CASE REPORT

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Immune-complex deposits in pANCA glomerulonephritis: a pediatric case report

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Abstract

A 15-year-old boy is admitted to the hospital for clinical signs that suggest a pulmonary-renal syndrome (fever, cough, hemopthoic expectoration, oliguria, gross hematuria). A crescentic pANCA positive glomerulonephritis was configured. However, dense subendothelial deposits were identified in electronic microscopy and immunofluorescence staining showed granular deposits of IgG and C3, kappa and lambda in the capillary loops. Although the treatment was strictly followed, after three years and three months of good clinical state, he manifested signs of kidney failure being transplanted. His case represents a specific pattern of rapidly progressive glomerulonephritis leading to kidney failure and emphasizes the importance of clinical attendance especially in a case of two associated glomerulopathies.

Keywords: crescentic glomerulonephritis, rapidly progressive glomerulonephritis, pANCA, immune-complex deposits, children.

Introduction

Anti-neutrophil cytoplasmic antibodies (ANCA) represent a group of autoantibodies to specific intracellular constituents of neutrophils and monocytes. They appear in certain autoimmune diseases, most commonly in vasculitis, such as Wegener's granulomatosis, Churg–Strauss syndrome, polyarteritis nodosa, and patients with idiopathic crescentic glomerulonephritis. They are identified in the blood by immunofluorescence. There are two major categories of ANCA, one with cytoplasmic staining (cANCA) and the other with artifactual perinuclear staining (pANCA) [1–3].

Besides immunofluorescence in a rapidly progressive glomerulonephritis (RPGN) it is mandatory to evaluate the patient by kidney biopsy [4]. Severe glomerular injury in a RPGN involves microscopic appearance of the characteristic features of glomerular crescents (crescent-shaped scars).

ANCA-related glomerulonephritis is the most common form of crescent glomerulonephritis in adults. It is framed between pauci-immune crescentic glomerulonephritis [5] with minimal evidence of immune complex deposition. On immunofluorescence microscopy, in ANCA-related glomerulonephritis, there is little or no glomerular staining for Igs or complement and absence of immune deposits by electron microscopy [6]. Presence of immunoglobulins IgG and of complement C3 in a positive ANCA glomerulonephritis raise suspicion of other associated glonerular pathologies [7]. Unlike adults, ANCA positive glomerulonephritis are very rare in children. However, 25% of patients with crescentic immune complex glomerulonephritis, may present both electronodense immune-complex deposits and positive ANCA serology [8, 9]. The presence of this dual glomerulopathy in the evolution of a rapidly progressive glomerulonephritis is rare and some cases described so far have been mostly in adults [4, 10, 11].

Patient, Methods and Results

A 15-year-old boy was referred to our Nephrology Department with a 10-day history of fever, cough, hemoptoic expectoration, oliguria, gross hematuria, palpable legs purpura and general malaise in January 2007. Past medical and family histories were insignificant.

Seven days earlier, he had received oral Penicillin for acute pharingitis. Weight 75 kg, height 175 cm, BMI (body mass index) 24.5 kg/m^2 (<90%), blood pressure 130/60 mm/Hg (90–95%), heart rate 80 bpm. The boy also presented fatigue and pallor. He had oliguria (200 mL urine/day), fever (38.5^{0}C), presented myalgia and joint pain, without important joint swelling (bilateral lower extremity pitting edema, and minimal facial edema) and crackles at the basis of the lungs.

The laboratory results were: Hb 7 g/dL, Ht 21%, hypochromia, WBC 20.5×10^3/μL (neutrophils 78%), Plt 291×10^3/μL, serum urea 301.2 mg/dL, creatinine 10.72 mg/dL, fibrinogen 639 mg/dL, C-reactive protein 12 mg/dL, erythrocyte sedimentation rate 92 mm. Urine analysis showed constant hematuria and proteinuria

(1.99–2.3 g/24 h), and RBC casts. Immunologic work-up including rheumatoid factor, C3 and C4 complement levels, lupus anticoagulant antibody, antinuclear antibody, anti-double stranded DNA antibody, antistreptolysin O, and viral serology (hepatitis B, C, and HIV) were negative. Antiglomerular basement membrane antibody and cryoglobulin test were negative; pANCA – 299.06 EU/mL (positive ≥5 EU/mL); cANCA – normal. A chest X-ray demonstrated lung infiltrates in pulmonary bases.

