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Case Report

Myocardial dysfunction and thrombocytopenia, rare manifestations of acute post-streptococcal glomerulonephritis: case report

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ABSTRACT

In this case report, we present two rare cases of acute post-streptococcal glomerulonephritis with unusual manifestations in the form of myocardial dysfunction and thrombocytopenia. APSGN typically follows Streptococcal infections and is characterized by inflammation of glomeruli. These cases, however, exhibited additional complexities. The first case involved a 12-year-old male with fever, shortness of breath, and cough. He presented with pedal edema, pallor, and hypertension. Laboratory findings revealed thrombocytopenia, anemia, and decreased C3 levels, while echocardiography indicated grade-3 diastolic dysfunction. The second case featured a 5-year-old female with icterus, fever, and body swelling. She had a palpable liver, pleural effusion, and thrombocytopenia. Both cases were diagnosed with APSGN, congestive heart failure, and thrombocytopenia. Thrombocytopenia is a rare finding in APSGN, and its etiology remains debated. Treatment included decongestive therapy and antihypertensive medication. Notably, thrombocytopenia in both cases improved without specific intervention, challenging the necessity of steroids or IVIg therapy. This report illuminates on the atypical presentation of APSGN, highlighting the potential coexistence of glomerulonephritis and thrombocytopenia. It underscores the need for further research to better understand this association and determine appropriate treatment protocols. These cases emphasize the importance of considering diverse clinical manifestations in the context of APSGN, calling for a broader understanding of this condition.

Key words: APSGN, Thrombocytopenia, Myocardial dysfunction, Congestive heart failure, Raised ASO titre, Low C3

INTRODUCTION

Group A beta-hemolytic streptococcal infections are common in children. It can cause Streptococcal sore throat and scarlet fever, impetigo, type II necrotizing fascitis, cellulitis, streptococcal toxic shock syndrome, acute rheumatic fever, post-streptococcal glomerulonephritis. Acute post-streptococcal glomerulonephritis is immunologically-mediated, nonsuppurative, delayed sequela of pharyngitis or skin infections caused by nephritogenic strains of GABHS. *Streptococcus pyogenes* of M types 1, 2, 4, and 12 were associated with epidemic nephritis resulting from upper respiratory infections, and M types 47, 49, and 55 were associated with epidemic nephritis following pyoderma. It is the best-studied immune complex-mediated glomerulonephritis. It is the most common glomerulonephritis in children worldwide with an estimated global burden of 450,000 cases annually with most of the cases occurring in children.[1] Globally, the prevalence of acute post-streptococcal glomerulonephritis (APSGN) has declined, especially in affluent nations where it is now uncommon and only affects adult patients with severe diseases. Because of improved hygiene, streptococcal infections may be treated more easily and quickly. However, in developing countries, the annual burden of APSGN remains at a level of at least 9.3 cases per 100,000 inhabitants.[2] It is most common in children

ages 5-12 years and uncommon before the age of 3 years.[3] Male to female ratio is 2:1.[4] The patient develops an acute nephritic syndrome 1-2 weeks after antecedent streptococcal pharyngitis or 3-6 after a streptococcal pyoderma.[3] Because of moderate symptoms or the resolution of those symptoms without the need for specific treatment or medical care, the history of a particular infection may not be present. Regarding how immune complexes injure glomeruli, there are now 3 leading hypotheses. The first hypothesis proposes that group A *streptococci* (GAS) antigen and antibody complexes form in the circulation and are subsequently trapped in the glomeruli. The second hypothesis proposes that GAS antigens are first deposited into glomerular components, followed by subsequent in-situ antibody binding, which creates immune complexes. The third hypothesis is that some GAS antigens in serum resemble parts of the glomerular basement membrane, a phenomenon known as molecular mimicry, which results in the production of cross-reacting antibodies and the formation of complexes in the glomeruli.

