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Additional Refinement of CKD Prognostication Using Lymphatic Vessel Density: IgA Nephropathy as the Role Model?

Andreas Kronbichler[1,2], Jae Il Shin[3] and Duvuru Geetha[4]

[1]Department of Medicine, University of Cambridge, Cambridge, UK; [2]Vasculitis and Lupus Clinic, Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK; [3]Department of Pediatrics, Yonsei University College of Medicine, Seoul, Republic of Korea; and [4]Division of Nephrology, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

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IgA nephropathy (IgAN) is the most common form of glomerulonephritis in most parts of the world. The disease course is variable because of differences in the pathophysiological pathways ranging from nonprogressive, often asymptomatic microhematuria to progressive IgAN forms leading to end-stage kidney disease (ESKD). Several intervention trials highlighted the need of an optimized conservative therapy with renin–angiotensin system inhibition. Despite improved strategies mitigating progression of chronic kidney disease (CKD), the prognosis of patients with IgAN remains poor. Follow-up of the STOP-IgA trial found that 47.7% of patients reached the composite end point of 40% decline of estimated glomerular filtration rate (eGFR), ESKD, or death during a median follow-up of 7.4 years. Among 149 participants, 37 (24.8%) progressed to ESKD and no difference was found among patients randomized to receive supportive care or additional immunosuppression.[1] The implementation of the Oxford Classification of IgAN kidney biopsies in 2009 aided in prognostication of an individual patient and was further refined after addition of crescents (C) in a revision in 2016. In addition to the crescents, the Oxford Classification evaluates mesangial hypercellularity (M), endocapillary cellularity (E), segmental sclerosis (S), and interstitial fibrosis/tubular atrophy (T).[2] The addition of clinical and demographic parameters to the M, E, S, and T score provides the basis for the International IgAN Prediction Tool and includes eGFR, blood pressure, proteinuria, use of renin–angiotensin system inhibition and immunosuppression at the time of biopsy, and age of the patient. In international cohorts (derivation and validation), the IgAN Prediction Tool predicted the 5-year risk of the primary outcome, which is defined as 50% reduction in eGFR or ESKD. Overall, after 4.8 and 5.8 years of follow-up, progression to ESKD was observed in 13.4% and 13.5% in the derivation and validation cohort, respectively, and patients belonging to the higher and highest risk groups achieved the primary outcome more frequently, with approximately 13.9% and 46.5%, respectively, in the full model, including race/ethnicity.[3] Calculation of the International IgAN Prediction Tool has become standard when evaluating risk of progression of an individual patient with IgAN.

In the current issue of *KI Reports*, Rodas *et al.*[4] evaluated the density of lymphatic vessels on kidney biopsies and their role in outcome prediction in a cohort of 76 patients with IgAN. Baseline proteinuria of patients was 1.3 g/d, 89% received renin–angiotensin system inhibition, whereas a minority (21%) received glucocorticoids. On kidney biopsy evaluation, the median density of lymphatic vessels per mm^2 was 2.8 and correlated with the area of lymphatic vessels. Histopathologic features of poor prognosis, such as mesangial hypercellularity ≥ 50% (3.4 vs. 2.0/mm^2), segmental sclerosis (4.6 vs. 2.3/mm^2), and higher degrees of interstitial fibrosis/tubular atrophy (>50%, 4.8/mm^2; 25%–25%, 3.1/mm^2, and <25%, 1.9/mm^2) correlated with density of lymphatic vessels. A cutoff of lymphatic vessel density of 8/mm^2 predicted the outcome, progression to ESKD, and the best, and this was reached by 12 patients (15.8%). Progression to ESKD was reported in 53% of patients with a lymphatic vessel density of ≥8/mm^2, whereas only 7% of those

Correspondence: Andreas Kronbichler, Department of Medicine, University of Cambridge, Cambridge, UK. E-mail: ak2283@cam.ac.uk