Pulmonary-renal syndrome was configured – hemopthysis, diffuse alveolar infiltrates, decreased hemoglobin and hematocrit, aggravating and persistent oliguric renal failure, active urinary sediment with RBC casts, proteinuria and hematuria. Hemodialysis was started.

Light microscopy (kidney biopsy) revealed massive extracapillary proliferation (cellular crescents) in 14/15 examined glomeruli (Figure 1).

Interstitial and tubular lesions were also apparent. Immunofluorescence staining showed granular deposits of IgG and C3, kappa and lambda in the capillary loops (Figure 2).

Dense subendothelial deposits and extracapillary proliferation were identified in electronic microscopy (Figure 3).

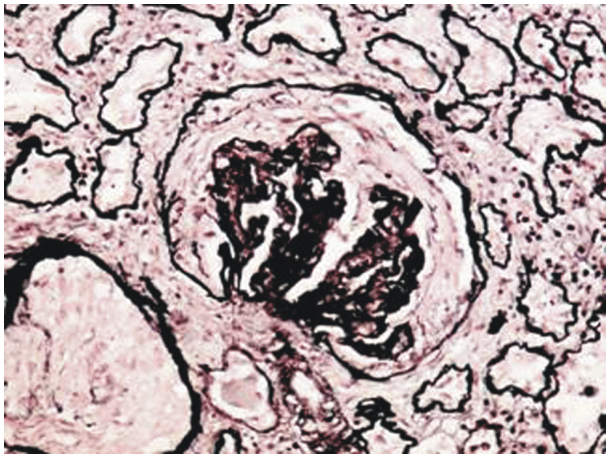

Figure 1 – ***Light microscopy on paraffin section. Glomerulus showing a circumferential crescent and centrally compressed capillaries. Silver-methenamine staining, 300×.***

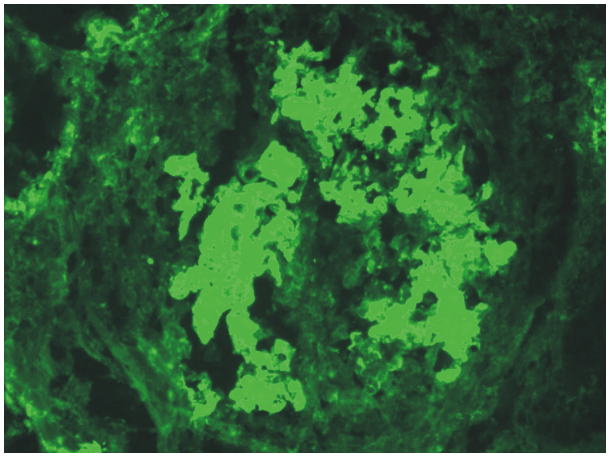

Figure 2 – ***Glomerulus. Anti-IgG FITC-conjugated antibody. Immunofluorescence, 200×.***

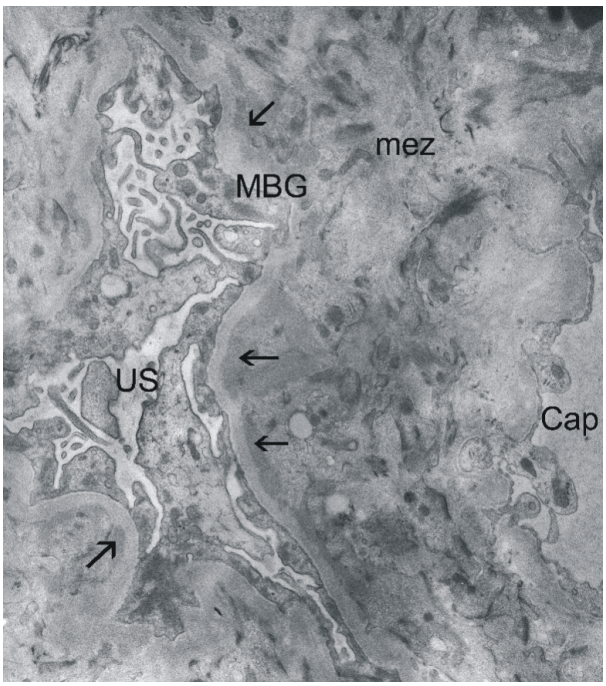

Figure 3 – ***Glomerulus. Subendothelial dense deposits (arrows). Glomerular basement membrane (MBG). Mesangial interposition (mez). Capillary lumen (Cap). Urinary space (US). Electron microscopy, 12 000×.***

