Con la colaboración de:

NOVARTIS

Sociedad Española de Reumatología

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ÁMSTERDAM JUNIO 2018

REVIEW

Annual European Congress of Rheumatology

AMPLIADO
SÍNDROME ANTIFOSFOLÍPIDO
SÍNDROME DE SJÖGREN

María José Cuadrado Lozano

Clínica Universidad de Navarra-Madrid

PLASMABLAST PROLIFERATION IS ASSOCIATED WITH TLR7 POLYMORPHISMS AND UPREGULATION OF TYPE I INTERFERON, CONTRIBUTING TO THE ANTIBODY PRODUCTION IN APS

- 26 primary APS, 18 SLE/APS patients and 10 healthy controls
- B cell and T cell subsets, (21 subsets), were evaluated in PBMC
- 21 single nucleotide polymorphisms (SNP), associated with autoimmune or thrombotic diseases, were analysed in genomic DNA
- IFN score was calculated based on the mRNA expression of Ly6e, Mx1, IFIT1 and IFIT3 in PBMC.
- To evaluate the aPL-producing capability of plasmablasts, PBMC obtained from APS patients were cultured following depletion of CD19 +CD20+ or CD19+CD20- cells and aPL were measured in the supernatants

PLASMABLAST PROLIFERATION IS ASSOCIATED WITH TLR7 POLYMORPHISMS AND UPREGULATION OF TYPE I INTERFERON, CONTRIBUTING TO THE ANTIBODY PRODUCTION IN APS

- Increased plasmablasts, Th2 and Th17
- Decreased memory B, regulatory B and regulatory T cells
- Genomic analysis revealed that the increase of plasmablasts (p=0.032) and the decrease of memory B cells (p=0.013) were more pronounced in patients with a risk allele of SNP in toll like receptor 7 (TLR7) gene (rs3853839).
- IFN score was significantly higher in the TLR7 SNP risk allele carriers, confirming the downstream signalling of TLR7 (p=0.029)
- aPL, including anti-cardiolipin/β2-glycoprotein I were present in the culture supernatant of CD19 +CD20+depleted PBMC from APS patients, but not in that of CD19 +CD20 depleted cells.
- Important role of plasmablasts in the production of aPL. Plasmablast proliferation was associated with TLR 7 and type I IFN, suggesting a common pathophysiology in SLE and APS.
- Targeting plasmablasts might be a novel, immunological therapeutic approach in the treatment of APS.

IS HYPERHOMOCYSTEINEMIA (HHC) ADDITIONAL RISK FACTORS OF THROMBOSES IN PATIENTS WITH SLE/ APS

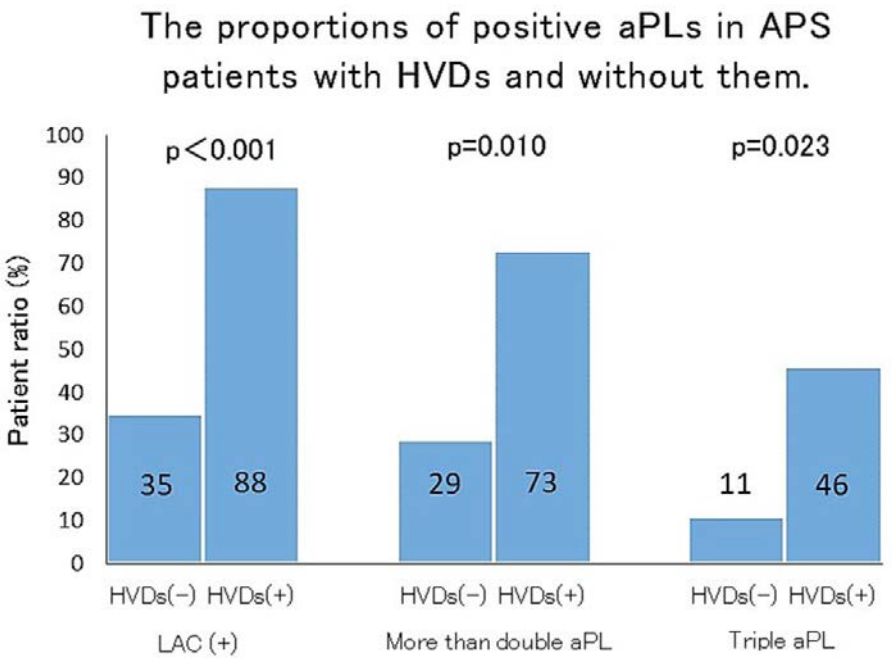
- 125 patients: group 1 – SLE patients (n=51); group 2 – SLE +APS patients (n=49); group 3 – primary APS patients (n=25)
- HHC: 82 of 125 (66%) patients: 59% SLE, 67% SLE+APS, 76% APS.
- HHC and digital necrosis: 80% with DN vs 57% without DN (p=0.03).
- HHC: 43 of 55 (78%) APS patients with thromboses vs. 9 of 19 (47%) aPL-positive SLE patients without thromboses (p=0.03).
- HHC in patients with arterial thromboses (in all 14 patients) vs venous thromboses – in 16 of 23 (69.9%) (p=0.03)
- HHC was associated with thromboses of cerebral (90%), peripheral arteries (84%) and myocardial infarction (79%) vs. 47% of patients without thromboses (p=0.005; p=0.04, p=0.04 respectively).

