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A novel case of acute glomerulonephritis with concurrent acute non-rheumatic myocarditis following group a streptococcal infection

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Abstract

Streptococcal infection is a common cause of acute glomerulonephritis. Cardiac damage associated with streptococcal infection commonly occurs in acute rheumatic fever. However, cases of acute non-rheumatic streptococcal myocarditis have been reported in recent years. We report a novel case of concurrent acute glomerulonephritis and non-rheumatic myocarditis following streptococcal infection. A good prognosis was achieved with antibiotic and immunosuppressive therapy, indicating that *Streptococcus* causes cardiorenal syndrome type 5 *via* an immune-mediated response. A better understanding of post-streptococcal cardiorenal syndrome is warranted to enable the early diagnosis and treatment of affected patients.

Keywords

Group A streptococcus, post-streptococcal glomerulonephritis, acute non-rheumatic streptococcal myocarditis, cardiorenal syndrome, cardiac damage, immunosuppressive therapy

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Introduction

Type III hypersensitivity reaction following group A streptococcal infection represents the main mechanism of post-streptococcal glomerulonephritis (PSGN).[1] Cardiac damage associated with streptococcal infection mainly occurs in the context of acute rheumatic fever. In recent years, cases of acute non-rheumatic streptococcal myocarditis (ANRSM) have been reported. Although the mechanism of ANRSM remains unclear, most studies propose the involvement of streptococcal toxins.[2,3] We hereby report a novel case of concurrent acute PSGN and ANRSM after streptococcal infection.

Case report

A 17-year-old boy complained of rhinobyon and nonproductive cough for a week and presented with a 3-day history of pharyngodynia, fever, palpebral edema, and fatigue. Ibuprofen was taken as an antipyretic. He had no past medical or family history, and he denied any chest pain, dyspnea, rash, or musculoskeletal pain. Physical examination on admission revealed a body temperature of 36.7°C, a heart rate of 77 beats/min, a respiratory rate of 20 breaths/min, and blood pressure of 105/74 mmHg. Palpebral edema and bilateral non-suppurative tonsillar enlargement (grade 1) were noted, but no rash or pustules were observed.

All laboratory test results on admission are presented in Table 1. The patient had mild anemia, an increased serum creatinine level, hypoalbuminemia, a significantly increased anti-streptolysin O (ASO) titer, decreased complement C3 and C4 levels, and a slightly increased C-reactive protein level and erythrocyte sedimentation rate. Antinuclear antibodies were weakly positive (1:100). The patient's brain natriuretic peptide (BNP) level was elevated, whereas his high-sensitivity troponin T (TnT) and lactate dehydrogenase levels were normal. Viral causes of myocarditis, such as echovirus and Coxsackie virus, were all seronegative. Proteinuria (3+) with 24-hour protein excretion of 6.5 g/24 hour, hematuria (164/high-power field [HPF]), and leukocyturia (256/HPF) was observed on urinalysis. Electrocardiogram was unremarkable, whereas chest X-ray (Figure 1a) revealed an enlarged heart shadow with small amounts of bilateral pleural effusion. Echocardiography disclosed whole-heart enlargement, mild regurgitation of the mitral, tricuspid, and aortic valves, and mildly increased pulmonary arterial pressure. Blood and pharyngeal swab cultures were negative.

Renal biopsy performed on day 3 of hospitalization confirmed a diagnosis of acute PSGN (Figure 2). However, the patient's clinical condition gradually worsened (Table 2), and he experienced chest pain, exertional shortness of breath, and lower-limb edema. Increases in blood pressure (140/80 mmHg) and serum creatinine (194 μmol/L), TnT (0.017 mg/L), lactate dehydrogenase (392 U/L), and BNP levels (550 pg/mL) from baseline were observed. In addition, a decrease in the estimated glomerular filtration rate (42.36 mL/min) was observed. Repeat echocardiography revealed further enlargement of the cardiac chambers, mainly of the right heart, and pulmonary hypertension (48 mmHg), suggesting fulminant myocarditis. As such, a diagnosis of acute PSGN with concurrent ANRSM was confirmed.

