

Very Late Recurrence of Dense Deposit Disease after Kidney Transplantation

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A woman in her 40s with kidney failure secondary to biopsy-proven dense deposit disease (DDD) with positive C3 nephritic factor (C3Nef) and no complement gene defect received a kidney transplant from a deceased donor. Eighteen years after transplantation, laboratory workup revealed new-onset microscopic hematuria, with 547 red blood cells/ μ L (normal <25), and proteinuria, with a urine protein-to-creatinine ratio of 1.0 g/g creatinine (normal <0.150), increasing to 7.5 g/g within a few months. Glomerular filtration rate, estimated from the CKD-EPI equation, was normal (88 mL/min/1.73m²). Serum C3 level was very low (0.09 g/L, N 0.90 -1.80), while serum C4 level was normal. Screening for monoclonal gammopathy, BK viremia and circulating donor-specific antibodies, was negative.

A kidney allograft biopsy was performed, and light microscopy demonstrated a membranoproliferative pattern, with a characteristic ribbon-like appearance of the glomerular basement membrane (Figure 1A). Immunofluorescence studies showed isolated and bright deposits of C3 along glomerular basement membranes with the pathognomonic 'ring' pattern (Figure 1B). The C4d staining was negative, and no immunoglobulin deposits were detected. Electron microscopy analysis confirmed the membranoproliferative pattern of the glomerulus and revealed electron dense deposits thickening irregularly the lamina densa of the glomerular basement membrane (Figure 1C). These features were consistent with the diagnosis of recurrent DDD in the allograft.

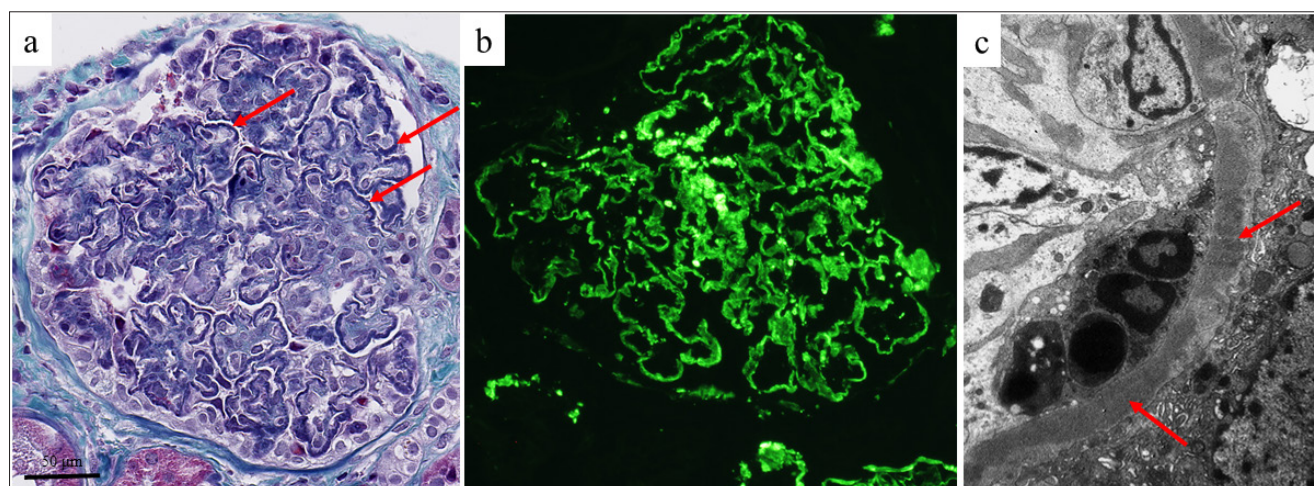


Figure 1: Kidney allograft biopsy (a) Light Microscopy demonstrates a membranoproliferative pattern, with a characteristic ribbon-like appearance of the glomerular basement membrane (red arrows). (b) Immunofluorescence microscopy shows bright deposits of C3 along the glomerular basement membrane. (c) Electron microscopy reveals in the glomerular basement membrane, electron dense deposits thickening the lamina densa (red arrows).

DDD is a form of C3 glomerulopathy caused by genetic or acquired dysregulation of the alternative complement pathway. Pathogenesis includes- as in our patient- the C3Nef autoantibody that stabilizes C3 convertase C3bBb, or factor H deficiency or inactivation, leading to reduced decay of the complex C3bBb. The defining histopathologic finding is C3 dominance with minimal or absent immunoglobulin deposition on immunofluorescence staining¹ and a distinctive pattern of dense deposits in the glomerular membrane on electron microscopy. The clinical manifestations include proteinuria of variable degree and/or hematuria, increased or preserved creatinine, and/or low serum C3 levels with normal C4 levels². Incidence of recurrence on the allograft has been reported to be 67%-84%, after a median time of 14-28 months from kidney transplantation³. Recurrence often results in graft loss, typically within 2.5 years of transplantation⁴. The use of eculizumab, a humanized C5 monoclonal antibody, for recurrence after transplantation remains controversial, but in the absence of other treatment options, it can be considered for patients at high risk of graft loss. An oral complement factor B inhibitor (iptacopan) has shown clinical efficacy in a phase II trial (NCT03832114)⁵ and the potential efficacy of a C3 inhibitor (pegcetacoplan) is currently tested in the VALIANT phase III study (NCT05067127).

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