AN UNUSUAL CAUSE OF NEPHROTIC SYNDROME ACCOMPANYING HEMATURIA: ENDOCARDITIS-ASSOCIATED GLOMERULONEPHRITIS

Hematürili Nefrotik Sendromun Nadir bir Prezentasyonu: Endokardit İlişkili Glomerülonefrit

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ABSTRACT

Endocarditis-associated glomerulonephritis (EGN), a specific sub-subtype of post-infectious glomerulonephritis (PIGN) is very rare in children. Nephrotic syndrome is a rare presentation for EGN with a reported frequency of 6%. In this case, an 8-year-old girl patient presented with nephrotic syndrome accompanying hematuria is mentioned. She was hospitalized with fever, mild azotemia, acute phase elevation and hypocomplementemia. Aggregatibacter Actinomycetemcomitans has grown in blood culture. Echocardiogram revealed third-degree tricuspid regurgitation and vegetations on the tricuspid valve. She was commenced on ceftriaxone therapy with a diagnose of EGN. At the end of the six-week treatment, the patient was discharged with normal laboratory values except for non-nephrotic proteinuria. Cardiac vegetations had completely disappeared. PIGN is still an important cause of morbidity for developing countries. EGN is rarely seen especially in childhood with the presence of predisposing conditions. With timely diagnosis and correct treatment, satisfactory results are possible in terms of kidney health.

Keywords: *Post-Infectious Glomerulonephritis; Infective Endocarditis; Hacek; Endocarditis-Associated Glomerulonephritis; Aggregatibacter Actinomycetemcomitans*

ÖZET

Post-infeksiyöz glomerülonefritin (PIGN) spesifik bir alt tipi olan endokardit-ilişkili glomerülonefrit (EGN), çocuklarda çok nadir görülür. Nefrotik sendrom, %6 sıklık ile EGN için nadir bir prezantasyondur. Bu olguda hematürili nefrotik sendrom ile başvuran 8 yaşında bir kız hastadan bahsedilmiştir. Ateş, hafif azotemi, akut faz yükselmesi ve hipokomplementemisi olan hasta nefrotik sendrom kliniğinde yatırıldı. Kan kültüründe Aggregatibacter Actinomycetemcomitans üredi. Ekokardiyogramda triküspit kapakta üçüncü derece triküspit yetersizliği ve vejetasyonlar görüldü. EGN tanısı ile seftriakson tedavisine başlandı. Altı haftalık tedavi sonunda hasta nefrotik olmayan proteinüri dışında normal laboratuvar değerleri ile taburcu edildi. Kardiyak vejetasyonlar tamamen kaybolmuştu. PIGN gelişmekte olan ülkeler için hala önemli bir morbidite nedenidir. EGN özellikle çocukluk çağında predispozan koşulların varlığı ile nadiren görülür. Zamanında teşhis ve doğru tedavi ile böbrek sağlığı açısından tatmin edici sonuçlar alınması mümkündür.

Anahtar Kelimeler: *Post-Enfeksiyöz Glomerülonefrit; Enfektif Endokardit; Hacek; Endokardit İlişkili Glomerülonefrit; Aggregatibacter Actinomycetemcomitans*

INTRODUCTION

Endocarditis-associated glomerulonephritis (EGN) is very rare in children due to the widespread use of antibiotics and the increase in early diagnosis possibilities (1,2). Although the classic presentation of post-infectious glomerulonephritis (PIGN) is acute nephritic syndrome, it may present as nephrotic syndrome in 2-4% of patients. The most common feature of EGN, a specific sub-subtype of PIGN, reported as acute kidney injury. Nephrotic syndrome is a rare presentation for EGN with a reported frequency of 6% (3,4). In this case, a girl patient presented with nephrotic syndrome accompanying hematuria is mentioned.

