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ORIGINAL ARTICLE

A 25-year experience with pediatric anti-glomerular basement membrane disease

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Abstract Anti-glomerular basement membrane (anti-GBM) disease, which is extremely uncommon in children, is characterized by rapidly progressive glomerulonephritis (RPGN) and autoantibodies against GBM collagen. Pulmonary hemorrhage is the third component in Goodpasture Syndrome. Cigarette smoking and exposure to hydrocarbons have been linked to anti-GBM disease in adults, but such an association has not been established in children. We reviewed renal biopsy and autopsy specimens over 25 years from a major tertiary care U.S. children's hospital, diagnosing anti-GBM by clinical RPGN, crescentic glomerulonephritis, and linear immunofluorescence (IF) immunoglobulin G staining in patients under 18 years of age. We identified four patients, with and without pulmonary manifestations. The sole autopsy case showed diagnostic IF despite undetectable serum anti-GBM antibodies and positive testing for serum anti-neutrophil cytoplasmic antibodies (ANCA). Three patients have survived 1–18 years following diagnosis, one of whom is recovering renal function. One adolescent had a history of smoking cigarettes and one had a probable hydrocarbon exposure. Anti-GBM disease is unusual in children, and the relationship to inhaled agents is incompletely understood. Serum anti-GBM antibodies are typically present, but cases with undetectable levels can occur. Some patients are anti-GBM and ANCA positive, with a small subset ANCA-positive, anti-GBM-negative. Ours is the first such described pediatric case.

Keywords Anti-glomerular basement membrane disease · Pediatric · Goodpasture syndrome · Rapidly progressive glomerulonephritis · Anti-GBM · Cigarette smoking · Hydrocarbon exposure · Etiology

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Introduction

Anti-glomerular basement membrane (anti-GBM) disease is characterized by glomerulonephritis and the formation of autoantibodies against the α3 chain of type IV collagen [α3 (IV) NC1 domain] in the GBM [1, 2]. Diagnosis is typically based on serologic detection of circulating antibodies by commercial assay and/or direct immunofluorescence (IF) staining of kidney biopsy specimens, combined with the clinical presentation of rapidly progressive glomerulonephritis (RPGN). As autoantibodies react with the same epitope in alveolar basement membrane (ABM) [3], pulmonary hemorrhage is the third component of the triad in Goodpasture syndrome and is variably present.

The mean age of onset of anti-GBM disease is 20–30 years, with a male predominance; a second peak occurs later at 50–70 years, with a female predominance [2, 4]. Anti-GBM disease is rare in children, and limited published data are available on its clinical course and histopathology among patients in this age group. Some authors have proposed that structural differences in the GBM exist in childhood, which transition to the adult type over ages 3 months to 3 years, contributing to the exceedingly rare diagnosis of anti-GBM disease in younger children [5]. However, patients have been reported in the literature aged

from 11 months to 5 years [6–8]. The youngest reported patient (11 months) presented with acute kidney injury, requiring plasmapheresis and progressing to end-stage renal disease (ESRD) and ultimately renal transplantation [6]. The U.S. Renal Data System (USRDS) reports that 0.4% (24/6,560) ESRD cases in children (2002–2006) were attributable to Goodpasture syndrome, presumably anti-GBM disease, as other causes of pulmonary–renal syndrome are listed separately [9]. By some accounts, crescentic glomerulonephritis is present in 5–15% of pediatric renal biopsies, of which anti-GBM disease represents yet a smaller component [10].

In adults, cigarette smoking is implicated in the development of the pulmonary component [11]. In children, this association is not clear. Exposure to inhaled hydrocarbons has otherwise been postulated as an inciting agent of the pulmonary manifestations, although a definitive link is uncertain [12, 13]. Here, we report four cases of anti-GBM disease in the pediatric population; these represent all of the cases treated at our institution in more than 25 years.

