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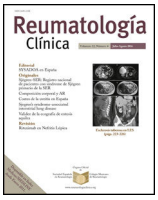

Letters to the Editor

Revisiting the association between systemic lupus erythematosus and gout

Revisitando la asociación entre lupus eritematoso sistémico y gota

Dear Editor,

In the literature there have been few case reports of systemic lupus erythematosus (SLE) and gout occurring concomitantly in the same patient.[1–3] Hyperuricaemia is relatively frequent in SLE, with a reported prevalence of 25–41%,[4] for which there are several predisposing factors: many patients have nephritis and renal insufficiency, receive diuretics and some are on low-dose aspirin, all contributing to decreased uric acid excretion.[1–3] Nevertheless, they rarely develop gout clinically. Besides age and gender distribution of both diseases, many other factors may play a role in this association.

First, it is known that the inflammatory response in acute gouty arthritis largely arises from the interaction between polymorphonuclear leukocytes and monosodium urate (MSU) crystals. In SLE, it has been demonstrated that these cells have impaired chemotactic activity and phagocytosis, which may hamper the reaction to MSU crystals.[4]

Secondly, it is thought that complement plays an important role in the pathogenesis of gouty arthritis, as MSU crystals activate both classical and alternative pathways of complement in synovial fluid.[5] As active SLE is characterized by decreased serum and synovial complement levels, in these situations it is expected that inflammatory response to MSU crystals will be impaired. This view is further supported by the fact that most cases of gout occur when SLE is quiescent, with complement levels in the normal range.[1,3]

Alterations in the structure of MSU crystals may provide another explanation. It has been demonstrated that Apo B lipoprotein binds to the crystal surface, thereby physically inhibiting particle–cell interaction and subsequent phagocytosis of MSU and membrane activation.[3] Apo B lipoprotein levels may be elevated in SLE, by a process that can be related to the disease itself and/or induced by corticosteroids, one of the cornerstone treatments in these patients.[6]

Additionally, it is well known that corticosteroids are powerful suppressors of the inflammatory response, blocking vasodilatation and increased vascular permeability and reducing neutrophils chemotaxis and phagocytosis, and likely impede clinical typical gout attacks.[3]

Furthermore, in clinical practice routine microscopy evaluation of synovial fluid is unfortunately underused, so gout attacks may be misdiagnosed as lupus arthritis flares. Consequently, gout diagnosis is late, with high rates of tophaceous forms.[2,4]

More recently, the knowledge about inflammasome contribution to the pathogenesis of certain diseases has progressed. Inflammasome is a term used to describe multimeric cytoplasmic protein complexes that detect pathogen-associated and danger-associated molecular patterns (PAMPS and DAMPs respectively) and mediate the activation of caspase-1, the primary enzyme responsible for activation of the pro-inflammatory cytokines IL-1β and IL-18. Several types of inflammasomes exist, but the best studied is the Nod-like receptor protein 3 (NLRP3) inflammasome.[7,8] The importance of inflammasome and IL-1 β activation in gout is clearly established, however in SLE it is an emerging concept. It is noteworthy that both uric acid and DNA are DAMPs, and both induce NLRP3 inflammasome, although the exact molecular details of this pathway in both conditions are not entirely known. It has been demonstrated that NLRP3 plays an important role in lupus nephritis animal models.[9] Moreover, it has been shown that anti-dsDNA antibodies activate NLRP3 inflammasome in monocytes/macrophages by binding to toll-like receptor 4 and inducing the production of mitochondrial reactive oxygen species.[10] As gout and SLE share this pathway in their pathogenesis, that appears to be related with SLE activity and nephritis,[9,10] it seems reasonable to think that it could play a role in the interplay between both diseases. As previously stated, gout attacks are less common in active lupus. The authors hypothesize there could be a counterregulatory mechanism in inflammasome pathway. However, further research is needed to clarify this subject.

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Valvulopathy in scleroderma is not always autoimmunity☆

Valvulopatía en la esclerodermia, no siempre es autoinmunidad

Dear Editor,

Cardiac complications in scleroderma (SD) are associated with a poor prognosis. Up to 15% of patients, generally with limited forms and anticentromere antibodies, develop pulmonary hypertension (PHT). Early diagnosis improves the prognosis, so that routine transthoracic echocardiograms (TTE) are recommended.[1] Pericardial bleeding has also been described, as have valvulopathies, myocarditis and hypertrophy or myocardial fibrosis.[2,3] We believe it is of interest to present the case of a patient with limited SD who developed mitral-aortic valvulopathy that was finally attributed to ergotamine toxicity.

