

## Antibrush Border Antibody Disease: A Case Report and Literature Review



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Anti-brush border antibody (ABBA) disease, also called anti–low-density lipoprotein receptor-related protein 2 (anti-LRP2) nephropathy, occurs due to the formation of antibodies against brush border antigens of the renal proximal convoluted tubule. We report a case of ABBA disease in a male farmer in his 30s who presented with 2 years of polyuria, dysuria, nocturia, and urinary urgency. He described a history of long-term occupational exposure to pesticides and silica, evolving into possible pneumoconiosis, and prior pulmonary tuberculosis. At presentation, he had reduced kidney function (serum creatinine 3.6 mg/dL) with hyponatremia, hypokalemia, hypophosphatemia, a normal anion gap, metabolic acidosis, and respiratory acidosis, and 2.2 g/day of urine proteinuria. The kidney biopsy was consistent with ABBA, showing amorphous immune-deposits in the tubular basement membrane and strong positivity on indirect immunofluorescence in the brush border of the proximal tubules. The trigger for production of ABBA is still unknown, but it may be associated with chronic conditions such as pulmonary tuberculosis and occupational exposures such as silica and pesticides, as seen in the patient in this report. Most cases do not respond to immunosuppression, and the prognosis is poor.

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### INTRODUCTION

Anti-brush border antibody (ABBA) disease/anti–low-density lipoprotein receptor-related protein 2 (anti-LRP2) nephropathy is a rare form of kidney disease that affects older patients and is characterized by acute kidney injury (AKI) and progressive renal tubular injury associated with immunoglobulin G (IgG) immune complex deposits along the basement membrane of proximal tubules, and circulating autoantibodies to the proximal tubule brush border protein LRP2 (megalin).<sup>1</sup> Morrison et al<sup>2</sup> first described the disease in 1981 with the case of a patient with myasthenia gravis associated with AKI, whose indirect immunofluorescence results showed positivity on the tubular basement membrane (TBM). Biopsy samples demonstrated advanced tubulointerstitial nephritis and indirect immunofluorescence positivity for immunoglobulins and C3 only in the proximal tubules. Since then, ABBA disease has been reported in the literature rarely; herein, we report a case of a man in his 30s with AKI and proteinuria, whose serum showed strong positivity in the proximal tubules' brush border when applied on kidney tissue from a control.

### CASE REPORT

A male farmer in his 30s sought evaluation due to 2 years of urinary symptoms: polyuria, dysuria, nocturia, and urinary urgency. He confirmed long-term occupational exposure to pesticides and silica, evolving into possible pneumoconiosis. Spirometry showed severe mixed ventilatory disorder, and the pulmonary biopsy was inconclusive. He was in the last month of empirical treatment for

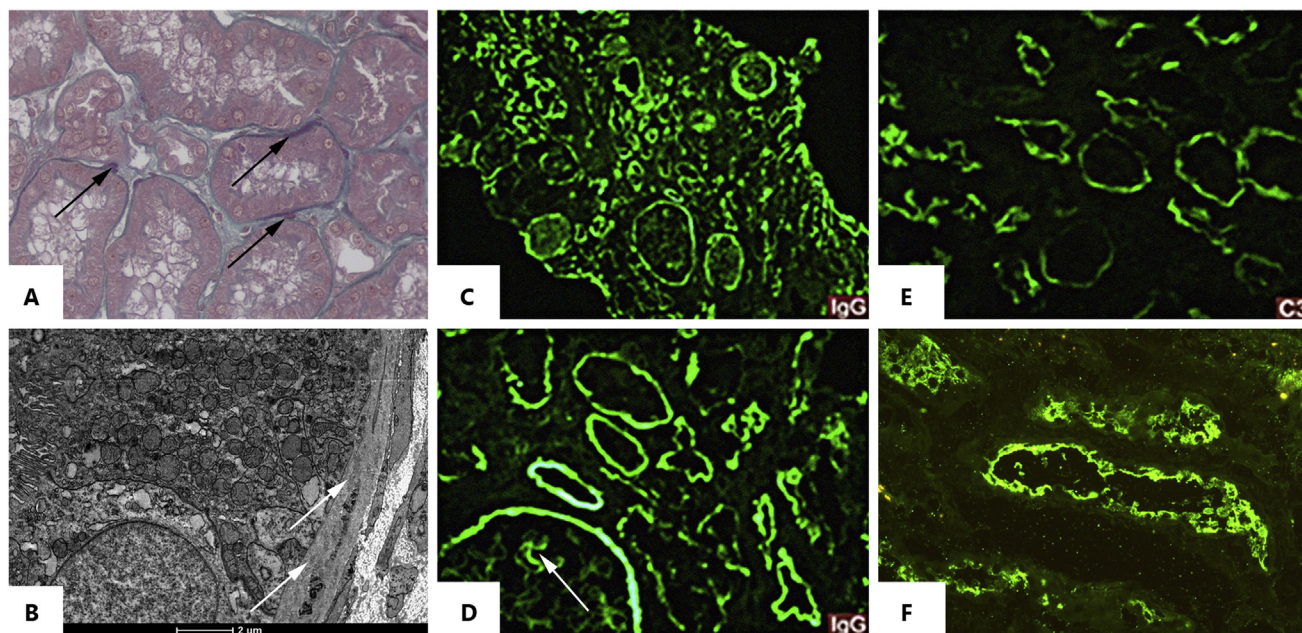
pulmonary tuberculosis, did not report previous smoking, and had two siblings both with undiagnosed pneumopathy and with similar occupational exposures.

