LES o Vasculitis

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Antecedentes personales

- **Estudiada en HSO en 2004** por elevación persistente de VSG (> 100) y PCR en varias determinaciones y elevación muy moderada de GGT junto con astenia y febrícula persistente.
  - Anemia moderada persistente posiblemente ferropénica.
  - ANA persistentemente + a titulo bajo o medio (hasta 1/160) con AntiDNA y ENAs negativos y complemento normal.
  - Proteinuria persistente en muestras aisladas y con frecuencia hematuria y leucocituria con aislamiento en varias ocasiones asintomático de E. coli sin deterioro de función renal.
  - Mantoux + con Rx normal e imagen de adenopatía calcificada.
- Gestación gemelar en 2004 sin incidencias. No antecedentes de abortos. Proteinuria más llamativa durante la gestación con microhematuria.

Enfermedad actual

- Una semana antes de su ingreso cefalea y sensación de mal estar general.
- Progresivamente afectación del estado general con aparición en las siguientes 72 horas de lesiones cutáneas dolorosas en EEII de coloración violáceo y posteriormente en EESS y cara anterior de abdomen.
- Fiebre elevada de hasta 39ºC precedida de tiritona y escalofríos.
- Artralgias de grandes articulaciones.
- Edemas en ambas EEII con escasa respuesta gravitatoria.
- Además desde hace dos meses y de forma progresiva nota astenia intensa que le dificulta sus actividades diarias

Exploración física

- TA: 118/79 pulso: 111 Tª: 38,2ºC
- No adenopatías cervicofaciales.
- AC: Rítmico, no soplos ni extratonos
- AP: Expansión simétrica de tórax. MVC, no roncus ni sibilancias
- ABDOMEN: Blando, globuloso, depresible, no masas ni megalias. PPRB y Murphy (-), no peritonismo, dolor a la palpación en epigastrio y FII. RHA (+). Cicatriz de apendicectomía.
- MMII: no edemas, dorsal pedio bilateral presente y simétrico. No signos de TVP. Lesiones en piernas y brazos compatible con eritema nodoso.
- E. neurológica básica normal.

Análisis en Urgencias

- Proteina C Reactiva 15.1 mg/dL, Urea 45 mg/dL, Creatinina 1.60 mg/dl, GGT 432 U/L, LDH 143 U/L.
- Sistemático de orina: Proteínas Positivo (+3), Hemoglobina Positivo (+3), Leucocitos en orina Positivo (+1), Nitritos Positivo (+2).
- Sedimento urinario: Piuria y hematies de 10/15 x c.
- Hemograma: Hemoglobina 8.5 g/dl, VCM 77.2 fl, Recuento de plaquetas 186 10E3/µl, (N 81.3 %, L 9.8 %, M 8.3 %, Eo 0.3 %, B 0.3 %).
- Estudio de coagulación: Tiempo de protrombina 13.0 s, Actividad de protrombina 87 %, INR 1.09, Tiempo de tromboplastina parcial activado 39.8 s, Fibrinógeno calculado 865.0 mg/dl

En planta

- Urea 45 mg/dL, Creatinina 1.50 mg/dL.
- Factor reumatoide 12 mUI/mL,
- Serologías negativas.
- Complemento C3 137 mg/dl, Complemento C4 22.5 mg/dl.
- Hemograma: Hemoglobina 7.8 g/dl, VCM 78.2 fl.
- VSG: VSG 1ª hora 122 mm.
- Sedimento urinario Hematíes : > 50 Hematíes por campo, Sedimento urinario Leucocitos : 11 - 20 Leucocitos por campo, Sedimento urinario Células epiteliales : Abundantes, Proteinuria en orina aislada 139.6 mg/dl, Proteinuria/Creatininuria 3.09, Creatininuria en orina aislada 45.2 mg/dL

Inmunidad

- **ANTICOAGULANTE LUPICO POSITIVO**
- PROTEINOGRAMA/ELECTROFORESIS: Hipoproteinemia con hipoalbuminemia.
- AUTOINMUNIDAD: **Ac. antinucleares Positivo** 1/80 Patrón homogéneo
- **Ac. anti-PR3 Positivo**, Ac. anti-MBG Negativo,
- Antiestreptolisina (ASLO) 57 UI/mL,
- Complemento C3 119 mg/dl, Complemento C4 14.5 mg/dl.

