Bibliografía

1. Munra S, Christophe-Stine L. Pregnancy in myositis and scleroderma. Best Pract Res Clin Obstet Gynaecol. 2019, http://dx.doi.org/10.1016/j.bpobgyn.2019.10.004.
2. Che WG, Hellgren K, Sephansson O, Lundberg IE, Holmqvist M. Pregnancy outcomes in women with idiopathic inflammatory myopathy, before and after diagnosis—a population-based study. Rheumatology. 2020;59:2572–80.
3. United Nations Statistics Division. Geographic regions. USA, New York; 2020. https://unstats.un.org/unsd/methodology/m49/ [accessed 30.12.20].
4. Iba-Ba J, Mayi-Tsonga S, Bignoumba IR, Diallo T, Kombila M, Coniquet S, et al. Dermatomyosite et grossesse: une observation au Gabon. Med Trop. 2009;69:603–5.
5. Kaddour N, Marzouk S, Frigui M, Chaabouni Y, Maazoun F, Ben Salah R, et al. Grossesse au cours des dermatomyosites et polymyosites. Rev Méd Intern. 2009;30:S97.
6. Ousmane C, Makhtar BEH, Fatoumata B, Massi GD, Lémine DSM, Soda DSM, et al. Polymyositis and anti-SRP antibodies and pregnancy about 2 cases. PAMJ. 2016;24:192.
7. Awatef K, Salim G, Zahra MF. A rare case of dermatomyositis revealed during pregnancy with good outcome. PAMJ. 2016;23:117.
8. Cisse L, Karabinta Y. Neonatal lupus in an infant of a mother followed up for dermatomyositis: medical images. PAMJ. 2018;31:117.
9. Iba Ba J, Nseng N, Ntsame N, Igala M, Kombila U, Malekou M, et al. Grossesses au cours de maladies auto-immunes en zone subsaharienne à travers l'expérience du service de médecine du CHU de Libreville. Médecine Santé Trop. 2019;29:206–12.

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The Value of a Negative Antinuclear Antibody (ANA) Test: An Often Forgotten Result

El valor de una prueba de anticuerpos antinucleares (ANA) negativa: un resultado a menudo olvidado

Dear Editor:

It is quite clear that medicine is biased towards positive results and the same applies to the practice of pathology.[1] One of the ubiquitous tests in autoimmunity, the antinuclear antibody (ANA) suffers from this very same fate. A number of guidelines report on the clinical utility of a positive ANA and dissuade clinicians from requesting this test in the setting of low pre-test probability for an ANA-associated autoimmune disorder (AAD).[2] This is certainly sound advice and prevents unnecessary investigations and healthcare expenditure. Yet, it is important to realise the clinical importance and pitfalls of a negative ANA results which sometimes becomes forgotten.

The internationally-accepted "gold standard" to measure ANA is via indirect immunofluorescence on HEp-2 cells.[3] A negative ANA test on HEp-2 substrate usually means that there is no significant detection of IgG ANA (in the nucleus) at a specified dilution of serum – usually 1:80 to 1:160. There is a move to also classify positive cytoplasmic and mitotic staining of the HEp-2 substrate as ANA positive.[3,4] This may improve the sensitivity of detecting AADs and prompt appropriate further testing and follow-up (Fig. 1).[3]

