C4d in Proliferative Glomerulonephritis

There was a time when "diffuse proliferative and exudative pattern of glomerular injury" was considered synonymous with post infectious glomerulonephritis (PIGN). However, in recent years as we better understand underlying pathophysiology, it is clear that not all diffuse proliferative and exudative glomerulonephritis behave like the classical PIGN. It is a common discussion point between the renal pathologist and nephrologist whenever such glomerular injury pattern is noted, with the question being "Is this PIGN?" to which the most likely answer is— If the patient gets better, it is.

The diffuse proliferative and exudative pattern of glomerular injury is the response of the glomerulus to immune complexes in a subendothelial and mesangial location (subepithelial deposits are those that escape through the glomerular basement membrane).[1] An infectious trigger and its immunoglobulin response could cause such deposits, which set the ball rolling for the activation of the complement pathways including classical (CP), alternative (AP), and lectin pathways (LP). All the pathways would finally converge into the formation of C3, which deposits in the glomeruli. Along the way, activation of the CP would also result in the deposition of C1q and C4d, which can be detected, and LP activation would bring in C4d too.

What we expect in a classical PIGN is a transient deposition of immune complexes and complement components, which then clear out of the glomeruli with complete resolution of the glomerulonephritis (GN). Recent studies into patients who do not behave in this typical manner have resulted in the term "atypical post infectious GN" in whom underlying abnormality in the AP has been found in the majority of cases.[2] It is hypothesized that the abnormality may be mild and so ultimately the disease resolves, though it takes longer. What is even more ominous is that with a more severe AP abnormality some cases of dense deposit disease/C3 glomerulonephritis may present with a similar pattern of injury. These may represent the early phase of the GN, which will progress to a more usual membranoproliferative pattern of injury over time.[3] The infectious trigger with a history of febrile illness may also be present in these cases.

The role of the nephrologist and renal pathologist team is to, therefore, stratify the risk of progressive glomerular disease and advise AP evaluation in selected cases, which is itself challenging in the Indian context due to the lack of complement genetics and antibody testing in most centers. Practically, we rely on clinical parameters such as sustained low serum C3 (with normal C4 levels), lack of clinical remission; and pathology parameters such as an isolated C3 immunofluorescence pattern without accompanying immunoglobulins and abnormal electron microscopic findings inconsistent with the diagnosis of classical PIGN for risk stratification. Again, electron microscopy is not readily available in most centers.

Therefore in the hunt, for more tissue markers to help resolve the differential diagnosis Bansode *et al.*[4] have objectively evaluated C4d in 104 cases of diffuse proliferative and exudative GN, hypothesizing that low-intensity C4d staining (cut off of 1.45 defined by statistical modeling) would suggest AP activation. They found that these patients did poorly compared to cases with higher C4d staining. The caveat here is that a few cases with significant C4d staining also did not remit. A previous study on C4d in PIGN showed slightly less than 50% cases were C4d negative, however, no follow up data or complement testing was available.[5]

So will C4d (specifically the lack of it) be the marker for the renal pathologist to suggest underlying abnormality in AP and thus poor prognosis in patients with "diffuse proliferative and exudative pattern of glomerular injury?" The answer is complicated due to the following –

1. An infectious trigger may likely result in a CP/LP activation even in a patient with an underlying AP abnormality such as dense deposit disease, which would give a C4d positivity (with or without immunoglobulins)
2. The role of the lectin pathway is still unresolved in this form of glomerulonephritis. Abnormalities in this pathway may contribute to positive C4d with variable prognosis.

From Bansode *et al.*[4] and our own experience,[6] the value of the lack of C4d is significant in indicating a potential abnormality in the AP in proliferative glomerulonephritis, however, its presence should not give false reassurance. In our practice, based on a combination of clinical and pathology features including C4d, the first step is to perform electron microscopy in suspect cases and at the very least advise a close clinical follow-up with serial serum C3/C4 estimation.

We expect that more renal pathologists will use C4d in the evaluation of glomerulonephritis in combination with routine immunofluorescence in the future.

Geetika Singh

Department of Pathology, All India Institute of Medical Sciences, New Delhi, India

Address for correspondence:
Dr. Geetika Singh,
Department of Pathology, All India Institute of Medical Sciences, New Delhi, India.
E-mail: drsingh.geetika@gmail.com

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