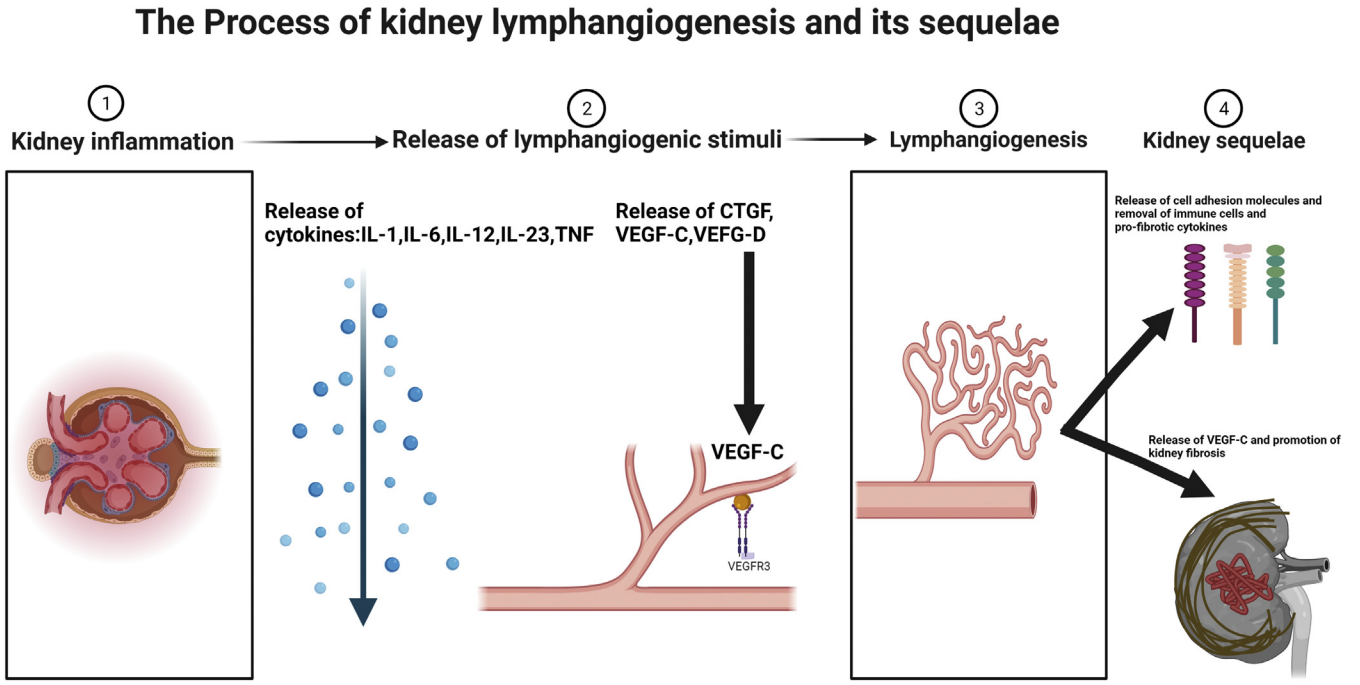

Figure 1. Kidney inflammation is in part triggered by proinflammatory cytokines, which are stimulated by immune cells in a positive feedback loop. A release of unspecific inflammatory cytokines such as interleukins and tumor necrosis factor alongside more specific factors implicated in development of lymphatic vessels (connective tissue growth factor, VEGF-C, and VEGF-D), together with VEGFR3, eventually establish "lymphangiogenesis." The presence of lymphatic vessels and the density thereof have been associated with fibrotic kidney changes, and it remains poorly defined if this is a protective adaption to clear inflammatory infiltrates or contribute to progression of chronic kidney disease. CTGF, connective tissue growth factor; IL, interleukin; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor; VEGFR3, vascular endothelial growth factor receptor 3.

with values $< 8/mm^2$ reached ESKD 3 years after biopsy. These patients presented with higher proteinuria values (3.5 vs. 1.2 g/d), lower eGFR (26 vs. 64 ml/min per 1.73 m^2), and were younger at time of presentation. Higher density of lymphatic vessels predicted the International IgAN Prediction Tool, with a median score of 25.7 in those with lymphatic vessel density of $\geq 8/mm^2$ and 6.0 in those with lower vessel density. In a multivariable regression analysis, the significant association between lymphatic vessel density and early progression to ESKD in patients with IgAN was confirmed, whereas the International IgAN Prediction Tool had limited validity. These findings are in line with an investigation comparing infiltrates of patients with IgAN and interstitial nephritis. Lymphatic vessels were present in inflammatory areas, interstitial fibrosis, or around sclerotic glomeruli. The number was in general higher as compared with biopsies taken from patients with interstitial nephritis, whereas the appearance was more focal in IgAN.[5]

