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All About ABBA: New Insights Into Antibrush Border Antibody Disease

Vivette D. D'Agati[1]

[1]Renal Pathology Laboratory, Columbia University Irving Medical Center, New York, New York, USA

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Major diagnostic considerations in a patient with acute kidney injury and acute tubular injury on kidney biopsy include ischemic and toxic tubular insults. Autoimmune forms of acute tubular injury are rarely considered and poorly characterized. Proximal tubular injury mediated by antibodies directed to proximal tubular antigens and resulting in detectable immune complex formation has emerged as a rare subset of acute kidney injury.

Autoantibody directed to the low-density lipoprotein receptor-related protein 2 (LRP2), also known as megalin, is a newly recognized cause of human autoimmune tubular injury. This entity has been termed antibrush border antibody (ABBA) disease or anti-LRP2 nephropathy. LRP2/megalin is a 517 kD transmembrane glycoprotein member of the subfamily of giant low-density lipoprotein receptor-related proteins with endocytic roles in absorptive epithelia of multiple organs, including kidney, thyroid, parathyroid, and pulmonary alveoli.[1] Cryo-electron microscopic studies have elucidated how the LRP2 homodimer undergoes dramatic pH-dependent conformational changes between states of ligand capture at the cell surface and ligand release within endosomes.[1] LRP2 is a receptor for over 75 putative ligands and is best known for its role in proximal tubular endocytosis of albumin; vitamin-binding protein complexes; and low molecular weight proteins such as β-2-microglobulin, cystatin-C, light chains, and hormones.

Similar to many discoveries in medicine, the concept of autoimmunity to megalin causing acute tubular injury is in part a rediscovery of experimental data performed decades ago. The Heymann nephritis model developed in Lewis rats is mediated by binding of ABBA to megalin expressed in the clathrin-coated pits of both the brush border of proximal tubules and the soles of podocyte foot processes, producing glomerular subepithelial immune complexes and membranous nephropathy.[2] Often forgotten is the associated injury to proximal tubular cells. This is relevant to human ABBA disease because in human kidney, LRP2/megalin is expressed only in proximal tubular brush border and is undetectable in podocytes. Classic studies in this model describe the evolution of proximal tubular injury.[3] Immediately following the onset of proteinuria, patchy binding of IgG to proximal tubular brush border occurs, followed by IgG deposition along the tubular basement membranes (TBMs) of proximal tubules only. By light and electron microscopy, proximal tubules undergo extensive destruction and loss of the apical brush border with sparse residual swollen and blunted microvilli, intraluminal shedding of cellular debris, decreased pinocytotic vesicles, tubular cell flattening or simplification, and the appearance of electron dense deposits within proximal TBMs. A sparse mononuclear inflammatory cell infiltrate and mild lymphocytic tubulitis can also occur.[3] These tubulointerstitial changes closely resemble human ABBA disease.

ABBA disease was first described in case reports by Morrison *et al.*[4] in 1981 and Rosales *et al.*[5] in 2016. It was further characterized in 2018 in a series of 10 patients by Larsen *et al.*[6] with identification of LRP2 as the major inciting autoantigen. In that cohort, antibody specific for LRP2/megalin was demonstrated by immunoprecipitation of patients' serum with tubular extract.[6] LRP2 was detected by immunofluorescence (IF) within the TBM deposits. Indirect IF using patient sera applied to sections of normal kidney showed binding of patient's IgG to normal proximal tubular brush border. Thus, both immunostaining for LRP2 to demonstrate the autoantigen within the TBM deposits and

Correspondence: Vivette D. D'Agati, Renal Pathology Laboratory, Columbia University Irving Medical Center, 630 W. 168th, New York, New York 10032, USA. E-mail: Vdd1@cumc.columbia.edu