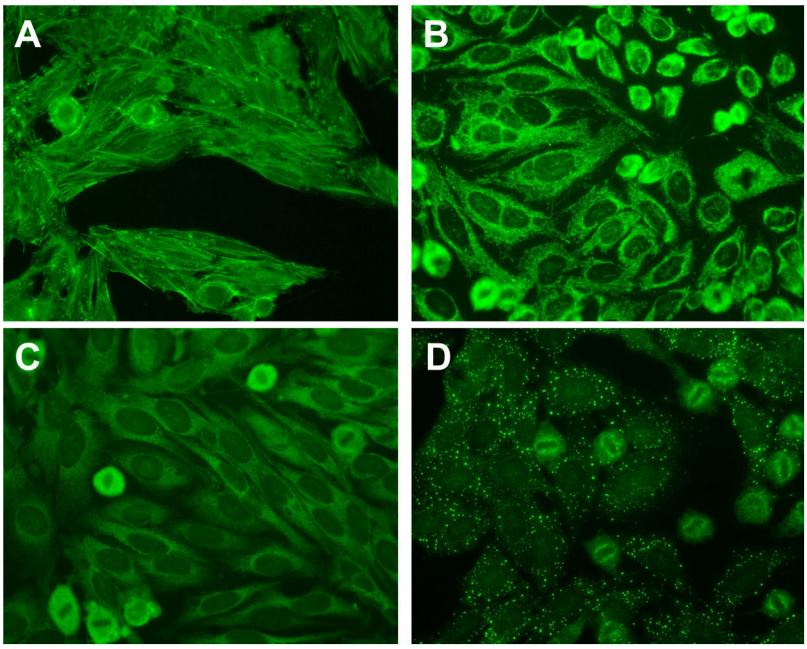

Fig. 1. Example cytoplasmic staining on the HEp-2 substrate. (A) F-actin staining suggesting the presence of smooth muscle antibodies found in autoimmune hepatitis and related disorders. (B) Coarse, granular cytoplasmic staining suggestive of anti-mitochondrial antibodies found in primary biliary cirrhosis. (C) Smooth, homogenous cytoplasmic staining suggestive of anti-ribosomal P antibodies found in systemic lupus erythematosus. (D) Large cytoplasmic dots staining suggestive of anti-GW bodies. All micrographs are taken at a magnification of 400×.

The high sensitivity and negative predictive value (NPV) for systemic lupus erythematosus (SLE) makes the ANA test a good "rule out" test to essentially exclude this disorder if it is negative.[5] Indeed, the most recent European League Against Rheumatism/American College of Rheumatology guidelines for the diagnosis of SLE mandates a positive ANA (≥1:80) on the HEp-2 substrate to be considered for this diagnosis.[6] Sensitivities for detecting other AADs is low-moderate at best; yet also demonstrates very high NPVs.[7] Unless there has been a significant change in clinical picture or there is a suspicion of a laboratory issue, there is little value in repeating an ANA that is initially negative.[8]

A pitfall is that ANA is a screening test and may, in rare instances, miss low-level specific autoantibodies/anti-extractable nuclear antigens (ENAs) if more sensitive assays are not performed,[9] or miss anti-ENA that do not produce a characteristic ANA pattern e.g., anti-Ro52. Therefore, the substrate should be specified in the report since substrates such as the HEp-2000® (Immunoconcepts) which has transfected Ro60 increase the detection of anti-Ro60 and hence, a negative result makes the presence of anti-Ro60 less likely.[10]

If there is a high clinical suspicion for an AAD, the clinician should request further anti-ENA tests and the overall clinical picture and physician's interpretation of the patient should prevail. This is especially of importance since commercial HEp-2 substrates, whilst generally demonstrating excellent inter-assay and inter-laboratory agreement, display subtle staining differences that affect the microscopist's final interpretation.[11] The significance of low levels of anti-ENA with negative ANA is not well established.

To conclude, clinicians should be aware of the value, implications and pitfalls of a negative ANA result when considering AADs. They should also be aware of their laboratory's definitions of a "negative" ANA result, the substrate used and whether they report non-nuclear patterns which may have important implications for their patients. Importantly, the overall clinical picture of the patient should be taken into considerations when deciding on the relevancy of a negative ANA test.