At physical examination, he was normotensive. The admission examinations showed creatinine at 3.6 mg/dL, hyponatremia (133 mEq/L), hypokalemia (2.7 mEq/L), hypophosphatemia (2.7 mg/dL), and mixed acidosis (pH 7.22, bicarbonate 18.1 mEq/L, and pCO<sub>2</sub> 43.2 mm Hg) with normal anion gap. The urine test revealed pH of 6.0, glucose (+), and 24-hour proteinuria was 2.2 g.

Hepatitis B, hepatitis C, human immunodeficiency virus, and autoimmune diseases tests (antinuclear-antibody, anti–smooth-muscle antibody, anti-DNA antibody, anti-glomerular basement membrane [GBM] antibody, anti-cardiolipin IgM and IgG, lupus anticoagulant, and anti-neutrophil cytoplasmic antibody) were negative. Serum complement was normal. Plasma protein electrophoresis showed an increase in the region of gamma globulins, but negative immunofixation.

Ultrasound showed a normal left kidney and a right kidney with reduced dimensions, high echogenicity, and with loss of corticomedullary differentiation. He had normal renal arteries by Doppler ultrasound, and his urodynamic was unremarkable. On kidney biopsy, the light microscopy showed 47 glomeruli: 16 were globally sclerosed, and some had segmental sclerosis. His arterial vessels showed slight thickening of the middle layer. There was fibrosis and tubular atrophy in about 20 % to 30 % of the parenchyma with interstitial mononuclear inflammatory infiltrate.

Indirect immunofluorescence was negative in the glomerular compartment and was positive in the



**Figure 1.** (A-B) Kidney needle biopsy, buffered 10 % formal paraffin process. (A) Fuchsinophilic “smudgy” appearance deposits on tubular basement membrane (Masson Trichrome stain; original magnification,  $\times 40$ ). (B) Electron microscopy shows mild tubular basement membrane deposits. (C-F) Kidney biopsy fixed in Michel’s solution. (C-D) Diffuse IgG deposits along Bowman capsule, tubular basement membrane, and segmental granular capillary wall (arrow). (E) Complement fraction C3 with weak stain along tubular membrane. (F) Indirect immunofluorescence microscopy from a separate patient’s normal kidney tissue. For the test, it was preincubated with serum from the studied patient and posteriorly incubated with IgG-FITC (fluorescein isothiocyanate). The staining along the brush border proves the presence of anti-brush border antibody in the serum.

segmental peripheral capillary wall and Bowman’s capsule staining. There was granular staining in TBM and in Bowman’s capsule for IgG (+++/3+), C3 (++/3+), and  $\kappa$  and  $\lambda$  (+++/3+). Electronic microscopy showed amorphous immune-deposits in the TBM. Indirect immunofluorescence was performed using the patient’s serum and kidney tissue from a control, which showed strong positivity in the proximal tubules’ brush border (Fig 1). After 4 months, the patient developed terminal respiratory failure and died.

## DISCUSSION

ABBA disease, or anti-LRP2 nephropathy, is a rare kidney disease associated with tubular dysfunction and progressive kidney failure, potentially manifesting with hyponatremia, hypokalemia, hypophosphatemia, proteinuria, and acidosis. This report describes a case of advanced chronic kidney disease associated with a decrease in serum levels of various electrolytes (sodium, potassium, magnesium, phosphorus, and loss of bicarbonate), which refers to the hypothesis of tubulopathy. The findings on kidney biopsy were consistent with ABBA disease/anti-LRP2 nephropathy.

After the first reports in 1981 and 1982,<sup>2-4</sup> the next report was in 2016 when Rosales et al<sup>5</sup> described a patient with end-stage kidney disease and negative serologies with kidney biopsy findings compatible with ABBA disease.

Subsequently, in 2018 Larsen et al<sup>6</sup> described the largest series of the disease: a cohort of 10 cases (including the report by Rosales et al<sup>5</sup>). All the patients were elderly and had reduced kidney function associated with subnephrotic proteinuria. Immunoprecipitation and mass spectrometry analysis showed that the serum from 9 of the 10 patients had an antigen-antibody reaction with a high-molecular-weight protein present on the renal tubular brush border known as megalin or LRP2, which formed a highly sensitive and disease-specific marker associated with ABBA disease. Therefore, a new nomenclature for the disease was proposed: anti-LRP2 nephropathy.<sup>6</sup>

In 2019, Dinesh et al<sup>7</sup> published a case describing a novel feature of the disease: abundant IgG4-positive interstitial plasma cells. This feature was accompanied by the classic combination of TBM deposits, tubulointerstitial nephritis, and segmental glomerular subepithelial immune deposits. Light microscopy identified large TBM deposits, and IgG staining of apical aspects of proximal tubules using immunofluorescence microscopy pointed to the correct diagnosis of anti-LRP2 nephropathy.

