Kidney Medicine

Antibrush Border Antibody Disease: A Case Series

Michelle Pengshung, Vivek Charu, Megan L. Troxell, Shreeram Akilesh, Kelly D. Smith, and J. Ashley Jefferson

Antibrush border antibody (ABBA) disease is a rare cause of kidney disease characterized by progressive renal tubular injury associated with immune complex deposition along the basement membranes of the proximal tubule and circulating autoantibodies to brush border antigens. Several antigens have been identified as targets of autoantibodies in this disease, including low-density lipoprotein receptor related protein 2 (LRP2), cubilin, and amnionless proteins. We present 9 patients from 2 academic medical centers and describe the clinicopathologic characteristics and outcome data. All patients presented with acute kidney injury and proteinuria. Pathology confirmed immune complex deposition along proximal tubular basement membranes in all patients, but the majority (6/8) also showed segmental glomerular subepithelial immune complexes. Two of 3 patients treated with rituximab demonstrated stabilization of kidney function; 1 of these patients had mantle cell lymphoma. One patient with lung cancer showed stabilization of disease after treatment of the malignancy. The remaining patients progressed to end-stage kidney disease with either conservative therapy (3 patients) or immunosuppression with glucocorticoids (2 patients). This series highlights the poor prognosis of ABBA disease, but a potential benefit of anti-B cell therapy or treatment of an underlying malignancy in some cases.

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INTRODUCTION

Antibrush border antibody (ABBA) disease is a rare kidney disease first described in case reports in the early 1980s.[1] Initial reports described a tubulointerstitial nephritis induced by an antibody directed against the brush border of the proximal tubule. Since then, several individual case reports and small case series have further characterized this rare disease.[2-9] In 2018, the low-density lipoprotein receptor related protein 2 (LRP2, megalin) was identified as the major target of the circulating autoantibodies in ABBA disease, and the condition was briefly renamed anti-LRP2 nephropathy.[8] LRP2/megalin is a large multiligand endocytic receptor found in clathrin-coated pits at the base of microvilli in proximal tubule brush border. In 2022, cubilin (CUBN) and amnionless (AMN) proteins were identified as additional antigens implicated in the pathogenesis of ABBA disease.[10]

The disease typically presents in older adults with acute kidney injury (AKI) leading to progressive renal tubular damage and is associated with antibody binding along the brush border of proximal tubules and immune complex deposition along the tubular basement membranes.[8] With few cases reported, there are limited data on the natural history, treatment options and outcomes of this disease. This article presents a case series of patients diagnosed with ABBA disease at 2 academic medical centers on the West Coast of the United States.

MATERIALS AND METHODS

The kidney pathology biopsy databases from the University of Washington (UW), Seattle, Washington and Stanford University, Stanford, California, were queried to identify cases of ABBA disease (2000-2022). Clinical history was acquired through review of medical records. The patient's serum was tested for ABBA autoantibodies using indirect immunofluorescence on normal kidney tissue sections. Undiluted patient serum as well as serial dilutions of the serum were overlaid onto acetone-fixed frozen sections and localized using fluorescein-labeled antiserum against human antibodies to confirm the diagnosis of ABBA disease. Immunostaining of biopsy tissue with anti-LRP2 antibodies was not performed.

RESULTS

Clinical Findings

We identified 9 patients with ABBA disease (Table 1). The patients were in their 60s-80s at time of diagnosis with 4 men and 5 women in the cohort. All presented with AKI (median serum creatinine level 3.2 mg/dL, range 1.9-9.6 mg/dL) and proteinuria (median 2.3 g/g, range 1.1-16.2 g/g). Hypertension was present in 6/9 individuals. Comorbid conditions included autoimmune disease (n = 4) (Grave's disease, prior antineutrophil cytoplasmic antibody (ANCA) vasculitis, immune-related myositis and rheumatoid arthritis), malignancy (n = 2) (mantle cell lymphoma, breast cancer/squamous cell lung cancer in 1 patient), and diabetes (n = 3). Three patients were positive for antinuclear antibody (ANA) but did not meet criteria for systemic lupus erythematosus. Four patients had a positive antineutrophil cytoplasmic antibody (pANCA) without features of active ANCA-associated vasculitis. Case 3 had a monoclonal kappa band identified and was later found to have a recurrence of their mantle cell lymphoma. Positive ABBA titers were identified in the 6 patients tested (not performed in 3 patients).