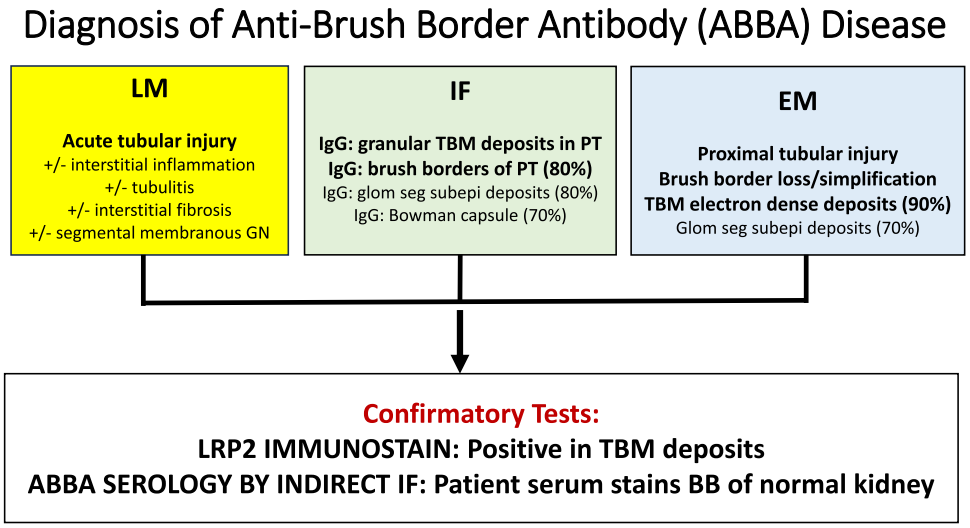

Figure 1. Pathologic diagnosis of antibrush border (ABBA) disease by light microscopy (LM), immunofluorescence (IF) and electron microscopy (EM). Findings by all 3 modalities are listed, with the major features bolded and percentages rounded to the nearest ten percent. Suspected diagnosis of ABBA disease should be corroborated by immunostain for LRP2 or ABBA serologic testing by indirect IF performed on normal kidney sections. ABBA, antibrush border antibody; BB, brush borders; glom, glomerular; seg, segmental; subepi, subepithelial; PT, proximal tubule; TBM, tubular basement membrane.

indirect IF as a serum assay for brush border antibody have become useful confirmatory tests in clinical practice. The authors now enlarge their series to 67 patients gleaned from the Arkana Laboratory archives, corresponding to a biopsy incidence of only 0.05%.[7] This large cohort provides valuable new insights into the clinicopathologic characteristics and outcomes of this rare, underrecognized disease.[7]

Diagnostic inclusion criteria are as follows: (i) acute tubular injury; (ii) the presence by IF of TBM deposits staining for IgG, with or without proximal tubular brush border staining for IgG; and (iii) positive IF staining for LRP2 within TBM deposits or serologic confirmation of anti-LRP2 antibodies by indirect IF performed on normal human kidney (Figure 1). By sequentially diluting the patient serum to the point at which staining disappears, the titer of ABBA can be determined. This serologic test is not commercially available; however, it can be performed by a pathologist when a kidney biopsy exhibits findings suspicious for ABBA disease (i.e., acute tubular injury with positivity for IgG involving TBM deposits and tubular brush border). In cases where patient sera are unobtainable, diagnostic confirmation requires demonstration of positive IF staining of the TBM deposits for LRP2 using monoclonal antihuman LRP2 antibody. Interestingly, immunostaining for cubilin and amnionless also showed positivity in the TBM deposits of 1 case from this cohort, indicating the rare potential for epitope spreading to complexed brush border antigens.[8]

ABBA disease most commonly afflicts elderly White males. In this cohort, 75% were male and median age was 72 years. Although ages ranged from 24 to 91 years, only 12% of patients were <60 years of age. Nineteen patients (representing 41% of cases with available data) had monoclonal gammopathy, which is a nearly 8-fold higher rate than expected for this age group and may have lowered the clinical threshold for biopsy in the elderly patient with acute kidney injury or slowly progressive chronic kidney disease. An additional 11 patients had solid organ malignancies. Together, these findings raise the question of ABBA disease developing as a paraneoplastic syndrome. Other autoimmune diseases were also common, found in 10 of 62 patients, including 5 with hypothyroidism; 2 with polymyalgia rheumatica; and 1 each with immune thrombocytopenia, myasthenia gravis, and systemic lupus erythematosus, possibly representing poly-autoimmunity or potential effects of LRP2 expression in other organs.

Presentations were most often acute kidney injury and/or progressive chronic kidney disease, with mean estimated glomerular filtration rate of 26.6 ml/min and median serum creatinine of 2.7 mg/dl.[7] Surprisingly, despite the targeted injury to proximal tubules, no patient manifested overt Fanconi syndrome. Although 95% of patients had proteinuria >500 mg, only 22% had nephrotic syndrome that was related to associated glomerular diseases. Hypocomplementemia was identified in 8 patients, 3 of which had

concurrent glomerular disease. A total of 50% of patients had positive antinuclear antibody and 3 had positive PR3 antineutrophil cytoplasmic antibodies.