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Conflict of interests

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Bibliografía

1. Vawdrey DK, Hripcsak G. Publication bias in clinical trials of electronic health records. J Biomed Inform. 2013;46:139–41.
2. Solomon DH, Kavanaugh AJ, Schur PH. Evidence-based guidelines for the use of immunologic tests: antinuclear antibody testing. Arthritis Rheum. 2002;47:434–44.
3. Agmon-Levin N, Damoiseaux J, Kallenberg C, Sack U, Witte T, Herold M, et al. International recommendations for the assessment of autoantibodies to cellular antigens referred to as anti-nuclear antibodies. Ann Rheum Dis. 2014;73:17–23.
4. Damoiseaux J, Andrade LEC, Carballo OG, Conrad K, Francescantonio PLC, Fritzler MJ, et al. Clinical relevance of HEp-2 indirect immunofluorescent patterns: the International Consensus on ANA patterns (ICAP) perspective. Ann Rheum Dis. 2019;78:879–89.
5. Leuchten N, Hoyer A, Brinks R, Schoels M, Schneider M, Smolen J, et al. Performance of antinuclear antibodies for classifying systemic lupus erythematosus: a systematic literature review and meta-regression of diagnostic data. Arthritis Care Res. 2018;70:428–38.
6. Aringer M, Costenbader K, Daikh D, Brinks R, Mosca M, Ramsey-Goldman R, et al. 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus. Ann Rheum Dis. 2019;78:1151–9.
7. Slater CA, Davis RB, Shmerling RH. Antinuclear antibody testing: a study of clinical utility. Arch Intern Med. 1996;156:1421–5.
8. Lee AYS, Hudspeth AR, Adelstein S. The concordance of serial ANA tests in an Australian tertiary hospital pathology laboratory. Pathology. 2016;48:597–601.
9. Lee AYS, Beroukas D, Brown L, Lucchesi C, Kaur A, Gyedu L, et al. Identification of a unique anti-Ro60 subset with restricted serological and molecular profiles. Clin Exp Immunol. 2021;203:13–21.
10. Lee AYS, Beroukas D, Roberts-Thomson PJ. Utility of the HEp-2000 antinuclear antibody substrate. Ann Rheum Dis. 2020;79:e67.
11. Copple SS, Giles SR, Jaskowski TD, Gardiner AE, Wilson AM, Hill HR. Screening for IgG antinuclear autoantibodies by HEp-2 indirect fluorescent antibody assays and the need for standardization. Am J Clin Pathol. 2012;137:825–30.

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¿Cómo manejan la remisión los reumatólogos españoles? Encuesta de conocimientos y abordaje antes y después de un taller formativo

How do Spanish Rheumatologists handle remission? Survey of knowledge and approach before and after a training workshop

Sr. Editor:

La finalidad del tratamiento de la artritis reumatoide (AR) es alcanzar la remisión, pero los criterios para su determinación son diversos, complejos y de desigual rigurosidad[1], con la consiguiente complicación de su manejo. Los principales criterios son los puntos de corte de los índices compuestos (DAS28, SDAI o CDAI), los criterios booleanos de ACR/EULAR, la remisión sin tratamiento o la remisión ecográfica[2]. Tras alcanzar la remisión, las guías recomiendan reducir la dosis sin interrumpir ningún fármaco (ACR[3]), disminuir inicialmente los glucocorticoides y luego el tratamiento biológico (EULAR[1]) o reducir los glucocorticoides (no la de FAME clásicos) y establecer un plan de reducción de dosis de terapia biológica (SER[4]).

Hace 2 años nos propusimos analizar los conocimientos de los reumatólogos sobre la remisión de la AR y su influencia en el manejo terapéutico en la consulta externa. Los reumatólogos completaron una encuesta doble (material suplementario) antes y 3 meses después de asistir a 4 talleres científicos sobre la remisión y el manejo de los pacientes en remisión (incluida la herramienta RedoSER)[5]. Se dispuso que los encuestados tenían conocimientos elevados cuando ≥ 70% respondían correctamente y que el aumento o disminución de 10 puntos de las respuestas correctas antes y después del taller implicaba una variación.

Los resultados señalaron que los reumatólogos españoles tienen un conocimiento adecuado de la remisión (antes del taller, al menos el 70% respondió correctamente el 67% de las preguntas) y que un porcentaje muy elevado de estos especialistas considera que la valoración de la remisión debe incluir imagen, la perspectiva del paciente y biomarcadores. La remisión se valora sobre todo con el DAS28 o sus componentes y muy poco con imagen o con PRO