The implementation of lymphatic vessel density analysis to current standards in histopathologic examination of IgAN or other glomerular diseases is easily achievable, as antibodies to podoplanin (D2–D40), a membrane glycoprotein expressed by the lymphatic endothelial cells, are commercially available. But how does this aid to refine prognostication in patients with IgAN? The picture of IgAN becomes more complex, as there is a "resuscitation" of systemic immunosuppression and there is a need to provide tailored therapy to those who might benefit from corticosteroids or other immunosuppressive measures. The TESTING trial included patients with proteinuria $>$ 1 g/d and an eGFR of $>$20 ml/min per 1.73 m^2. Administration of low-dose methylprednisolone (initial dose 0.4 mg/kg body weight, maximum 32 mg, with subsequent taper) reduced the composite end point of 40% decrease in eGFR and ESKD by 47%. Recent evidence underlines that the intensity of the glomerular infiltrate predicts response to immunosuppression. A prospective study of 621 Chinese patients with IgAN indicated that the intensity of the macrophage markers CD206 and CD68 on kidney biopsy specimen outperformed clinical data in combination with the M, E, S, and T-C score in prediction of therapeutic response. Combination of both markers yielded an area under the curve of 0.84 and 0.86 in a derivation and validation cohort, respectively, and the addition of clinical and histopathologic data

added minimal additional improvement of the area under the curve (0.87 in both cohorts).[6] It is hypothesized that activated macrophages can promote lymphangiogenesis. Further investigations focusing on addition of lymphatic vessel density to macrophage infiltrate of glomeruli are needed to evaluate potential additional benefits in refining prognostication in IgAN. In contrast, lymphangiogenesis might already indicate irreversible damage and these patients might benefit more from intensification of conservative therapy as opposed to immunosuppression.

The pathogenicity of kidney-related lymphangiogenesis is discussed controversially, and both protective and detrimental effects of lymphatic vessels are proposed. In active inflammatory processes, lymphangiogenesis is induced by the release of proinflammatory cytokines and specific factors leading to development of new lymphatic vessels (such as vascular endothelial growth factor-C or vascular endothelial growth factor-D; Figure 1) and aims to remove inflammatory cytokines and immune cells and to reduce activation of proapoptotic signals in tubule epithelial cells. In contrast, chronic lymphangiogenesis as probably observed in IgAN results in disorganized lymphatic expansion and thereby poor lymphatic functioning. This may lead to a reduction in immune cell and fluid clearance and propagates an inflammatory feedback loop, which in turn augments the progressive fibrotic processes found in CKD progression (Figure 1).[7] The latter would underline the association of poor prognosis with segmental sclerosis and higher degrees of interstitial fibrosis/tubular atrophy as found in the study by Rodas *et al.*,[4] hallmarks of irreversible kidney damage. This will finally lead to nephron overload of remaining vital renal structures, which might induce lymphangiogenesis. The specificity of lymphatic vessel density to IgAN remains obscure[4] and might simply indicate a consequence of chronic damage. In such scenario, a reduction in remnant nephron overload is warranted and stepwise initiation of renin–angiotensin system inhibition and sodium-glucose cotransporter 2 inhibition, alongside optimization of risk factors implicated in CKD progression, such as salt intake, obesity, poorly controlled hypertension, diabetes, among others, need to be considered.[8] Efficacy data of sodium-glucose cotransporter 2 inhibition in IgAN stem from a subanalysis of the DAPA-CKD trial, a landmark trial improving outcome of patients with CKD. A total of 270 participants had a diagnosis of IgAN, which was confirmed by biopsy in most cases (94.1%). The primary end point of DAPA-CKD was a composite of sustained eGFR decline of 50% or more, ESKD, or death from a kidney disease-related or cardiovascular cause. Occurrence of the primary end point was reported in 6 participants (4%) on dapagliflozin and 20 (15%) on placebo, with a mean rate of eGFR decline of −3.5 and −4.7 ml/min per 1.73 m^2 per year.[9] A dedicated randomized controlled trial of sodium-glucose cotransporter 2 inhibition with dapagliflozin (in combination with an endothelin A receptor antagonist) is currently in the set-up phase and will further our understanding of IgAN.

The study by Rodas *et al.*[4] has some limitations, inherent with its retrospective design. In addition, the sample size of the study was low, the results could not be validated in an independent cohort of patients with IgAN, and there was no comparison to other entities leading to progressive kidney function decline, such as diabetic kidney disease. Such investigations are necessary to understand the specificity of lymphatic vessel density as a prognostic factor for IgAN, rather than a factor implicated in the common final pathway of CKD. Moreover, the impact of higher density and the responsiveness to immunosuppression rather than optimization of conservative therapy need to be investigated in larger cohorts of patients with IgAN and other forms of CKD. The finding of an independent association with CKD progression of IgAN is interesting and helps to refine our understanding of IgAN. Notably, patients in the group with the highest lymphatic vessel density had a significantly lower eGFR at baseline and higher proteinuria values, both associated with a reduced kidney survival. But these patients were younger (32 years, on average) and have a longer duration living with CKD, which highlights the unmet need to provide optimized management options in this subset of patients with IgAN.

DISCLOSURE

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