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**Computerized interstitial fibrosis quantification is the most powerful histological predictor of renal outcome in ANCA-associated vasculitis**

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**Introduction.**—Renal involvement in ANCA-associated vasculitis (AAV) is characterized by necrotizing crescentic glomerulonephritis (GN). Although a new glomerular-based histological classification has been proposed, its prognostic value is still debated. The aim of this study was to evaluate the prognostic value of computerized color image analysis of renal biopsies in AAV.

**Patients.**—We included 65 patients with AAV and biopsy-proven renal involvement. All renal biopsies were centrally classified according to the recently defined classification and divided in local GN (fGN = 50% normal glomeruli), crescentic GN (cGN = 50% crescent), mixed GN (mGN) or sclerotic GN (sGN = 50% globally sclerotic). Computerized interstitial fibrosis (IF) was analyzed with a specific software, using a colour segmentation imaging technique. The IF score was expressed as the ratio of fibrotic tissue area/total renal tissue area.

**Results.**—Renal function was defined by a mean serum creatinine of 433 ± 265 μmol/L. ANCA specificity was mostly anti-MPO (65%). Pathological classification showed fGN in 40%, cGN in 30%, mGN in 25%, sGN in 5% of patients. Mean IF score was 29 ± 11.6. If score was statistically associated with a former history of diabetes or hypertension, with anti-MPO, with arteriosclerotic lesions on the renal biopsy. There was no correlation between IF score and glomerular classification. Renal prognosis was defined as the proportion of patients with CKD stage 4/5 at 12 months. This endpoint was reached by 19% of patients. We found that the presence of sGN is associated with a poorer outcome, but we did not observe significant differences between the other categories. On the contrary, the IF was statistically associated with renal prognosis: the IF score was 35 ± 10% among patients with subsequent CKD 4/5, vs. 25 ± 10% (P < 0.01).

**Conclusion.**—Our study failed to correlate the glomerular classification with renal outcome. We show that quantification of IF on the renal biopsy, with a computerized method, can predict 1-year kidney function in AAV.

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**The necessity of the addition of interstitial pathological parameters on the glomerular histological classification to predict the long-term outcome in MPO-ANCA-associated RPGN cohort in Japan**

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**Introduction.**—The newly proposed classification categorized into focal, crescentic, mixed, and sclerotic classes showed prognostic value for 1- and 5-year renal outcomes in European cohort [1]. However, this is not adaptable in Japanese cohort dominant with microscopic polyangiitis (MPA) showing no significant difference between crescentic and mixed group and mixed showed more favorable prognosis [2]. The evaluation whether the addition of tubule-interstitial parameters is more predictive for renal outcome was performed in Japanese cohort.

**Patients.**—Eighty-seven patients, diagnosed ANCA-associated glomerulonephritis were analyzed retrospectively. All glomeruli obtained were categorized in four groups proposed by Berden et al. [2]. In addition, the severity of interstitial fibrosis and tubular atrophy was categorized into three grades (<50%, 50–74%, 75%). Estimated GFR and renal survival were analyzed at onset, 6 months, 1 year and 5 years after renal biopsy.

**Results:**

- all were MPA in Japan;
- in mixed group, 5 years outcome of patients with severe interstitial damage were significantly poorer than those with mild damage;
- in focal group, those with high interstitial fibrosis showed low eGFR from entry to 5 years;
- in sclerotic group, almost cases accompanied severe interstitial fibrosis with very low eGFR from entry.

**Discussion.**—MPA and GPA might have different progression course of renal injury, partly due to pre-existing nephrosclerosis in MPA which often occurs in more elderly patients than in GPA. The evaluation based on only glomerular lesion is not enough for long-term renal prognosis in Japan dominant with MPA.

**Conclusion.**—In Japanese MPA oriented AAV patients with GN, histological classification combining with glomerular and chronic tubulo-interstitial parameters might bring about more predictive potential for long-term renal outcome, especially in mixed group.

**References**


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**Long-term outcome in patients with both ANCA and GBM positivity**

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**Introduction.**—Anti-GBM disease is now considered a form of vasculitis [1]. The co-existence of anti-GBM and ANCA antibodies is rare. There are few data regarding long-term outcomes of these patients [2]. We assessed the long-term outcome of “double positive” patients in our centre.