Methods

This was a retrospective review of renal biopsy and autopsy specimens, extending over a 25-year period, from a large midwestern U.S. children's hospital. The diagnosis of anti-GBM disease was based on the clinical presentation of RPGN, light microscopic (LM) demonstration of crescentic glomerulonephritis, and direct IF demonstration of linear anti-immunoglobulin G (IgG) staining of glomerular capillary loops. Findings were correlated with the clinical history as well as laboratory and serologic data. Pediatric patients were defined as being ≤18 years of age. Renal biopsy and autopsy specimens were stained for LM with hematoxylin/eosin (HE) and periodic acid Schiff (PAS) at the very minimum, with Lillie's allochrome, Masson's trichrome, and Jones' silver stains available on select cases as per institutional protocol at the time of presentation. Crescentic glomerulonephritis was defined as the presence of cellular crescents in 50% or more of non-obsolescent glomeruli. Direct IF with fluorescein-conjugated antisera was performed in all cases, with a positive result being the presence of linear GBM staining for IgG. In one case, IF microscopy was non-diagnostic due to extensive necrosis of glomerular tufts; however, as there was a significantly elevated serologic anti-GBM antibody level, the case was included in the series. Serologic anti-GBM antibody values were available for all cases. Quantitative serum anti-GBM antibody levels for patients 1 and 3 were performed at the ARUP reference laboratory (Salt Lake City, UT), via multi-analyte fluorescent detection using the following reference interval: ≤19 AU/mL = negative, 20–25 AU/mL = equivocal, ≥26 AU/mL = positive. For patient 2, serum anti-GBM antibody was performed at the ARUP reference laboratory using an enzyme-linked immunosorbent assay (ELISA) with the following reference interval: 0–20 EU = negative, 21–30 EU = weak positive, >30 EU = positive. For patient 4, fewer records of the anti-GBM antibody testing methodology were available: testing was performed using an enzyme immunoassay with the following reference interval: <10 units = negative, 10–19 units = weakly positive, >20 units = positive.

Results

In our institution, close to 2,000 pediatric medical renal biopsies are estimated to have been performed over a 25-year period. Over the past 7 years, between 67 and 85 pediatric medical renal biopsies were performed annually. An average of 5.25 cases of crescentic glomerulonephritis were diagnosed per year over the same 7-year time period, including cases of pauci-immune vasculitis, anti-GBM disease, and immune-mediated glomerulonephritis. Of these cases, we identified three patients who presented with anti-GBM disease, with one additional case identified at autopsy. The patients ranged in age from 8 to 17 years and had a male to female ratio of 3:1 (Table 1).

Table 1 Patient characteristics

Patient	Gender	Age (years)	IgG IF	Serum anti-GBM antibody	Serum ANCA	Pulmonary hemorrhage	Exposure history	% crescents	Days from first symptoms to tissue sample
1	F	8	+	-	+	+	-	83	4
2	M	10	+	+	-	-	Engine exhaust/ gasoline	87	18
3	M	17	+	+	-	+/-	Prior cigarette smoking	100	21
4	M	10	NA	+	NA	+	-	100	56

IgG, Immunoglobulin G; IF, immunofluorescence; GBM glomerular basement membrane; ANCA, anti-neutrophil cytoplasmic antibodies; F, female; M, male; NA, not available