The major biopsy finding by light microscopy was acute tubular injury. Although the majority (70%) of biopsies had little or no interstitial inflammation, about a quarter of cases had associated mild features of acute interstitial nephritis with tubulitis. In chronic phases, acute tubular injury persisted on a background of prominent interstitial fibrosis. TBM deposits were not typically visible by light microscopy but were readily identified by IF as granular staining of proximal TBMs for IgG, kappa, and lambda (indicating polyclonal deposits); and by electron microscopic demonstration of electron dense granular or confluent TBM deposits. IF had greater sensitivity than electron microscopy for identification of TBM deposits due to its larger tissue sampling and earlier detectability of small immune deposits. IgG subclass staining showed dominance of IgG1 in 41% of biopsies and of IgG4 in 25%, with IgG1 and IgG4 codominance in the remainder. Because IgG1 is a strong complement activator whereas IgG4 is not, this might explain the variable codeposition of C3 in the TBM deposits. IgG was detected along TBMs in virtually all cases and highlighted the proximal tubular brush borders in 77%, whereas C3 was detected along TBMs in 64% of cases. The absence of detectable brush border staining for IgG in nearly a quarter of cases may reflect extensive autoimmune destruction of brush border integrity. It remains unclear how antibody to a brush border antigen can lead to deposits in TBMs. Theoretically, this could involve a process of immune complex shedding from damaged tubular cells. Analogy can be drawn to the TBM deposits of IgG that form during immune response to BK polyoma virus infection of tubular epithelium.[9]

A characteristic finding was the presence of segmental membranous features with glomerular subepithelial deposits detected in nearly 80% of biopsies, as well as deposits in Bowman's capsule in 72%.[7] This is surprising, given that LRP2 expression has not been definitively demonstrated by highly sensitive molecular techniques in normal human podocytes or flat parietal epithelial cells; moreover, staining for LRP2 was negative in the distribution of the glomerular deposits in all but one case. These results suggest potential plasticity in gene expression among a subset of human parietal epithelial cells and podocytes.

A major new observation from this cohort was the existence of concurrent pathologic diagnoses in 57% of biopsies.[7] Coexistent glomerular diseases were diverse, including global membranous nephropathy, minimal change disease, primary focal segmental glomerulosclerosis, diabetic glomerulosclerosis, IgA nephropathy, proliferative lupus nephritis, crescentic pauci-immune glomerulonephritis and light chain amyloidosis. Tubulointerstitial diseases included acute or granulomatous interstitial nephritis and rare interstitial infiltration by B-cell lymphoma. The high number of coexistent diseases raises intriguing questions about pathogenesis. Hypothetically, conformational changes in LRP2/megalin stimulated by proteinuria might influence its immunogenicity to incite autoimmunity. Concurrent glomerular diseases causing proteinuria could provide a mechanism whereby circulating anti-LRP2 antibody reaches the apical membrane of the proximal tubule. The high rate of concurrent disease also begs the question how often ABBA disease is an incidental finding in biopsies performed for another dominant disease process and therefore runs the risk of being overlooked.

ABBA disease is a challenging pathologic diagnosis that must be differentiated from other entities with TBM deposits. Because it causes acute tubular injury and progressive chronic tubular damage, the staining of the brush border for IgG seen by routine IF can be easily missed if it is focal and limited to better preserved tubules, especially in small biopsy samples. The staining of the TBM deposits by IF may be so densely confluent and pseudolinear that it mimics anti-TBM nephritis. Differential diagnosis of TBM deposits also includes graft versus host disease and IgG4-related tubulointerstitial nephritis (both of which can have concurrent membranous nephropathy), Sjogren disease, and membranous lupus nephritis, especially in those ABBA cases with positive antinuclear antibody and plasma cell-rich infiltrates. Therefore, pathologists could benefit from lowering their threshold for performing LRP2 staining and ABBA serologic testing in difficult diagnostic situations.

The outcome of ABBA disease is poor and treatment guidelines are lacking. Of the 51 patients with follow-up data, 53% progressed to end-stage kidney disease or death.[7] The majority (59%) of patients received at least 1 immunosuppressive agent. Among these, 12 patients received corticosteroids alone, 3 received rituximab alone, and 15 received combination therapy (corticosteroids plus mycophenolate mofetil, tacrolimus and/or rituximab). Patients who received combination therapy were more likely to achieve complete or partial remissions, including 23% complete, 31% substantial, 15% partial, and 31% no remission. Among the 14 untreated patients, 12 had no

remission. The authors interpret these data as suggesting potential benefit of immunosuppressive therapy, although they acknowledge that coexistent glomerular disease may have influenced the rapidity and likelihood of receiving immunosuppression, as well as outcomes. Clearly, longitudinal data from more cohorts are needed to inform optimal therapy. The development of recurrent ABBA disease in 2 of the 4 patients with end-stage kidney disease who received a kidney transplant represents yet another focus for future study.

DISCLOSURE

VDD serves on the editorial board of *Kidney International*.

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