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Migratory arthralgia as the initial sign of systemic toxicity associated with chronic nitrofurantoin treatment☆

Artralgias migratorias: manifestación inicial de toxicidad sistémica asociada al tratamiento crónico con nitrofurantoína

Dear Editor,

Nitrofurantoin is an antibiotic widely used in the treatment and prevention of urinary tract infections (UTI). The most common adverse effects are gastrointestinal but cases of pulmonary and hepatic[1] toxicity, and even vasculitis[2] have been reported.

We present the case of a 63-year-old woman with a history of repetitive UTI, with no other relevant medical history. Prophylaxis with nitrofurantoin had been initiated a year prior to the presentation of symptoms. She was referred to the rheumatology department for migratory asymmetrical arthralgias of 4-month onset. During examination she referred to dyspnoea with moderate effort which had appeared after the arthralgias. Auscultation revealed bilateral crackling sounds. A chest X-ray showed a bilateral interstitial pattern and high resolution computerised tomography (HRCT) showed ground glass areas corresponding to acute/sub acute interstitial pneumonia (Fig. 1). Blood tests highlighted GOT 360 U/l, GPT 432 U/l and GGT 279 U/l with normal abdominal ultrasound. The hepatropos virus serology and autoimmune antibody study tested negative. Autoimmunity studies detected ANCA+ 1/640 perinuclear staining (negative anti-myeloperoxidase and anti-proteinase 3). Due to these findings toxicity by nitrofurantoin was suspected and the drug was withdrawn. Treatment with prednisone was established, with a good response at respiratory level, a drop in hepatic enzymes and a complete resolution of arthralgias. During follow-up, the transaminase values remained normal, respiratory symptoms disappeared and posterior lung imaging tests were normal. The arthralgias abated and the ANCAs tested negative.

There have been case reports of concomitant pulmonary and hepatic toxicity attributed to the use of nitrofurantoin.[3] Pulmonary toxicity and hepatic toxicity have 2 types of presentations: acute and chronic. Chronic pulmonary toxicity symptoms develop after several months of treatment. The most common are dyspnoea, irritative cough and fatigue. Crackling sounds, especially around the lung bases[4] are usually the result of auscultation. All types of radiographic anomalies in most patients exist, mostly in inferior and bilateral fields. In the HRCT scan ground glass areas may be observed, together with septal enlargement and traction bronquiectasias.[5]

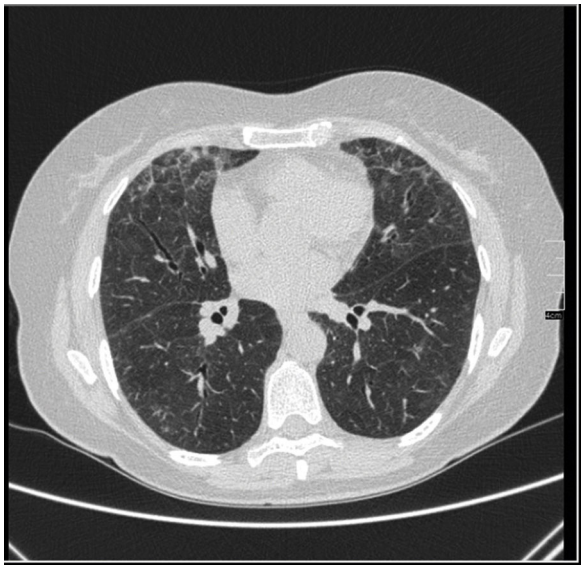

Fig. 1. High resolution computerized tomography. Axial slice at lung base level. Ground glass pattern is observed which corresponds to acute/sub acute pneumonia. There are no areas of fibrosis or any distortion of the lung architecture.

