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Case Report

Severe acute kidney injury induced by crescentic glomerulonephritis in a child with infective endocarditis

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ABSTRACT

Background. Kidney involvement related to infective endocarditis (IE) may present with different clinical findings. The most common histopathological finding of renal involvement is a combination of proliferative and exudative glomerulonephritis. However, severe acute kidney injury (AKI) induced by crescentic glomerulonephritis (CGN) is extremely rare in children with IE. To date, only 4 pediatric cases with IE-induced CGN had been reported. We present a 14-year old girl with IE-induced CGN.

Case. A 14-year old girl with fever, macroscopic hematuria, oliguria, and acute kidney injury (AKI) was admitted to our clinic. The medical history revealed that the patient had undergone several cardiac interventions due to truncus arteriosus type 1, and she recovered from IE-induced glomerulonephritis following antibiotherapy six months ago. During admission, the patient was diagnosed with IE according to one major (positive imaging finding) and three minor (fever, predisposing cardiac disease, and immunological criterion) criteria. Immediate antibiotic treatment was initiated. A kidney biopsy was performed, which showed crescentic glomerulonephritis (CGN with crescents, >50%). Daily pulse steroid (3 days), monthly pulse cyclophosphamide (6 doses), and oral steroid (2 mg/kg/day) therapy were initiated with gradual dose tapering. The patient underwent 12 hemodialysis sessions until the 38th day of the treatment. She was discharged on the 45th day of treatment with normal kidney function tests and negative acute phase reactants. Treatment was maintained with mycophenolate mofetil (MMF) after a 6-month course of cyclophosphamide. MMF was discontinued in the 12th month. At the 18th-month follow-up visit the patient had mild proteinuria, and was on ramipril therapy.

Conclusions. The occurrence of CGN should be considered in children with predisposing cardiac disease, who develop hematuria, proteinuria, and severe AKI. Although antibiotic therapy alone is often sufficient in this immune complex GN induced by infection, early initiation of additional immunosuppressive therapy in the presence of CGN may be beneficial for long term preservation of kidney functions.

Key words: infective endocarditis, crescentic glomerulonephritis, children, vegetation.

Infective endocarditis (IE) and related kidney involvement may present different clinical findings. Hematuria and/or proteinuria constitute the initial clinical findings in these patients. The most common histopathological finding is proliferative and exudative glomerulonephritis.[1-8] Severe acute kidney injury (AKI) caused by crescentic glomerulonephritis (CGN) is extremely rare in children with IE.[1-3] To the best of our knowledge to date, only four cases with IE-induced CGN have been reported in PubMed/MEDLINE, Scopus, and Google Scholar databases. In this case report, CGN, related severe AKI, and the difficulties of the clinical course and treatment in a girl who had undergone several cardiac interventions due to the truncus arteriosus type 1 are discussed along with similar cases in the literature.

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Case Report

A 14-year old girl, who was referred from another health center due to macroscopic hematuria and gradual impairment in kidney functions was admitted to our clinic. Her medical history revealed that she had undergone five surgeries starting at two months of age due to the truncus arteriosus type 1 and underwent three cardiac homograft implants.

Six months ago while she was under treatment in the city in which she lived, the patient had convulsions due to a diagnosis of immune thrombocytopenic purpura (ITP) and urinary system infection presenting with macroscopic hematuria and thrombocytopenia. Cranial imaging displayed hemorrhage involving left parasagittal area. During this period, the patient was hospitalized in our clinic because of a high fever and impaired kidney function. She was diagnosed with bacterial endocarditis according to the Duke's criteria consisting of one major (*Staphylococcus aureus* growing in the blood culture) and three minor (predisposing cardiac disease, glomerulonephritis, and high fever) findings.[9] She recovered after 6-weeks of treatment with teicoplanin and cefotaxime antibiotherapy. She was discharged with normal kidney function tests and microscopic hematuria. After six months, the patient was re-hospitalized due to macroscopic hematuria and impaired kidney functions. Her physical examination revealed body weight 29 kg (<3p), height 130 cm (<3p), temperature 36.7°C, blood pressure 110/70 mmHg, oxygen saturation 99%, 4/6 pansystolic murmur in all cardiac auscultation points, and splenomegaly. Laboratory examination showed anemia, thrombocytopenia, hypocomplementemia, elevated acute phase reactants, negative antinuclear antibody (ANA) and direct Coombs tests, elevated urea and creatinine levels, proteinuria, hematuria, and elevated rheumatoid factor (RF) titration (Table I). However, the blood culture was negative. The cardiac imaging showed vegetation in the aortic valve (Fig. 1).

