A Child with Post-streptococcal Acute Glomerulonephritis Complicated by Coombs Positive Autoimmune Hemolytic Anemia

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Citation

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Abstract

The simultaneous occurrence of acute post-streptococcal glomerulonephritis (PSAGN) and autoimmune hemolytic anemia (AIHA) is rare. A 5-year-old African-American boy was admitted with acute renal failure, hematuria, nephrotic syndrome and severe hemolytic anemia. The patient also had a low serum level of complement 3 (C3) and elevated anti-streptolysin O (ASO) titer. Kidney biopsy confirmed post-infectious glomerulonephritis with diffuse hypercellularity, sub-endothelial and sub-epithelial deposits. The patient received three blood transfusions and his hematocrit became stable without the necessity of steroid treatment. Renal function rapidly improved and his serum level of C3 returned to normal within two months and his proteinuria disappeared in 4 months. This case illustrates the rare occurrence of severe AIHA in association with PSAGN. This association suggests a potential role of anti-streptolysin O in the pathogenesis of the hemolytic anemia.

CASE

A 5-year-old African-American boy was referred to the Le Bonheur Children's Medical Center emergency department for acute onset of anemia. He was initially seen by his primary care physician four days prior to admission with headache, runny nose, cough and occasional vomiting. He denied sore throat and Streptococcal screening was negative. He was diagnosed with a viral infection and started on symptomatic treatment with acetaminophen. He had on and off fever up to 102°C for the following four days and was noticed by his parents to have increasing fatigue and a decrease in both oral intake and urine output. He was seen again by his primary care physician on the day of admission. He appeared pale and his hematocrit at the office was 14%. He denied any history of unexplained bruising, gross hematuria or blood in the stool. Past medical history was unremarkable and history was negative for sick contacts, insect bite and travel. He did not have sickle cell disease or any previous history suggestive of thalassemia. On physical examination, his body weight was 26.4 kg (95 %) and his height was 122.7 cm (95 %). His body temperature was normal at 37°C. He had tachycardia with heart rate of 123 per minute, and his respiratory rate was 24 per minute. His blood pressure was 111/68 mm Hg (95% for age and height was 117/76 mmHg). He was pale and had peri-orbital and pedal edema and abdominal distension suggestive of ascites. He had no icterus or splenomegaly, and the rest of his systemic examination was unremarkable. His admission laboratory results are depicted in Table One.

Figure 1

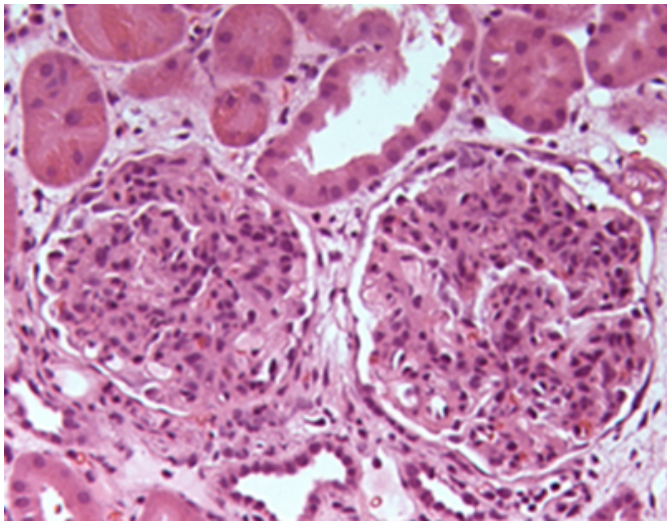
Table 1: Initial laboratory results including sepsis work-up after admission