Case reports

Patient 1

The first patient, an 8-year-old female, presented to her primary care physician with initial complaints of productive cough and sore throat. She was subsequently treated with oral amoxicillin for presumed *Streptococcal* pharyngitis. She developed abrupt respiratory failure, fever, and productive cough without hemoptysis, requiring intubation in transit from the community to children's hospital. Her past medical history was remarkable for asthma and recurrent pneumonia. Physical examination revealed diffuse rhonchi, gurgles, and bibasilar crackles in the lungs; skin pallor was diffuse. Chest X-ray revealed near-complete opacification of both lung fields (Fig. 1a). Laboratory findings were remarkable for: hemoglobin, 2.8 g/dL; platelets, 368 k/mm^3; serum creatinine, 7.7 mg/dL; blood urea nitrogen (BUN), 141 mg/dL; potassium, 6.0 mmol/L. Mechanical ventilation was difficult, although suctioning of the airway did not reveal gross blood. In the operating room, during dialysis catheter placement, she rapidly developed massive hemorrhage via the endotracheal tube and died within a few hours after receiving medical attention at our hospital. Gross autopsy examination revealed diffuse petechiae of the capsular surface of the kidneys (Fig. 1b) and massive intraalveolar pulmonary hemorrhage. LM demonstrated crescentic glomerulonephritis (83% of non-obsolescent glomeruli) (Fig. 2a) and massive intraalveolar pulmonary hemorrhage with acute capillaritis (Fig. 2b). Discontinuity of both GBM and ABM was detectable by Jones' silver staining (Fig. 2c). IF microscopy of kidney tissue revealed positive linear staining with anti-IgG (3–4+ intensity in a range scored from zero to 4+) (Fig. 3a). Similar IgG staining (3–4+) was observed in the alveolar walls but in an interrupted pattern (Fig. 3b). The quantitative serum tests were negative for anti-GBM antibody level (0 AU/mL) and positive for perinuclear anti-neutrophil cytoplasmic antibody (p-ANCA) with anti-myeloperoxidase antibody (MPO) of 182 AU/mL. Anti-nuclear antibody (ANA) titer was negative; complement C3 and C4 were normal.

Patient 2

The second patient, a 10-year-old male, was previously healthy until 6 days prior to admission, when he developed gross hematuria and was taken to a local urgent care center. He had no abdominal pain, back pain, dysuria, or edema. The hematuria was attributed to participation in Go-Kart racing 2 weeks prior to admission. Subsequently, he developed pallor, nausea, and vomiting. He continued to void bloody purple urine at 2 days prior to admission, developing eyelid edema and cough without hemoptysis on the night prior to admission. The patient was taken to the emergency department.

Initial examination revealed scattered pinpoint petechiae on the skin of his left chest, abdomen, back, thigh, and dorsum of the feet. Laboratory findings were remarkable for: hemoglobin, 11.5 g/dL; platelets, 58 k/mm^3; serum creatinine, 11.5 mg/dL; BUN, 146 mg/dL; potassium, 6.5 mmol/L. Tests for ANA and ANCA were negative, and those for C3, C4 and ASO were normal. Chest X-ray revealed clear lung fields.

After the initial management of hyperkalemia, the patient was taken to the operating room, a Tenckhoff catheter was placed, and peritoneal dialysis was immediately initiated. A renal ultrasound revealed slightly enlarged and echogenic kidneys. As hemoglobin and hematocrit continued to deteriorate and schistocytes were identified by peripheral smear, atypical hemolytic–uremic syndrome was considered. However, kidney biopsy revealed diffuse crescentic glomerulonephritis (affecting all glomeruli) with 3–4+ linear IgG staining of glomerular basement membranes by IF. Data on the quantitative serum anti-GBM