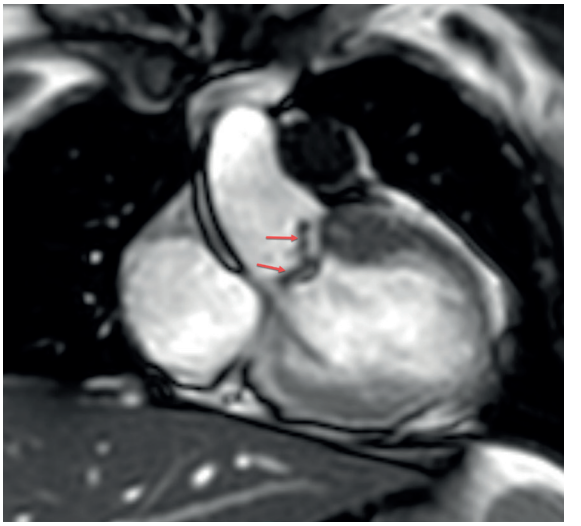

Fig. 1. Magnetic resonance imaging of left ventricular outflow tract (LVOT) showing vegetations in the aortic valve (arrows).

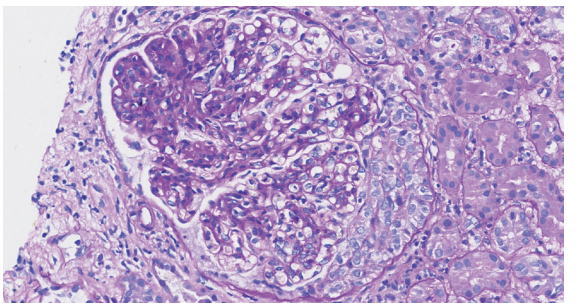

Fig. 2. Cellular crescent and mesangial proliferation (Periodic acid – Schiff statining, x400).

At this admission to our clinic, although blood culture was negative, considering other major (positive imaging finding) criterion of Duke's criteria[9] and three minor (fever, predisposing cardiac disease, and immunological) criteria, IE, and immune complex-mediated glomerulonephritis secondary to IE were diagnosed; teicoplanin and cefotaxime were initiated. However, progressive impairment in kidney function was observed. The creatinine level increased to 6.3 mg/dl, and oliguria developed. The kidney biopsy revealed diffuse endocapillary proliferation along with 56% cellular crescents (Fig. 2). The immunofluorescence images showed granular C3 and IgM deposition on the basement membrane zone. The patient was diagnosed

Table I. Laboratory findings of the patient at first admission.

Complete blood count		Serological tests	
WBC (4-12 x10^3/mm^3)	39.4	Anti-HBs Ab	positive
Hemoglobin (12-16 g/dl)	7.2	HBsAg	negative
MCV (80-100 fl)	70	Anti HCV IgM	negative
Hematocrit (35-49 %)	22	Anti HAV IgM	negative
Platelet (100-400 x10^3/mm^3)	89	Anti HIV	negative
Biochemical parameters		CMV IgM	negative
Urea (16-40 mg/dl)	98	EBV IgM	negative
Creatinine (0.57-0.87 mg/dl)	2.7	Parvovirus-B19	negative
eGFR (ml/min./1.73 m^2)	26	Anti-nuclear antibody (ANA)	negative
Total protein (6.6-8.7 g/dl)	6.4	Anti-ds DNA	negative
Albumin (3.2-4.5 g/dl)	3.2	p- ANCA	negative
Sodium (135-145 mEq/L)	138	c- ANCA	negative
Potassium (3.5-5.1 mEq/L)	3.3	Anti-phospholipid antibodies	negative
Chloride (98-107 mEq/L)	106	Direct Coombs	negative
Phosphorus (2.9-5.1 mg/dl)	5.8	Urine analysis	
Magnesium (1.7-2.2 mg/dl)	1.3	Proteinuria-24 hours (0.140 gr/day)	2.04
Uric acid (2.4-5.7 mg/dl)	7.7	Spot urine protein/creatinine ratio (<0.2 mg/mg)	3
ALP (50-117 IU/L)	66	Proteinuria-24 hours (<4 mg/m^2/hour)	73
LDH (135-214 U/L)	301	Microscopy	>50 RBC/hpf
AST (<32 IU/L)	12	Acute phase reactants	
ALT (<33 IU/L)	4	Erythrocyte sedimentation rate (<20 mm/hour)	23
Calcium (8.4-10.2 mg/dl)	7.8	C-reactive protein (<5 mg/L)	70
ASO (<200 IU/ml)	34	Fibrinogen (200-393 mg/dl)	292
Triglycerides (<200 mg/dl)	226	Serum complements	
Cholesterol (<200 mg/dl)	188	Complement 3 (0.88-1.55 g/L)	0.09
Rhematoid factor (<14 IU/ml)	146	Complement 4 (0.12-0.32 g/L)	0.04

