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Recurrence of anti factor H associated C3 glomerulonephritis in the kidney allograft

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In the last issue of the Journal Magriço et al. reported the case of a patient with C3 glomerulonephritis (C3GN) and evidence of recurrence in his second kidney allograft. Patient is presently being considered for a third allograft (first allograft lost due to thrombosis).

As it is nicely described in the manuscript, we now recognize C3GN as a distinct clinical and histologic entity associated with uncontrolled activation of the central complement component C3. Most often, the pathogenic process involves incomplete regulation of the alternative complement pathway. However, it is becoming clear that multiple anomalies of complement activation, not necessarily affecting the alternative pathway, may result in a similar clinical and histologic picture. Furthermore, it is likely that in patients with these complement anomalies a triggering event, such as perhaps an infection, is needed to develop the disease.

Based on the current understanding of C3GN, work up of these patient should try answer the following questions: 1) Are the glomerular C3 deposits the result of dysregulation of which complement activation pathway: classical, lectin or alternative?; 2) Are there glomerular immunoglobulin deposits "hidden" by the C3 deposits?; 3) Are there monoclonal proteins present in the glomerulus and/or in serum?; 4) What is the mechanisms of complement over-activation in each particular patient, possibilities including: a) genetic; b) autoimmune (C3Nef, C4Nef, anti-Factor H); or c) other, often unknown? The first question is best addressed by staining the kidney biopsy for C4d. In C3GN which is C4d positive the classical or lectin pathways are activated and often there is an association with monoclonal proteins and/or C4 nephritic factor. At times, an apparent C3GN is associated with immunoglobulin glomerular deposits that can be visualized by immunofluorescence only after pronase treatment of the tissue. The search of monoclonal proteins and studies on the mechanism of complement dysregulation are nicely described in this case report. In the patient presented here the dysregulation of C3 activation appeared to relate to an autoantibody against Factor H a critical regulator of the alternative pathway C3 convertase (C3bBb).

However, I confess to be a bit puzzled with the fact that the patient's C4 (classical pathway) was low at initial presentation but not thereafter. C3GN often recurs following kidney transplantation. However, its behavior in the allograft is variable, perhaps due to variability in the pathogenesis of the disease. This particular patient likely had early recurrence, manifested by proteinuria, and slow progressive disease. It is our practice to do allograft biopsies at the earliest manifestations of graft glomerulonephritis in patients with high recurrence risk.

Admittedly, we have very limited therapeutic choices for C3GN. Thus, it could be argued that early diagnosis may not lead to a change in therapy. Conversely, as this case illustrates (likely), biopsies done at the time of overt clinical manifestations (high grade proteinuria, rising creatinine) often show advanced disease unlikely to benefit from any available therapy.