Table 1. Clinical Characteristics at Time of Presentation Along With Treatment and Outcomes in Patients with ABBA Disease

Case	Age, Sex	Kidney Involvement	Comorbid Conditions	Paraprotein Workup	Autoimmune Workup	ABBA Titer	Treatment	Outcomes
1	63, male	S_{Cr} 1.9 mg/dL, proteinuria (1.1 g/g), microhematuria	Grave's disease	Negative	+ ANA	1:40	Rituximab 1 g x 2 doses 2 weeks apart x 3 courses	S_{Cr} 1.9 mg/dL; proteinuria 0.7 g/g (at 27 months)
2	68, female	S_{Cr} 1.3 mg/dL, proteinuria (16.2 g/g)	Hypertension, diabetes, prior ANCA vasculitis	Negative	ANCA negative (previously + 10 years ago)	1:10	Rituximab, then tacrolimus and corticosteroids	Dialysis treated with dialysis (at 14 months)[a]
3	69, male	S_{Cr} 3.2 mg/dL, Proteinuria (2.5 g/g)	Mantle cell lymphoma, diabetes	Monoclonal kappa band	+ ANA (1:640) + pANCA	1:640	Treatment of mantle cell lymphoma with bendamustine and rituximab	S_{Cr} 1.6 mg/dL (at 14 months)
4	65, female	S_{Cr} 1.9 mg/dL, proteinuria (6.5 g/g), microhematuria	Breast cancer, squamous cell lung cancer, RA	Negative	+ ANA (1:320)	1:160	Chemoradiation and immunotherapy for lung cancer	S_{Cr} 1.7 mg/dL; proteinuria 1.8 g/g (at 10 months)
5	83, female	S_{Cr} 4 mg/dL, proteinuria (1.9 g/g)	Hypertension, immune-related myositis	Negative	+ pANCA	ND	Corticosteroids	S_{Cr} 3.7 mg/dL (at 12 months)
6	83, female	S_{Cr} 5.8 mg/dL, proteinuria (3+ protein on urinalysis)	Hypertension	Negative	Negative	1:100	Corticosteroids	S_{Cr} 3.5 mg/dL (at 11 months)
7	76, male	S_{Cr} 3.5 mg/dL, proteinuria (1.1 g/g)	Hypertension	Negative	Negative	Undiluted	Conservative management	Lost to follow-up
8	70, male	S_{Cr} 2.6 mg/dL, proteinuria (1.5 g/g UACR), microhematuria	Hypertension, diabetes	Free light chain ratio 2.2 mg/L	ND	ND	Conservative management	eGFR 22 (at 3.5 months)
9	79, female	S_{Cr} 9.6 mg/dL, proteinuria (3.6 g/g)	Hypertension, diabetes, cirrhosis	Negative	+pANCA (1:80)	ND	Hospice	Death (at 2 months)

Abbreviations: ABBA, antibrush border antibody; ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; ND, not done; RA, rheumatoid arthritis; S_{Cr}, serum creatinine; UACR, urinary albumin-creatinine ratio.
[a]Suspected that diabetic nephropathy was also contributing.

Pathology Findings

Light microscopy revealed acute tubular injury in 5 out of 9 patients with evidence of interstitial nephritis in 4 out of 9 patients (Table 2). Patients had varying degrees of tubular atrophy and interstitial fibrosis (Fig 1A). Case 3 with a history of mantle cell lymphoma was found to have a monomorphic lymphoplasmacytic infiltrate replacing their renal parenchyma. Cases 2 and 9 also had evidence of mesangial nodular glomerulosclerosis consistent with diabetic nephropathy. Immunofluorescence in all patients showed prominent staining of proximal tubular basement membranes (TBM) and brush borders for IgG, C3, kappa, and lambda light chains (Fig 1D). There was also segmental granular peripheral capillary wall staining in the glomeruli for IgG, C3, kappa and lambda light chains in 6 out of 9 patients (Fig 1B). Electron microscopy confirmed discrete immune deposits in the TBM in all patients (TBM was not visualized in one patient) (Fig 1E), whereas 6 patients also demonstrated segmental subepithelial deposits in the glomerular capillary loops in a segmental membranous nephropathy pattern (Fig 1C).