Intravenous methylprednisolone therapy (0.25 g/day for 3 days and 40 mg/day sequentially for 2 weeks) was administered. Other supportive measures, including antibiotics, irbesartan, and furosemide, were also used during hospitalization. After discharge, the patient received oral methylprednisolone 40 mg, and he was tapered to withdrawal for a total course of 8 months.

Table 1. Laboratory findings.

Parameter	Value	Reference range
Blood analysis		
White blood cell count ($\times 10^9$/L)	5.46	3.5–9.5
Hemoglobin (g/L)	105	115–150
Platelets ($\times 10^9$/L)	131	94–268
Lymphocytes ($\times 10^9$/L)	0.82	0.8–4.0
Creatinine (μmol/L)	129.1	57.0–97.0
Cystatin C (mg/L)	1.75	0.0–1.26
Serum albumin (g/L)	27.4	40.0–55.0
Alanine aminotransferase (U/L)	12.7	15–40
Aspartate aminotransferase (U/L)	6.4	9–50
Lactate dehydrogenase (U/L)	162.2	120.0–250.0
Creatine kinase isoenzymes (mg/L)	0.91	0.1–4.94
T cardiac troponin T (mg/L)	0.01	0.0–0.14
Brain natriuretic peptide (pg/mL)	486	0–100
Total cholesterol (mmol/L)	2.29	3.1–5.72
Triglycerides (mmol/L)	1.1	0.3–1.7
C-reactive protein (mg/L)	26	0–8
Procalcitonin (ng/mL)	0.14	0.0–0.25
Soluble interleukin-6 receptor (pg/mL)	3.02	0–7
Erythrocyte sedimentation rate (mm/h)	19	10.0–15.0
Ferritin (ng/mL)	116.54	13–150
Serum iron (μmol/L)	8.9	11.0–30.0
Total iron-binding capacity (μmol/L)	33.4	50.0–77.0
Antinuclear antibody	Weakly positive (titer 1:100)	Negative
Anti-dsDNA antibody	Negative	Negative
Anti-Sm antibody	Negative	Negative
Anti-Sjögren's syndrome-related antigen A and B antibody	Negative	Negative
Complement C3 (g/L)	0.06	0.79–1.52
Complement C4 (g/L)	0.06	0.16–0.38
Rheumatoid factor (KIU/L)	<20	0–30
Anti-streptolysin O test (KIU/L)	786	0–116
Anti-neutrophil cytoplasmic antibody	Negative	Negative
Anti-cardiolipin antibody	Negative	Negative
Anti-glomerular basement membrane antibody	Negative	Negative
Immunofixation electrophoresis	Negative	Negative
Fibrinogen (g/L)	3.37	2.0–4.0
D-dimer (μg/L)	245.1	0.0–232.0
Respiratory virus	Negative	Negative
EBV DNA (IU/mL)	5.19×10^3	Negative
Cytomegalovirus DNA	Negative	Negative
TORCH test	Negative	Negative
Hepatitis B DNA, hepatitis C RNA, hepatitis E RNA	Negative	Negative
TRUST and HIV	Negative	Negative
Blood and urine culture	Negative	Negative

(continued)

Table 1. Continued.

Parameter	Value	Reference range
Urinalysis		
Urine protein	3+	Negative
Urine RBC/HPF	164	0–10
Urine WBC/HPF	256	0–10
Urine microalbumin/creatinine ratio (mg/g·Cr)	3618.60	0.0–30.0
Twenty-four–hour urine protein (g/24 h)	5.6	0.0–0.1
Imaging study		
Electrocardiogram	Negative	Negative
Chest X-ray	Thickened lung texture, full heart shadow, small amount of bilateral pleural effusion	Negative
Heart ultrasound		
Left atrial diameter (mm)	38	<30
Left ventricular diameter (mm)	54	45–50
Right inner diameter (mm)	36	33–41
Internal diameter of right ventricle (mm)	37	7–23
Ejection fraction (%)	63	55–80
Heart valve lesions	Negative	Negative
Aortic valve mouth reflux area (cm^2)	1.0	Negative
Mitral valve mouth reflux area (cm^2)	3.0	Negative
Mitral valve mouth reflux area (cm^2)	1.0	Negative
Pulmonary arterial pressure (mmHg)	37	15–28
Pericardial effusion	Negative	Negative

EBV, Epstein–Barr virus; TORCH, toxoplasmosis, rubella, cytomegalovirus, and herpes simplex virus TRUST: toluidine red unheated serum test; HIV: human immunodeficiency virus.