More recently, authors have described ABBA disease/anti-LRP2 nephropathy associated with lupus,<sup>8</sup> minimal change disease,<sup>9</sup> and lymphoma,<sup>10</sup> and highlighted the diagnostic difficulty faced by nephrologists and pathologists in the identification of this rare but likely under-recognized disease<sup>11,12</sup> (Table 1).

**Table 1.** Literature Review of ABBA Cases

Case	Reference	Age, Sex	Comorbidities	Kidney Impairment	Autoimmunity	Kidney Biopsy	Treatment and Outcome
1	Morrison et al <sup>2</sup> (1981)	59, Male	Thymoma, myasthenia gravis	<ul style="list-style-type: none"> <li>Scr not informed (described as in AKI)</li> <li>Urine sediment with proteinuria 3+</li> <li>6-8 RBCs/field</li> </ul>	<ul style="list-style-type: none"> <li>Indirect IF (+) on TBM brush border</li> <li>ANA (-)</li> </ul>	<ul style="list-style-type: none"> <li>OM: marked TIN, interstitial fibrosis and tubular atrophy, AKI, slight expansion of mesangial matrix</li> <li>IF: IgG (+) in BC; C3 (+) in BC and TBM</li> <li>EM: focal fusion of podocytary process, intramembranous subepithelial deposits in GBM, TBM disrupted</li> </ul>	<ul style="list-style-type: none"> <li>Hemodialysis</li> <li>Death</li> </ul>
2	Douglas et al <sup>3</sup> (1981)	31, Male	None	<ul style="list-style-type: none"> <li>Scr 1.5 mg/dL</li> <li>Proteinuria/24 h 1.1 g</li> <li>No description of hematuria</li> </ul>	<ul style="list-style-type: none"> <li>Indirect IF (+) on TBM brush border</li> <li>ANA (-)</li> </ul>	<ul style="list-style-type: none"> <li>OM: not described</li> <li>IF: IgG and C3 (+) in glomerular capillaries and more intensely in BC and TBM</li> <li>EM: electro-dense subepithelial and intramembranous glomerular deposits in BC and proximal TBM</li> </ul>	Not described
3	Rosales et al <sup>5</sup> (2016)	73, Male	DM, HTN, CAD	<ul style="list-style-type: none"> <li>Scr 15.2 mg/dL</li> <li>Proteinuria/24 h 1.3 g</li> <li>Hematuria 1+</li> </ul>	<ul style="list-style-type: none"> <li>Indirect IF (+) on TBM brush border</li> <li>ANA (-)</li> <li>Anti-DNA (-)</li> <li>ANCA (-)</li> <li>Anti-GBM (-)</li> </ul>	<ul style="list-style-type: none"> <li>OM: marked interstitial inflammation and fibrosis; slight tubulitis with accentuated tubular atrophy; acute tubular injury.</li> <li>IF: IgG (IgG1, IgG2, IgG4), C3, κ and λ (+) in TBM, IgG (+) focal and segmental glomerular impairment</li> <li>EM: electro-dense deposits in TBM, sparse and focal subepithelial deposits with no spicules</li> </ul>	<ul style="list-style-type: none"> <li>Corticotherapy without success</li> <li>Kidney transplantation with posttransplant recurrence of primary disease</li> </ul>
4	Larsen et al <sup>6</sup> (2018)	68, Male	Recent infection by bacillus cereus	<ul style="list-style-type: none"> <li>Scr 8.8 mg/dL</li> <li>Proteinuria/hematuria not evaluated</li> </ul>	<ul style="list-style-type: none"> <li>Indirect IF (+) on TBM brush border</li> <li>ANA (-)</li> <li>Anti-DNA (-)</li> <li>ANCA (-)</li> </ul>	<ul style="list-style-type: none"> <li>OM: slight tubulitis and interstitial inflammation; slight fibrosis and tubular atrophy; acute tubular injury</li> <li>IF: IgG (+) in GBM and BC, IgG and C3 (+) in TBM, IgG (-) in proximal tubular brush border</li> <li>EM: electro-dense deposits in TBM</li> </ul>	<ul style="list-style-type: none"> <li>Corticotherapy</li> <li>Hemodialysis</li> </ul>
5	Larsen et al <sup>6</sup> (2018)	78, Male	DM, HTN	<ul style="list-style-type: none"> <li>Scr 3.0 mg/dL</li> <li>Proteinuria/24 h 3.3 g</li> <li>Hematuria 1+</li> </ul>	<ul style="list-style-type: none"> <li>Indirect IF (+) on TBM brush border</li> <li>ANA (-)</li> <li>Anti-DNA (unperformed)</li> <li>ANCA (+) borderline</li> </ul>	<ul style="list-style-type: none"> <li>OM: moderate interstitial fibrosis and tubular atrophy; acute tubular injury</li> <li>IF: IgG (+) in GBM and BC, IgG and C3 (+) in TBM, IgG (+) in proximal tubular brush border</li> <li>EM: electro-dense deposits in TBM</li> </ul>	<ul style="list-style-type: none"> <li>Corticotherapy and cyclophosphamide;</li> <li>Scr 2.0 mg/dL and ABBA's negated at indirect IF (disease remission) after 12 months of treatment and FU</li> </ul>
6	Larsen et al <sup>6</sup> (2018)	76, Male	COPD	<ul style="list-style-type: none"> <li>Scr 1.7 mg/dL</li> <li>Proteinuria/24 h 0.5 g</li> <li>Hematuria 1+</li> </ul>	<ul style="list-style-type: none"> <li>Indirect IF (+) on TBM brush border</li> <li>ANA 1:320</li> <li>Anti-DNA (-)</li> <li>ANCA (unperformed)</li> </ul>	<ul style="list-style-type: none"> <li>OM: mild interstitial fibrosis and moderate tubular atrophy; acute tubular injury</li> <li>IF: IgG (+) in GBM and BC; IgG and C3 (+) in TBM; IgG (-) in proximal tubular brush border</li> <li>EM: electro-dense deposits in TBM</li> </ul>	<ul style="list-style-type: none"> <li>Rituximab</li> <li>Hemodialysis</li> <li>Death</li> </ul>

