythropoietin in type 2 diabetic patients with mild to moderate renal failure. Clin Neurol Neurosurg. 2012;114:663–7.
4. Wu Z, Mata M, Fink DJ. Prevention of diabetic neuropathy by regulatable expression of HSV-mediated erythropoietin. Mol Ther. 2011;19:310–7.
5. Ybarra J, Crespo M, Torregrosa JV, Fuster D, Campistol JM, Oppenheimer F. Reflex sympathetic dystrophy syndrome in renal transplanted patients under immunosuppression with tacrolimus. Transplant Proc. 2003;35:2937–9.
6. Molina MG, Diekmann F, Burgos D, Cabello M, Lopez V, Oppenheimer F, et al. Sympathetic dystrophy associated with sirolimus therapy. Transplantation. 2008;85:290–2.
7. Vanacker A, Vandewiele I, Aerts P, de Groof J, Maes B. Reflex sympathetic dystrophy in a renal transplant patient treated with sirolimus. Nephrol Dial Transpl. 2007;22:2709–12.

Ana Coloma[a], Nuria Sánchez[b,*], David Fuster[b], Cristina Ruiz[b], Marc Xipell[c], John Orozco[b], Andrés Tapias[b], José V. Torregrosa[a]

[a] *Unidad de Trasplante Renal, Hospital Clínic, Barcelona, Spain*

[b] Departamento de Medicina Nuclear, Hospital Clínic, Barcelona, Spain
[c] Departamento de Nefrología, Hospital Clínic, Barcelona, Spain

* Corresponding author.
E-mail address: nusanchez@clinic.ub.es (N. Sánchez).

https://doi.org/10.1016/j.nefroe.2017.10.003

Kidney damage due to the use of anabolic androgenic steroids and practice of bodybuilding☆

Consecuencias renales del uso de esteroides anabolizantes y práctica de culturismo

Dear Editor,

We report the case of a patient, male with acute kidney failure and haemolytic anaemia in the context of secondary malignant hypertension (HTN) and anabolic steroid user.

Malignant HTN is a disease characterised by a marked rise in blood pressure (BP) (systolic > 180–190 mmHg and diastolic > 120–130 mmHg), grade III–IV hypertensive retinopathy and abnormal kidney function.[1,2] It is often accompanied by microangiopathic haemolytic anaemia (schistocytes in peripheral blood) with high LDH, undetectable haptoglobin, reticulocytosis, thrombocytopenia and a negative Coombs test. There may be proteinuria and micro- or macrohaematuria. An immunology study is usually negative and is useful to rule out connective tissue diseases. Lesions often develop in other target organs, leading to, for example, left-sided heart failure or hypertensive encephalopathy. Therefore, it is necessary to perform an electrocardiogram, a chest X-ray, an echocardiogram or a brain scan.[3]

Furthermore, the use of anabolic steroids has risen to alarming proportions in recent decades. Although effects on kidney function are uncommon, some cases have been documented in which a combination of anabolic steroids and creatine supplements has caused kidney damage. Anabolic steroids have a known effect on hypernatraemia, accompanied by an increase in urinary excretion of potassium and hydrogen ions, resulting in hypokalaemic alkalosis.[4,5]

We report the case of a 37-year-old male with hypertension known for the last 10 years, with no treatment, who regularly practised bodybuilding; took intramuscular anabolic steroids (testosterone and stanozolol), growth hormone and oral creatine; and followed a protein-rich diet. He visited the Emergency Department due to signs and symptoms of general malaise, nausea, headache and blurred vision that had lasted for one week. He was found to have high BP (250/180 mmHg) and severe acute kidney failure. Complementary tests revealed anaemia and thrombocytopenia (haemoglobin 9.9 g/dl, haematocrit 28.4%, platelets 91,000/mm^3) as well as the above-mentioned kidney failure (urea 246 mg/dl, creatinine 23.5 mg/dl). An immunology study was negative (except for a slight decrease in C3 and C4 fraction), with proteinuria of 1.7 g/24 h and oligoalbuminuria of 491 mg/l. A peripheral blood smear showed real thrombocytopenia and schistocytes (2.1%). Venous blood gases were normal and potassium levels were at the lower limit of normal (this was likely an effect of the anabolic steroids). Given his haemolytic anaemia with mild thrombocytopenia and schistocytes on smear testing, the patient was thought to have microangiopathic haemolytic anaemia. A brain CT scan was performed (to rule out brain damage secondary to HTN). The scan showed a punctiform image in the caudate nucleus that was not suggestive of acute haemorrhagic lesion.

Despite intravenous hypotensive treatment (labetalol and nitrites), the patient's BP levels remained high. Therefore, it was decided to admit the patient to the Intensive Care Unit and start acute haemodialysis and plasmapheresis simultaneously on an emergency basis. A dilated eye fundi examination was performed and yielded a result consistent with grade IV hypertensive retinopathy. A kidney ultrasound showed destructured kidneys with poor corticomedullary differentiation and obvious asymmetry. An angio-CT scan (Fig. 1) ruled out left renal artery stenosis, but revealed an aneurysm in the left renal artery 2 cm in diameter with a calcified and thrombosed wall. An ECG showed signs of left ventricular hypertrophy and diastolic overload, and an echocardiogram showed severe concentric LV hypertrophy with preserved systolic function.

DOI of original article:
http://dx.doi.org/10.1016/j.nefro.2017.03.004.
☆ Please cite this article as: Merino García E, Borrego Utiel FJ, Martínez Arcos MÁ, Borrego Hinojosa J, Pérez del Barrio MP. Consecuencias renales del uso de esteroides anabolizantes y práctica de culturismo. Nefrología. 2018;38:101–103.