The patient had a good prognosis (Table 2). He was discharged after 2 weeks, and significant relief of chest pain and dyspnea was achieved together with decreased TnT and BNP levels and remission of cardiac chamber enlargement, pulmonary hypertension, and valve regurgitation on echocardiography. TnT and BNP levels and echocardiographic findings returned to normal after 1 month, and these findings were confirmed by chest computed tomography (Figure 1b). The patient nearly regained hypocomplementemia within 1 month, and baseline kidney function was restored by 3 months. Meanwhile, urinary protein decreased to 1+ after 5 months, although small amounts of urinary red blood cells persisted.

This case report was approved by the Ethics Committee of Daping Hospital [Approval No.: 97 (2022), Approval date: 14 April 2022]. We have obtained written informed consent for publication from the patient. The reporting of this study conforms to CARE guidelines.[4]

Discussion

This study presented a novel case of cardiorenal syndrome type 5 following streptococcal infection, which stimulated an immune-mediated response that resulted in cardiac and renal damage. Cardiorenal syndrome type 5 refers to combined kidney and heart dysfunction attributable to acute or chronic systemic illness, which affects the

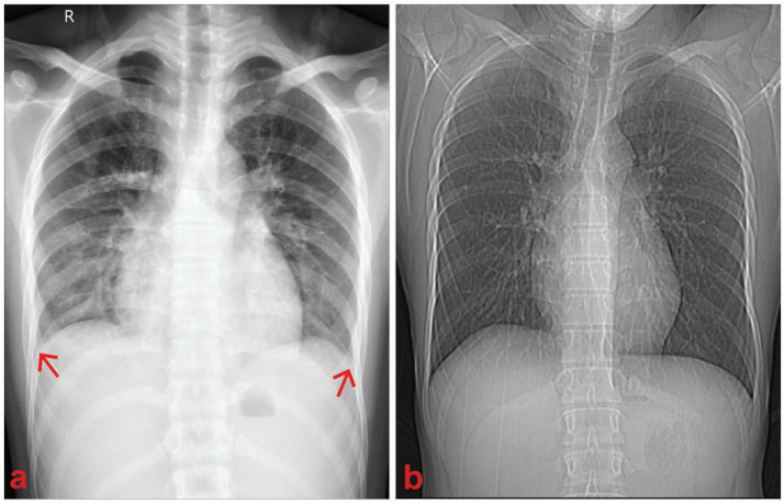

Figure 1. Radiographic findings. (a) Chest X-ray revealed an enlarged heart shadow with small amounts of bilateral pleural effusion (red arrow) on admission and (b) Chest computed tomography revealed a normal heart shadow after 1 month.

function of both organs in parallel, leading to a common clinical picture.[5]

Palpebral edema, hematuria, proteinuria, elevated ASO levels, reduced complement levels, and the findings of renal biopsy supported the diagnosis of PSGN. Systemic lupus erythematosus (SLE) and C3 glomerulopathy were excluded according to The 2019 American College of Rheumatology (ACR) criteria, and the patient rapidly regained hypocomplementemia.[6,7] Importantly, concurrent cardiac damage was observed with increased BNP levels on admission. The patient subsequently developed chest pain and dyspnea and exhibited increased levels of myocardial injury markers such as TnT and lactate dehydrogenase, and progressive cardiomegaly was observed on echocardiography. According to the three-tiered clinical classification for the diagnosis of myocarditis based on the level of diagnostic certainty, the patient was considered probable for acute myocarditis. Moreover, we attempted to identify the cause of myocarditis. Streptococcal infection and cardiac disease are most commonly associated with acute rheumatic fever, which is diagnosed using the modified Jones criteria consisting of major, minor, and supportive criteria. The patient did not meet the modified Jones acute rheumatic fever standard because he had no persistent fever, arthritis chorea, and erythema, and his erythrocyte sedimentation rate was <26 mm/hour. Viruses are the most common causes of myocarditis. Respiratory virus, Epstein–Barr virus, and TORCH (toxoplasmosis, rubella, cytomegalovirus, and herpes simplex virus) tests were negative in our patient. Other systemic causes, such as SLE and Sjögren's syndrome, were excluded, which raised the suspicion of acute non-rheumatic streptococcal myocarditis.[8–10]