Clinical features can vary from asymptomatic microscopic haematuria with normal renal function to gross haematuria with acute renal failure. The most common presentation is an acute nephritic syndrome are edema, hypertension, and gross haematuria. The nephritic syndrome is when the glomeruli get inflamed and the function of filtration is impaired because the epithelial cell (podocyte) is damaged, as a result, large molecules such as RBCs (haematuria) and proteins (proteinuria) start to filter through it thus causing it to appear cola-like in color. Between 65% and 90% of patients are said to have edema but it is short-lived and lasts about 7-10 days.[1] It is because of too much fluid and sodium retention rather than a significant loss of protein in the urine. Although less common, pulmonary edema can occur in more serious circumstances. Up to 50% of cases have also been reported to have congestive heart failure. Both pulmonary edema and heart failure present as respiratory distress, orthopnoea and cough. Hypertension occurs in between 60% and 80% of PSGN patients, and around half of these cases necessitate treatment.[1] Mechanism of hypertension is the same as edema- retention of salt and water. It usually only lasts for a short period about 10 days, on average. Hypertension can also cause complications like hypertensive encephalopathy and heart failure. Hypertensive encephalopathy presents as blurred vision, severe headaches, altered mental status and new onset seizure. Hematuria is virtually present in all patients of PSGN be it gross or microscopic. Gross hematuria described as tea or cola-colored urine is present in 1/3rd cases and may last up to 10 days, the microscopic hematuria may persist for 1-2 years after initial presentation.[3] In a typical case of post-streptococcal nephritis, improvement is noticed after 2-7 days when the volume of urine increases, which is swiftly followed by the edema clearing up and the blood pressure returning to normal. In a minority of cases, APSGN may be manifested by nephrotic syndrome; and in rare cases, by a rapidly progressive (crescentic glomerulonephritis). Asymptomatic disease may be manifested by microscopic hematuria and a fall in serum complement levels and is 4-5 times more common than clinical disease in non-epidemic conditions.[4,5] On urine analysis hematuria, proteinuria, RBC casts, and polymorphonuclear leukocytes are found. C3 level is significantly reduced in >90% of patients in the acute phase which returns to normal in 6-8 weeks after the onset. C4 is either normal or only mildly depressed. Diagnosis is confirmed by clear evidence of prior streptococcal infection- a positive culture for streptococcus, rising antibody titre to streptococcal antigens such as anti-streptolysin-o and anti-ribonuclease, or positive streptozyme screen (which measures multiple antibodies to different streptococcal antigens). Hematological changes are not typical for APSGN. Anemia, frequently seen in children with APSGN, is not real and is due to circulatory congestion and consequent hemodilution. It improves spontaneously after induction of diuresis. Idiopathic thrombocytopenic purpura (ITP) is often related to sensitization by viral infections. Thrombocytopenia with ASPGN had not been reported in the literature much. In this case report we present two cases of ASPGN with thrombocytopenia.

CASE REPORT

In case report 1: the patient was a 12-year-old male who presented to paediatric emergency of JNMCH with complaints of fever for 3 days, shortness of breath, and cough for 2 days. There was no history of bleeding from any site including petechiae. There was no history of sore throat. He had no history of chronic disease. Family history of thrombocytopenia and chronic systemic disease including renal disease was not significant. On general examination, the child was sick-looking with pedal edema and pallor. Vitals were as follows-PR-136/min, RR- 24/min, SPO2-98% at Room Air, BP-127/104 (>95th +12 centile, stage 2 HTN) and temperature-101.1 degrees Fahrenheit. Anthropometry revealed a weight of 61 kgs (90th to 97th) a height of 159 cm (50th to 90th) and a BMI of 24.1 kg/m2 (23rd-27th). Systemic examination-respiratory system examination showed bilateral decreased air entry and bilateral basal crepitations. A cardiovascular examination showed tachycardia and muffled heart sounds. Abdominal examination and CNS examination were normal. Laboratory findings were as follows - hemoglobin-8.8 gm/dl, total leucocyte count-7610/mm^3 differential count-N71%, L23%, E 03%, M03%, platelet count-64000/mm^3, MCV-77.14 fl, MCH-27.94 pg and MCHC-36.2 g/dl, Peripheral blood smear does not show features of hemolysis, platelets were reduced by smear with few large platelets. reticulocyte count was 1%. Blood urea nitrogen-26 mg/dl, creatinine 1.2 mg/dl. Liver function test: ALT-21 U/l, AST-34 U/l, Alkaline phosphatase-192 U/l, and TSB-0.3 mg/dl. Urine