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CASE REPORT

An 8-year-old girl, referred to nephrology department with macroscopic hematuria and proteinuria. It was learned from her history that she was diagnosed with type 1 diabetes three years ago. She referred to a hospital with fever, vomiting and abdominal pain two months ago. Anemia, increase in acute phase reactants and hypoalbuminemia were detected. The patient received red blood cell transfusions four times during the last 2 months, then directed to pediatric nephrology. On physical examination, her blood pressure was 110/70 mmHg. She was pale in appearance. She had grade 2 pansystolic murmur on cardiac examination. The liver was 3-4 cm palpable below the right mid-costal margin. Laboratory analysis revealed microcytic anemia (WBC: 7500/µL, hemoglobin7.4 gr/dL, platelet 291000/µL), hypoalbuminemia, mild azotemia and hypocomplementemia (urea: 45 mg/dL, creatinine: 0.49 mg/L, total protein: 43g/L, albumin: 16.4 g/L, C3: 37 mg/L, C4: 5 mg/L, ASO: 27). Acute phase reactants (CRP: 107 mg/L, sedimentation: 47 mm/s) were high. Urinalysis showed that urine color was red, density 1009, pH: 5.5, and +++ positive protein on dipstick. Microscopic evaluation of urine was 212 RBC/hpf, 34 WBC/hpf with negative urine culture. There was a nephrotic range proteinuria with a ratio of spot urine/creatinine of 9.7 mg/mg creatinine. Direct Coombs was negative. Ultrasonographic evaluation revealed bilateral increase in kidney size and parenchymal echogenicity (Grade 2).

The patient was hospitalized with a diagnose of nephrotic syndrome with macroscopic hematuria accompanying anemia, mild azotemia, and acute phase elevation. Meropenem and gentamicin was initially started to cover gram-positive and negative agents empirically. Antinuclear antibodies (ANA) and Anti-double stranded DNA (Anti-dsDNA) tests were negative. Tests for other infectious causes such as hepatitis B and C, HIV, syphilis, mycoplasma, mycobacteria were negative. Bone marrow smears of the patient performed to investigate malignancy, revealed hyperplasia (myeloid erythroid ratio 4/1) and histiocyte increase in myeloid series. No atypical cells were seen. Echocardiogram of the patient revealed third-degree tricuspid regurgitation (Figure 1) and vegetations on the tricuspid valve (Figure 2). A fever up to 39 °C was observed and Aggregatibacter Actinomycetemcomitans has grown in blood culture. EGN was considered in the patient. Antibiotic therapy was changed to ceftriaxone and the treatment period completed to 6 weeks. Macroscopic hematuria resolved on the 7th day of the treatment, and microscopic hematuria resolved in the 4th week. Complement values returned to normal in the 4th week of treatment. Proteinuria regressed to non-nephrotic level. Angiotensin converting enzyme inhibitor was added. At the end of the six-week treatment, the patient was discharged with normal laboratory values except for non-nephrotic proteinuria (urea: 24 mg/dl, creatinine: 0.41 mg/dl, total protein: 65 g/L, albumin: 38.6 g/L, and spot urinary protein excretion

Figure 1. Third degree tricuspid regurgitation on Echocardiogram

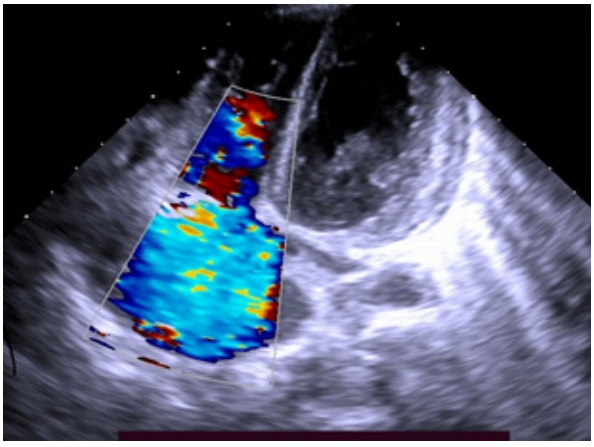
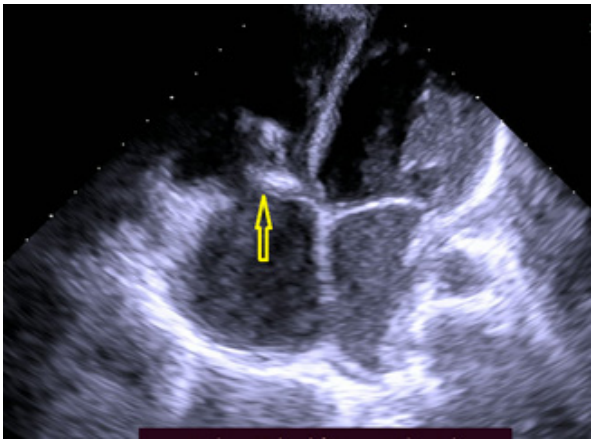


Figure 2. Two vegetations on the tricuspid valve on Echocardiogram



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0.8 mg/mg creatinine). Cardiac vegetations had completely disappeared. Proteinuria had completely resolved at the first month of discharge.