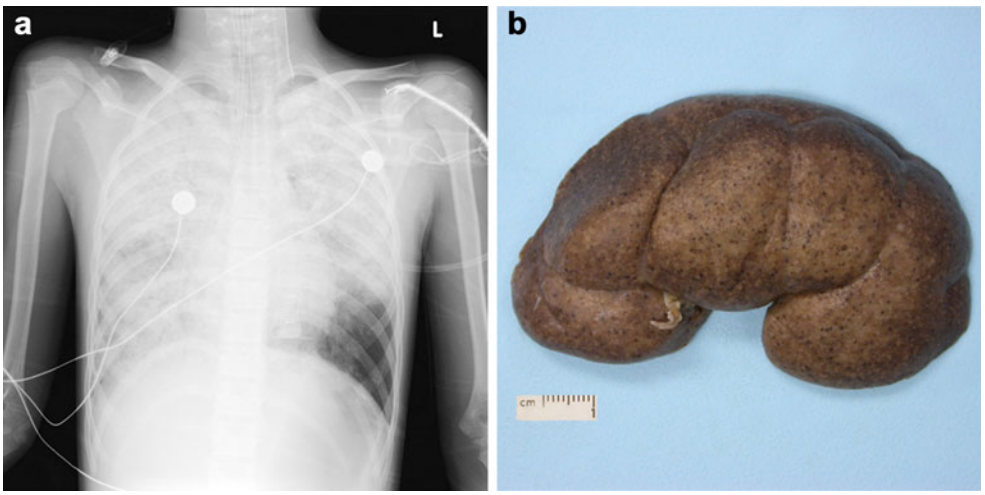

Fig. 1 Patient 1. **a** Chest X-ray. **b** Gross kidney specimen with petechial hemorrhages observed after formalin fixation

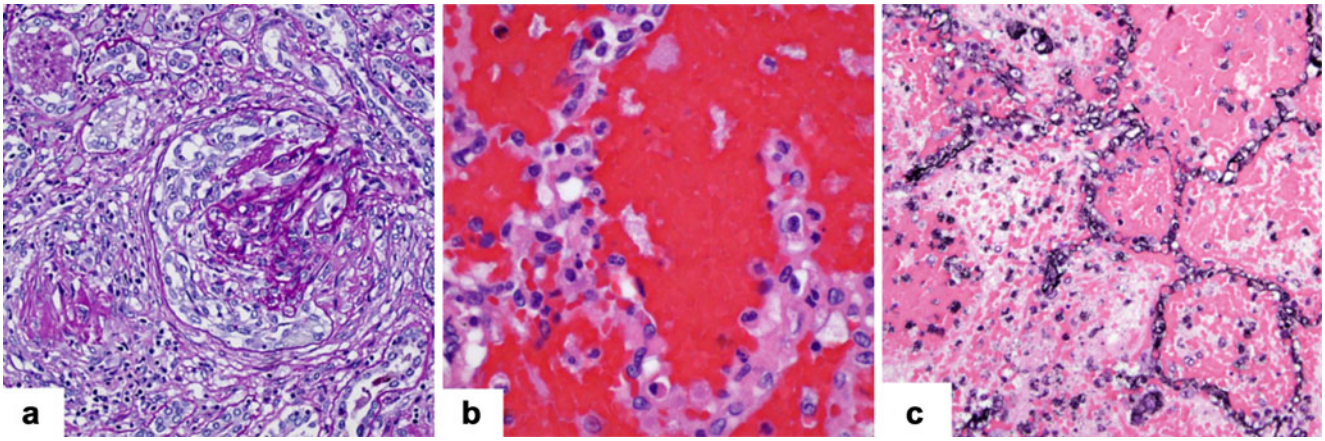

Fig. 2 Patient 1. **a** Kidney, 200× magnification, periodic acid Schiff (PAS) stain. **b** Lung, 600× magnification, hematoxylin/eosin (HE) stain; neutrophils and apoptotic debris indicate acute capillaritis. **c** Lung, 400× magnification, Jones silver stain; discontinuity of alveolar basement membrane

antibody level became available later, revealing an elevated level at 97 EU. Methylprednisolone 1 g intravenous (IV) was given as six doses every other day, continued with prednisone 60 mg every other day on a weaning regimen and cyclophosphamide 100 mg daily orally for 12 weeks. The patient underwent 12 plasmapheresis exchanges of a single plasma volume, performed daily for the first 5 days and then on alternate days for the remaining seven treatments, using a combination of fresh frozen plasma and 5% albumin as the replacement fluid. Anti-GBM antibody levels were monitored until negative. Throughout his stay the patient did not have hemoptysis.

