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Necrotizing Glomerulonephritis Secondary to Henoch-Schönlein Purpura and Streptococcal Infection with A Successful Response to Cyclophosphamide Treatment: A Case Report

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Abstract

Henoch-Schönlein Purpura (HSP) is a systemic vasculitis that commonly involves the kidneys. Streptococcal infection might cause typical acute post-infectious glomerulonephritis and could induce abnormal IgA immune response similar to HSP. Both HSP and Post-Streptococcal Glomerulonephritis (PSGN) histological examination reveal a broad spectrum of renal pathologies including necrotizing glomerulonephritis. Coexisting diseases might result in severe nephritis as shown in our case.

We describe the case of a seven-year-old boy who developed purpuric rash, abdominal pain and arthralgia typical for HSP following a confirmed streptococcal infection. Shortly after presentation, he developed acute renal failure requiring referral for dialysis. Renal biopsy showed full-blown immune complex-mediated necrotizing glomerulonephritis. He had dramatic improvement and full recovery after steroids and cyclophosphamide treatment.

Introduction

Henoch-Schönlein Purpura (HSP) is clinically characterized by purpura, abdominal pain, arthralgia or arthritis, and nephritis. Renal histological examination reveals a broad spectrum of pathologies including necrotizing glomerulonephritis [1]. However, predominant IgA and complement C_3 deposits in mesangial lesions are characteristic.

The possible etiologies of HSP include infections, drugs, allergies and other factors [2], but the pathogenesis is still unknown. Streptococcal infection could induce abnormal IgA immune responses like HSP, quite similar to typical acute Post-Infectious Glomerulonephritis (AGN) [3,4]. Indeed, hypocomplementemia that is typical of AGN has been also described in HSP [5].

We report the case of a young child who presented with acute renal failure following typical HSP clinical presentation that was preceded by upper respiratory tract infection symptoms a week earlier. He was found to have positive throat culture for group A beta hemolytic streptococcus and positive streptococcal serological tests. Renal biopsy showed necrotizing glomerulonephritis. He had dramatic response to steroid and immunosuppressant.

Case Presentation

A previously well seven-year-old boy presented initially to a local hospital with 2-3 days' history of generalized fatigability, myalgia, non-blanchable purpuric rash over the dorsum of the feet, back of the legs, and buttocks, progressive bilateral ankle swelling, abdominal pain, and vomiting. He had upper respiratory tract infection in form of sore throat, mild cough and fever 1 week prior to his presentation for which he received cefixime course for 5 days. Family history was negative for renal diseases. He was vaccinated up to date with no recent vaccinations. He had tracheoesophageal fistula repair and left orchiopexy at the age of 3 and 4 years respectively.

There was no history of diarrhea, bloody stool, hematuria, headache, seizure, behavior or personality change, chest pain, shortness of breath, malar or discoid rash, photosensitivity, oral

ulcers, or other joints involvement.

He was admitted as a case of Henoch-Schonlein Purpura (HSP). Abdominal ultrasonography ruled out intussusceptions and showed normal kidneys size and differentiation with slightly increased cortical echogenicity. During hospitalization, he developed acute renal failure manifested as oliguria (urine output of 0.5 mL/kg/hr), hypertension, abnormal renal function (BUN of 49.5 mmol/L, creatinine of 211 µmol/L, and potassium of 5 mmol/L), hematuria, and proteinuria. At that time, he received one dose of methylprednisolone (30mg/kg) in addition to supportive care then he was transferred to our hospital 5 days later for second opinion and possible dialysis. Upon arrival to our hospital, he was having minimal periorbital edema, hypertension and fading petechial rash over the feet and buttocks.