**Patients.**—Double positive patients with a minimum of 2 years follow-up at our centre, were identified. Electronic and paper records were reviewed and outcome data collated. A comparison was made with
data obtained for patients presenting with AAV over the same time period.

Results.—Eleven patients were identified, nine female, with an average age of 57 years and average follow-up of 80 months. Seven patients had antibodies to MPO and GBM and three to PR3 and GBM. One patient had antibodies to GBM, PR3 and MPO. All patients had renal involvement with a mean serum creatinine of 473 µmol. Five out of eleven patients required dialysis at presentation and one of these patients recovered renal function by 6 months. Two patients presented with pulmonary haemorrhage and 45% had radiological evidence of interstitial lung disease. Fifty-five percent of patients relapsed, all of whom had antibodies to PR3 and all relapses were associated with rising PR3 titres in the absence of anti-GBM antibodies. Five and 10 year renal survival was 100% in patients presenting dialysis independent and 20% of patients presenting dialysis dependent had independent renal function at 5 years. Overall renal survival, compared with AAV, is shown on figure 1.

![Renal survival graph](image)

Discussion.—This cohort of patients with “double positivity” experienced better overall patient and renal outcomes at one year than previously reported cohorts. They were generally treated as per local protocols for anti-GBM disease with 82% undergoing plasma-exchange. There was significantly reduced renal survival compared with AAV patients. GbM antibodies should be sought in any patients with AAV since double positive patients may require plasmapheresis despite the absence of organ threatening disease.

References


Discussion—This study aimed to identify genetic determinants of granulomatosis with polyangiitis (Wegener’s, GPA).

Methods.—We carried out a genome-wide association study (GWAS) on 459 cases of GPA and 1503 healthy controls (white subjects of European descent), followed by replication of the most strongly associated signals in an independent cohort of 528 cases of GPA and 1228 controls.

Results.—Genome-wide significant associations were identified in thirty-two single nucleotide polymorphic (SNP) markers across the HLA region, the majority of which were located in the HLA-DPB1 and HLA-DPA1 genes encoding the major histocompatibility complex (MHC) class II, DP beta chain 1, and DP alpha chain 1 proteins, respectively. Peak association signals in these two genes, emanating from the rs9277554 (for DP beta chain 1) and rs9277341 (DP alpha chain 1) SNPs were strongly replicated in an independent cohort (Pcombined = 2.09 × 10^{-10} and 2.18 × 10^{-39}, respectively). Imputation of classical HLA alleles and conditional analyses revealed the SNP association signal to be fully accounted for by the classical HLA-DPB1*04 allele. An independent single SNP, rs26595, near the SEMA6A (semaphorin 6A) gene on chromosome 5, was also associated with GPA, reaching genome-wide significance in a combined analysis of the GWAS and replication cohort (Pcombined = 2.09 × 10^{-8}).

Conclusion.—We identified the SEMA6A and HLA-DP loci as significant contributors to risk for GPA, with the HLA-DPB1*04 allele almost completely accounting for the MHC association. These two associations confirm the critical role of immunogenetic factors in the development of this disease.

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A41 ANCA-associated vasculitis in Hispanics: An unrecognized severity

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Introduction.—ANCA-associated vasculitis (AAV) is now increasingly recognized in diverse ethnic populations. However, little is known about AAV and its severity among minorities in particular the Hispanic population in the United States. This study aims to describe the clinical severity and disease outcome in a group of Hispanic patients with AAV compared to a cohort of Caucasians living in the same geographical area.

A40 Granulomatosis with polyangiitis (Wegener’s) is associated with HLA-DPB1*04 and EMA6A gene variants. Evidence from a genome-wide analysis


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Introduction—ANCA-associated vasculitis (AAV) is now increasingly recognized in diverse ethnic populations. We identified the SEMA6A and HLA-DP loci as significant contributors to risk for GPA, with the HLA-DPB1*04 allele almost completely accounting for the MHC association. These two associations confirm the critical role of immunogenetic factors in the development of this disease.

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