(Continued)

**Table 1 (Cont'd).** Literature Review of ABBA Cases

Case	Reference	Age, Sex	Comorbidities	Kidney Impairment	Autoimmunity	Kidney Biopsy	Treatment and Outcome
7	Larsen et al <sup>6</sup> (2018)	69, Female	DM	<ul style="list-style-type: none"> <li>Scr 2.7 mg/dL</li> <li>Proteinuria/24 h 1.5 g</li> <li>Hematuria 1+</li> </ul>	<ul style="list-style-type: none"> <li>Indirect IF (+) on TBM brush border</li> <li>ANA (-)</li> <li>Anti-DNA (-)</li> <li>ANCA (-)</li> </ul>	<ul style="list-style-type: none"> <li>OM: slight tubulitis and moderate interstitial inflammation and fibrosis, with tubular atrophy; acute tubular injury</li> <li>IF: IgG (+) in GBM and BC, IgG and C3 (+) in TBM, IgG (+) in proximal tubular brush border</li> <li>EM: electro-dense deposits in TBM</li> </ul>	<ul style="list-style-type: none"> <li>Corticotherapy</li> <li>Scr 4.2 mg/dL at 15-month FU</li> </ul>
8	Larsen et al <sup>6</sup> (2018)	72, Male	DM	<ul style="list-style-type: none"> <li>Scr 5.0 mg/dL</li> <li>Proteinuria/24 h 0.8 g</li> <li>Hematuria 1+</li> </ul>	<ul style="list-style-type: none"> <li>Indirect IF (+) on TBM brush border</li> <li>ANA 1:40</li> <li>Anti-DNA (-)</li> <li>ANCA (-)</li> </ul>	<ul style="list-style-type: none"> <li>OM: interstitial inflammation with marked fibrosis and tubular atrophy, acute tubular injury</li> <li>IF: IgG (+) in GBM and BC, IgG and C3 (+) in TBM; IgG (+) in proximal tubular brush border</li> <li>EM: electro-dense deposits in TBM</li> </ul>	<ul style="list-style-type: none"> <li>Corticotherapy</li> <li>Hemodialysis</li> <li>Death</li> </ul>
9	Larsen et al <sup>6</sup> (2018)	70, Male	HTN, gout, nephrolithiasis	<ul style="list-style-type: none"> <li>Scr 2.2 mg/dL</li> <li>Proteinuria/24 h 1.1 g</li> <li>Hematuria 1+</li> </ul>	<ul style="list-style-type: none"> <li>Indirect IF (+) on TBM brush border</li> <li>ANA 1:640</li> <li>Anti-DNA (weak +)</li> <li>ANCA (-)</li> </ul>	<ul style="list-style-type: none"> <li>OM: high interstitial inflammation, fibrosis and tubular atrophy, acute tubular necrosis</li> <li>IF: IgG (+) in GBM and BC, IgG and C3 (+) in TBM; IgG (-) in proximal tubular brush border</li> <li>EM: electro-dense deposits in TBM</li> </ul>	<ul style="list-style-type: none"> <li>No specific treatment</li> <li>Scr 2.3 mg/dL at 10-month FU</li> </ul>