Urinalysis and microscopy revealed: significant hematuria (+3 with RBC > 50/hpf), proteinuria (24-hour urine protein of 104.3 mg/m^2/hr) with hyaline and granular casts. He had abnormal renal function with BUN of 22.9 mmol/L (normal range 2.3-6.7 mmol/L), creatinine 289 µmol/L (normal range 26-58 µmol/L), potassium 5.9 mmol/L (normal range 3.5-5 mmol/L), bicarbonate 18 mmol/L (normal range 22-31 mmol/L), and phospohate 2.59 mmol/L (normal range 1-1.75 mmol/L). Other laboratory findings showed low hemoglobin at 10.5 g/L, normal white cell count 9×10^9/L, normal platelet count 235×10^9/L, high Erythrocyte Sedimentation Rate (ESR) and C-Reactive Protein (CRP) at 29 mm/hr and 4.6 mg/L respectively, positive Streptozyme test, positive Antistreptolysin-O (ASO) titer at 1:400 IU/mL (normal titer less than 1:200), and high Anti-DNAse at 1:1280 (normal less than 1:80). Throat culture grew group A beta hemolytic streptococcus. Antinuclear antibodies (ANA), anti-DNA, anti-Smith, anti-Ro, anti-La, Anti-neutrophil Cytoplasmic Antibodies (ANCAs), and antiphospholipid (anticardiolipin, anti-phosphatidyl serine and anti-beta 2 glycoprotein) antibodies were negative. Complements assay showed low C_3 at 0.64 g/L (normal range 0.9-1.8 g/L) and C4 at 0.07 g/L (normal range 0.1-0.4 g/L). Repeated abdominal ultrasound at our hospital showed enlarged both kidneys with increased echogenicity. From the radiology point of view, differential diagnoses included HSP nephritis and post-streptococcus glomerulonephritis. Renal biopsy showed Diffuse Proliferative Glomerulonephritis (DPGN) with foal segmental necrotizing lesions involving 60% of the glomeruli with full immune complex deposition including all IgG, IgM, IgA and C3, C1q, kappa and lambda (Figure 1-3). Electron microscopy showed sub endothelial deposits and foot processes effacement of podocytes (Figure 4). The biopsy picture was suggestive of immune complex-mediated disease like Systemic Lupus Erythematosus (SLE) however, lupus workup was negative.

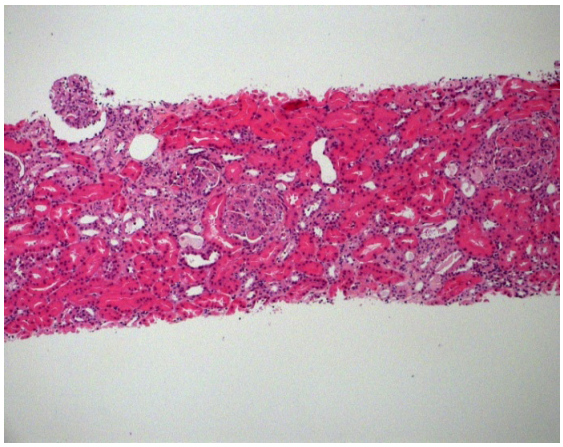

Figure 1: H&E stain: showing diffuse proliferative glomerulonephritis.

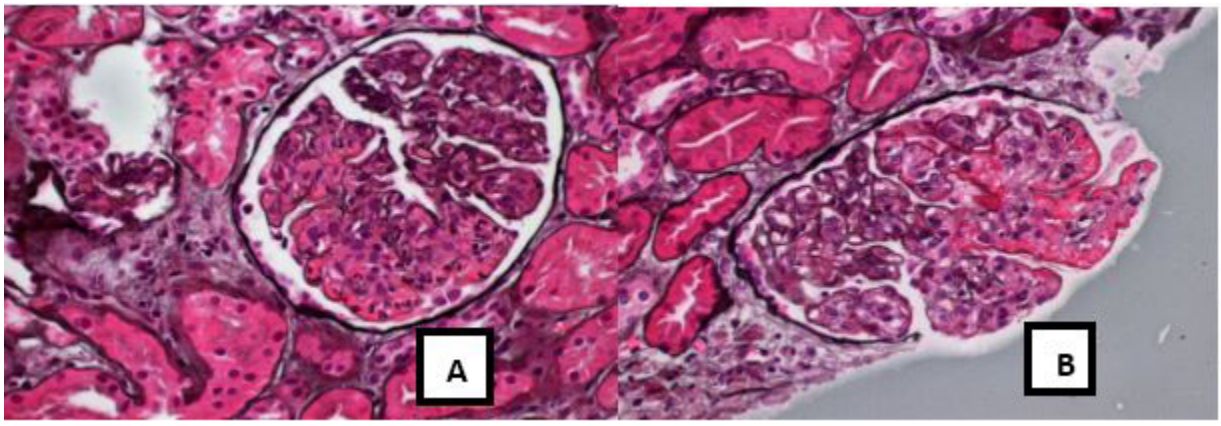

Figure 2: Low power, Silver stain: **A**, showing a glomerulus that is more cellular and lobulated with influx of inflammatory cells. **B**, showing area of necrosis.