DISCUSSION

The development of immune-mediated glomerular damage as a result of the host response to a non-renal infection is defined as PIGN. The most common cause of glomerulonephritis in children is PIGN, with more than 95% being post-streptococcic glomerulonephritis (PSGN) (2,5). EGN was defined as case reports in the early 1900s, and at that time it was thought to be acute kidney injury mainly due to embolism (2,6).

Over time, it has been understood that immune-mediated damage also plays an important role in the pathogenesis of the disease. Boils et al. published an article in 2015 on patients with EGN who underwent kidney biopsy; Accordingly, most common biopsy findings were necrotizing and crescentic GN and endocapillary proliferative GN (4).

The most common feature of EGN reported as acute kidney injury. Nephrotic syndrome is a rare presentation for EGN with a reported frequency of 6% (3,4). In this case, apart from the classic course of PIGN and EGN, there was nephrotic range proteinuria accompanied by severe hypoalbuminemia. This clinic of the patient was thought to be related to the late diagnosis Although infective endocarditis (IE) in children is also much less common than in adults, it is still an important and complex clinical problem in children due to its mortality rate between 5% and 10%. It usually occurs in children with underlying congenital heart disease, presence of prosthetic valve, immune deficiency, and diabetes (7). The fact that our patient had both a previously undiagnosed valve regurgitation and a history of type 1 diabetes were evaluated as predisposing factors. Since the patient has nephrotic syndrome, hematuria, anemia, and low complement (C3 and C4) levels, glomerulonephritis such as systemic lupus erythematosus (SLE) nephritis, PIGN, MPGN, bacterial endocarditis, cryoglobulinemia and shunt nephritis should be considered in differential diagnosis (8,9). Antinuclear antibodies (ANA) and Anti-double stranded DNA (Anti-dsDNA) tests were negative in the patient studied for the differential diagnosis of SLE nephritis. The patient did also not have other signs and symptoms such as such as malar and discoid rash, photosensitivity, oral ulcer, arthritis, serositis suggestive of SLE. ASO titer, valuable in diagnosis of PSGN was in normal range.

The most common agents of IE are still gram-positive bacteria, such as streptococci and staphylococci, with a frequency of 80%. Microorganisms known as the HACEK group are the most common causes of gram-negative endocarditis with a frequency of 1-3%. 'HACEK' is an abbreviation for agents in the oral mucosa that cause IE, including Haemophilus spp., Aggregatibacter spp., Cardiobacterium hominis, Eikenella corrodens and Kingella kingae. Studies have reported that the mean age of HACEK endocarditis (HE) is much younger than non-HE patients, and Aggregatibacter Actinomycetemcomitans is more common in the presence of underlying heart disease, as in our patient (10,11).

Treatment of EGN is mainly based on the treatment of IE with antibiotics. Although some reports mention immunosuppressive treatment and plasmapheresis in resistant cases, there is no consensus on this issue due to the risk of worsening of the underlying infection (5,12). The treatment should be selected according to the antibiotic susceptibility of the organism detected in the culture. European Society of Cardiology (ESC) IE guidelines recommend considering ampicillin-resistant organisms, as the susceptibility of the HACEK group is difficult to detect, and the probability of ampicillin resistance is high. The standard treatment for HE is monotherapy with intravenous ceftriaxone for 4-6 weeks. Although gentamicin is no longer recommended due to its nephrotoxic risks, the combination of ampicillin and gentamicin for 4-6 weeks is also an alternative option if HACEK organisms are not β-lactamase producers (10,13). Complete renal recovery was reported only in about 1/3 of the EGN in a study. However, the fact that the study group was selected only from patients who underwent biopsy and mostly adult population, suggests that the rate of kidney damage may be overestimated (4). In this case, disappearance of vegetation, normalization of complement values, and the disappearance of hematuria and proteinuria suggested a complete response to the treatment and good renal outcome.

PIGN is still an important cause of morbidity for developing countries such as our country. EGN is rarely seen especially in childhood with the presence of predisposing

conditions such as underlying congenital heart disease, presence of prosthetic valve, immune deficiency, and diabetes. However, with timely diagnosis and treatment of the disease, the prognosis for kidney health can be promising.

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