The patient continued home peritoneal dialysis after discharge from the hospital, with cyclophosphamide and oral steroids on a weaning regimen. The anti-GBM antibody level remained negative. Nine months after his initial presentation, he received a living-related kidney transplant. His post-transplant course was unremarkable, without any episodes of acute rejection or significant infections. He has been maintained on an immunosuppression regimen consisting of tacrolimus, mycophenolate mofetil, and prednisone. His kidney function 3.5 years posttransplant is excellent, with a creatinine level of 0.8 mg/dL.

Patient 3

The third patient, a 17-year-old previously healthy male, was transferred to our hospital from an outside pediatric inpatient unit. He presented to his primary care physician with 3 weeks of fatigue and feeling ill. He had noticed decreased urine output with darkening color, but still reported urinating approximately four times a day. He denied gross hematuria or recent illnesses, including pharyngitis, abdominal pain, chest pain, shortness of breath, rashes, or peripheral swelling. Notably, the patient admitted quitting smoking 1 month prior to admission after an episode of hemoptysis. The primary care physician initiated a work-up, which revealed a creatinine level of 13.9 mg/dL. Renal ultrasound showed borderline enlargement of the kidneys with poor corticomedullary differentiation, consis-

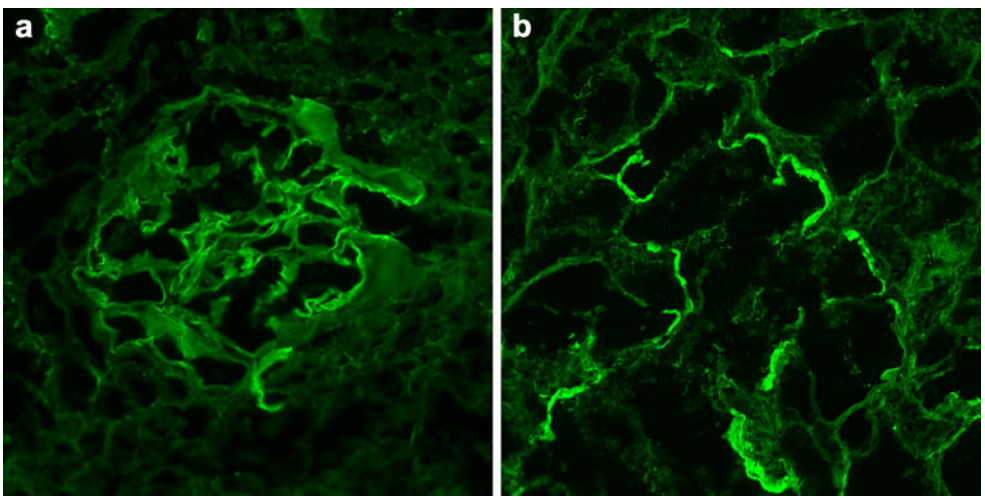

Fig. 3 Patient 1. **a** Glomerulus, 400× magnification, immunoglobulin G immunofluorescence (IgG IF). **b** Alveolus, 400× magnification, IgG IF

tent with acute medical renal disease. The patient was started on methylprednisolone IV and transferred to our hospital for further care and management.

Upon admission, the patient had mild pretibial edema. Laboratory findings were remarkable for: hemoglobin, 7.1 g/dL; platelets, 257 k/mm^3; serum creatinine, 13.4 mg/dL; BUN, 70 mg/dL; potassium, 4.4 mmol/L. Tests for ANA and ANCA were negative, and those for C3, C4 and ASO were normal. Chest X-ray demonstrated mild perihilar opacities.

