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Case Report

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IgA Nephropathy and Atypical Anti-GBM Disease: A Rare Dual Pathology in a Pediatric Rapidly Progressive Glomerulonephritis

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IgA nephropathy · Anti-GBM disease · Rapidly progressive glomerulonephritis · Rare disease · Crescentic glomerulonephritis

Abstract
Introduction: Anti-GBM nephritis in the pediatric age group is exceedingly rare with concurrent additional pathologies being even rarer. Tissue diagnosis requires a combination of crescentic histomorphology, immunofluorescence showing "paint brush stroke" pattern of linear IgG or rarely IgA, and serum anti-GBM antibodies subject to the disease course and treatment. The authors describe one such case with a dual pathology involving IgA nephropathy and atypical anti-GBM disease. ***Case Presentation:*** A 13-year-old girl presenting with features of rapidly progressive glomerulonephritis underwent a renal biopsy showing a mesangioproliferative histology with crescents and an immunofluorescence pattern indicating a dual pathology of IgA nephropathy and anti-GBM nephritis. Additional ancillary testing including staining for IgG subclasses and galactose-deficient IgA (KM55) helped to confirm the diagnosis. She responded to steroid pulses and plasma exchange therapy, was off dialysis after 8 weeks with a serum creatinine level of 1.5 mg/dL, and however remains proteinuric at last follow-up. ***Conclusion:*** Concurrent anti-GBM nephritis and IgA nephropathy is a rare occurrence and possibly arises from a complex interaction between the anti-GBM antibodies and the basement membrane unmasking the antigens for IgA antibodies. Additional newer techniques like immunofluorescence for KM55 are helpful in establishing the dual pathology.

Introduction

Pediatric anti-glomerular basement membrane (anti-GBM) disease is a rare occurrence accounting for 0.5% cases of end-stage renal disease in pediatric population [1]. Most cases in the pediatric age group tend to occur in teenagers with a male preponderance [2–6] with the youngest patient being 11 months of age [7]. It results from antibodies directed against NC1 domains of alpha 3 type IV collagen, and in its typical form presents with disruptive GBM necrotizing lesions/crescents in the kidney and pulmonary hemorrhage [8]. Tissue diagnosis re-

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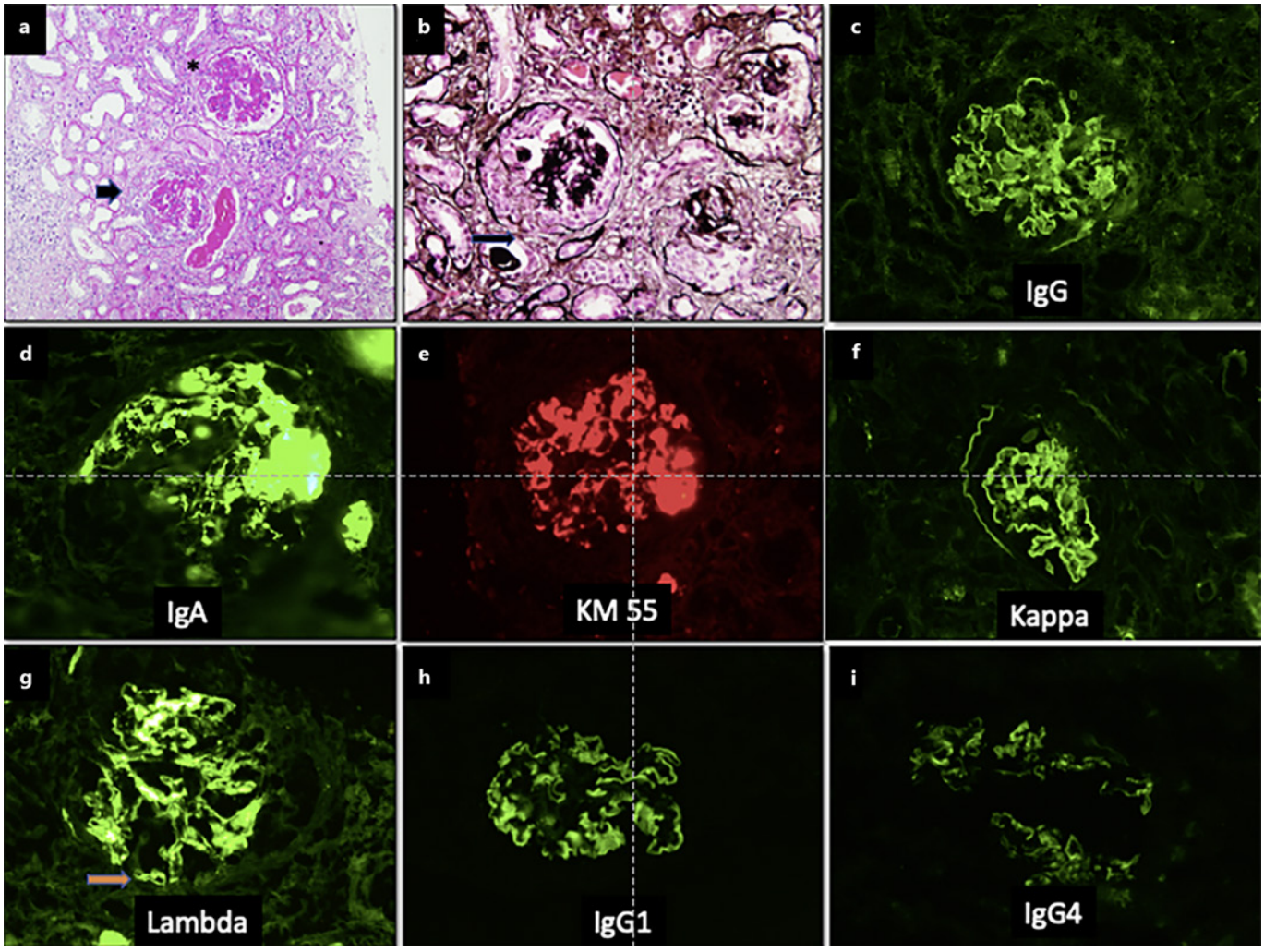