HIGH RISK OF MISTAKEN CLASSIFICATION OF PRIMARY APS AS SLE ACCORDING TO THE SLICC CRITERIA: ANALYSIS OF A COHORT OF 214 ANTIPHOSPHOLIPID PATIENTS

- “SLE-specific” manifestation (biopsy-proven SLE nephropathy, arthritis, cutaneous, neurologic SLE, pericarditis, AHA, oral and nasal ulcers, non-scarring alopecia, anti-dsDNA, and anti-Sm antibodies)
- Excluded patients with SLE specific manifestation or other CTD (114)
- 28% met at least 4 SLICC classification criteria and could be classified as SLE
- Any future classification for SLE should specifically require at least one SLE-specific criterion for patients with aPL.

RISK FACTORS FOR HEART VALVE DISEASES IN APS PATIENTS

- 43 patients underwent echo.
- Six patients were primary APS, 36 were secondary APS (35 SLE, 1 SS)
- HVDs in 26 (60.5%) 20 MR, 8 AR and 1 Libman-Sacks endocarditis.
- No clinical differences (use of prednisolone, miscarriages, arterial or venous thrombosis.
- No significant difference in anti-dsDNA antibody or ENA antibodies.
- Positivity of aCL or anti-β2GPI was not different
- Positive LA was much higher in patients with HVDs (88.5% vs 35.3%, p<0.01);
- Double and triple positive tests of aPLs significantly more frequently (p=0.010 and p=0.023)
- Hospitalisation risk in patients with HVDs because of heart failure or syncope were 0.011/patient year.



B-CELLS DEPLETION AS RESCUE THERAPY FOR EXTRA-CRITERIA MANIFESTATIONS OF PRIMARY APS

- 7 PAPS patients (median age 53)
- Six patients presented with severe thrombocytopenia (plaquetas <50.000/mm3)
- 1 patient presented with recurrent superficial venous thrombosis (3 events in 6 months despite ongoing anticoagulation therapy with VKA)
- Full response after treatment with RTX in 6 out of 7 patients (86%, 5 with thrombocytopenia and 1 with recurrent superficial thrombosis)

	Age	aPL profile	Clinical manifestations of APS	Extra-criteria manifestations	RTX Protocol	Adverse events	Previous Immuno modulant Therapy	Anticoagulant therapy	Time free from relapse (months)
Patient 1 (male)	45	Triple positivity	1 episode of TVP and PE, 1 episode of retinal thrombosis	Recurrent superficial venous thrombosis	CYC 750mg/weekly for 2 weeks and RTX 375 mg/m2 weekly for 4 weeks + 2 monthly infusions	None	IVIG	Warfarin, target INR 2,5-3,5	10-ongoing
Patient 2 (female)	38	Triple positivity	1 episode of stroke	Severe thrombocytopenia	RTX 375 mg/m2 weekly for 4 weeks + 2 monthly infusions	None	IVIG	Warfarin, target INR 2-3	94-ongoing
Patient 3 (female)	46	Triple positivity	1 retinic haemorrhage, 1 thrombosis of dural venous sinuses, 1 thrombosis of the Jugular vein	Severe thrombocytopenia	RTX 1g/15 days, 2 infusions in total	None	IVIG, high doses of steroids	Warfarin 2,5-3,5, then Fondaparinux	12
Patient 4 (female)	53	LA positive	Recurrent miscarriages, Thrombosis of the Abdominal aorta	Severe thrombocytopenia	RTX 1g/15 days, 2 infusions in total	None	IVIG, high doses of steroids	Warfarin, target INR 2-3	4-ongoing
Patient 5 (female)	58	Triple positivity	1 episode of TVP and PE, 1 recurrence of TVP	Severe thrombocytopenia	RTX 375 mg/m2 weekly for 4 weeks + 2 monthly infusions	None	None	Warfarin, target INR 2-3	43-ongoing
Patient 6 (female)	60	Triple positivity	1 episode of stroke	Severe thrombocytopenia	RTX 375 mg/m2 weekly for 4 weeks + 2 monthly infusions	None	IVIG	Warfarin, target INR 2-3	97-ongoing
Patient 7 (female)	66	Triple positivity	1 episode of TVP	Severe thrombocytopenia	RTX 375 mg/m2 weekly for 4 weeks	None	High doses of steroids	Warfarin, target INR 2-3	0