			Ref. Range
White Cell Count	6.1	$10^3/mm^3$	(5 – 13)
Hemoglobin	4.5	g/dL	(11 – 16)
Hematocrit	13.0	%	(33 – 48)
Platelet Count	254	$10^3/mm^3$	(140 – 450)
Reticulocyte Count	3 %		(< 0.25%)
Blood Smear	Spherocytosis, poikilocytosis, anisocytosis		
Sodium	131	mmol/L	(135 – 145)
Potassium	5.6	mmol/L	(3.5 – 5.0)
Chloride	100	mmol/L	(98 – 107)
Carbon Dioxide	18	mmol/L	(18 – 27)
BUN	172	mg/dL	(6 – 20)
Creatinine	4.0	mg/dL	(0 – 0.9)
Glucose	93	mg/dL	(60 – 115)
Calcium	8.3	mg/dL	(8.6 – 11.0)
Total Protein	6.0	g/dL	(6.3 – 8.6)
Albumin	2.4	g/dL	(3.7 – 5.6)
Total Bilirubin	1.3	mg/dL	(0.2 – 1.0)
Lactate Dehydrogenase	213	IU/L	(45 - 85)
AST	23	IU/L	(15 – 40)
ALT	13	IU/L	(2 – 15)
Alkaline Phosphatase	109	IU/L	(96 – 437)
Haptoglobin	49.3	mg/dL	(27 - 139)
Cholesterol	237	mg/dL	(124 - 170)
Complement 3	4.8	mg/dL	(90 - 207)
Complement 4	23.6	mg/dL	(10 - 40)
Anti-streptolysin O titer	925	Todd units	(< 500)
DAT, Broad Spectrum Coombs	Positive		Negative
DAT, Anti-IgG Coombs	Negative		Negative
Direct Coombs, Anti-C3b-C3d	Positive		Negative
Anti-nuclear Antibody	Negative		Negative
Parvovirus IgG/IgM	Negative/Negative		Negative
Arbovirus Titer	Negative		Negative
Hepatitis B srface Antigen	Negative		Negative
Blood Viral Culture	Negative		Negative
Blood Culture	Negative		Negative
Urine Culture	Negative		Negative
Stool bacterial/viral Cultures	Negative		Negative
Urinalysis	Blood 3+, Protein 3+		
Urine Protein to Creatinine Ratio	11.6		(< 0.2)

In summary, he was found to have hyponatremia, elevated blood urea nitrogen (BUN) and creatinine, severe anemia with spherocytosis, proteinuria, pyuria and hematuria. His initial haptoglobin was not low, probably secondary to acute phase reaction. He had positive broad spectrum direct Coombs test and anti-C3b-C3d. His anti-IgG Coombs test was negative. Renal ultrasound showed normal kidneys and bladder. His chest X-ray revealed bilateral pleural effusions. He was initially admitted to the intensive care unit and subsequently received three blood transfusions. Further laboratory tests showed hypocomplementemia and a high ASO titer. His hemoglobin stabilized after the blood transfusion and his BUN and creatinine improved after fluid resuscitation. On day 3 of his hospitalization, he developed hypertension that required antihypertensive treatment. A renal biopsy done one week after admission showed a marked increase in cellularity resulting from both inflammatory cell infiltration and cell proliferation (Figure 1). Ten percent of the glomeruli had crescent formation. Only mild interstitial inflammation was noticed. Immunostaining showed marked IgG and C3 staining. Both subendothelial and subepithelial deposits were observed by electron microscopy. The histology was compatible with post-infectious glomerulonephritis.

Figure 2

Figure 1: Diffuse inflammatory cellular infiltration and mesangial hypercellularity (Hematoxylin and Eosin Staining: original magnification X 200)



Since his hematocrit stabilized after the transfusions, no steroids were administered. All cultures done during hospitalization were negative. At the time of discharge, his hemoglobin level was stable at 9.5 g/L and his serum creatinine level was 0.9 mg/dL. His medications included amoxicillin, amlodipine and ranitidine. At follow up 2 weeks after discharge, his hemoglobin level was 9.9 g/L. Subsequently, his C3 complement level was normal by 8 weeks and proteinuria had disappeared by 12 weeks.