Fig. 1. a Light microscopy showing glomeruli in various stages of sclerosis ranging from open with mesangial hypercellularity to sclerosed (*) with overlying crescent (arrow) (PAS stain, ×10). **b** Silver stain showing a cellular crescent with Bowman's capsule disruption (arrow), adjacent glomeruli showing variable sclerosis (Jones Silver Methenamine stain, ×40). **c** Immunofluorescence for IgG shows "paint brush stroke" linear deposition of IgG (3+). **d** IgA shows mesangial deposits (2–3+) with capillary wall extension. **e** KM55 performed shows mesangial positivity with capillary wall extension (3+). Similar linear capillary wall immunofluorescence observed in kappa (3+) (**f**) and lambda (3+) (**g**) (arrow) along with mesangial deposits more so in lambda compared to kappa. IgG subclasses show capillary wall linear deposition of IgG1 (3+) (**h**) and IgG4 (2+) (**i**).

quires immunofluorescence demonstration of linear GBM staining for IgG, without detectable deposits on electron microscopy. Additional concurrent glomerular pathologies have been rarely described in the adult setting, with the hypothesis that the glomerular injury unmasked antigens in the GBM resulting in the development of anti-GBM antibodies and a renal limited disease. This brief report describes the rare combination of an IgA nephropathy with atypical anti-GBM nephritis in a pediatric patient and challenges in its diagnosis and management.

Case Report

The patient is a 13-year-old girl who presented with generalized puffiness and cola-colored urine for 2 weeks associated with oliguria and headache for 1 week. There was no history of rash, arthralgia, oral ulcers, nasal discharge or stuffiness, cough, dyspnea, or hemoptysis; past history was not contributory. Physical examination did not reveal any abnormality except mild edema and hypertension stage 1 (130/90 mm Hg). Hematological and biochemical investigations indicated microcytic hypochromic anemia (hemoglobin 7.4 g/dL without schistocytes on peripheral smear), total leukocyte count 8,200/mm^3, platelet count 400 × 10^3/mm^3, deranged renal function (urea 69 mg/dL, creatinine 3.4 mg/dL), and

hypoalbuminemia (albumin 2.4 g/dL). Urinalysis showed proteinuria (2+ qualitative) and hematuria (80–90 red cells/high power field), with no casts or crystals; the urine protein/creatinine ratio was 8.2 mg/mg. Complement C3 and C4 levels were within normal limits (97 mg/dL and 26 mg/dL), and ANA, anti-dsDNA, and anti-neutrophil cytoplasmic (anti-PR3 as well as anti-MPO) antibodies by enzyme linked immunoassay (ELISA) were negative. The Direct Coombs Test was negative. Ultrasound examination of the kidney showed normal size and echogenicity. With an empiric diagnosis of rapidly progressive glomerulonephritis, severe anemia, and oliguria, hemodialysis and methylprednisolone pulsing were started and a kidney biopsy performed.