ANRSM was first reported by Gore *et al.* in 1947,[11] and its reported clinical manifestations are diverse. Most patients present with anginal chest pain, exertional shortness of breath, ST-segment elevation on electrocardiogram, and increased TnT levels but no evidence of stenosis on coronary angiography. Ultrasonographic findings have included cardiomegaly, decreased

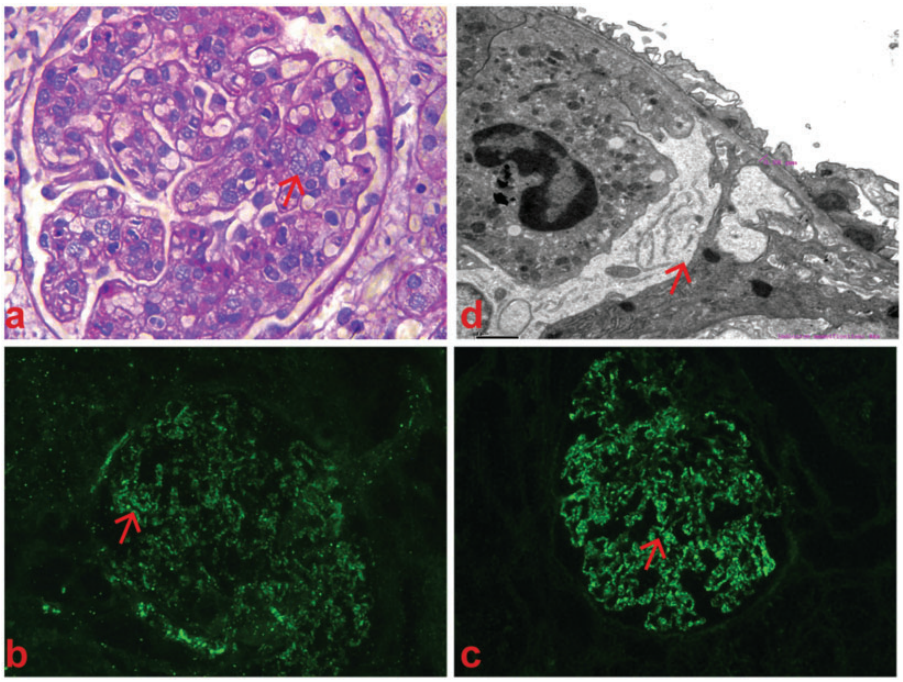

Figure 2. Microscopic images of renal biopsy specimens. (a) Light microscopy of periodic acid–Schiff staining revealed glomerular lobulation attributable to mild mesangial cell and matrix hyperplasia, as well as capillary endothelial cell hyperplasia, mononuclear cell and neutrophil infiltration of the glomerulus, and granular epithelial cell and vacuolar degeneration (red arrow). (b, c) Immunofluorescence staining for C3 revealed granules along the capillary walls and a few granules in mesangial staining with lesser degrees of IgG positivity and (d) Electron microscopy demonstrated swollen visceral epithelial cells; extensive fusion of foot processes; and electron-dense deposition in the mesangial, subepithelial, and medial basement membranes (red arrow). Original magnification: a–c, ×400; d, ×8000.

systolic function, and pericardial effusion. In severe cases, acute heart failure, systemic multiple organ dysfunction, and even sudden cardiac death can occur.[2,3,12,13]