Biopsia cutánea

- DESCRIPCIÓN MICROSCÓPICA
- Las secciones histológicas muestran un fragmento cutáneo con presencia en dermis media de arterias de pequeño y mediano tamaño con tumefacción de células endoteliales e infiltración de la pared por células inflamatorias constituidas por neutrófilos, linfocitos e histiocitos. La dermis superficial muestra edema y un discreto infiltrado inflamatorio crónico perivascular.
- DIAGNÓSTICO ANATOMOPATÓLOGICO. Cuña de piel de miembro inferior izquierdo: Fragmento cutáneo con una **ARTERITIS DE PEQUEÑO y MEDIANO VASO**

Biopsia renal

- **DIAGNÓSTICO ANATOMOPATÓLOGICO**

  Glomerulonefritis lúpica proliferativa focal, clase III-S (ISN/RPS 2004), con índice de actividad 9/24 y de cronicidad 0/12 según esquema NIH.

Evolución

- Desde su ingreso y ante la sospecha inicial de eritema nodoso se inició tratamiento con esteroides a dosis bajas con respuesta de la fiebre y mejoría de las lesiones cutáneas
- Además en los hemocultivos recogidos en Urgencias se apreciaban en ¾ frascos la presencia de bacterias cocos + gram positivos. En el contexto de la paciente y hasta recibir los estudios ulteriores podría ser encuadrable dentro de una endocarditis bacteriana por lo que se instauró tratamiento antibiótico acorde y realizó ecocardiograma sin alteraciones y una valoración del fondo de ojo que fue normal recibiendo posteriormente los aislamientos siendo estos compatibles con una contaminación

Evolución

- Deterioro del filtrado glomerular hasta aclaramientos de 56 ml/min con Cr 1.46
- Clínica y analítica compatible con síndrome nefrótico por lo que se solicitó biopsia renal

Resumen

- ANA + a título bajo y patrón homogéneo
- ANCA PR3 +
- Elevación severa de reactantes de fase aguda con PCR alta y VSG de 133
- Anemia severa microcítica
- Deterioro de función renal con características glomerulares e intersticiales (proteinuria significativa nefrótica, hematuria, leucocituria y FG 58 ml/min)
- Radiografía con pequeño derrame pleural posterior (serositis?)

Resumen

- Sospecha de LES
- 5 criterios:
  - ANA+
  - Anticoagulante lúpico + anticardiolipina +
  - Anemia severa???
  - Nefritis: síndrome nefrótico
  - Serositis

Tratamiento

- 5 bolus de Metilprednisolona
- Inducción: 1 bolo de ciclofosfamida 750 mg/m2

- Excelente evolución clínica con importante mejoría de la anemia, desaparición del tercer espacio, normalización del FG y práctica normalización de reactantes de fase aguda así como importante mejoría subjetiva

Dudas

- Es un LES? o una PAM? o un Wegener?
- Es frecuente la vasculitis en el LES?
- Se eligió el mejor tratamiento?
- Seguiríamos con CFM o mejor con MM?

