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Editorial

Erythrocyte sedimentation rate and C-reactive protein as useful markers in the determination of the etiology of fever in patients with systemic lupus erythematosus

Velocidad de sedimentación globular y proteína C reactiva como marcadores útiles en la determinación de la etiología de la fiebre en pacientes con lupus eritematoso sistémico

Systemic lupus erythematosus (SLE) is a systemic chronic autoimmune disease characterized by the diversity of clinical presentations that it can generate, based on organic and tissue involvement, in which the renal, cutaneous and hematological commitment stands out.[1] These manifestations are caused by alterations in the immune response, both innate and adaptive, in addition to genetic predisposition factors and environmental elements that together lead to the triggering of autoimmunity.[2] In addition, it is a pathology characterized by the development of cycles of remission and relapses of the activity, which can generate cumulative sequelae in the patients that affect the associated morbidity and mortality.[1] It has been calculated an incidence of SLE of 0.3–31.5 cases per 100,000 people/year, and a prevalence of 50–100 cases per 100,000 inhabitants.[2]

During the follow-up of the patients, it is of great importance to carry out active surveillance that allows the early detection of comorbidities, which can be triggered as a direct consequence of the disease, or by the medications used to control it.[1] One of the main comorbidities are the infections, which can be directly associated with changes in the immune response generated by the disease and also with the use of medications, especially immunosuppressants, being one of the main causes of morbidity, mortality and death.[2] For example, in the EuroLupus cohort, it was estimated that 30% of the deaths during follow-up were caused by infections. Among the infections, around 80% are caused by bacteria, which mainly affect the respiratory tract, the skin tissue and the genitourinary tract.[3]

One of the clinical scenarios which is most difficult to manage is when the patients with SLE have fever. This is due to the fact that fever can be triggered by a relapse of the disease or by an infection. Being able to establish the etiology with certainty is a diagnostic challenge, given that the management for each scenario will be different and diametrically opposed. On some occasions it will be possible to differentiate between both situations, if a specific focus or source of infection can be identified, or when patients present clear manifestations of lupus activity. However, there are scenarios in which specific infectious foci are not identified, or the manifestations are ambiguous, which makes decision making difficult.[3,4]

In search of tools that can help in the differentiation between infections and lupus inflammatory activity, different biomarkers have been evaluated, among which the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), procalcitonin, complement levels (C3, C4), cytokine levels (IFN-α, IL-6, IL-10, IL-15, IL-18, BLyS/BAFF, TNF) and urinary markers stand out. The majority of biomarkers are focused on the assessment of the disease activity.[5] Two of these markers that are most evaluated due to their ease of measurement and low associated cost are ESR and CRP.

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ESR measures the rate at which the erythrocytes settle in the plasma of a sample of anticoagulated blood over a specific period of time. One of the limitations of this measure is that its result can be altered by different factors, which makes it vulnerable to misinterpretations that do not reflect the real scenario of the patient and make it not very specific.[6] With respect to SLE, the ESR levels tend to be elevated in the case of active disease, which is why it is included in some validated activity scores. These increases are related to changes in serum proteins or also to changes in the erythrocytes.[5]

CRP is a pentraxin-type acute phase reactant that functions as a pattern recognition protein, facilitating complement binding and phagocytosis. It is produced and synthesized in the liver in response to stimulation by cytokines such as IL-1, IL-6, TNF-α, among others. Due to the above-mentioned, CRP levels tend to increase in a manner directly proportional to the degree of inflammation present, which makes it a sensitive marker.[5] In the case of SLE, it has not been used to measure the disease activity, but rather as a marker of infectious processes. In general, only lupus activity involving active serositis, arthritis, or myositis is associated with elevated CRP.[5] Some hypotheses about the low elevation of CRP include the suppression generated by the high levels of IFN-α, the sustained production of IL-6 that impacts the synthesis of CRP by the hepatocytes and the development of anti-CRP antibodies.[7]