10	Larsen et al <sup>6</sup> (2018)	66, Female	DM, HTN	<ul style="list-style-type: none"> <li>Scr 6.7 mg/dL</li> <li>Proteinuria/24 h 0.9 g</li> <li>Hematuria 1+</li> </ul>	<ul style="list-style-type: none"> <li>Indirect IF (+) on TBM brush border</li> <li>ANA (-)</li> <li>Anti-DNA (-)</li> <li>ANCA (-)</li> </ul>	<ul style="list-style-type: none"> <li>OM: mild interstitial inflammation, marked interstitial fibrosis and tubular atrophy, acute tubular injury</li> <li>IF: IgG (+) in GBM and BC, IgG and C3 (+) in TBM, IgG (+) in proximal tubular brush border</li> <li>EM: electro-dense deposits in TBM</li> </ul>	<ul style="list-style-type: none"> <li>No specific treatment</li> <li>Scr 2.5 mg/dL at 3-month FU</li> </ul>
11	Larsen et al <sup>6</sup> (2018)	77, Female	Sarcoidosis	<ul style="list-style-type: none"> <li>Scr 2.3 mg/dL</li> <li>Proteinuria/24 h 0.6 g</li> <li>Hematuria 1+</li> </ul>	<ul style="list-style-type: none"> <li>Indirect IF (+) on TBM brush border</li> <li>ANA (-)</li> <li>Anti-DNA (-)</li> <li>ANCA (-)</li> </ul>	<ul style="list-style-type: none"> <li>OM: moderate interstitial fibrosis and tubular atrophy; acute tubular injury</li> <li>IF: IgG (-) in GBM and (+) in BC, IgG and C3 (+) in TBM, IgG (-) in proximal tubular brush border</li> <li>EM: electro-dense deposits in TBM</li> </ul>	<ul style="list-style-type: none"> <li>No specific treatment</li> <li>Scr 2.1 mg/dL at 6-month FU</li> </ul>
12	Larsen et al <sup>6</sup> (2018)	80, Male	HTN	<ul style="list-style-type: none"> <li>Scr 14.7 mg/dL</li> <li>Proteinuria/hematuria not evaluated</li> </ul>	<ul style="list-style-type: none"> <li>Indirect IF (+) on TBM brush border</li> <li>ANA (-)</li> <li>Anti-DNA (-)</li> <li>ANCA (-)</li> </ul>	<ul style="list-style-type: none"> <li>OM: medium interstitial inflammation and fibrosis, slight tubulitis and tubular atrophy, acute tubular injury</li> <li>IF: IgG (+) in GBM and BC, IgG and C3 (+) in TBM, IgG (+) in proximal tubular brush border</li> <li>EM: electro-dense deposits in TBM</li> </ul>	<ul style="list-style-type: none"> <li>Corticotherapy</li> <li>Hemodialysis</li> </ul>
13	Dinesh et al <sup>7</sup> (2019)	90, Female	HTN, HLD, AV block, OP, PMR	<ul style="list-style-type: none"> <li>Scr 4.4 mg/dL</li> <li>PTN/Scr ratio 2.4 g/g</li> <li>5 RBCs/field</li> </ul>	<ul style="list-style-type: none"> <li>Indirect IF (+) on TBM brush border</li> <li>ANA (-)</li> <li>Anti-GBM</li> <li>Anti-DNA (weak +)</li> <li>ANCA (-)</li> </ul>	<ul style="list-style-type: none"> <li>OM: mild tubulitis and mild to moderate interstitial fibrosis and tubular atrophy; acute tubular injury</li> <li>IF: IgG (+) (mainly IgG4), κ and λ light chains, and C3 (+) in TBM, IgG (+) also in GBM</li> <li>EM: immune deposits in TBM, subepithelial immune deposits within glomeruli and BC</li> </ul>	<ul style="list-style-type: none"> <li>Corticotherapy</li> <li>Rituximab</li> <li>Hemodialysis</li> </ul>