Clinical Course

Follow-up was available for 8 out of 9 patients (median 14 months, range 3-27 months) (Table 1). Three patients were treated with rituximab. Case 1 achieved stable kidney function over 27 months follow-up with proteinuria improving from 1.1 to 0.7 g/g. Case 2 was treated with rituximab and then received maintenance therapy with tacrolimus and prednisone. At 14 months of follow-up, the patient had progressed to dialysis. Case 3 had mantle cell lymphoma and was treated with a combination of bendamustine and rituximab with an improvement in serum creatinine levels from 3.2 to 1.6 mg/dL noted at 14 months of follow-up. Case 4 had squamous cell lung cancer and underwent chemoradiation and immunotherapy with serum creatinine levels improving slightly from 1.9 to 1.7 mg/dL and proteinuria improving from 6.5 to 1.8 g/g. Cases 5 and 6 were treated with corticosteroids, but continued to have significant advanced kidney disease at 12 and 11 months of follow-up, separately. Two patients were not treated with any immunosuppression because of already advanced disease (Case 7 and 8). Case 9 was transitioned to hospice care given multiple other medical comorbid conditions and died after 2 months.

DISCUSSION

This case series describes 9 patients with ABBA disease identified at 2 West Coast academic medical centers. The patients in this case series confirm the typical clinical presentation of ABBA disease, predominantly affecting elderly patients presenting with AKI with subnephrotic range proteinuria.[8] Two patients presented with nephrotic range proteinuria but also had evidence of diabetic glomerulosclerosis on biopsy. We also highlight the association with glomerulopathy in the majority of cases.

ABBA disease has been described in case reports and one larger case series, but remains a rare entity.[2-9] The full pathophysiologic spectrum of ABBA disease remains unknown; however, several antigens have been identified as targets, including LRP2, CUBN, and AMN proteins. Both CUBN and megalin interact with AMN to form a multireceptor complex on proximal tubular cells responsible for the uptake of albumin and other filtered proteins.[10,11] Rather than a single disease entity, it has been proposed that ABBA disease represents a morphologic pattern of injury because of autoantibodies against several proximal tubular antigens causing an in situ immune complex-mediated tubulointerstitial nephritis.[10] It is unclear how circulating pathogenic autoantibodies are able to pass through the glomerular filtration barrier and access antigens on the proximal tubule brush border within the urinary space. It is possible that an associated glomerulopathy is also required. In this series, 2 patients had evidence of diabetic glomerulopathy, and 6 patients had scattered subepithelial immune deposits consistent with a segmental membranous nephropathy. The segmental membranous nephropathy cases are of particular interest in that megalin was initially identified as the target podocyte antigen in Heymann nephritis, a rat model of membranous nephropathy, but was excluded in human disease, as megalin was initially not found to be expressed on human podocytes.[12] However, more sensitive techniques have demonstrated low level megalin expression on human podocytes.[13] Segmental subepithelial immune deposits have been previously described in LRP2-associated ABBA disease but do not stain with anti-LRP2 antibodies, and the presumed podocyte antigen(s) have not been identified.[8,14] Staining for the phospholipase A2 receptor (PLA2R) or other podocyte antigens known to be associated with membranous nephropathy was not performed in this series.

The mechanism for the development of autoantibodies also remains unknown. Associations with malignancies and autoimmune disorders have been proposed as possible triggers for autoantibody formation along with preexisting kidney injury.[15] Two of the patients in this case series had an underlying malignancy (one with recurrence of mantle cell lymphoma and the other with newly diagnosed squamous cell lung cancer). Both patients received chemotherapy for their cancers and noted improvement in their kidney function and proteinuria. It is unclear whether the improvement was related to nonspecific immunosuppressive effects of the chemotherapy or effects on the tumor itself. Three cases of ABBA disease associated with concurrent kidney infiltration by low-grade B cell lymphoma have previously been described.[7,14] ABBA disease has also been reported with renal clear cell carcinoma.[3] LRP2/megalin is expressed in a wide range of tissues, including the choroid plexus, the lung alveoli, the thyroid and parathyroid glands, and retina, in addition to proximal tubular cells within the kidney, and has been implicated in tumorigenesis in a range of human cancers, including colorectal cancer, melanoma, and lung cancer.[16-18]

Table 2. Pathologic Characteristics of Kidney Biopsies with ABBA Disease at Initial Diagnosis