The patient underwent placement of a Tenckhoff catheter for the initiation of peritoneal dialysis the following day and was subsequently temporarily changed to hemodialysis due to pericatheter leakage of the dialysis fluid. Methylprednisolone IV was continued at 1 g per dose for six consecutive doses every other day. Kidney biopsy revealed diffuse crescentic glomerulonephritis affecting 87% of glomeruli (13/15) with 4+ linear IgG staining of the GBM by IF. Data on the quantitative serum anti-GBM antibody level later became available, revealing a markedly elevated level at 173 EU. The patient underwent 11 plasmapheresis exchanges of a single plasma volume, daily for the first 5 days and then on alternate days for the remaining six treatments, using a combination of fresh frozen plasma and 5% albumin as the replacement fluid. His anti-GBM antibody level decreased to 25 EU. IV methylprednisolone was continued with prednisone 20 mg three times a day and cyclophosphamide 150 mg daily orally. Throughout his stay, the patient did not have any hemoptysis. The patient was discharged home to continue hemodialysis on an outpatient basis three times a week.

A month after discharge from the hospital, the patient resumed peritoneal dialysis, performing four manual exchanges per day and maintaining a creatinine level of 2.6-3.3 mg/dL. His treatment regimen included prednisone 40 mg every other day on a weaning schedule and cyclophosphamide 150 mg daily for 12 weeks, continued with azathioprine. One year after his acute presentation he was able to discontinue dialysis, as his creatinine level was 2.1 mg/dL. Anti-GBM antibody levels have remained negative.

Patient 4

The fourth patient, a 10-year-old male previously reported in the transfusion medicine literature [14], presented with low-grade fever and persistent cough for 2 months without hemoptysis, continued by abdominal pain, vomiting, and headache. Treatment of a right lower lobe lung infiltrate with oral antibiotics resulted in no improvement. Upon admission, the patient had mild periorbital edema. Laboratory findings were remarkable for: hemoglobin, 9.4 g/dL; platelets, 737 k/mm^3; serum creatinine, 6.2 mg/dL; BUN, 75 mg/dL. The test for ANA was negative, and that for ASO was normal. Chest X-ray demonstrated a right lower lobe infiltrate. Blood cultures were negative. Samples were sent for anti-GBM antibody testing, but not for ANCA. Early in the hospitalization period, the patient developed hemoptysis, respiratory distress, and increasing pulmonary infiltrates, requiring intensive care, intubation, and the placement of chest tubes. Kidney biopsy revealed diffuse crescentic glomerulonephritis affecting all glomeruli (20). IF microscopy was non-diagnostic due to extensive necrosis of glomerular tufts. Lung biopsy demonstrated massive, confluent intraalveolar pulmonary hemorrhage with hemosiderin-laden macrophages. Data on the quantitative serum anti-GBM antibody level became available later, revealing an elevated level at 41 EU. The patient underwent treatment with methylprednisolone at six doses of 30 mg/kg/dose on alternate days, continued with prednisone on a weaning regimen, oral cyclophosphamide for 12 weeks (125 mg/day), and plasmapheresis. He underwent six plasmapheresis exchanges on alternate days of 1.5 plasma volumes, using 5% albumin as the replacement fluid. The treatment regimen resulted in undetectable anti-GBM antibody levels and complete resolution of the pulmonary infiltrates, as revealed by imaging. His hospital course continued to improve [14].

Following discharge, the patient was maintained on peritoneal dialysis for 1 year, with the anti-GBM titer remaining undetectable. His renal function did not improve, and he received a living-related renal allograft 1 year after initial presentation, which failed 12 years later due to financial difficulties and an inability to obtain immunosuppressant medication. He continues peritoneal dialysis and has since been relisted for renal transplantation.