(Continued)



**Table 1 (Cont'd).** Literature Review of ABBA Cases

Case	Reference	Age, Sex	Comorbidities	Kidney Impairment	Autoimmunity	Kidney Biopsy	Treatment and Outcome
14	Dvanajscak et al <sup>8</sup> (2020)	55, Male	DM, HTN, HLD	<ul style="list-style-type: none"> <li>Scr 1.2 mg/dL</li> <li>Proteinuria/24 h 5.7 g</li> <li>Hematuria 2+</li> </ul>	<ul style="list-style-type: none"> <li>Indirect IF (+) on TBM brush border</li> <li>ANA (+)</li> <li>Anti-dsDNA (+)</li> <li>Anti-Smith (+)</li> <li>Anti-histone (+)</li> <li>Anti-SSA/Ro (-)</li> <li>Anti-SSB/La (-)</li> <li>Anti-cardiolipin (-)</li> <li>ANCA (-)</li> </ul>	<ul style="list-style-type: none"> <li>OM: glomeruli with diffuse mesangial hypercellularity and mesangial matrix expansion; fibrinoid necrosis with a cellular crescent in a glomerulus; interstitium devoid of a significant inflammatory infiltrate</li> <li>IF: diffuse, granular, predominantly mesangial and lesser capillary loop "full-house" staining; extraglomerular granular IgG deposits focally present along the TBMs and BCs and the apical brush border of numerous proximal tubules; anti-LRP2 antibody (+) along the apical brush border of the proximal tubules and focal granular positivity along the TBMs</li> <li>EM: numerous mesangial electro-dense deposits but no discrete electro-dense deposits seen along peripheral GBMs</li> </ul>	<ul style="list-style-type: none"> <li>Corticotherapy</li> <li>Mycophenolate mofetil</li> <li>Cyclophosphamide</li> <li>Scr decreased to within normal limits (1.0-1.1 mg/dL), marked reduction in proteinuria (UPCR 0.8 g/g)</li> </ul>
15	Caliskan et al <sup>9</sup> (2020)	79, Male	HTN, hemochromatosis, PMR, BPH	<ul style="list-style-type: none"> <li>Scr 3.2 mg/dL</li> <li>Protein/Scr ratio 9.0 g/g</li> <li>3-5 RBCs/field</li> </ul>	<ul style="list-style-type: none"> <li>Indirect IF (+) on TBM brush border</li> <li>ANA (-)</li> <li>Anti-PLA<sub>2</sub>R (-)</li> <li>Anti-GBM, proteinase 3 and myeloperoxidase antibodies (-)</li> <li>Serum cryoglobulin (-)</li> </ul>	<ul style="list-style-type: none"> <li>OM: glomeruli with largely unremarkable appearance; mild interstitial fibrosis and tubular atrophy involving 20 % of cortex; moderate interstitial edema without significant interstitial inflammation; Congo red stain (-)</li> <li>IF: staining along proximal tubular brush borders seen for IgG, κ and λ light chains, equal throughout the tubulointerstitium; staining for LRP2 showed similar granular TBM deposits along the proximal tubules and brush borders</li> <li>EM: global podocyte foot process effacement</li> </ul>	<ul style="list-style-type: none"> <li>Corticotherapy</li> <li>Rituximab</li> <li>Hemodialysis</li> </ul>
16	Gamayo et al <sup>10</sup> (2019)	74, Male	WM, LPL	<ul style="list-style-type: none"> <li>Scr 3.8 mg/dL</li> <li>Protein/Scr ratio 2.0 g/g</li> <li>No description of hematuria</li> </ul>	<ul style="list-style-type: none"> <li>Indirect IF (+) on TBM brush border</li> <li>SPEP demonstrated IgM monoclonal protein and elevated κ free light chain;</li> <li>C3 levels low</li> </ul>	<ul style="list-style-type: none"> <li>OM: glomeruli with segmental membranous features; tubulointerstitium with diffuse inflammatory infiltrate; acute tubular injury; foci of mild tubulitis and occasional large TBM deposits; moderate tubular atrophy and interstitial fibrosis</li> <li>IF: segmental granular peripheral capillary wall and BC staining for polytypic IgG and C3; widespread granular to chunky, near-circumferential staining of TBMs for polytypic IgG and C3; tubular brush borders with focal reactivity with polytypic IgG</li> <li>EM: TBM and subepithelial immune deposits, with associated podocyte foot process effacement</li> </ul>	<ul style="list-style-type: none"> <li>Bortezomib</li> <li>Dexamethasone</li> <li>Rituximab</li> <li>Hemodialysis</li> </ul>

(Continued)