	Light Microscopy				Immunofluorescence			Electron Microscopy	
Case	Acute Tubular Injury	Interstitial Inflammation	Interstitial Fibrosis and Tubular Atrophy	Other Findings	Glomerular Capillary Wall staining	Bowman's Capsule Staining	TBM and Brush Border Staining	Segmental Subepithelial Deposits Present	TBM and Bowman's Capsule Deposits Present
1	No	Yes	No		Segmental IgG, C3, kappa, and lambda	Strong granular staining for IgG, C3, kappa, and lambda	Strong staining for IgG, C3, kappa, and lambda	Yes	Yes
2	Yes, focal	No	Yes, mild	Nodular mesangial glomerulosclerosis	None	None	Strong staining for IgG	No	Yes
3	No	No	No	Entire renal parenchyma replaced by monomorphic lymphoplasmacytic infiltrate	Segmental granular staining for IgG, C3, C1q, kappa, and lambda	None	Diffuse granular deposits for IgG, C3, C1q, kappa, and lambda	Yes	Yes
4	No	Yes	Yes, mild		Granular staining for IgG, C3, kappa, and lambda	Granular staining for IgG, C3, kappa, and lambda	Staining for IgG, C3, C1q, kappa, and lambda	Yes	Yes
5	Yes, focal	Yes, patchy	Yes, moderate		Segmental granular staining for IgG, IgG4, C3, kappa, and lambda	Strong staining for IgG	Strong staining for IgG	Yes	Yes
6	Yes, focal	No	Yes, diffuse and severe		Rare segmental staining for IgG and kappa	Staining for IgG, kappa, and lambda	Staining for IgG, kappa, and lambda	Yes	Not able to be visualized
7	Yes	Yes, focal	Yes, severe		None	Focal segmental trace staining for IgG, kappa, and lambda	Granular staining for IgG, C3, kappa, and lambda	No	Yes
8	Yes, focal	No	Yes, mild and patchy		Segmental staining for IgG, kappa, and lambda		Strong staining for IgG, kappa, and lambda	Yes	Yes
9	Yes	No	Yes, moderate	Moderate nodular mesangial glomerulosclerosis	None	None	Strong staining for IgG, kappa, and lambda	No	Yes

Abbreviations: BM, basement membrane; GBM, glomerular basement membrane; IF, immunofluorescence; TBM, tubular basement membrane.

However, data remain limited in determining an association between malignancy and ABBA disease.

An association of ABBA disease with autoimmune disorders has also been suggested. One case report described a patient with both ABBA disease and lupus nephritis.[6] In the largest case series reported to date, 30% of the patients were ANA positive.[8] In our series, 3 patients (33%) had a positive ANA but did not meet criteria for systemic lupus nephritis, and 4 patients (44%) were positive for ANCA. Other autoimmune disorders in our patients included Grave's disease, prior ANCA vasculitis (though current ANCA testing was negative), immune-related myositis, and rheumatoid arthritis. Anti-LRP2 is a common autoantibody that has been detected in many autoimmune diseases, including rheumatoid arthritis, systemic lupus nephritis, systemic sclerosis, and Bechet disease, and one could postulate that the absence of glomerulopathy in these patients prevents the development of ABBA disease.[19]

Given the rarity of this disease, the natural history and optimal treatment are uncertain. In prior reported cases, a range of immunosuppressive therapies, including glucocorticoids, rituximab, and cyclophosphamide, have been used.[2] Only one patient achieved immunologic remission when treated with a combination of corticosteroids and cyclophosphamide. The overall prognosis for this disease remains poor. In the largest case series to date, 5 out of 10 patients reached dialysis despite a variety of treatments with an average follow-up of 11 months, leading to the conclusion that patients progressed rapidly.[8] In our series, all patients had chronic kidney disease or reached dialysis. One patient who had concomitant diabetes with ABBA disease had worse outcomes progressing to dialysis in 14 months. The 2 patients who were treated for their underlying malignancy demonstrated interval improvement in their creatinine levels and proteinuria.

ABBA disease is difficult to diagnose given its rarity and relatively nonspecific clinical presentation. Kidney biopsy remains the gold standard diagnostic test as there are no clinically available biomarkers at present. Notably, many older patients with subacute AKI and low-grade proteinuria may not undergo kidney biopsy, and this condition may be missed. The differential diagnosis on biopsy for this disease includes lupus nephritis and IgG4-related disease as both may demonstrate tubulointerstitial nephritis with TBM deposits. The characteristic brush border granular IgG staining identifies ABBA disease. Detection of antibodies to LRP2, and the newly identified CUBN and AMN, may play an important role in the diagnosis of ABBA disease in the future, though testing at this time is currently limited to specialty laboratories.