Values in parenthesis represent normal range
eGFR: estimated glomerular filtration rate, hpf: high power field, RBC: red blood cell, WBC: white blood cell.

with IE-induced and immune complex-mediated crescentic glomerulonephritis.

The previous incident of bacterial endocarditis (*S. aureus*) and secondary glomerulonephritis were treated only with antibiotics. However, this time, due to remarkable increase in serum creatinine during antibiotic treatment and the presence of CGN, pulse steroid therapy (3 days) and monthly pulse cyclophosphamide (6 months) were initiated. Oral steroid (2 mg/kg/day) were tapered gradually. Twelve sessions of hemodialysis were performed. On the 38th day of treatment, dialysis was stopped. On the 45th day of treatment, urea and creatinine levels dropped to 58 mg/dl and 0.5 mg/dl, respectively; and the patient was discharged with negative acute phase reactants on the same day. The treatment was maintained with mycophenolate mofetil (MMF, 1200 mg/m^2) after six months of cyclophosphamide treatment. In the seventh month, a repeat kidney biopsy revealed global sclerosis in 2 of 14 glomeruli and fibrous crescents and 30% fibrosis in three glomeruli. MMF treatment was discontinued in the 12th month. At the 18-month follow-up control, proteinuria was mild (12 mg/m^2/hour) and urea and creatinine levels were 33 and 0.6 mg/dl, respectively. The levels of complement and rheumatoid factor (RF) were within normal limits. The patient is still receiving 4 mg/m^2 ramipril.

Informed parental written consent was taken for case publication.

Discussion

Severe AKI is extremely rare in patients with IE-induced immune complex-mediated glomerulonephritis. Only four case reports on severe AKI in children with IE-induced immune complex-mediated glomerulonephritis (Table II) have been published in the literature.[1-3]

Immune complex processes are responsible for the pathogenesis of IE-induced acute glomerulonephritis.[4] The infections are responsible for the development of renal disorders and they require antibiotherapy which makes the decision difficult with respect to the immunosuppressive treatment needed for the treatment of the immune complex-mediated GN. Monotherapy of IE with antibiotics may occasionally contribute to the recovery of immune complex-mediated kidney lesions. However, as CGN can potentially lead to chronic renal failure, it requires immunosuppressive therapy, therefore, it should be administered in combination with antibiotherapy.[5-7]

During the investigation of the cases reported in the literature, it was noticed that the cases with IE-induced CGN seem to occur between the ages of 6 and 14. In all cases, fever was the most important first finding and the general findings of cardiac disease were usually observed.[1-3]

The first case in the literature was reported by Sadikoglu et al.[1] A 6-year old male patient, who had undergone cardiac surgery due to pulmonary atresia and ventricular septal defect, underwent a kidney biopsy because of persistent fever and impaired kidney function. The histopathological findings were interpreted in favor of crescentic immune complex-mediated glomerulonephritis. The patient recovered by antibiotherapy, intravenous methylprednisolone (followed by tapering doses of prednisone), and intravenous cyclophosphamide.

Table II. Clinical profile of the patients reported in literature with subacute bacterial endocarditis and crescentic glomerulonephritis.