Vasculitis y LES

Vasculitis in Systemic Lupus Erythematosis

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Abstract. *Vasculitis in connective tissue diseases is not an uncommon complication. Vasculitis complicates both rheumatoid arthritis and systemic lupus erythematosis (SLE) in about 4% of cases.[1] Cutaneous lesions, representing small-vessel involvement, are most common; however, widespread, necrotizing visceral medium-and large-vessel involvement, mimicking primary vasculitic syndromes, may also occur. Connective tissue disease-associated vasculitis is separated from primary vasculitis syndromes in classification schemes. Granulomatous large-vessel disease does not occur in connective tissue diseases, suggesting a different pathogenesis.[2] In most disorders, the etiology of vascular inflammation in not completely understood, but basic pathogenic mechanisms can often be distinguished. The role of immune complexes in the inflammatory manifestations of SLE is recognized, and other pathogenic factors such as antineutrophil cytoplasmic antibodies, common in other vasculitides, are infrequent. A diverse spectrum of clinical features, due to inflammatory involvement of arterial and venous vessels of all sizes, characterize several connective tissue diseases including Behçet's disease and SLE. The recognition of disease manifestations due to vasculitis in these disorders has important implications for treatment and may be critical to reduce morbidity and mortality.*

Clinics in Dermatology • 2004;22:148–156

ANCA y LES

1: Am J Nephrol. 2000 Jan-Feb;20(1):57-63.

Clinical implications of antineutrophil cytoplasmic antibody test in lupus nephritis.

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To elucidate the prevalence and clinical implications of antineutrophil cytoplasmic antibody (ANCA) in lupus nephritis (LN), we examined ANCA by indirect immunofluorescence and by ELISA against antilactoferrin (anti-LF) and antimyeloperoxidase (anti-MPO) antibody. To discriminate perinuclear ANCA (pANCA) with antinuclear antibody (ANA), all the ANCA-positive sera were tested again after incubating patients' sera with single-stranded (SS) and double-stranded (ds) DNA. These results were compared with clinicopathologic manifestations and clinical courses of LN. ANCA was positive in 19 (37.3%) of 51 LN patients. Among these LN patients, 3 had cytoplasmic ANCA (cANCA) and 16 had pANCA. ANCA was not found in 8 SLE patients without nephritis and 30 normal controls. The presence of ANCA, particularly pANCA, was associated with the presence of nephritis (18/51 cases vs. 0/8 cases, $p < 0.05$), especially with diffuse proliferative lupus nephritis, WHO class IV (17/18 cases vs. 21/31 cases, $p < 0.05$) as well as the presence of anti-dsDNA antibody (17/19 cases vs. 18/30 cases, $p < 0.05$). Patients with ANCA frequently had deterioration of renal function (3/16 vs. 0/26 cases). Anti-LF antibody was positive in 13 patients. Among those, 12 patients had nephritis. Five patients with anti-LF antibody did not have ANCA, but 7 had pANCA, and 1 had cANCA. Patients with anti-LF antibody had lower initial creatinine levels than those without it [serum creatinine (mg/dl): 0.78 (0.6-1.0) vs. 1.43 (0.5-5.0), $p < 0.05$]. Anti-MPO antibody was positive in only 1 patient, suggesting that MPO is a rare antigen for ANCA in LN. Copyright 2000 S. Karger AG, Basel

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ANCA y LES

1: J Assoc Physicians India. 2004 Jul;52:533-7.

Anti-neutrophil cytoplasmic antibodies (ANCA) in systemic lupus erythematosus: prevalence, clinical associations and correlation with other autoantibodies.