In summary, we present the second largest series of patients with ABBA disease, which adds to the currently

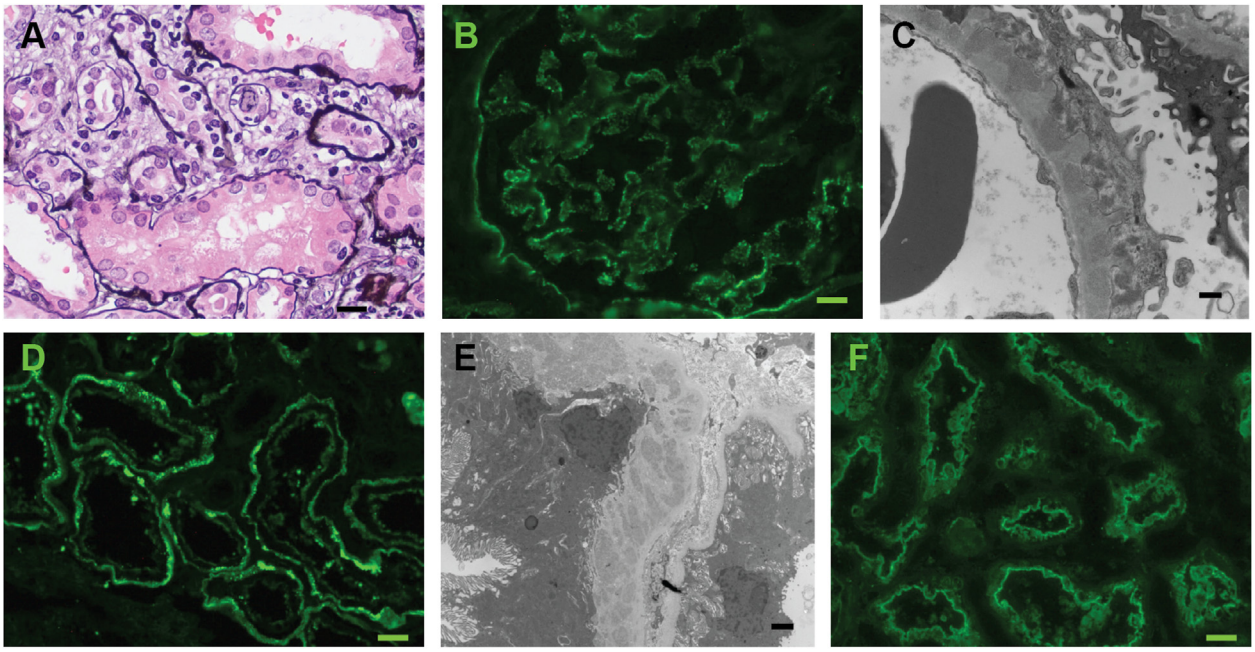

Figure 1. Representative histopathology images of ABBA disease. (A) Light microscopy demonstrating typical findings of tubulointerstitial nephritis, tubular injury, tubular atrophy, and interstitial fibrosis (bar = 20 μm). (B) Immunofluorescence staining of glomeruli demonstrates granular capillary wall IgG immune deposits (bar = 20 μm). (C) Electron microscopy shows small subepithelial immune deposits and podocyte foot process effacement (bar = 500 nm). (D) Direct immunofluorescence for IgG shows positive staining in proximal tubular basement membranes and brush borders (bar = 40 μm). (E) Electron microscopy demonstrates electron dense immune deposits within the tubular basement membranes (bar = 2 μm). (F) Indirect immunofluorescence staining of normal human kidney with patient's serum demonstrates positive staining in proximal tubular epithelial cell brush borders (bar = 40 μm). ABBA, Antibrush border antibody.

available literature.[2-9] It confirms the typical clinical presentation and histological features, and highlights the overall poor prognosis for this disease. Future studies identifying circulating antibodies may permit diagnosis at an earlier stage in the disease course and hopefully improve the prognosis for this uncommon condition.

ARTICLE INFORMATION

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