Spontaneous MCP-1 production by nephritic glomeruli ex vivo was reduced following incubation with R406, the active metabolite of FOS, in a dose-dependent manner. IHC was positive for SYK in diseased rodent and human renal tissue (anti-GBM and AAV) but not in healthy controls.

Discussion.— SYK inhibition reverses CGN and prevents LH in EAG, by inhibiting both the induction of humoral autoimmunity and the effector immune response. We believe this is the first report that SYK inhibition reduces autoantibody production in a genuine model of autoimmunity. SYK is expressed in comparable human glomerular diseases. Conclusion.— SYK inhibition may warrant further investigation as a treatment strategy in human autoimmune glomerular diseases, such as AAV and anti-GM1 disease.

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A8 Serum biomarkers signature identifies patients with overt B-cell non-Hodgkin lymphoma associated with mixed cryoglobulinemia in chronic HCV infection


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Introduction.— Hepatitis C virus (HCV) is associated with B-cell disorders, including mixed cryoglobulinemia (MC) and B-cell non-Hodgkin lymphoma (B-NHL). Early diagnosis of B-NHL in HCV-infected patients is critical. We hypothesized that combination of serum biomarkers could be used to identify B-NHL associated with MC in patients with chronic HCV infection.

Methods.— One hundred and fifty-five HCV-infected patients have been exposed to drugs known to cause disease: 46 (33%) received PTU, sulfasalazine and as recently described by our group, levaquin, however, drug-induced forms of disease exist. Reported culprits include hydralazine, minocycline, penicillamine, propylthiouracil (PTU), sulfasalazine and as recently described by our group, levaquin. Our group has been the main clinical ANCA laboratory in New England and evaluation of positive patient, a limited discussion was held with the ordering clinician to review implications of the positive test and to identify exposure to any known culprit drugs (discussions noted in MGH ANCA clinician to review implications of the positive test and to identify exposure to any known culprit drugs (discussions noted in MGH ANCA test registry were used for initial data analyses).

Results.— A total of 2257 patients with positive ANCA tests were included, with and without MC and/or B-NHL. We measured serum levels of eight markers previously described to be increased in patients with B-NHL i.e. sCD22, sCD27, sIL-2Rα, sCD137, free-light chains of Ig, heavy chains of Ig, gammaglobulins and C4 complement fraction. We used a multiparametric analysis to determine a signature that identifies patients with overt B-NHL.

Discussion.— Serum levels were significantly different between patients without MC, patients with asymptomatic MC, patients with MC vasculitis and those with MC vasculitis and B-NHL: sCD22 (6.7 vs. 11.9 vs. 20.8 vs. 36.4 ng/ml, P < 0.0001), sCD27 (71.9 vs. 75.7 vs. 122.9 vs. 263.9 U/ml, P < 0.0001), sIL-2Rα (877 vs. 1035 vs. 2206 vs. 4044 pg/ml, P < 0.0001), sCD137 (296 vs. 426 vs. 539 vs. 763 pg/ml, P < 0.0001), free-light chains of Ig (ratio κ/λ: 1.13 vs. 1.08 vs. 1.79 vs. 3.01, P < 0.0001), heavy chains of Ig (ratio IgMκ/IgMλ: 1.90 vs. 1.85 vs. 3.13, P < 0.0001), gammaglobulins (14.1 vs. 17.0 vs. 12.1 vs. 6.0 g/L, P < 0.0001) and C4 complement fraction (0.23 vs. 0.16 vs. 0.07 vs. 0.04 g/L, P < 0.0001).

Conclusion.— Using multiparametric analysis, we identified a signature involving sCD27, sIL-2Rα, gammaglobulins and C4 levels associated with the presence of overt B-NHL in HCV-infected patients. This signature had a sensitivity of 100%, specificity of 63%, and positive and negative predictive values of 94 and 100% for discriminating patients with overt B-NHL and those without B-NHL.

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Introduction.— The etiology of vasculitides associated with anti-neutrophil cytoplasmic autoantibodies (ANCA) remains largely unknown; however, drug-induced forms of disease exist. Reported culprits include hydralazine, minocycline, penicillamine, propylthiouracil (PTU), sulfasalazine and as recently described by our group, levaquin in the presence of cocaine. Our group has been the main clinical ANCA laboratory in New England and evaluation of positive patients is needed to identify exposures to known and potential culprit drugs.

Patients.— We conducted a systematic retrospective analysis of patients from 1989–2012 with an initial positive ANCA test by indirect capture ELISA directed against either MPO and/or PR3. For each new ANCA-positive patient, a limited discussion was held with the ordering clinician to review implications of the positive test and to identify exposure to any known culprit drugs (discussions noted in MGH ANCA test registry were used for initial data analyses).

Results.— A total of 2257 patients with positive ANCA tests were identified: 1428 (63%) were MPO-ANCA, 793 (35%) PR3-ANCA, and 38 (2%) dual MPO- and PR3-ANCA. 139 (6%) patients were positive for any drug. We measured serum levels of eight markers previously described to be increased in patients with drug-induced vasculitis: sCD22, sCD27, sIL-2Rα, sCD137, free-light chains of Ig, heavy chains of Ig, gammaglobulins and C4 complement fraction. We used a multiparametric analysis to determine a signature that identifies patients with overt B-NHL.

