Mesangial C1q Deposition in IgA Nephropathy: Does the Classical Complement Pathway Play an Independent Role?

Dear Editor,

We read with great interest the review article by Roberts *et al.* entitled "IgA nephropathy: Emerging Mechanisms of Disease."[1] This is an in-depth and comprehensive review of the treatment of immunoglobulin A nephropathy (IgAN), focusing on the complex pathological mechanisms underlying IgAN in order to move to increasingly targeted treatments.

We would like to contribute by commenting on an aspect that has not been specifically mentioned, namely the relationship between IgAN and glomerular complement component 1q (C1q) deposition.

A renal biopsy performed in a three-year-old boy presented only for persistent macrohematuria (with no other current or past medical/laboratory history) showed microscopically mesangial hypercellularity with glomerular deposits on immunofluorescence for IgA and C1q [Figure 1]. All other histologic structures, both glomerular (capillaries, basal membrane, podocytes, urinary space, Bowman's capsule) and non-glomerular (tubules, interstitium, vessels), were negative for any lesions, as were negative immunofluorescence findings for IgG, IgM, C3, and C4d: the diagnosis was IgAN associated with mesangial C1q deposition.

Primary IgAN can progress to end-stage kidney disease in 14–39% of cases.[2] Disease progression correlates with the severity of histologic lesions according to the 2016 Oxford Classification: mesangial cellularity (M), endocapillary cellularity (E), segmental glomerulosclerosis (S), tubular atrophy/interstitial fibrosis (T), and crescents (C):[3] the described case was classified as M1,S0,T0,C0, highlighting the coexistence of glomerular C1q deposition.

In fact, IgAN/C1q co-occurrence is not so rare, and correlates with a worse outcome in terms of renal survival, in particular with a described correlation with crescent formation, both in native and posttransplant kidneys.[4–6]

A large part of the review by Roberts *et al.*[1] relies on the article by Suzuki *et al*., according to which four successive genetic molecular hits are required to reach the actual kidney damage in IgAN. Only the fourth hit, after glomerular deposition of immune complexes with IgA1, leads to complement activation and the resulting inflammatory cascade that increases kidney damage.[7] However, both articles focus on the alternative complement pathway, particularly the involvement of C3 and C5, with Roberts *et al.* stating that disease severity and progression correlates with glomerular C3 deposition and concluding the argument by writing that "the absence of C1q deposition suggests that the activation of the complement cascade does not involve the classical pathway in IgAN,"[1] and Suzuki *et al.* stating that components of the classical complement pathway, including C1q, are typically absent in IgAN.[7] This pathogenetic approach is in line with what Zhang *et al.* write in a very similar recently published