Multiple studies focused on establishing greater relevance to the measurement of CRP and ESR, either by the recorded levels, or by means of instruments that combine both markers, for the evaluation of the activity or the presence of infections in SLE have been published. Firooz et al. assessed the relationship between high-sensitivity CRP levels and ESR levels, with lupus activity and the presence of infections, and they observed that ESR levels did not vary significantly between patients with infections and disease activity, while the levels of CRP were lower in patients with activity, compared with those who presented infection, and this makes them a good predictor of active infection in patients with SLE.[8]

Also, Beça et al. developed and validated an algorithm to help calculate the risk of presenting a relapse vs. infection in patients with SLE who present fever. Among the variables used as predictors of relapses that showed high performance, CRP was identified.[9]

Littlejohn et al. carried out a retrospective study to clarify the usefulness of ESR and CRP, alone or in combination, in order to distinguish between relapses and infections in patients with SLE, and reported that in febrile patients with high levels of ESR/CRP ratio there was an association with lupus activity, while low levels were associated with infectious etiology. The foregoing is a signal of a high usefulness of this relationship as a composite marker.[10] Meanwhile, Schäfer et al. evaluated the usefulness of ESR in the context of lupus activity, infection, or both at the same time, and found that ESR levels alone failed to make the distinction between activity and infection, while CRP levels did achieve good discrimination. However, the use of the ESR parameter (cutoff points are defined based on age and sex) did achieve better discrimination, mainly to identify the presence of relapses due to activity.[11]

Mehta et al., for their part, evaluated the reliability of multiple widely available, low-cost and routine markers in the differentiation between lupus activity and infection, in order to develop a compound score with these markers in patients with fever, and observed that CRP levels were significantly higher in patients with infection, mainly with levels higher than 2 mg/dL. Only the patients with activity who presented serositis and musculoskeletal involvement had elevated CRP. In addition, the compound model that included the total leukocyte count, together with CRP levels and age, achieved good performance to differentiate between lupus activity and infection.[12]

In the current edition of the Colombian Journal of Rheumatology (*Revista Colombiana de Reumatología*), the group of Gustavo León et al., from the Rheumatology Service of the *Hospital Nacional Edgardo Rebagliati Martins* in Lima (Perú), published the results of the study of diagnostic accuracy in febrile patients with SLE, in order to determine the usefulness of ESR and CRP levels in the discrimination between infection and lupus activity as the etiology of the fever. To do this, they obtained retrospective data from patients with SLE who had been hospitalized due to fever, primarily to obtain information on the paraclinical and clinical findings that led to the final diagnosis within the first 10 days of hospitalization. The capture of the information in a period between the years 2010 and 2019 was performed. Being fever the main variable measured, a categorization was made between patients with fever due to infection and those without fever, for the evaluation of diagnostic accuracy. In addition, the levels of ESR, CRP, ESR parameter, and the ESR/CRP ratio were measured in order to compare them between both groups. The ROC curves of performance were calculated for the 4 parameters and the most appropriate cut-off points, in addition to the values of sensitivity and specificity, as well as the predictive values of each parameter.[13]

As it was expected, high levels of CRP were present in fever of infectious etiology, while high values of ESR/CRP ratio were found in febrile patients with only lupus activity. These researchers also found that the most common cause of fever due to activity was kidney involvement (52.2%), while the most common infection was pneumonia (25%). Regarding the cut-off points for each parameter, they found that CRP > 5.4 mg/dL has a sensitivity of 76.9% and a specificity of 85.7% to identify a patient with infection, while an ESR/CRP > 21.42 is associated with a sensitivity of 78.6% and a specificity of 84.6% to identify lupus activity.[13]

The study conducted by León et al. represents a great contribution, by establishing the usefulness of widely available and low-cost markers in Latin American countries, such as ESR and CRP, in the discrimination of febrile etiology, which can be a great diagnostic challenge in clinical practice. In their study, they were able to corroborate the behavioral patterns of the markers that have been seen in other populations, in addition to providing cut-off points that achieve a good discrimination between infection and lupus activity. It is expected that, with this information available, it will be possible to improve the care of patients with SLE in the hospital setting, and thus help to improve the associated morbidity and mortality, based on early detection of the etiology of the fever.

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