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AB0471 ELEVATED EXPRESSION OF PYRUVATE KINASE M2 IN GIANT CELL ARTERITIS

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Background: Giant Cell Arteritis (GCA) is an inflammatory disease of large and medium vessels. In GCA, expression of interleukin-6 (IL-6), a systemic marker of inflammation, is elevated and it has been shown that treatment with IL-6 receptor blockade (Tocilizumab) is beneficial for GCA patients.¹ To investigate the role of the IL-6 signaling pathway in GCA pathogenesis in more depth, we focused on the metabolic enzyme Pyruvate Kinase M2 (PKM2). PKM2 may exist as a tetramer, a dimer and/or a monomer in the cell. Tetrameric PKM2 acts as a glycolytic enzyme and catalyzes the last steps of glycolysis by converting phosphoenolpyruvate (PEP) to pyruvate and ATP. On the other hand, dimeric PKM2 translocates to the nucleus and mediates gene regulation via its non-canonical protein kinase activity. Dimeric PKM2 regulates hypoxia, IL-1 β expression and, phosphorylates signal transducer and activator of transcription 3 (STAT3) which functions downstream of the IL-6 signaling pathway.²

Objectives: To investigate the role of PKM2 in GCA diagnosis and pathogenesis.

Methods: Immunohistochemical staining for PKM2 was performed on inflamed (n=8) and non-inflamed (n=4) temporal artery biopsies (TAB) from GCA patients and on TAB from non-GCA (n=9) patients. To detect soluble, dimeric PKM2 in plasma commercially available dimeric PKM2 specific ELISA kit was used. To determine the modulation of dimeric PKM2 by treatment, samples of GCA patients at baseline (n=44), at 6 weeks (n=32) and at 1 year (n=31) after treatment were compared to samples from age- and sex-matched healthy controls (HC, n=45). As a positive control, samples from melanoma patients (n=8) were used. To investigate the role of dimeric PKM2 in the pathogenesis of GCA, we correlated PKM2 plasma levels with markers of inflammation (CRP, IL-6) and markers of angiogenesis (Angpt2, VEGF, YKL40). Statistical analysis included the Mann-Whitney U test for comparing different groups while the Wilcoxon rank test was used for paired samples. Correlations were assessed by Spearman's rank correlation coefficient.

Results: High expression of PKM2 was found in inflamed and non-inflamed TABs of GCA patients, while in non-GCA TABs PKM2 was sparsely expressed. Circulating levels of dimeric PKM2 were found elevated in melanoma and in GCA patients at baseline/active disease compared to those in healthy controls. Analysis of 6 weeks and 1 year follow up plasma samples showed that plasma levels of dimeric PKM2 significantly decreased upon treatment. Dimeric PKM2 weakly correlated with CRP at baseline ($r=0.399$, $p=0.048$) but not with angiogenesis markers.

Conclusion: Dimeric PKM2 plasma levels were found elevated in GCA patients at baseline. PKM2 plasma levels were down modulated by treatment. PKM2 plasma levels weakly correlated with inflammation marker CRP. The data suggest that PKM2 as a marker of glycolysis may have relevance in GCA at diagnosis and for monitoring disease activity. Future studies should aim to validate PKM2 in an independent cohort. Additional studies are needed to determine the molecular mechanism underlying the increase in elevated dimeric PKM2 levels and how this may contribute to IL-6 signaling.

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AB0472 INFECTIOUS PROFILE IN PATIENTS WITH ANCA-ASSOCIATED VASCULITIS: RETROSPECTIVE ANALYSIS IN A REFERRAL CENTRE

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Background: The antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) are rare multisystem autoimmune diseases of unknown cause, characterised by inflammatory cell infiltration causing necrosis of blood vessels. The treatment of AAV requires prolonged immunosuppressive therapy. Infections remain a major cause of morbidity and mortality.

Objectives: The aim of our study was to investigate the prevalence and characteristics of infection, and analyse the factors associated with infection in patients with AAV from Northern of Spain.

Methods: Retrospective, descriptive study of patients with AAV followed in a specific Systemic Autoimmune Diseases and Thrombosis Unit from January 2000 to December 2019. Demographic, laboratory, microbiology, treatment and clinical data were collected from the medical records. AAV was diagnosed according to the definitions of the Chapel Hill nomenclature and designated as granulomatosis with polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis (EGPA), microscopic polyangiitis (MPA) or pauci-immune necrotizing and/or crescentic glomerulonephritis without systemic vasculitis (renal-limited vasculitis, RLV). Disease activity of AAV was evaluated by Birmingham Vasculitis Activity score (BVAS). The infection episode was considered on the basis of clinical, laboratory, microbiology, radiology information, and response to therapy. Different episodes of infection in one patient were independently reflected. Data were analysed using SPSS 25.0

