A PANEL OF BIOMARKERS FOR THE PREDICTION OF DISEASE PROGRESSION IN IGA NEPHROPATHY

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Introduction and Aims

IgA nephropathy (IgAN) is a common glomerular disease with a heterogeneous clinical course that challenges a straightforward approach to therapeutic options. Besides established clinical and histological predictors, a number of molecules have recently been shown to be involved in the pathogenesis and progression of IgAN. We selected C4d (a complement lectin pathway activation marker in IgAN), CD3 (a T-cell marker, traducing interstitial inflammation), Transglutaminase 2 (TGase2, a calcium dependent enzyme involved in tissue fibrosis development), and p-ERK 1/2 (a protein kinase intracellular signaling molecule) to evaluate the potential value of a panel of immunohistological biomarkers for the prediction of the disease course.

Methods

Paraffin sections from 74 renal biopsy cases with the clinical diagnosis of IgAN were retrieved for C4d, CD3, TGase2 and p-ERK 1/2 immunohistochemistry staining. Association between score analysis of these parameters and disease presentation, as well as progression, was assessed through univariate and multivariate analysis, considering baseline clinical (age, gender, macroscopic haematuria, hypertension, estimated glomerular filtration rate - eGFR, urine protein) and histological data (M, E, S, T as defined in the Oxford Classification; and Immunohistology – IgA, IgG, IgM, C1q, C3).

Immunohistochemical Score analysis was performed as follows - for C4d as negative (0) or positive (1) for each case (positive case in biopsies with>50% glomeruli positive for C4d). For glomerular and tubulointerstitial TGase2 (TGase2 G and TGase2 T, respectively) semiquantitative methods were applied (0 to 2 and 0 to 5, respectively), as well as for p-ERK1/2 (0 to 3). For tubulointerstitial CD3 score, pictures covering the whole slide length of cortical area were analysed using Image J software v1.47, and the mean score of all fields was considered as the patient's CD3 tubulointerstitial staining score.

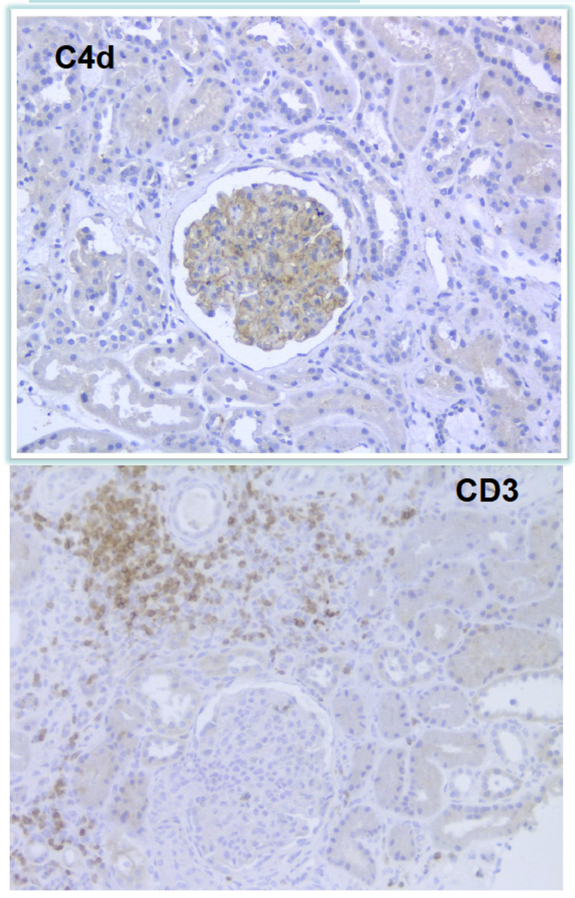
Statistical analysis was performed using SPSS v21 - For univariate analysis Mann-Whitney, Chi-Square, or Fisher's exact Test were used as needed. Multivariate models using logistic regression and Cox regression analysis were performed including all correlated covariates identified in the univariate analysis. The non-significant variables were eliminated from the model one at a time. Survival to progressive state was also assessed through Kaplan-Meier survival analysis.

Results

C4d positivity was associated with higher baseline proteinuria, T 1-2 (Oxford Classification) and IgG. TGase2 G and TGase2 T were both associated with lower eGFR, higher proteinuria and T1-2. Higher CD3 score was associated with T1-2, decreased eGFR and higher proteinuria at presentation. Progressive kidney disease, defined as a decline of at least 50% in the eGFR or progression to ESRD during the follow-up period, was found in 20 patients (27%).

Results (cont.)

Clinical and Pathological Data	Progressive Kidney Disease (n=20)	Non Progressive Kidney Disease (n=54)	P-value
Age	45 ± 16	37 ± 13	0,053
Female	20%	34,6%	0,23
Hypertensive	90%	49,1%	0,001
Previous macroscopic hematuria	33,3%	40,4%	0,6
eGFR (ml/min per 1.73m2)	31 ± 22	81 ± 31	<0,005
Proteinuria (g/day)	3,907 ± 2,155	1,835 ± 1,372	<0,005
Immunosupressive therapy	26,3%	23,4%	≅1
IgM positivity	50%	34%	0,21
IgG positivity	26,3%	26,9%	0,96
C1q positivity	10,5%	16%	0,715
S1 score	40%	53,7%	0,295
E1 score	15,0%	9,3%	0,674
T1-2 score	85%	15,4%	<0,005
C4d positivity	55%	27,5%	0,029
TGase-2 G score	1,35 ±0,26	1,26 ±0,29	0,19
TGase-2 T score	2,8 ±1	1,6±0,7	<0,005
p-ERK ½ score	1,33±0,68	1,32±0,54	0,9
CD3 score	66273±39311	19322±20632	<0,005



A multivariate model with the biomarkers (TGase2 T, CD3, and C4d) that showed univariate correlation with progressive kidney disease, revealed that these remained independently associated with progression. In a multivariate analysis including the previous 3 biomarkers with eGFR and T1-2 (the clinical and pathological parameters that remained independently associated with progression), only eGFR, C4dG and CD3 were independently associated with progressive kidney disease.

Conclusions

C4d and CD3 immunostaining panel can be a powerful predictor of IgAN course. It is both technically simple to perform, and a refined pathophysiological approach to diagnosis, making it a potential valuable tool for clinical decisions in this disease.

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