Light microscopy revealed a total of 16 glomeruli, of which 3 were globally sclerosed, 1 was segmentally sclerosed, and the remainder showed cellular crescents (5/16, 31.2%), fibrocellular crescents (3/16, 18.75%), and one fibrous crescent. The crescents were associated with Bowman's capsule disruption. However, no giant cells were observed in the glomeruli or adjacent to the disrupted Bowman's capsules. Underlying tufts displayed mesangial expansion and hypercellularity. No endocapillary hypercellularity, neutrophilic infiltration, or active tuft necrosis was noted. Interstitial fibrosis and tubular atrophy occupied 25–30% of the biopsied cortex with dense chronic interstitial inflammation, interstitial edema, and diffuse acute tubular injury with presence of RBC, hyaline, and granular casts (Fig. 1a, b).

Direct immunofluorescence on the tissue showed coarse mesangial deposits of IgA (2–3+) and C3 (2–3+) along with capillary wall linear "paint brush stroke" positivity for IgG (3+) with a subclass profile of IgG1 (2–3+) and IgG4 (1–2+). Coarse mesangial and linear capillary wall positivity was also observed for both light chains, kappa and lambda. IgM and C1q were negative. No extraglomerular (tubular basement membrane or vascular) staining was observed for IgG or any of the IgG subclasses. Immunofluorescence for galactose-deficient IgA (KM55) was positive in the same location and with similar intensity as the IgA, confirming the galactose-deficient nature of IgA [9] (Fig. 1e). Ultrastructural examination of the tissue could not be performed due to lack of glomeruli in the core sent. Electron microscopy on the paraffin embedded tissue was not contributory due to extensive anatomic distortion. A final diagnosis of IgA nephropathy with anti-GBM nephritis was rendered.

Based on the biopsy, (post-pulse) sera testing for anti-glomerular basement membrane antibodies was performed by indirect immunofluorescence and ELISA, however was negative. Chest radiograph and high-resolution computerized tomography chest performed excluded pulmonary involvement.

Following kidney biopsy, 7 sessions (5 daily and 2 alternate day) of double volume therapeutic plasma exchange were performed with continued methylprednisolone pulses to a cumulative dose of 140 mg/kg (6 doses) and later switched to oral prednisolone (1 mg/kg/day). Once the child was shifted to alternate day plasma exchange, cyclophosphamide pulse (500 mg/m^2) was also initiated. Hemodialysis was discontinued after 8 weeks. At the latest follow-up, which was 5 months from presentation, blood urea was 41 mg/dL, serum creatinine 1.26 mg/dL, and serum albumin 3.4 g/dL; 24-h urine protein was 5.6 g. Medications at the last follow-up included prednisolone at 10 mg and amlodipine 5 mg once daily.

Discussion

Concurrent anti-GBM disease and IgA nephropathy is a rare occurrence and the subject of isolated case reports in adult patients [10–12]. So far, only 10 cases have been reported in the literature with an average age of 43 years and a slight female preponderance (1.15:1) [10]. In the pediatric age group, this combination is even rarer with only one other case reported in a 12-year-old post-transplant patient [13].

Association between the two diseases is hypothesized to be due to GBM damage and exposure of target antigens by the preexisting IgA nephropathy [14]. Wang et al. [15] proposed increased antigen synthesis and exposure of cryptic antigens as a possible mechanism. Another study placed the pro-inflammatory milieu in the mesangium responsible for GBM conformational changes [13]. Imperative for the diagnosis of this rare dual pathology is a sensitive immunofluorescence. Additional newer diagnostic modalities like KM55 (galactose-deficient IgA) and IgG subclasses helped to confirm the two pathologies of IgAN and anti-GBM nephritis, respectively, even in the absence of electron microscopy [16, 17]. The lack of serum positivity for anti-GBM antibodies may be related to post-pulse sampling or may be truly negative as described in a small subset of patients labeled "atypical anti-GBM nephritis" [9]. Nevertheless, with regard to prognosis, the combination has been found to have a better outcome compared to patients with anti-GBM disease in isolation [10].

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We acknowledge the efforts from our technical staff for their support and crisp diagnostic staining which was the cornerstone of making this difficult diagnosis.

Statement of Ethics

Written informed consent was obtained from the patient's parent (patient being a minor) for publication of this case report and any accompanying images. Ethical clearance in this case was not sought as this was a single case, and all investigations performed were a part of the patient workup and diagnosis and were provided to the patient, and no additional diagnostic material was obtained for research purposes.

Conflict of Interest Statement

The authors declare no conflicts of interest.

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Author Contributions

Conception and design of the work: Geetika Singh and Varun Bajaj. Data collection and imaging: Varun Bajaj and Shilpi Thakur. Data analysis and interpretation: Geetika Singh, Adarsh Barwad, and Varun Bajaj. Drafting the article: Geetika Singh and Varun Bajaj. Critical revision of the article: Geetika Singh and Aditi Sinha. Final approval of the version to be published: Geetika Singh, Aditi Sinha, and Arvind Bagga.

Data Availability Statement

All data pertaining to the case have been included in the manuscript and are part of the case report.

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