Monthly induction therapy with high-dose corticosteroids and Cyclophosphamide was prescribed for six months. Initially, the patient received three pulses of Methylprednisolone (1000 mg/day), with Prednisone 60 mg every other day on a weaning regimen, and monthly therapy of Cyclophosphamide 750 mg/dose pulsed IV. The maintenance phase consisted of Mycophenolate Mofetil (1000 mg/day) and oral Prednisone administrated in alternate-day low-dose regimen, along with angiotensin-converting inhibitors. The boy was discharged from hospital after eight weeks with normal blood tests, minimal proteinuria and microscopic hematuria. The global glomerular filtration rate (GFR) of 107.8 mL/min./1.73 m^2, appreciated by Tc-99m diethylenetriamine pentaacetic acid renal scan, defines chronic kidney disease stage 1, according to the *National Kidney Foundation Kidney Disease Outcomes Quality Initiative* (*NKF KDOQI*) *Guidelines* (www.kdoqi.org).

Subsequent clinical and laboratory records showed obvious improvement (Hb 11 g/dL, serum creatinine 1.5–2 mg/dL), and the treatment was strictly followed for the following three years.

In March 2010, the patient developed anemia, progressive uremia, and proteinuria. Estimated GFR creatinine clearance value of 12 mL/min./1.73 m^2 reflected end stage kidney failure according to the *NKF KDOQI Guidelines*. Hemodialysis restarted, and soon after, he underwent a transplant from a living related donor.

Discussion

Although little is known regarding pulmonary-renal syndrome (PRS) in children, some diseases primarily seen in childhood, such as Henoch–Schönlein purpura,

hemolytic uremic syndrome, IgA nephropathy, and RPGN, may present pulmonary and renal features [12, 13].

The alarming clinical beginning of the disease as PRS increased by RPGN evokes the associated inflammatory and immunological mechanisms. An overview of the symptoms and laboratory data at admission suggests that a case of PRS is associated with small-vessel vasculitis. Therefore, Henoch–Schönlein purpura, Wegener granulomatosis, Goodpasture syndrome, cryoglobulinemia, Churg–Strauss syndrome, and microscopic polyangiitis were successively excluded because of specific clinical, laboratory data, and pathological pattern. In our case, the pANCA level was very high and kidney biopsy showed strong granular immune deposits with massive cellular extra-capillary proliferation, resulting into a multitude of squashy glomeruli with interstitial inflammatory infiltrates and tubular lesions. The high-level of deposition and cellular proliferation indicate the severity, while the extensive crescent formation and interstitial fibrosis signal probable irreversible renal failure in pediatric glomerulonephritis [14–16]. Although ANCA-associated glomerulonephritis is classically pauci-immune, our case demonstrated IF staining for IgG and C3 deposits.

In a meta-analysis, ANCA-associated glomerulonephritis with IF staining were selected, and 281 biopsies were described in patients with ANCA-associated glomerulonephritis, from 10 relevant articles [11]. Only 54% showed positive IF for IgG, IgM, IgA, and/or complements. In another study on 126 renal biopsies from patients with ANCA-associated glomerulonephritis, half of them had immune-complex deposits and IgM was the most common immunoglobulin found [17].

Pathophysiological role of immune deposits in patients with ANCA vasculitis is not well understood. This combination of the two glomerulopathies, both with immune complexes, either deposits of IgG or IgA mesangial deposits, in an ANCA glomerulonephritis, was mentioned as a criterion of severity [18–20].

There seems not to be a correlation between the type of ANCA identified (pANCA or cANCA) and histological and immunopathological type of lesions. Also appears to be similar pathological evolution. This was comparatively studied on a group of 135 patients with ANCA-associated vasculitides by kidney biopsy light microscopy and immunofluorescence [21].

All these studies imply the existence of a potentiating effect between immune complexes and ANCA to justify more aggressive evolution associated forms and a worse renal function in the subsets with immune deposits [11, 15]. The decline of renal function in advanced chronic renal disease in child may be 50% before severe clinical signs and elevated serum urea and creatinine manifest [22].

Conclusions

The bad clinical status and laboratory results at admission and afterwards evoke progressive, subclinical loss of renal function accompanying a progressive glomerulopathy, and evince the dramatic evolution towards renal failure in immune complex crescentic ANCA-positive glomerulonephritis in this pediatric case. The message of this case report is that, in children, the progressive decline of renal function is not apparent and demands mandatory medical attendance. This emphasizes the importance of clinical attendance even in the absence of renal failure signs especially in a case of two associated glomerulopathies.

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