The pathogenesis of ANRSM remains unclear. Myocardial biopsy is mainly characterized by mononuclear cell infiltration, cardiomyocyte edema, and regional necrosis with the absence of streptococci, indicating the lack of direct myocardial infection.[11] *Via* bioinformatics analysis, Malnick *et al.* recently identified common epitopes between cardiac Ca^{2+} ATPase and M proteins of group A *Streptococcus* cell walls, suggesting a role of the immune-mediate mechanisms by which *Streptococcus* causes acute myocarditis.[14] Similarly, cross-reactivity between streptococcal M proteins and the glomerular basement membrane has been suggested as a potential mechanism of PSGN.[15] In our patient, a good prognosis was achieved with immunosuppressive therapy. We therefore speculate that group A streptococcal M proteins share a common epitope with the Ca^{2+} ATPase proteins of both the glomerular basement membrane and cardiomyocytes. Cross-immune responses of the heart and kidneys with M proteins might have been the pathogenesis of simultaneous cardiac and renal damage following streptococcal

Table 2. Clinical follow-up.

Parameter	1 week	2 weeks	1 month	4 months	Reference range
Blood analysis					
Creatinine (μmol/L)	194.9	274	234	93.9	57.0–97.0
Serum albumin (g/L)	25.2	26.7	32.8	46	40.0–55.0
Alanine aminotransferase (U/L)	29.1	30.5	65.3	18.5	15–40
Aspartate aminotransferase (U/L)	33.5	41.9	16.7	36.7	9–50
Lactate dehydrogenase (U/L)	248.8	278	392	189.9	120.0–250.0
Creatine kinase isoenzymes (mg/L)	0.51	1.34	1.89	0.97	0.1–4.94
T cardiac troponin T (mg/L)	0.017	0.023	0.02	0.006	0–0.014
Brain natriuretic peptide (pg/mL)	550	405	119.97	29.76	0–100
Complement C3 (g/L)		0.07	0.74	1.14	0.79–1.52
Complement C4 (g/L)		0.16	0.24	0.3	0.16–0.38
Anti-streptolysin O test (KIU/L)		683	388	247	0–116
Urinalysis					
Urine protein	3+	3+	3+	2+	Negative
Urine RBC/HPF	1528	11,449	4707	1622	0–10
Urine WBC/HPF	36	771.5	279	30	0–10
Urine microalbumin/creatinine ratio (mg/g·Cr)	3618	2861	4432	502	0.0–30.0
Twenty-four–hour urine protein (g/24 h)			3.8	0.35	0.0–0.1
Heart ultrasound					
Left atrial diameter (mm)	39		36	35	<30
Left ventricular diameter(mm)	55		52	50	45–50
Right inner diameter(mm)	43		35	30	33–41
Internal diameter of right ventricle(mm)	43		38	28	7–23
Ejection fraction (%)	64		63	61	55–80
Heart valve lesions	Negative		Negative	Negative	Negative
Aortic valve mouth reflux area (cm^2)	3.4		5.1	5.1	Negative
Mitral valve mouth reflux area (cm^2)	5.3		4.8	2	Negative
Mitral valve mouth reflux area (cm^2)	4.7		2.5	3.3	Negative
Pulmonary arterial pressure (mmHg)	48		28	18	15–28
Pericardial effusion	Slight		Slight	Slight	Negative

infection. Unfortunately, given the negative throat swab culture, the pathogenic *Streptococcus* species failed to be obtained for further analysis.

In conclusion, we report a novel case of concurrent acute glomerulonephritis and ANRSM after group A streptococcal infection. We propose the potential role of cross-immune reactivity between streptococcal M proteins and Ca^{2+} ATPase in both the glomerular basement membrane and cardiomyocytes as the pathogenesis of cardiorenal syndrome type 5 following streptococcal infection.

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Author contributions

Shihui Hou, Huanzi Dai, Jie Yang, and Fei Xiao diagnosed and treated the patient. Shihui Hou and Huanzi Dai collected the data. Fei Xiao completed the staining of kidney tissue. Huanzi

Dai and Shihui Hou edited and submitted the manuscript. All authors read and approved the final manuscript.

Consent for publication

We have obtained informed consent for publication from the patient. A copy of the consent form is available for review by the Editor of this journal.

Data availability statement

The data are openly available in a public repository.

Declaration of conflicting interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethics approval and consent to participate

This case report was approved by the Ethics Committee of Daping Hospital. A copy of the medical research ethics approval document is available for review by the Editor of this journal, and it can be provided on request. All authors read and approved the final manuscript.

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