Title: *Unmasking the Brush Border: Anti-LRP2 (Megalin) Nephropathy in the Setting of Immune Checkpoint Inhibitor Therapy*

Authors: Chenyang Yu[1], Arley F Diaz[2,3], Cherry Starling[4], Sujal I Shah[1,5]

Affiliations:

1. Department of Pathology, Brigham and Women's Hospital, Boston, MA
2. Department of Nephrology, Cooley Dickinson Hospital, Northampton, MA
3. UMass Chan Medical School - Baystate, Springfield, MA
4. Arkana Laboratories, Little Rock, AR
5. Harvard Medical School, Boston, MA

Introduction: Anti-brush border antibody (ABBA) disease is an exceedingly rare autoimmune tubulopathy driven by autoantibodies against low-density lipoprotein receptor-related protein 2 (LRP2/megalin), or less frequently, cubilin and amnionless protein, all being components of the proximal tubular brush border. The etiology is poorly understood, but ABBA has been reported in setting of autoimmune and neoplastic conditions. Immune checkpoint inhibitors (ICIs) typically trigger acute interstitial nephritis (AIN), though there are increasing reports of glomerular immune complex disease. Here, we report a patient who developed anti-LRP2-mediated ABBA disease in the setting of combination ICI and Tyrosine Kinase Inhibitor (TKI) therapy for renal cell carcinoma (RCC).

Case Description: An 82-year-old male with metastatic papillary RCC developed severe acute kidney injury (peak serum creatinine 11.2mg/dL) three weeks after initiating pembrolizumab and lenvatinib. Kidney biopsy was performed. Light microscopy (Figure 1A) revealed severe chronic-active interstitial nephritis alongside acute tubular injury with focal necrosis. Glomeruli showed mild mesangial expansion but otherwise appeared unremarkable. Direct immunofluorescence (Figure 1B) demonstrated prominent, granular polytypic IgG deposits, with IgG4 and weaker IgG1 staining, along the proximal tubular basement membranes (TBM) and segmentally along glomerular capillary loops. LRP2 staining (Figure 1C) showed granular reactivity along the TBM. Electron microscopy revealed dense deposits in the TBM and glomeruli. The findings were consistent with ABBA disease. Both oncologic agents were held and steroids were initiated, with complete renal recovery to baseline without requiring renal replacement therapy. The patient was subsequently treated with TKI monotherapies (cabozantinib, then tivozanib) without evidence of renal relapse.

Discussion: While separating paraneoplastic from drug-induced nephrotoxicity is challenging, the tight temporal onset following immunotherapy and complete renal recovery upon treatment cessation strongly implicate the ICI as a key immunologic catalyst. This case further supports the possibility of immunotherapy-related immune complex-mediated diseases and suggests that deposition may not be limited to glomeruli.

Figure 1, Pathologic diagnostic features of ICI-associated ABBA disease. (A) Hematoxylin and Eosin (H&E) staining (10x objective). (B) IgG staining (20x objective). (C) LRP2/megalin staining revealing expected staining along the apical brush border accompanied by ectopic deposition along the tubular basement membrane (Arrows; 40x objective).