Author	Age/Sex	Urinalysis	C3/C4	ANA/ ANCA	Blood culture	Treatment	Percentage of glomeruli with crescents	Light microscopy	Outcomes
Sadikoglu (2006)	6/M	Hematuria,	Low/N	-/-	-	Ab, Cs, CYC	80%	Crescentic immune complex glomerulonephritis	Full recovery
Mantan (2013)	11/M	Proteinuria	Low/N	-/-	-	Ab, Cs, CYC	21%	Immune complex-mediated proliferative glomerulonephritis	Full recovery
Krishnamurthy (2017, Case 1)	8/F	Hematuria, Proteinuria	Low/N	-/-	-	Ab, Cs	1%	Diffuse endocapillary exudative proliferation;	Full recovery
Krishnamurthy (2017, Case 2)	9/F	Hematuria, Proteinuria	Low/N	-/-	-	Ab, Cs, HD, CYC	70%	Crescentic glomerulonephritis	Predialysis CKD, Proteinuria, Hematuria (microscopic)
Our patient	14/F	Hematuria, Proteinuria	Low/ Low	-/-	-	Ab, Cs, HD, CYC, MMF	56%	Crescentic immune complex glomerulonephritis.	Proteinuria, Hematuria (microscopic) Normal creatinine

ANA: antinuclear antibodies, Ab: antibiotic therapy, ANCA: anti-neutrophil cytoplasmic antibody, Cs: corticosteroids, CKD: chronic kidney disease, CYC: cyclophosphamide, HD: hemodialysis, MMF: mycophenolate mofetil.
–: negative, +: positive, N: normal

Mantan et al.[3] reported an 11-year old male patient with acyanotic heart disease. The patient was treated with antibiotics and oral prednisolone for four weeks due to a highly impaired kidney function and fever that persisted for the last 15 days. As proteinuria and edema persisted, a kidney biopsy was performed in the sixth week, and the patient was diagnosed with crescentic glomerulonephritis. The steroid treatment was continued combined with oral cyclophosphamide (8 weeks).

Krishnamurthy et al.[2] reported two cases. The first case was an 8-year old girl with mitral insufficiency (MI) secondary to rheumatic heart disease and was on antibiotic treatment because of fever; she underwent a kidney biopsy as the serum creatinine increased rapidly on the 5th day of treatment. The biopsy displayed diffuse endocapillary exudative proliferation and segmental crescents. The patient was treated with intravenous methylprednisolone and oral prednisolone; without dialysis.

The second case, a 9-year old girl, was under follow-up with a diagnosis of perimembranous ventricular septal defects (VSD), and had fever, hematuria, oliguria, and edema. The kidney biopsy revealed severe CGN with 70% crescent formation. The patient was treated with pulse methylprednisolone, monthly pulse cyclophosphamide and oral prednisolone. Residual renal injury developed despite aggressive immunosuppressive treatment. In the fourth month of the follow-up, her serum creatinine level was still elevated along with proteinuria and microscopic hematuria, and the need for antihypertensive treatment continued.

In our case, endocarditis was diagnosed twice, and at the first admission of bacterial endocarditis (*S. aureus*) and secondary glomerulonephritis were treated only with antibiotics. However, during the second admission, she had to take antibiotics and aggressive immunosuppression together with hemodialysis.

IE and secondary immune complex glomerulonephritis may be treated with antibiotics and/or surgical restoration of the predisposing cardiac disorder. Thereby, the kidney lesions resolved as a result of the decrease in or disappearance of the circulating immune complexes. However, it has been previously reported that aggressive immunosuppressive treatment was necessary for IE-related CGN in adults.[5] Although plasma exchange combined with the immunosuppressive treatment has been widely discussed, the benefits of this approach were demonstrated only in a few adult patients.[8,10] In our case and other pediatric cases reported in the literature, plasma exchange was not necessary. Although there is no evidence on immunosuppressive agent treatment to be initiated (high dose steroid monotherapy or in combination with cyclophosphamide), it seems that the decision should be made according to clinical and laboratory findings. In our case, considering the ongoing immune complex formation, we implemented maintenance therapy with high-dose steroids and then gradually tapered the oral steroids while we added an intensive induction treatment with monthly pulse cyclophosphamide. In addition, we maintained the immunosuppression with MMF until the 12th month.

In conclusion, CGN or severe diffuse proliferative glomerulonephritis should be considered in children who have predisposing heart disease concomitant with hematuria, proteinuria, and severe AKI. In patients with severe AKI, antibiotic treatment and early initiated aggressive immunosuppressive treatment following the kidney biopsy may be useful for long-term preservation of kidney functions.

Ethical approval

Informed parental written consent was taken for case publication.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: SY, NY; data collection: NY, SY, DG, İG, TB, MY, FU, GG; analysis and interpretation of results: SY, NY; draft manuscript preparation: SY, NY. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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