**Table 1 (Cont'd).** Literature Review of ABBA Cases

Case	Reference	Age, Sex	Comorbidities	Kidney Impairment	Autoimmunity	Kidney Biopsy	Treatment and Outcome
17	Gamayo et al <sup>10</sup> (2019)	70, Male	HTN, DM, hypothyroidism, CLL	<ul style="list-style-type: none"> <li>• Scr 2.1 mg/dL</li> <li>• Protein/Scr ratio 0.47 g/g</li> <li>• Hematuria +</li> </ul>	<ul style="list-style-type: none"> <li>• Indirect IF (+) on TBM brush border</li> <li>• Elevated <math>\kappa</math> free light chain and an elevated <math>\kappa</math>:<math>\lambda</math> ratio</li> <li>• SPEP negative</li> <li>• Urine protein electrophoresis demonstrated monoclonal <math>\kappa</math> light chain</li> </ul>	<ul style="list-style-type: none"> <li>• OM: segmental membranous features; acute tubular injury; mild tubulointerstitial inflammation; large, wedge-shaped TBM immune deposits and a background of moderate tubular atrophy and interstitial fibrosis</li> <li>• IF: corticomedullary junction without glomeruli; bright, granular to chunky TBM staining for polytypic IgG and C3, with tubular brush border staining for IgG; IgG subclasses with IgG1 dominance and lesser staining for IgG2 and IgG4; IgG3 (-)</li> <li>• EM: TBMs and segmental subepithelial deposits without mesangial or subendothelial deposits</li> </ul>	<ul style="list-style-type: none"> <li>• Rituximab</li> </ul>
18	Gallan et al <sup>11</sup> (2020)	76, Male	HTN, DM, CKD	<ul style="list-style-type: none"> <li>• Scr 8.0 mg/dL</li> <li>• Proteinuria/24 h 1.1 g</li> <li>• No description of hematuria</li> </ul>	<ul style="list-style-type: none"> <li>• Indirect IF (+) on TBM brush border</li> <li>• ANCA (-)</li> <li>• Normal complement levels</li> </ul>	<ul style="list-style-type: none"> <li>• OM: glomeruli showing only ischemic changes; proximal tubules with extensive attenuation with loss of the brush borders; patchy mild interstitial inflammation; diffuse and frequently marked interstitial fibrosis and tubular atrophy</li> <li>• IF: diffuse granular to confluent TBM deposits staining for IgG, C3, and <math>\kappa</math> and <math>\lambda</math> light chains</li> <li>• EM: numerous large collections of electron-dense deposits in proximal TBMs without an identifiable substructure</li> </ul>	<ul style="list-style-type: none"> <li>• Hemodialysis</li> </ul>
19	Zhu et al <sup>12</sup> (2020)	29, Female	None	<ul style="list-style-type: none"> <li>• Scr 0.5 mg/dL</li> <li>• Proteinuria/24 h 3.8 g</li> <li>• Hematuria 14.4/HPF</li> </ul>	<ul style="list-style-type: none"> <li>• Indirect IF (+) on TBM brush border</li> <li>• ANA (-)</li> <li>• Anti-dsDNA (-)</li> <li>• Anti-GBM (-)</li> </ul>	<ul style="list-style-type: none"> <li>• OM: glomeruli without morphologic abnormalities; no tubular injury; no tubulitis, interstitial inflammatory infiltration, or fibrosis</li> <li>• IF: deposits of IgG along the brush border of proximal tubular cells and some segments of TBM and BC, with equal staining of <math>\kappa</math> and <math>\lambda</math> chains; a few segmental granular deposits of IgG also observed along the GBM</li> <li>• EM: small granular electron-dense deposits within the proximal tubule TBMs, and podocyte foot process effacement</li> </ul>	<ul style="list-style-type: none"> <li>• Corticotherapy</li> <li>• Cyclophosphamide</li> </ul>
20	Arcoverde Fechine Brito et al (2021)	35, Male	Silicosis, pulmonary TB, exposure to pesticides	<ul style="list-style-type: none"> <li>• Scr 3.6 mg/dL</li> <li>• Proteinuria/24 h 2.2 g</li> <li>• No hematuria</li> </ul>	<ul style="list-style-type: none"> <li>• Indirect IF (+) on TBM brush border</li> <li>• ANA (-)</li> <li>• Anti-DNA (-)</li> <li>• ANCA (-)</li> </ul>	<ul style="list-style-type: none"> <li>• OM: mild TIN, slight interstitial fibrosis and tubular atrophy; one-third of glomeruli globally sclerotic, some with segmental sclerosis</li> <li>• IF: IgG, C3, <math>\kappa</math> and <math>\lambda</math> (+) in TBM and BC</li> <li>• EM: amorphous immune-deposits in TBM</li> </ul>	<ul style="list-style-type: none"> <li>• No specific treatment</li> <li>• Death</li> </ul>

Abbreviations: ABBA, anti-brush border antibody; AKI, acute kidney injury; ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; anti-GBM, antiglomerular basement membrane; AV block, atrioventricular block; BC, Bowman's capsule; BPH, benign prostatic hyperplasia; CAD, coronary arterial disease; CKD, chronic kidney disease; CLL, chronic lymphocytic leukemia; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; dsDNA, double-stranded DNA; EM, electron microscopy; FU, follow-up; GBM, glomerular basement membrane; HDL, hyperlipidemia; HPF, high-power field; HTN, hypertension; IF, immunofluorescence; IgG, immunoglobulin G; IgM, immunoglobulin M; LPL, lymphoplasmacytic lymphoma; LRP2, low-density lipoprotein receptor-related protein 2 (megalin); OM, optical microscopy; OP, osteoporosis; PLA<sub>2</sub>R, M-type phospholipase A<sub>2</sub> receptor; PMR, polymyalgia rheumatic; RBC, red blood cell; Scr, serum creatinine; SPEP, serum protein electrophoresis; TB, tuberculosis; TBM, tubular basement membrane; TIN, tubulointerstitial nephritis; UPCR, urinary protein-creatinine ratio; WM, Waldenström's macroglobulinemia.

Our patient resembles the pattern of the cases described by Larsen et al<sup>6</sup>—a man with kidney failure and subnephrotic proteinuria who showed negative autoimmunity markers. In addition, he had a history of *Mycobacterium bacillus* infection, as did one of the patients in the case series in whom *Bacillus cereus* infection was documented. However, our patient contrasts with this cohort because he was not an elderly patient with ABBA disease.

In fact, the epidemiology of this disease is not well understood. It appears to affect mainly elderly people with comorbidities and subnephrotic proteinuria, situations in which kidney biopsy is hardly indicated. Thus, there is a high probability that this condition is underdiagnosed.