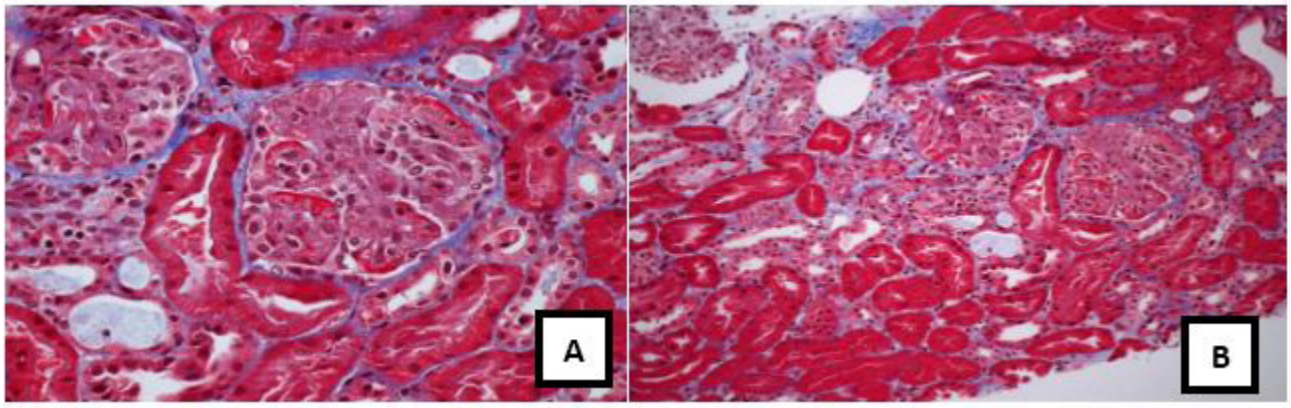

Figure 3: Trichrome stain: **A**, high power field. **B**, low power field. Both showing sub endothelial deposits that is rarely seen in post-streptococcal glomerulonephritis

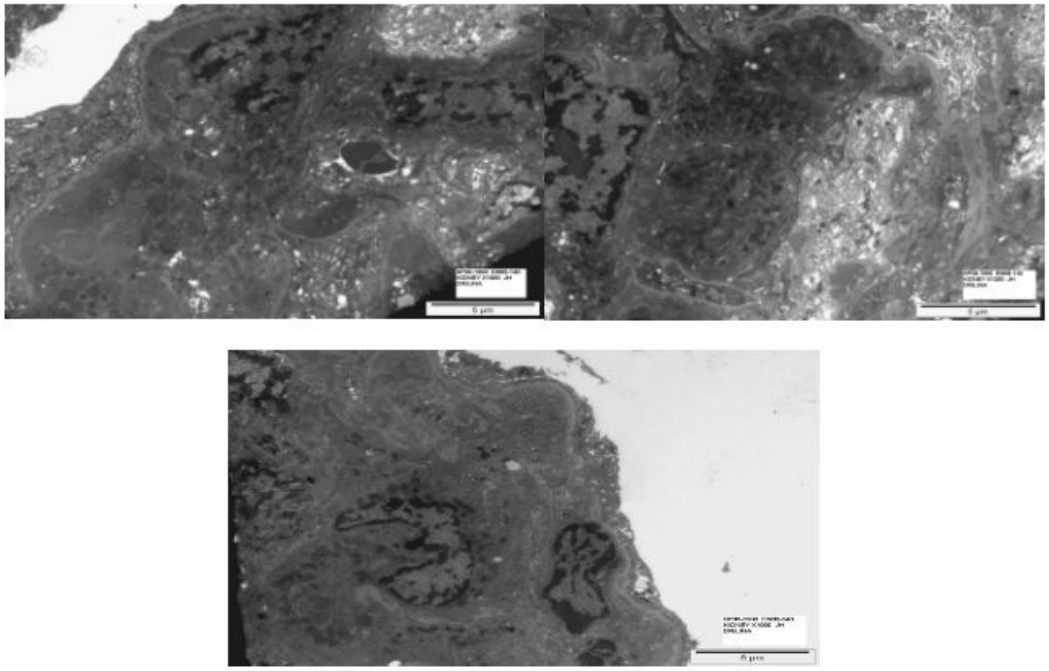

Figure 4: Electron microscopy: showing sub endothelial deposits and foot processes effacement of podocytes.