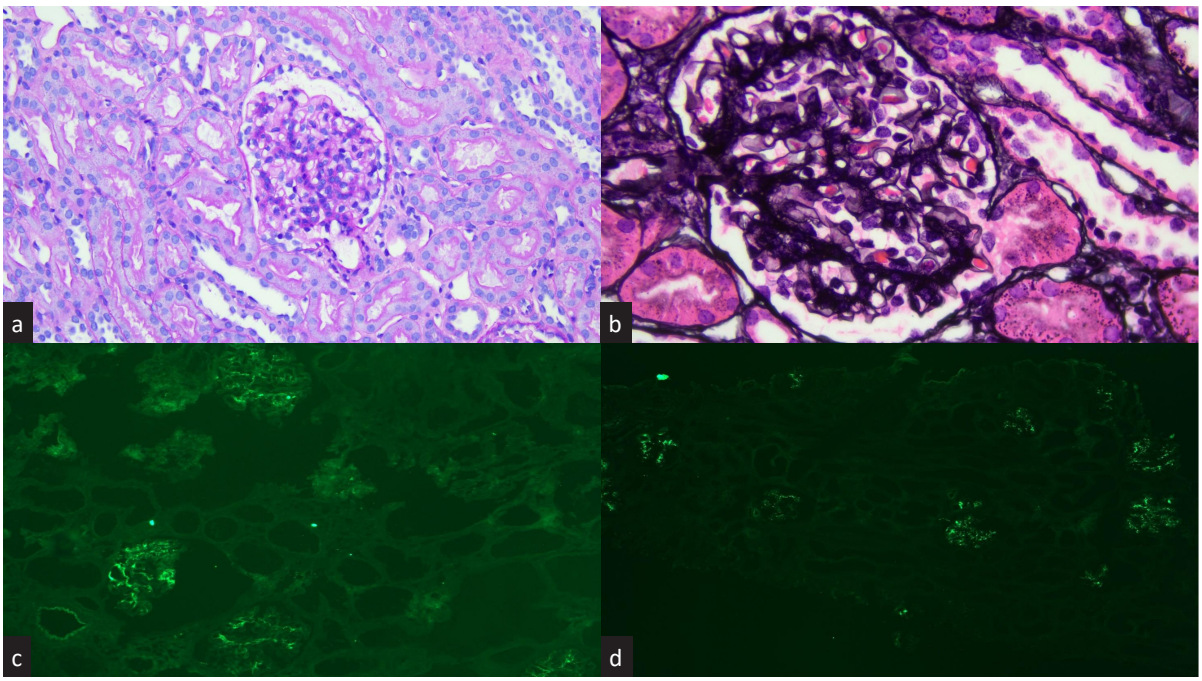

Figure 1: Histology and immunofluorescence. (a) Photomicrograph showing increased mesangial cellularity and normal endocapillary cellularity (PAS staining, 20x). (b) Photomicrograph showing a slight increase in mesangial reticular texture without true segmental sclerosis (PASM staining, 40x). (c) Positive immunofluorescence for IgA (10x). (d) Positive immunofluorescence for C1q (10x). PASM: Periodic schiff-methenamine silver; PAS: Periodic acid-schiff.

paper, referring to "ongoing therapeutic trials investigating inhibitors of components C3 and C5."[8]

However, recent data break this axiom and make it less rigid by introducing C1q as a possible building block in IgAN, suggesting both that it plays its own independent role (and we do not yet know whether this is mutually exclusive regarding alternative pathway activation as in our immunofluorescence findings)[4–6] and that C1q can therefore be considered in the ever-expanding landscape of IgAN target therapy. Finally, it confirms the role of microscopic examination of kidney biopsies (histopathology and immunofluorescence) not only for the prognostic aspects of the Oxford classification but also to identify cases where pathological glomerular IgA deposition is accompanied by C3 or C1q, thus differentiating patients with distinct potential therapeutic targets.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

Conflicts of interest

There are no conflicts of interest.

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Factor V Leiden Heterozygous Mutation and Hyperhomocysteinemia Presenting with Vascular Rejection and Renal Allograft Infarction

Dear Editor,

A 40-year-old male was diagnosed with end-stage kidney disease in 2020. He developed lower limb edema following femoral catheterization which resolved spontaneously. He underwent a kidney transplant in 2022. In October 2023, he presented with macroscopic hematuria and graft dysfunction. Graft biopsy revealed acute T-cell-mediated rejection (TCMR).

He was treated with methylprednisolone pulse and rabbit anti-thymocyte globulin. After initial response, his creatinine started increasing again. Graft biopsy revealed acute cortical necrosis with residual inflammation of TCMR. Doppler graft kidney and MRI revealed multiple cortical wedge-shaped infarcts [Figure 1].

Workup was negative for ANA and APLA, and complement levels were normal. Thrombophilia workup revealed hyperhomocsyteinemia 31.3 (1–5) micromol/L and factor V Leiden heterozygous mutation. There were no mutations in prothrombin gene (PGM) and MTHFR gene. Protein C and Protein S levels were normal. He was managed with oral Apixaban and folate. He stopped anticoagulation after a month and presented with recurrent DVT right lower limb and pulmonary thromboembolism.

Several studies have described FVL mutation and increased risk of transplant RVT. FVL mutation leads to fourfold rise in allograft thrombosis.[1] FVL mutation also predisposes to acute vascular rejection.[2,3] Possible mechanism involves delayed inactivation of FVL leading to microthrombi