The trigger for the production of ABBA is unknown, although it may be associated with other autoimmune diseases and chronic infections.<sup>13-23</sup> Our patient had no previous history of autoimmunity, but there was history of mycobacterial infection and occupational exposure to silica and pesticides. Mycobacterial infections are involved in mechanisms of “molecular mimicry” and consequent autoimmunity through cross reaction; therefore, it is possible that they are involved in the pathogenesis of diseases such as primary biliary cirrhosis, sarcoidosis, and systemic lupus erythematosus (SLE).<sup>14</sup> A study published in 2007 demonstrated a significant increase in autoantibodies in 47 patients with active pulmonary tuberculosis when compared with a control group.<sup>15</sup>

Silicosis can be associated with positivity of several autoantibodies, suggesting that it may be involved in changes of immunoregulation.<sup>16</sup> A meta-analysis involving 9 studies showed an increased risk of developing rheumatoid arthritis in individuals exposed to silica (combined relative risk of 3.43 [95 % CI, 2.25-5.22]), suggesting a causal relationship.<sup>17</sup> A study by Parks and Cooper<sup>18</sup> demonstrated a strong relationship between occupational exposure to silica and the appearance of autoimmune diseases such as SLE, scleroderma, rheumatoid arthritis, and others.

Regarding the correlation between exposure to pesticides and autoimmunity, in 1990 Broughton et al<sup>19</sup> reported the association of organochlorines with the appearance of autoantibodies, including ABBA. A study performed in 1993 demonstrated that hexachlorobenzene, another pesticide, induces increased levels of autoantibodies such as anti-DNA and rheumatoid factor in animal models.<sup>20</sup> Ten years later, Ezendam et al<sup>21</sup> demonstrated that hexachlorobenzene led to the formation of lymph node germinal centers in mice, with an expressive increase in B-cell and T-cell subpopulations.

Serologies are not diagnostic for ABBA disease.<sup>22</sup> Diagnostic confirmation occurs by kidney biopsy. On light microscopy, diffuse loss of the brush border of the proximal tubules is observed with signs of focal tubulitis and tubular atrophy; lymphocytic infiltrate is visible within the interstitium; the glomerular compartment has a normal pattern with a slight thickening of GBM.

On immunofluorescence, granular deposits of IgG, C3, and C4d are observed along the TBM and proportional light chain deposition, little to no deposition of IgA, IgM, C1q, and little to no immune deposits in the glomerular compartment are observed. Indirect immunofluorescence may show serum IgG reaction with antigens on a normal brush border.

On electronic microscopy, prominent amorphous electro-dense deposits are seen in TBM; discrete and limited glomerular deposits similar to the pattern of membranous glomerulonephritis can be seen in the glomerular compartment.<sup>22</sup> Our patient showed these characteristics, and in the glomerular compartment the findings were suggestive of focal segmental glomerulosclerosis (FSGS). However, it is known that any chronic glomerular or tubular disease can reduce the nephron's total function and result in adaptive FSGS superimposed on the primary disorder.<sup>23</sup>

Regarding indirect immunofluorescence, there was negativity in the glomerular compartment and strong positivity in the TBM and in the Bowman's capsule for IgG, C3, and kappa and lambda. To confirm the hypothesis of ABBA disease, indirect immunofluorescence was performed using the patient's serum and kidney tissue from a control, showing strong positivity in the proximal tubules' brush border.

The differential diagnoses of ABBA disease mainly include (1) SLE,<sup>22</sup> (2) IgG4 disease,<sup>24</sup> and (3) idiopathic hypocomplementemic tubulointerstitial nephritis.<sup>25</sup> In our patient, SLE was determined to be unlikely due to negative serologic markers and the fact that tubular deposits in the setting of lupus generally correlate with the presence of proliferative glomerular lesions,<sup>26</sup> which were not seen in our patient with anti-LRP2 nephropathy. IgG4-related tubulointerstitial nephritis is the entity with the most morphologic overlap, because both it and anti-LRP2 nephropathy can exhibit interstitial inflammation and glomerular deposits in addition to the tubular deposits.<sup>6</sup> However, systemic disease related to IgG4 was not clinically compatible with his presentation because of the absence of suggestive systemic signs. Finally, hypocomplementemic tubulointerstitial nephritis was ruled out because of the presence of normal serum C3 and C4 levels. Other common etiologies of tubulointerstitial nephropathy, such as drug-induced hypersensitivity reactions and sarcoidosis, do not show TBM IgG deposits in the majority of patients.<sup>6</sup>

Data are limited regarding therapeutics and outcomes. In the cases described before our report, one exhibited a decrease in the creatinine level after using cyclophosphamide and corticosteroids.<sup>4</sup> Three cases had stabilization of the disease, despite the absence of a specific treatment.<sup>6</sup> One of the 13 cases provided no description of the outcome.<sup>3</sup> All the others developed unfavorably (Table 1).<sup>2,5,6</sup> Rituximab was used in 2 cases unsuccessfully.<sup>6</sup> In another patient, the disease recurred in the kidney graft despite immunosuppression; even after

plasmapheresis and rituximab, there was progression of kidney disease. Pulse therapy with methylprednisolone and belatacept was attempted, but without success.<sup>5</sup>

ABBA disease is a rare and possibly underdiagnosed autoimmune disorder. There remains much to explore regarding its pathophysiology and predisposing factors. In addition, the cases described in the literature show variable evolution and reserved prognosis.

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