A 59 year-old woman diagnosed SD based on Reynaud's phenomenon, characteristic capillaroscopy and anticentromere antibodies. At the moment of diagnosis TTE showed insignificant aortic and mitral insufficiency, normal systolic function and the absence of PHT data. 11 years later the valvulopathy had evolved to become severe mitral and tricuspid insufficiency, moderate aortic insufficiency and severe PHT (PSAP: 75 mmHg). Two mechanical prostheses were therefore implanted at mitral and aortic levels.

Two years later she visited due to general syndrome and dyspnoea. She was treated with Furosemide, Ranolazine, Acenocumarol, Spironolactone, Omeprazol and Bromazepam.

Physical examination only found distal metacarpophalangeal sclerodactila, with no scarring, ulcers or telangiectasias, and mild cutaneous sclerosis on the legs.

Relevant analytical data are shown in Table 1.

A thoracic-abdominal CT scan showed an extensive area of retroperitoneal (RPF) and pelvic fibrosis with bilateral ureterohydronephrosis. Subsequently a PET-CT scan with ^{18}F-FDG (Fig. 1) confirmed the mass of soft tissues in front of the sacrococcygeal region, with low glucidic avidity (SUVmax: 2.16 g/ml).

Given these findings a double J catheter was implanted and the fibrotic retroperitoneal lesions were biopsied. In the valves resected 2 years previously and in the retroperitoneal lesions only areas of fibrosis with negative immunofluorescence for IgG4 were observed.

The patient then remembered taking Hemicraneal® (paracetamol, caffeine and 2 mg ergotamine tartrate) almost every day for several years in suppository format for headaches, without medical prescription.

It was finally assumed that the RPF as well as the valvulopathy were side effects of the ergotamines.

RPF is a fibroinflammatory disease that is now considered to be within the spectrum of diseases associated with IgG4, although it has also been associated with other systemic diseases.[4] Differential diagnosis of this disease includes carcinoid tumours, actinomycosis, radiotherapy or abdominal surgery and Erdheim-Chester's disease, although drugs also have to be considered. They include anti-migraine medication (metisergide and ergotamine), dopaminergic agonists used in Parkinson's disease (pergolide and cabergoline), anorexigenic drugs (fenfluramine, dexfenfluramine and benfluorex) and anti-TNF[5] drugs. However, the list includes recreational drugs as well, such as 3,4-methylenodioxymethamphetamine, known as ecstasy.[6] These drugs have strong affinity for the $5HT_{28}$ serotonin receptor that is found in valvular tissue, and they cause lesions similar to those observed in carcinoid tumours, with thickening and accumulation of collagen and the proliferation of myofibroblasts and smooth muscle cells.

Ergotamine is used as migraine prophylaxis. It is sold over the counter and its use is contraindicated in Raynaud as it causes vasospasm. The first case of valvulopathy due to ergotamines was described in 1974[5] and, although its toxicity is well-known, it is rarely diagnosed. It is probably under-diagnosed as it is taken without supervision, and its toxicity appears after prolonged use.[6,7]

Table 1
Analytical results.

Biochemistry		Haemogram		Immunology	
Creatinine	1.23 mg/dl	Haemoglobin	12.5 g/dl	ANA	Positive 1/1,280, centromere
AST	44 UI/l	Leukocytes	7,620	Anti-DNA, ENA, ANCA	Negative
AP	716 UI/l	Platelets	13,700	Anticardiolipin antibodies, anti-2-glycoprotein antibodies	Negative
GGT	290 UI/l	PCR	46 m/h	IgG4	Normal (0.05)
PCR	2.54 mg/dl	–	–	Plasmablasts in peripheral blood	Negative

ANA: antinuclear antibodies; ANCA: antineutrophile cytoplasm antibodies; Anti-DNA: anti-DNA antibodies; AST: aspartate aminotransferase; ENA: extractable nuclear antigens; AP: alkaline phosphatase; GGT: gamma glutamyl transpeptidase; PCR: polymerase chain reaction.

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