DISCUSSION

Our patient presented with a constellation of signs and

symptoms consisting of nephritic/nephrotic syndrome, acute renal insufficiency and severe anemia. Despite an absence of history of streptococcal pharyngitis, he had an increased ASO titer. His serum complement 3 level was decreased initially and returned back to normal within 8 weeks. The renal biopsy also showed classic histology of post-infectious glomerulonephritis. This clinical picture is compatible with PSAGN. Although PSAGN is usually a self-limiting illness, morbidity still occurs in a subgroup of patients. The most common hematological complication of PSAGN is anemia. While mild anemia probably secondary to hemodilution is very common in patients with post-streptococcal acute glomerulonephritis, severe anemia is rare. [1, 2] AIHA was first described by William Hunter in 1888 in a patient with pernicious anemia. Little was known about the pathogenic mechanism until the discovery of autohemagglutination in the presence of hemolysins in patients with acquired hemolytic anemia. Further investigations led to the understanding of the development of autoantibodies that cause immune hemolysis of red blood cells. AIHA is now defined as a process of accelerated red blood cell destruction due to the production of autoantibodies directed against the self red cell antigens. [3] The hemolysis can be mediated by either IgG or IgM autoantibodies. Our patient had a positive direct Coombs test, which indicated that fixed antibodies were found on the patient's red blood cells. The negative anti-IgG but positive anti-C3b-C3d indicates that the autoantibodies found on the red cell membranes were IgM in nature. [4] The etiology of autoimmune hemolytic anemia is variable. It had been described in various conditions including malignancies, rheumatic diseases, infections and drugs. [5, 6] Autoimmune hemolytic anemia in children is very rare. [7] In a recent study from Brazil, 17 children were diagnosed with autoimmune hemolytic anemia over a period of 15 years, and only 4/17 had autoimmune hemolytic anemia associated with an identifiable underlying disease, including systemic lupus erythematosus, autoimmune hepatitis, Hodgkin's lymphoma and Langerhans cell histiocytosis. [8]

The underlying pathogenic mechanism of AIHA in patients with PSAGN remains obscure. A cross reaction between antibodies induced by streptococcal infection against the red blood cells is possible but not confirmed. Bhakdi reported that streptolysin-O toxin is able to interact with the lipid layer of human red cells and insert into the membrane as a large polymerized molecule. [9] The membrane bound toxin was also able to form immune complexes on the membrane by attracting human IgG. The immune complexes formed from binding of the streptolysin O antigen and IgG antibodies are potent activators of the classical complement pathway. [9] Besides streptolysin O, NAD-glycohydrolase (NADase) may also play a role in causing hemolysis. Supernatant of the culture of streptococci that are able to generate NADase have enhanced erythrocyte cytolytic activities. [10] Thus, both streptolysin O and NADase may have significant roles in the pathogenesis of the hemolysis in our patient.

Steroids are usually administered to patients with autoimmune hemolytic anemia, since they induce prompt reduction in the rate of hemolysis in most patients. However, our patient's anemia stabilized after blood transfusion without recurrence and his hemoglobin stayed normal without the need for steroids.

Although hemolytic anemia due to hemolytic uremic syndrome has also been described in patients with PSAGN, it is unlikely to be the cause since the platelet count was normal in our patient. Our patient did not have sickle cell disease and he had no other signs or symptoms suggestive of malignancies or systemic lupus erythematosus. Negative cold agglutination did not favor the diagnosis of Mycoplasma infection and Parvoviral infection was also excluded. We therefore concluded that his AIHA was associated with PSAGN.

CONCLUSION

AIHA is a rare disorder associated with PSAGN and the pathogenesis is still obscure. However, in patients with post-infectious acute glomerulonephrits presenting with severe anemia, hemolysis should be sought. The anemia of our patient due to AIHA stabilized after the acute phase of the illness. Hence, rational approach of treatment should be individualized and steroid should only be used in refractory cases of hemolysis.

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