APS Antiphospholipid Syndrome, UC undifferentiated connective tissue disease, CYC cyclophosphamide, RTX rituximab, AZA azathioprine, MTX methotrexate, DVT deep vein thrombosis, PE pulmonary embolism

APS PLENARY SESION

- aPL carriers:
  -Riesgo de thrombosis: Low: 2.8/100 patients/year
  -LA strongest association with thrombosis
  -Role of aPS/PT
  -Role of Homocystein
  -LDA does not protect

APS PLENARY SESSION
SLE AND APL/APS

- 30-40% SLE will develop aPL
- 20% will develop APS
- Increased:
  - Organ damage (SLICC)
  - Mortality
  - Thrombotic events
  - Pregnancy morbidity
  - Heart Valve affections

- Increased:
  - Neurological symptoms
  - Thrombocytopenia
  - Complement activation
  - Circulating IFN type I and II
  - HLA-DRB1*04/*13, STAT4

APS PLENARY SESSION

- Kidney involvement in APS
  - Renal artery thrombosis
  - Renal vein thrombosis
  - Renal infarction
  - APS nefropathy (intrarenal vasculature)
- In primary APS: renal involvement ignored and very rarely biopsy
- In SLE: emphasis on GN

APS PLENARY SESSION

- Pathogenesis
  - Complement activation
  - Tissue factor overexpression
  - Toll like receptor
- Treatment: is anticoagulation indicated?
  - No agreement

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SJOGREN SYNDROME

BIOPSY STILL NEEDED IN SJOGREN SYNDROME?

- Labial gland or parotid gland biopsy included in the criteria
- 18-40% have a negative biopsy
- 5-10% of general population can have an abnormal biopsy
- Positive ultrasound and anti-Ro/La positive likely to fulfil criteria
- Biopsy higher sensitivity than US (95,5 vs 82,2%)
- Biopsy not needed if:
  - High clinical suspicious
  - anti-Ro/La positive
  - US findings consistent wit pSS

REASONS TO TAKE A BIOPSY

- Suspicion Maltoma (majority located in parotid gland)
- Diferential Diagnosis:
  - Non specific chronic sialadenitis (Atrophy, more difuse)
  - Obstructive sialadenitis (Neutrophilic infiltrate)
  - IG4-related disease (Fibrosis, many plasma cells)
  - Sarcoidosis (Non-ceasating granulomas)
  - Amyloidosis (Rojo Congo staining positive)

FACTORS ASSOCIATED WITH PULMONARY MANIFESTATIONS IN SJOGREN SYNDROME

- Approximately one-third of patients have respiratory symptoms (43%–75%), that are a cause of morbidity and conditioning quality of life.
- The SJOGREN-SER registry included 437 patients.
- 117 patients (26.8%) had pulmonary manifestations (19.2% airway disease and 9.8% pulmonary involvement). Ten patients presented both.
- Higher ESSDAI score , prolonged disease duration and ANA positive more frequently.
- Airway involvement preceded or occurred at the time of diagnosis in 46.4% of patients.

RESUMEN

- Síndrome antifosfolípido
  - Plasmoblasts therapeutic target
  - Homocystein in arterial thrombosis
  - aPL carriers low risk of thrombosis
  - TMA anticoagulation when acute lessions
  - Experience with Rituximab only in thrombocytopenia

RESUMEN

- Sjogren Syndrome
  - No biopsy if clinical, parotid US and anti-Ro/La positive
  - Biopsy if diferential diagnosis is needed or MALTOMA suspicious
  - Respiratory involvement in 30% of patients
  - Associated with higher ESSDAI score , prolonged disease duration and ANA positive