Results: Thirty-six patients of which 20 (55.6%) were males. Median follow-up was 42 months. The mean age at the diagnosis was 61.14 ± 17.49 years and mean BVAS was 18.81 ± 5.96 . 15 patients were diagnosed of GPA, 13 of MPA, 5 of EGPA and 3 of RLV. 72.2% MPO, 11.1% PR3. Lung involvement occurred in 75% of patients, upper airways was detected in 41.7%, skin involvement in 16.7%. Nervous system affection occurred in 33.3%. 30 patients (83.3%) had renal affection with a mean of 1.93 ± 1.66 gr/dl of Proteinuria and 2.9 ± 2.17 mg/dl of creatinine. We detected hypocomplementemia in 27.8% of patients (C3 in 19.4% and C4 in 16.7%). Regarding induction treatments, all patients received corticoids at high doses, 21 (58.3%) Cyclophosphamide, 3 (20%) Rituximab and 2 (13.3%) patients, Azathioprine. When we analyse infections, we detected 15 patients (41.66%) who presented any infection after the diagnosis of AAV, with a total of 71 episodes of infection. The most frequent were bacterial infections (29 episodes), specifically gram negative pathogens. The most frequent location was the respiratory (56.3%) followed by urinary (22.5%) and Skin (8.5%). Also opportunistic infections were described: 3 patients with *Aspergillus fumigatus* and one patient with *Cryptococcus neoformans*. 41 of these episodes needed hospitalisation with a median stay of 11 days. 6 episodes warranted intensive care unit (ICU) admission. Infection related mortality was 2.82%. We made latent tuberculosis screening and *Pneumocystis* prophylaxis in all our patients. No cases of Tuberculosis or *Pneumocystis* were recorded. Factors associated with increased risk of hospitalisation with statistical significance in univariate study were MPA, Hypocomplementemia and increased BVAS. But in the logistical regression study, only the value of the BVAS maintained statistical significance. The only factor associated with elevated risk of ICU admission was IgG deficit in the multivariate analysis. Neither immunosuppressive therapy nor age was associated with increased risk of infection in our study.

Conclusion: More than 50% of the episodes of infection needed hospitalisation in patients with AAV. Risk factors for hospitalisation and ICU admission were BVAS and IgG deficit respectively. Bacterial infections were the most frequent but fungal infections were the most severe.

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AB0473 "HALO SIGN" IN ULTRASOUND OF TEMPORAL, FACIAL AND AXILLARY ARTERIES: ASSOCIATIONS WITH CLINICAL SYMPTOMATOLOGY AND LABORATORY FINDINGS

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Background: Giant cell arteritis (GCA) has two subtypes, the cranial form ("cranial GCA") and the large-vessel form ("LV-GCA"). GCA can present with "cranial" symptoms (headache, visual symptoms, jaw claudication, scalp tenderness), constitutional symptoms (fever, fatigue), limb claudication and symptoms of polymyalgia rheumatica (PMR) and usually causes increased inflammation markers, anemia and thrombocytosis. Ultrasound (US) of the temporal and axillary arteries

has a well-established role in cranial GCA and LV-GCA diagnosis, respectively. However, it is unknown whether specific clinical and laboratory parameters are linked with US findings suggestive of vascular inflammation ("halo" sign).

Objectives: The aim of this study was to examine possible association between clinical and laboratory characteristics of the patients and detection of vessel wall inflammation in the US.

Methods: Patients ≥ 50 years old with elevated ESR (≥ 50 mm/h) and/or CRP (≥ 10 mg/L) that presented in our outpatient rheumatology clinics from July 2017 to December 2019 with possible clinical diagnosis of GCA were included. Three groups were compared: Patients with "cranial symptoms" (with or without PMR), patients with PMR symptoms only and patients with increased inflammation markers without specific symptoms indicative of GCA. Temporal arteries and their main branches, as well as facial and axillary arteries were evaluated by US bilaterally for the presence of non-compressible "halo sign" at the vessel wall. Clinical symptomatology and the occurrence of anemia and thrombocytosis were recorded.

Results: 52 patients were included. 71.2% were females, with a mean $\pm$ SD age of 71.0 ± 10.0 years. 17 patients had "cranial symptoms" (seven patients with concomitant PMR and ten without), 17 patients had PMR symptoms only, while 18 patients had non-specific symptoms (e.g. fever) (Table 1). Among 17 patients with "cranial symptoms", 7/7 (100%) with concomitant PMR had a positive temporal US, while only 3 out of 10 (30%) without PMR had a positive temporal US ($p<0.01$) and US was indeterminate in 2 of them (20%). Collectively, 10/17 (58.8%) of patients with "cranial symptoms" and systemic inflammation had a US examination compatible with GCA. No patient with "cranial symptoms" had a positive US of axillary arteries. No patient with only PMR symptoms, had "halo sign" in temporal and facial arteries, while 3 out of 17 (17.6%) had a positive axillary US. From the 18 patients with elevated ESR/CRP, one had a positive temporal US and another one had a positive axillary US. Regarding specific symptoms, positive temporal US was associated with new headache ($p=0.003$), vision impairment ($p=0.001$), jaw claudication ($p=0.05$), scalp tenderness ($p=0.01$) and fever ($P=0.002$), but not with PMR ($p=0.317$). Thrombocytosis was associated with an increased risk for "halo sign" detection in temporal ($p=0.04$) and facial ($p=0.007$) arteries, but not in axillary arteries ($p=0.52$).