examination showed amber-colored urine with pH-5.5, specific gravity-1.029, blood 3+, protein 3+, and sugar 1+. Microscopic examination of urine revealed numerous RBCs, 8-10 / HPF pus cells. The urine culture was sterile. Electrolytes were within normal range. Fever workup including dengue, malaria, and typhoid fever was negative. ASO titre was 470 Todd Units (12-166). C3 levels were decreased- 13.5 mg/dl (90-180). C4 was within normal range. Throat culture was negative. USG showed minimal left-sided pleural effusion, and kidney size, and architecture was within normal limit.

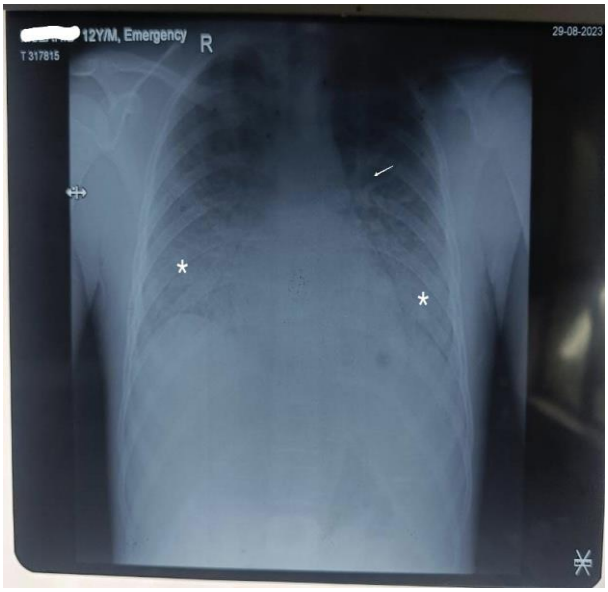

Figure 1: CXR showing increased CT ratio, basal pulmonary edema (asterisk), cephlisation of vessels (arrow), Pleural effusion (block arrow).

Renal Doppler was suggestive of normal blood flow. ECG showed relative bradycardia. Echo showed grade 3 Left ventricle diastolic dysfunction. In the view of above clinical laboratory findings, a diagnosis of ASPGN with Lower respiratory tract infection with Congestive heart failure with grade 3 diastolic function with thrombocytopenia was made. Differential diagnosis of HUS was kept. HUS was ruled out there was no history of preceding GI infection and no features of hemolysis on a peripheral blood smear. No features were suggestive of chronic systemic disease.

Treatment

The child was treated with supplemental oxygen and decongestive therapy was given in the form of IV furosemide (2 mg/kg/day) which was later switched to oral furosemide with spironolactone. Amlodipine (0.15 mg/kg/day) was given as an antihypertensive. The child was also started on an injection of ceftriaxone (100 mg/kg/day) and an injection of Azithromycin (10 mg/kg/day). The child's platelet count was kept under close watch along with the monitoring for any evidence of bleeding. No bleeding manifestation was noted during the hospital stay and in follow-up, so no steroids were started for thrombocytopenia. Shortness of breath improved after furosemide. BP improves gradually. Fever also responded to the course of antibiotics. On follow-up, thrombocytopenia and cardiac dysfunction were improved at end of 3rd month.