Treatment was initiated with methylprednisolone pulses therapy for 6 doses followed by oral prednisone (1 mg/kg/dose) twice daily along with Enalapril (5 mg daily). Cyclophosphamide infusion was started after the renal biopsy result then maintained monthly for total of 6 doses. Prednisone dose was tapered gradually. Complete recovery was achieved without the need for dialysis. Repeated ANA profile was persistently negative. Currently, he is off medications and on regular follow up in rheumatology clinic at our hospital without recurrences.

In summary, a seven-year-old boy with necrotizing immune-complex mediated glomerulonephritis most likely secondary to coexisting streptococcal infection and Henoch-Schonlein Purpura (HPS) nephritis. He had acute renal failure which responded well to methylprednisolone pulses and cyclophosphamide infusions with full recovery.

Discussion

The case described has, at least, four points of interest in HSP:

1) Initial presentation was preceded by streptococcal infection;
2) The finding of necrotizing glomerulonephritis on renal biopsy is not classical to HSP
3) The coexistence of streptococcal infection with HSP might give a severe form of renal involvement; and
4) There was complete response to cyclophosphamide along with steroids and Angiotensin Converting Enzyme Inhibitor (ACEI) in the presence of nephrotic syndrome. We are going to discuss these points in the following paragraphs.

Both acute Post-Streptococcal Glomerulonephritis (APSGN) and HSP nephritis could appear after antigen exposure with similar clinical presentation such as hematuria, edema and hypertension [3,6,7]. In this case, streptococcal infection was supported by clinical data and positive streptozyme test (high ASO titer and anti-DNAse). Also, the presence of hypocomplementemia would make APSGN to be a more likely diagnosis. Although in this GN the complement system is usually activated by alternative pathway, it has been described as the activation by classical pathway, characterized by low levels of C4 without decrease of C3, as we observed in our patient. Moreover, APSGN has also been described as having the presence of systemic vasculitis affecting skin, bowel, and other organs mimicking HSP [6,7]. On the other hand, the presence of purpura and absence of typical nephritic syndrome support the diagnosis of HSP. Indeed, it has been also described that ASO titer positivity is associated with a significant increase in the risk of HSP and renal involvement is more common among cases with positive elevated titers [8]. Also, in some patients with HSP nephritis transient hypo complementemia may appear [5].

Renal biopsy was essential to establish definitive diagnosis, as occurred in many glomerular diseases. The presence of diffuse proliferative glomerulonephritis with foal segmental necrotizing lesions involving 60% of the glomeruli with full house of immune complex deposition including all IgG, IgM, IgA and C_3, $C1_q$, kappa and lambda was a necessity to investigate more for other vasculitides. Knowing that necrotizing glomerulonephritis occurred significantly more often in the vasculitides including (systemic lupus erythematosus, HSP, Wegner's disease, Polyarteritis and others) than in all the other disorders put together [1]. Renal biopsy findings remark the importance of renal biopsy in the diagnosis of the majority of glomerular diseases because clinical manifestations may be similar in many different glomerular diseases [9].

Glomerulonephritis affects up to one third of children with HSP, but it is serious and potentially life-threatening in less than 10% [10]. The spectrum of features ranges from microscopic hematuria and mild proteinuria to the less-common nephrotic syndrome, acute nephritic syndrome, hypertension, or renal failure. The presence of streptococcal infection in HSP patient could have a role in the severity of the renal involvement as described in our patient.

The treatment of HSP is controversial and the use of steroids and immunosuppressive drugs must be reserved for cases with a severe form of presentation. Corticosteroids produce consistent benefits and reduce the odds of developing persistent renal disease [11]. Due to the severity of renal involvement in our patient cyclophosphamide was added to steroid therapy and the evolution was awesome. A low dose of Enalapril was added as an antiproteinuric measure and for high blood pressure.

Conclusion

Henoch-Schönlein purpura could be preceded by streptococcal infection and could give severe renal involvement in form of necrotizing glomerulonephritis mimicking lupus nephritis with an excellent response to steroids, cyclophosphamide and angiotensin-converting enzyme inhibitor.

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