Table 1. Symptomatology and ultrasound findings in the patients examined. PMR: Polymyalgia Rheumatica

Ultrasound	Symptoms			
	Cranial (n=17)		PMR only (n=17)	Non-specific symptoms (n=18)
	PMR (+) (n=7)	PMR (-) (n=10)		
Temporal (+)	7	3	0	1
Facial (+)	2	1	0	0
Axillary (+)	0	0	3	1

Conclusion: 60% of patients with "cranial symptoms" and elevated inflammation markers have US temporal findings indicative of GCA. This is more pronounced in patients with concomitant PMR symptoms and is associated with specific symptomatology. 18% of patients with only PMR symptoms might have LV-GCA, while those with high ESR/CRP without GCA-related symptoms rarely have "halo sign" in US.

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AB0474 CAROTID CONTRAST ENHANCED ULTRASOUND IN CASES OF TAKAYASU ARTERITIS COMPLICATED WITH BEHCET'S DISEASE

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Background: Carotid contrast enhanced ultrasound (CEUS) is used for diagnosis and activity determination of patients with Takayasu's arteritis (TA). However, very little is known about the carotid CEUS features of TA complicated with Behcet's disease (BD).

Objectives: This study reports the carotid CEUS features in cases of TA complicated with BD (TBD).

Methods: A total of 10 carotid CEUS examinations were performed on 4 patients of TBD. 10 TA patients complicated with no rheumatoid disease were included as control group. For each carotid artery lesion, the carotid CEUS features was graded as follows: Grade 0, artery wall shows no microbubbles, Grade 1, artery wall shows limited or moderate microbubbles, Grade 2, artery wall shows severe microbubbles.

Results: 2/10 patients in TBD group has oral ulcer during the CEUS examination, while all the other patients included in our study showed no clinical symptoms related to active TA or BD. The carotid wall thickness was greater of CEUS grade 2 than grade 1 in both group (TBD: 2.62 ± 0.74 mm vs 1.66 ± 0.22 mm, $p=0.001$; TA: 1.84 ± 0.31 mm vs 1.53 ± 0.5 mm, $p=0.136$). The carotid wall thickness

was significantly greater in TBD group than TA group, but there was no significant differences between the two groups in clinical data and CEUS grade (table 1).

Table 1. Clinical data and carotid CEUS features of both groups

	TBD	TA	p
Age (year)	32.5 $\pm$ 3.44	30.5 $\pm$ 9.2	0.487
Male	3	2	0.605
ESR (mm/h)	4(2, 10)	7(3.5, 11)	0.406
CRP (mg/L)	6.42(0.55, 15.38)	0.58(0.44, 5.05)	0.168
Wall thickness (mm)	2.10 $\pm$ 0.70	1.67 $\pm$ 0.44	0.030
CEUS grade 2	9	12	0.527

Conclusion: This study first shows carotid CEUS features in cases of TA complicated with BD, which may help with the comprehensive treatments of the disease.

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AB0475 CLINICAL RELEVANCE OF CLINICOPATHOLOGICAL PHENOTYPE AND ANTIBODY SPECIFICITY IN ANCA-ASSOCIATED VASCULITIS

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Background: Classification of ANCA-associated vasculitis (AAV) has emerged in order to identify more homogenous subgroups of patients with granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA). However, the exact value of classifying patients according to antibody specificity (proteinase 3 [PR3] or myeloperoxidase [MPO]) is still unclear.

Objectives: To assess demographic, clinical and prognostic differences among subgroups of AAV patients, according to clinicopathological classification (GPA vs. MPA) and antibody specificity (PR3 vs. MPO) in a single-centre cohort.

Methods: A clinical retrospective (1990-2019) observational analysis was performed. Among all patients with ANCA positivity, we analysed patients with GPA and MPA diagnosed according to 2018 Draft Classification Criteria for AAV¹, who were homogeneously treated and followed by the authors. Demographic, clinical and laboratory data, as well as disease outcomes, particularly BVAS, disease relapses and survival, were reviewed.

Results: Among a total 140 patients with any form of AAV, 32 were excluded for a diagnosis of isolated interstitial lung disease (n=10), cocaine-induced AAV (n=3), ANCA negative or undetermined disease (n=16), atypical ANCA or double PR3/MPO positivity (n=3). Finally, 108 patients with MPA (n=66) or GPA (n=42) were included (83 MPO, 25 PR3). GPA was associated with PR3 in 55% and MPO 45% of patients. MPA was associated with MPO in 97% and PR3 in 3% of patients. GPA patients with PR3 or MPO presented with similar clinical features, disease extent and BVAS. However, compared with GPA/PR3, GPA/MPO were more frequently women ($p=0.002$). MPA patients presented more frequent with renal involvement ($p=0.008$) and GPA patients with ENT/ocular involvement ($p<0.001$). Patients with MPO were older ($p=0.028$) and more frequently women ($p=0.001$) than PR3