In case report 2: a 5-year-old female patient presented to pediatric OPD with complaints of yellowish discoloration of eyes for 1 week, fever for 2 days, and generalized body swelling for 2 days. There was no history of sore throat. There was no history of bleeding from any site. There was no history of chronic systemic disease. Family history of thrombocytopenia and chronic systemic disease including renal disease was not significant. A general examination revealed a sick-looking patient with generalized body edema and icterus. Vitals were as follows- HR-130/min, RR-42/min, SP02-91% at room air and 97% with oxygen via mask, BP-110/68 (80) (stage 1) and temperature-101-degree Fahrenheit. On anthropometry weight was 15 kg (10th to 50th) and height was 104 cm (10 the top 50th) and BMI was 13.86 kg/m2 (10th to 50th). In systemic examination, on abdominal examination tenderness was present in the right hypochondrium and the liver was palpable 2 can below the costal margin with span of 7.5 cm. Respiratory examination revealed bilateral decreased air entry in the subscapular region and lower axillary region and bilateral basal crepitations. On Cardiac examination, tachycardia and muffled heart sounds were found. Laboratory findings were as follows: Hb- 10.4 g/dl, TLC-11800/mm^3, DLC- N60, L40, and platelet was 0.9 lakh/mm^3. BUN- 58 mg/dl, creatinine-1.5 mg/dl. LFT was as follows: ALP-378 U/l, ALT-160 U/l, AST-65 U/l. T.Bil-0.5 mg% PT-19.1 seconds, INR-1.663, and APTT-40.1 seconds. Total serum protein was 5.7 g%, albumin was 3.0 g%, globulin was 2.7 g%, and Albumin: Globulin ratio was 1.1. Fever workup for malaria, dengue, and typhoid was negative. HIV, HepB, and Hep C were negative. ASO Titre was raised-610 Todd Unit. C3 was low-74.89 (90-180). Throat culture was negative. Urine examination revealed blood 1+, protein 1+, bilirubin 3+, sugar negative, pH-6, specific gravity-1.029. Microscopic examination of urine revealed numerous RBCs and occasional WBCs. The urine culture was sterile. USG showed bilateral pleural effusion. Renal Doppler showed normal blood flow. ECHO showed trivial pericardial effusion with grade 1 diastolic dysfunction. In the view of above clinical and laboratory findings diagnosis of APSGN with congestive heart failure with mild hepatitis with bilateral pleural effusion with trivial pericardial effusion with thrombocytopenia was made.

The patient was put on oxygen support via a mask. Decongestive therapy was given in the form of IV furosemide (2 mg/kg/day) which was later switched to oral furosemide with spironolactone combination. Amlodipine (0.16 mg/kg/day) was given as an antihypertensive. The child was also started on broad

spectrum antibiotic in the form of injection cefotaxime (150 mg/kg/day) instead of ceftriaxone since the patient have evidence of mild hepatitis. During hospital stay respiratory distress improved gradually followed by anasarca. Hepatitis also improved. Thrombocytopenia improved gradually on its own without the need for steroids. The child is being followed up in OPD. In the 3 months of follow up, most of the parameters including cardiac function and thrombocytopenia were improved at the end of 2nd month except for microscopic hematuria.

DISCUSSION

We presented two cases of APSGN with congestive heart failure with thrombocytopenia. Congestive heart failure is an atypical finding of APSGN. It can be due to hypertension (the most common cause), hypervolemia, hyperkalaemia, administration of large quantities of fluids (especially when anuria or oliguria is present), or primary myocardial dysfunction.[6] In our first case, grade 3 diastolic dysfunction was present and stage 2 hypertension was also present. In our second case, trivial pericardial effusion was present with grade 1 myocardial dysfunction and stage 1 hypertension was also present. Singh et al studied 34 children with PSGN. CCF was found in nine participants in their investigation. On echocardiography, three patients, two of whom were normotensive, had reduced LVF.[7]