The acute form of hepatic toxicity generally presents after only a few weeks of treatment and is uncommon. It is usually accompanied by fever and rash.[6] Normally withdrawing the medication resolves this, although cases of fulminant hepatitis[3] have been known to exist. The more common chronic disorder may present months or years later. Symptoms are usually fatigue, muscle weakness and jaundice and an increase of transaminases in lab tests. Autoimmunity markers are occasionally detected (ANA+, anti-ML antibodies and elevated IgG).[1] Recovery after the removal of the drug is usually slow and hepatic damage may persist.[6]

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In the event of suspected diagnosis the temporary relationship between the onset of symptoms and exposure to the drug must be sought. Treatment is based on withdrawal of nitrofurantoin. Although glucocorticoids are usually combined with it, it is believed that the symptoms may cease after discontinuation of the drug.[1]

Prognosis is good if there is an early suspected diagnosis and exposure to the drug is limited. A case of cutaneous vasculitis and positive anti-MPO renal ANCA associated with the use of nitrofurantoin[2] has been reported. In our case the ANCAs tested positive although without vasculitis-associated specificity. Given the patient's favourable evolution no hepatic or pulmonary biopsies were performed which could have highlighted vasculitis. We did not find any cases of arthralgias with simultaneous pulmonary and hepatic involvement with positive ANCA related to the use of nitrofurantoin. In this case the arthralgias were the predominant symptom and led to the detection of concomitant pulmonary and hepatic toxicity. We therefore believe that the involvement of joints may suggest systemic toxicity and its early detection may improve prognosis.

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Comment on "Clinical practice guidelines for the treatment of systemic lupus erythematosus by the Mexican College of Rheumatology"

Comentario sobre "Guía de práctica clínica para el manejo del lupus eritematoso sistémico propuesta por el Colegio Mexicano de Reumatología"

Dear editor:

We read with high respect the recent publication of the Mexican Clinical Practice guidelines for the management of systemic lupus erythematosus (SLE).[1] This is a much-needed reference for Mexico, a country with a high number of SLE patients. From the nephrologist perspective, lupus nephritis (LN) is also of great concern to Latin America given the high percentage of LN observed in recent renal biopsy registries from the region.[2] It is known that LN affects 40–60% of patients with SLE and 10–20% will progress to end-stage renal disease within 10 years of diagnosis. These patients will receive some sort of renal replacement therapy (RRT): peritoneal dialysis (PD), hemodialysis (HD) or renal transplantation.[3]

In the LN management section, these new recommendations suggest "hemodialysis (HD) as the first option of renal replacement treatment in patients with chronic kidney disease (CKD) due to LN, given that peritoneal dialysis (PD) is associated with a higher number of complications and mortality due to immunosuppression (quality of evidence: moderate, strong recommendation)".

Studies in the nephrology community comparing patient survival on hemodialysis versus peritoneal dialysis in patients with end-stage renal disease from several etiologies have yielded conflicting results. Some underlying reasons encompass the differences in the included populations (e.g. incident vs. prevalent, diabetic vs. non-diabetic), differences in the methodology used (e.g. intention to treat vs. received dialysis modality) and importantly, the unavailability of complete information of important confounders (presence or severity of comorbidities, residual kidney function, administered dialysis dose, among others). Researchers have tried to overcome these difficulties with the use of multivariate modeling, multilevel modeling or the use of propensity scores. However, confounding remains a threat to validity of most studies.

The recommendation in these new guidelines is based on the study by Weng et al. from Taiwan.[4] This is a small observational report that found a higher number of infections and death among 24 SLE patients undergoing PD as compared to 12 SLE patients on HD. The study has multiple methodological limitations, the most notable being the absence of correction for the baseline differences with any of the aforementioned statistical techniques. Some other important limitations are mentioned in the manuscript's discussion, for example, the health system in Taiwan did not cover erythropoietin stimulating agents (ESAs) for PD patients as it did for the HD group. Several other studies have been performed to define the best dialytic modality for SLE patients, some of them with similar methodological limitations (Table 1).

The largest study to date that compared PD vs. HD in SLE patients was performed by Contreras et al.[5] with data from the US Renal Data System. In this study, 1352 SLE patients with PD were matched with a propensity score approach to 1352 SLE patients with HD. There was a similar 3-year mortality between both modalities (21.4% vs. 22.5%), with similar cardiovascular (10.5% vs. 9.5%) and infection-related mortality (3.0% vs. 4.4%). These results were not modified in a sensitivity analysis in the unmatched population by a Cox-regression analysis that included all the appropriate predictors.

Therefore, we believe there is not enough evidence to support the preference for HD over PD in SLE patients. Renal replacement therapy selection in most CKD patients requires a case-by-case evaluation by the healthcare team keeping in mind the patient preferences. It is clear that an effort should be made to transplant these patients as soon as possible due to the lower mortality achieved with renal transplantation.