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AIM: This study was undertaken to clarify the nature of anti-neutrophil cytoplasmic antibodies (ANCA) along with other autoantibodies in lupus nephritis (LN) patients and in systemic lupus erythematosus (SLE) patients without nephritis and to know their correlation with clinical manifestations and presence of other autoantibodies. MATERIAL AND METHODS: Fourty one LN patients and 18 SLE patients without nephritis were studied. LN patients were subdivided into diffuse proliferative glomerulonephritis (DPGN), focal proliferative glomerulonephritis (FPGN), rapidly progressive glomerulonephritis (RPGN) and membranoproliferative glomerulonephritis (MPGN). Anti-neutrophil cytoplasmic antibodies (ANCA) were detected by indirect immunofluorescence and confocal laser scanning microscope using PMN and HL60 cells. ANCA specificities like anti-myeloperoxidase (anti-MPO), anti-proteinase 3 (anti-PR3), anti-lactoferrin (anti-LF) and anti-cathepsin G (anti-CG) were detected by ELISA. Other autoantibodies like anti-nuclear antibodies (ANA), anti-double stranded DNA (anti-dsDNA), anti-single stranded DNA(anti-ssDNA), anti-ribonucleoproteins (anti-nRNP), anti-Smith antibodies (anti-Sm) and rheumatoid factor (RF) were also tested. RESULTS: ANCA was detected in 37.3% patients. The predominant ANCA pattern was perinuclear (p-ANCA). ANCA positivity was higher in LN patients and when confirmed by ELISA, 54.5% ANCA positives had anti-myeloperoxidase (anti-MPO). The cytoplasmic ANCA (c-ANCA) pattern was not seen in any patient. Two patients having FPGN with crescents showed atypical 'X-ANCA' pattern with dual specificity to anti-MPO and anti-PR3 by ELISA. The titers of ANCA were more in LN as compared to SLE without nephritis. LN cases having DPGN, FPGN, RPGN with crescents had higher titer p-ANCA positivity with corresponding anti-MPO antibodies, along with ANA, anti-dsDNA, anti-ssDNA and anti-Sm + anti-nRNP and also high SLEDAI scores. CONCLUSION: ANCA in SLE may be used as a serological marker along with clinical and histopathological assessment to differentiate vasculitides in LN cases from SLE without nephritis.

ANCA y LES

1: Clin Exp Rheumatol. 1998 Sep-Oct;16(5):541-6.

Anti-neutrophil cytoplasmic antibodies in 566 European patients with systemic lupus erythematosus: prevalence, clinical associations and correlation with other autoantibodies. European Concerted Action on the Immunogenetics of SLE.

Galeazzi M, Morozzi G, Sebastiani GD, Bellisai F, Marcolongo R, Cervera R, De Ramòn Garrido E, Fernandez-Nebro A, Houssiau F, Jedryka-Goral A, Mathieu A, Papasteriades C, Piette JC, Scorza R, Smolen J.

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OBJECTIVES: To evaluate, in a cohort of 566 patients with systemic lupus erythematosus (SLE) drawn from 11 European centres: (i) the prevalence of ANCAs and their subspecificities in a large series of European SLE patients; (ii) the possible associations of ANCA with the most common clinical manifestations of the disease; and (iii) whether ANCAs correlate with some of the autoantibodies commonly found in SLE. METHODS: ANCA detection was performed by indirect immunofluorescence (IIF), and by ELISA for lactoferrin (LF), myeloperoxydase (MPO), proteinase3 (PR3) and lysozyme (LZ) subspecificities. RESULTS: The prevalence of ANCA was 16.4% (IIF). The prevalence of LF was 14.3%, LZ 4.6%, MPO 9.3%, and PR3 1.7%. Our results show that ANCA is associated with certain clinical manifestations of SLE. In particular, positive correlations were found between IIF ANCA and serositis (p = 0.026), livedo reticularis (p = 0.01), venous thrombosis (p = 0.03) and arthritis (p = 0.04), while anti-LF antibodies were associated with serositis (p = 0.05) and livedo reticularis (p < 10(-3). Nevertheless, multivariate analysis demonstrated that other autoantibodies, such as aCL and SSA/Ro, are more closely correlated than ANCA with some of the aforementioned clinical features. CONCLUSION: Our results demonstrate that ANCA are detectable in SLE sera and that some of them are associated with particular clinical manifestations. Whether ANCA plays a direct pathogenetic role in the vascular damage of SLE or only represents an epiphenomenon or a marker of disease activity remains to be elucidated.

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