In research conducted by Banapurmath et al 13 out of 50 patients of APSGN developed CCF. Twelve of these children had hypertension. One child was normotensive and was suspected of having myocarditis based on muffled heart sounds and low-voltage complexes on an ECG.[6] Thrombocytopenia in the context of APSGN is a rare finding. The association between acute thrombocytopenia and APSGN was first reported by Kaplan and Esseltine.[8] They reported 2 cases who presented with bleeding manifestations such as petechiae, epistaxis, and gross hematuria. BP was normal, C3 was low and ASO titer was raised. Both were treated with prednisolone for 4-6 weeks. Thrombocytopenia improved on follow-up in both cases. In a similar study from Saudi Arabia by Rizkallah et al a child of ASPGN presented with gross hematuria, diffuse petechiae, and epistaxis.[9] The platelet count was 4000/mm^3. He was also treated with prednisolone for 4 weeks. In a case of 4-year-old boy reported from Turkey, the child was presented with epistaxis and petechiae. His platelet count was 1 thousand. He was treated with prednisolone for 4weeks.[10] Murugama et al reported a 4-year-old boy from Japan. The patient presented with gross hematuria. His minimum platelet count was 16 thousand. He was treated with Injectable hydrocortisone and then oral prednisolone for a total of 5 weeks. In his case remarkable increase of platelet-associated immunoglobulin G (PAIgG) was reported and the course of glomerulonephritis was mild which he explained by increased destruction of platelets bound with immunoglobulin.[11] This hypothesis cannot explain the more severe course of the nephritis in our case. Patients were treated with steroids except in the case reported from Hawai'i who treated his patient of APSGN with thrombocytopenia with I.V immune globulin (IVIG). In his patient, after treatment with IVIG patient's platelet count improved transiently and from the 7th day of treatment platelet count began to decrease again reaching a nadir of 15 thousand on day 38th. On day 39th patient was given dexamethasone (single dose) coincidentally for croup. After that patient‘s platelet count improved and became normal by day 66th.[12] Similarly, Bal A et al also treated their patient with IVIG. In all the cases thrombocytopenia improved on follow-up.[13] All these investigators consider thrombocytopenia as ITP.

The diagnosis of ITP in above reported cases has been a clinical one because assays measuring platelet-associated lgG have low sensitivity. So whether antiplatelet antibodies in a patient with APSGN with thrombocytopenia should be measured or not remains questionable. In our study children did not present with bleeding manifestations except for microscopic hematuria which need not necessarily be due to thrombocytopenia. The lowest platelet count in 1st patient was 36 thousand and in the second patient, it was 60 thousand. We kept both patients under observation for the progression of thrombocytopenia and bleeding manifestation. In both patients, thrombocytopenia improved on its own without the need for steroids or IVIG. Though the cause of thrombocytopenia in APSGN is not exactly known, Muguruma et al and Tasic and Polenakovic et al have hypothesized that autoantibodies cross-reactive against group A beta-hemolytic streptococci and platelets may play a role, for which reason, time-limited immune-modulating treatments appear to be beneficial.[10,11]

CONCLUSION

Hypertension is the most common contributory cause of circulatory congestion in acute glomerulonephritis. In rare circumstances, patients may develop CCF in the absence of hypertension, and primary heart dysfunction may be the genesis of CCF in such children. Systolic or diastolic myocardial dysfunction can occur. Myocardial dysfunction is usually transitory and it improves gradually in a few months. The etiology of the link between APSGN and ITP is still being debated. However, as the number of reported cases increases, a distinct clinical condition characterized by the coexistence of glomerulonephritis and thrombocytopenia following streptococcal infection may be discovered. In such circumstances measuring antiplatelet antibodies is also questionable. More studies are required to explore this association and to decide whether all cases of APSGN with thrombocytopenia, should be treated with steroids/ IVIG or observation is sufficient.

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