Discussion

Anti-GBM disease remains a very uncommon entity in the pediatric population. Our series identified only four cases over a 25-year span, at a medical institution where over 70 pediatric medical renal biopsies have been performed annually in recent years, accounting for probably close to 2,000 total biopsies over the entire study period. Interestingly, three of the cases occurred in the past 5 years. No clear etiologic factors were identified. Of the four patients, two developed overt pulmonary manifestations at presentation (Patients 1 and 4); however, neither had a documented history of smoking or other exposures, as is suggested in the adult literature. Conversely, Patient 3 reported recent smoking cessation after a prior episode of hemoptysis, despite having no further episodes of pulmonary hemorrhage at presentation or throughout admission. Documentation of passive inhalation of cigarette smoke was not

available for any of the remaining patients, although "second-hand" exposure may be a possible inciting agent in young patients. Patient 2 developed initial renal symptoms after participation in Go-Kart racing, which may represent a source of inhaled hydrocarbon vapors (automobile exhaust/gasoline), although he never developed overt pulmonary hemorrhage. In adult patients, a wide variety of agents have been linked to anti-GBM disease, including automobile exhaust, fuels (gasoline, jet fuel), paints, solvents (organic, degreasing, dry-cleaning, paint solvents), hair products (hair spray, hairdressing solvents), cleaners, glue, and insecticides [12, 13]. The association of hydrocarbons with anti-GBM disease remains unclear in children, as few cases have been reported.

Regarding treatment and prognosis of the disease, it has been noted in adults that early diagnosis and intervention correlate with improved outcome [15, 16]. Although all of the patients in our study exhibited extensive crescentic glomerulonephritis based on histological examination (>50% of glomeruli affected), Patient 3 was able to recover renal function. In support of the hypothesis that early intervention improves prognosis, the time period from the development of symptoms to hospital admission and treatment for this patient was shorter than that of Patient 4. In contrast, however, Patient 1 exhibited the most fulminant clinical course and died of massive pulmonary hemorrhage in the acute period. Of note, the previous history for this patient was remarkable for asthma and recurrent pneumonia, which may represent earlier manifestations of the disease. Pinpointing the precise onset of disease was challenging for these patients, as most experienced an ill-defined constellation of symptoms prior to the acute presentation. Our data are limited in definitively assessing this issue; however, a consideration of anti-GBM disease in young patients may avoid delay in diagnosis and therapy.

Notably, the serology tests revealed that Patient 1 had no demonstrable circulating anti-GBM antibodies, despite prominent linear IgG staining in both the GBM and ABM by IF. Along these lines, Salama et al. found that an estimated 2–3% of patients with anti-GBM disease may have circulating antibody levels that are undetectable by standard assays, yet detectable by a specialized, sensitive biosensor. In these cases, diagnosis of anti-GBM disease may be made based on biopsy findings in the appropriate clinical setting [17]. The same patient tested positive for p-ANCA with MPO, which can be seen concurrently with anti-GBM antibodies in 20–30% of adults, but has rarely been reported in children [18–20]. Of the three adult patients in Salama's series, one exhibited the same combination (anti-GBM antibody negative, perinuclear-ANCA positive) [17]. To the best of our knowledge, the case we present here is the first pediatric case to be reported. Alternatively, these results may be interpreted as overlapping ANCA vasculitis with anti-GBM disease or pure ANCA vasculitis if the IF findings are interpreted as falsely positive due to post-mortem changes or nonspecific antibody binding. However, Varis et al. examined IF findings in autopsy tissues sampled at up to 9 days after death and found only one example of pseudo-linear anti-IgG staining in a diabetic patient [21], a well-recognized phenomenon. In our case, autopsy tissue samples were obtained only 8 h postmortem, leading us to suspect that these findings are genuine.

Data in the literature on pediatric anti-GBM disease are primarily limited to case reports, likely attributable to the relative infrequency of this disease at any one institution. The USRDS figures suggest that a small but significant number of cases occur in children (ages 0–19 years) [9], although specifics regarding the diagnoses are unfortunately unavailable. If the age distribution of anti-GBM disease occurs in a manner approximating the normal (Gaussian) distribution, those cases seen in pediatric patients may represent the extreme tail of the curve. Structural differences in the GBM, as proposed by Anand et al. [5], may represent a compounding effect that makes anti-GBM disease uncommon, although not impossible in this population. Thus, although rare, anti-GBM disease should be considered in the differential diagnosis of pediatric patients with RPGN.

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