Discussion.— Serum levels were significantly different between patients without MC, patients with asymptomatic MC, patients with MC vasculitis and those with MC vasculitis and B-NHL: sCD22 (6.7 vs. 11.9 vs. 20.8 vs. 36.4 ng/ml, P < 0.0001), sCD27 (71.9 vs. 75.7 vs. 122.9 vs. 263.9 U/ml, P < 0.0001), sIL-2Rα (877 vs. 1035 vs. 2206 vs. 4044 pg/ml, P < 0.0001), sCD137 (296 vs. 426 vs. 539 vs. 763 pg/ml, P < 0.0001), free-light chains of Ig (ratio κ/λ: 1.13 vs. 1.08 vs. 1.79 vs. 3.01, P < 0.0001), heavy chains of Ig (ratio IgMκ/IgMλ: 1.90 vs. 1.85 vs. 3.13, P < 0.0001), gammaglobulins (14.1 vs. 17.0 vs. 12.1 vs. 6.0 g/L, P < 0.0001) and C4 complement fraction (0.23 vs. 0.16 vs. 0.07 vs. 0.04 g/L, P < 0.0001).

Conclusion.— Using multiparametric analysis, we identified a signature involving sCD27, sIL-2Rα, gammaglobulins and C4 levels associated with the presence of overt B-NHL in HCV-infected patients. This signature had a sensitivity of 100%, specificity of 63%, and positive and negative predictive values of 94 and 100% for discriminating patients with overt B-NHL and those without B-NHL.

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Discussion.— This study represents the first and largest of its kind. The true number of drug-induced cases is likely underrepresented given that medications in use at the time of a positive ANCA test, in many cases, were unknown. Most importantly, the number of cases of ANCA vasculitis associated with many of these drugs is of concern given their ubiquitous use in the general population.

Conclusion.— Based on these results, measures should be implemented to limit hydralazine and propylthiouracil use and counsel against cocaine use.

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A10 High genetic diversity in nasal Staphylococcus aureus isolates from Granulomatosis with Polyangiitis (GPA) patients


Introduction.— Chronic nasal carriage of the bacterium Staphylococcus aureus occurs in 60-70% of GPA-patients compared to 20-30% of healthy controls and is a risk factor for disease relapses. It is unknown whether specific strains are prevalent in GPA-patients. Therefore, we investigated the genetic diversity of nasal S. aureus isolates from GPA-patients.

Methods.— One hundred and thirty-eight S. aureus isolates, isolated between 1990–1996 and 2006–2012 from 71 patients (41 males, age 56.3 ± 15.3 y) with PR3-ANCA-positive GPA, were analyzed for genetic diversity by Multiple-Locus Variable number tandem repeat Fingerprinting (MLVF) and spa-typing.

Results.— Both typing methods demonstrated high genetic diversity of S. aureus isolates, with a total of 71 distinct MLVF patterns and 45 different spa-types. With the MLVF similarity cut-off value set at 70%, the MLVF patterns showed the highest concordance with the respective spa-types, leading to 39 MLVF clusters. Five clusters contained > 5 isolates (resp. 27, 21, ten, seven and six, derived from resp. 16, 14, five, five and five patients). The remaining 34 clusters, containing 1-4 isolates, were generally comprised of the isolates of one patient. The most frequent spa-types were 1084 (n = 23, 13 patients), 1064 (n = 22, 15 patients), 1091 (n = 10, 6 patients) and t012 (n = 9, 7 patients). Intriguingly, spa-types 1064 and 1091 were primarily found in isolates from 2006–2012, whereas spa-types 1084 and 1012 were solely found in isolates from 1990–1996. Out of 46 patients that provided > 1 isolate, 23 showed a shift in spa-types over time, whereas the remaining 23 carried the same spa-type over time. In 15 out of 23 patients this shift occurred when isolation dates were > 1 year apart.

Conclusion.— The results indicate a distinct neutrophil phenotype in S. aureus antigens is followed to define the role of S. aureus in GPA.

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A11 Neutrophils in ANCA vasculitis – old and apathetic

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Introduction.— Neutrophils play an important role in the pathogenesis of ANCA associated vasculitis (AAV). We have previously shown that neutrophils from patients with AAV have a different phenotype compared to healthy controls (HC) such as a longer lifespan, higher percentage of CD177/PR3 positive neutrophils and elevated neutrophil oxygen (ROS) species upon stimulation. In this study we have further characterized the neutrophil phenotype and measured their ability to produce reactive oxygen (ROS) species upon stimulation.

Methods.— Blood from 45 patients with AAV, 25 SLE and 36 HC were analyzed. FACS for surface expression of CD10, CD14, CD16, CD32, CD177, CD88, CD62L and CD11b. The ROS production was measured by Phagoburst kit.

Results.— AAV as well as SLE patients have a significantly lower proportion of newly produced granulocytes (CD16low/CD10low) compared to healthy individuals (3.8% vs. 8.5%, P < 0.0001). These cells also lack CD177 on their surface and can in part explain the higher percentage of CD177/PR3 positive cells in AAV patients. Furthermore, granulocytes from both AAV and SLE patients produce less ROS upon stimulation with E. coli or PMA compared to healthy controls. There were no correlation with steroid doses but patients with low B cell counts produced less ROS than patients with normal counts. Both CD62L and CD11b were normal but CD88 was expressed to a lower degree (MFI = 350 vs. 438, P = 0.04).

Conclusion.— The results indicate a distinct neutrophil phenotype in chronic auto-inflammatory diseases that differs from healthy controls. Our data suggests that the influx of newly produced neutrophils is lower.