The Clinicopathology and Outcome of Post-Infectious Glomerulonephritis: Experience in 36 Adults

Nattachai Srisawat MD*,
Laor Aroonpoonsub MD*, Songkiat Lewsuwan MD*,
Talengsak Kanjanabuch MD*, Yingyos Avihingsanon MD*,
Kearkiat Praditpornsilpa MD*, Kraing Tungsanga MD*,
Sawaluk Chusil MD*, Somchai Eiam-ong MD*

** Department of Medicine, Department of Pathology, Faculty of Medicine, Chulalongkorn University Hospital*

Post-infectious glomerulonephritis is one of the most common causes of acute glomerulonephritis. A retrospective study of post-infectious glomerulonephritis at King Chulalongkorn Memorial Hospital, Thailand was performed from January 1999 to December 2005. Among thirty six patients, eight cases were post-streptococcal glomerulonephritis and twenty eight cases were post non-streptococcal Glomerulo Nephritis (GN). Most cases present with edema, hypertension, gross hematuria and nephrotic-range proteinuria. C3 and CH50 commonly were low. Post-streptococcal glomerulonephritis had more aggressive pathology compared to the others. However, the long term outcome was excellent. In the present study the authors found ESRD in only 14.3% (4 out of 28 cases) that reflects the excellent prognosis of post-infectious glomerulonephritis. Of interest, all of the ESRD patients were caused by post non-Streptococcal GN. Even though, no statistic was achieved; it might reflect the aggressiveness of non-Streptococcal pathogen.

Keywords: *Post-infectious Glomerulonephritis, Post-streptococcal Glomerulonephritis, Outcome*

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Post-infectious glomerulonephritis (GN) is an immune-complex mediated GN caused by many different organisms. The best known pathogen is group A-beta hemolytic Streptococcus. The characteristic renal histopathology is diffuse proliferative GN, often exudation with IgG and C3 subepithelial and mesangial deposits. The pathogenesis of post-infectious GN is an interactive result of micro-organism and the host immune response[1]. Although the majority of the patients make a complete clinical recovery, a significant number, especially the elderly, continue to exhibit urinary abnormalities including sub-nephrotic range proteinuria, hypertension, and abnormal urine sediments. Recently, Nasr et al reported a worse prognosis of post-infectious GN complicating diabetic nephropathy. Four out of five cases developed ESRD. Of note, none of them arose from Streptococcal infection (3 *S. aureus* and 2 *S. epidermidis*) and IgA was the sole class of immunoglobulin that was deposited. Nowadays, there are growing evidences showing different prognosis between post-streptococcal GN and post-infectious GN.

The study aimed to compare the clinical manifestation, outcome, and histopathology between patients with post-infectious GN, caused by the organisms other than Streptococcal infection, and with post-streptococcal GN.

Material and Method

A retrospective study of 36 adult patients with post-infectious GN identified from 979 pooled native kidney specimens at King Chulalongkorn Memorial Hospital, Bangkok, Thailand during January 1998 - December 2005 was conducted. There were 16 males and 20 females.

The diagnosis of post-infectious GN was solely based on the clinico-pathology correlation and required the immunofluorescense (IF) findings of

Correspondence to : Kanjanabuch T, Division of Nephrology, Department of Medicine, Faculty of Medicine, Chulalongkorn University Hospital, Bangkok 10330, Thailand. Phone: 0-2256-4321, Fax: 0-2252-6920, E-mail: golfnephro@hotmail.com

granular C3 predominance or co-predominance with Ig and/or the electron microscopic (EM) features of subepithelial "humps" deposits. The patients were subsequently classified according to a potential pathogen into 2 groups: 1) post-streptococcal GN. The diagnosis required positive testing of recent group A-beta hemolytic Streptococcal infection by either Anti-Streptolysin O antibody (ASO), anti-DNase B antibody, or throat swab culture; 2) Post non-Streptococcal GN required none of the above being positive and occurred at the same interval or shortly after the episode of infection, others than group A-beta hemolytic Streptococcus either bacteria or non-bacterial organism.

The histological features by light microscopy (LM) were semi-quantified and were separately graded according to glomeruli, vascular, tubule, and interstitium. Degree of interstitial infiltration and interstitial fibrosis were classified by semi-quantitative scoring system: normal = 0, mild = 1 (involvement < 10%), moderate = 2 (10-40%), severe =3 (> 40%). The intensity of IF was graded by the quantity of intensity ranging from 0 to 4+ of IgG, M, A, C3, C1q, fibrinogen, and albumin. Mean percentage of glomerulosclerosis was the summation of glomeruli that contained global sclerosis or segmental sclerosis.

Statistical analysis was performed by using the SPSS statistical package (SPSS version 13.0). Results were presented as means with Standard Deviation (SD) for normally distributed data, or median with percentiles for non-normally distributed data. Generally, distributed continuous variables were compared using student t-test (if 2 dependent variables). All statistical tests were two-sided, with a p-value of less than 0.05 taken to indicate statistical significance. The survival analysis for time to ESRD or doubling serum creatinine, time to proteinuria less than 500 mg and time to serum creatinine less than 2 mg/dl were estimated by Kaplan-Meier methods. To determine statistical significance of the Kaplan-Meier analysis, the log-Rank test was performed.

Results

Thirty six cases of post-infectious GN were identified. The median age was 47 $\pm$ 16.9 years old with male predominant at a ratio of 1:1.3. The age ranged from 15 to 80 years. Eight cases were post-streptococcal GN and 28 cases were classified into non-Streptococcal GN. Most of the latter (24 out of 28 cases) could not identify causative pathogen. Nevertheless, none of those were positive neither of ASO nor anti-Dnase B Ab. One case was shunt nephritis, one case was ricket-sial associated GN, two cases were tuberculosis associated GN. Post-streptococcal GN manifested clinically and severely far more common than another did (Table 1 and 2). However, none of those obtained statistics. Proteinuria was detected in 97-100%, 60%of those achieved nephrotic range. Hence, microscopic hematuria was observed to be much less common in post non-streptococcal GN. The low level of C3, C4, and CH50 were detected in 42.3%, 15.4%, and 50%, respectively. Only C3 reached statistical difference. Level of C3 was lower in the patients with post streptococcal GN with statistical significance ($p < 0.05$).

The results of histopathology were summarized in Table 3. Post-streptococcal GN had significant higher semi-quantitative score of endocapillary proliferation than another did (p-value = 0.01). C3 was the most intense markers staining by IF in both groups of post-infectious GN. (See also Table 4).

The post-streptococcal GN had an excellent outcome. None of those developed ESRD. On the contrary, 1 and 4 out of 28 patients with post non-streptococcal GN developed CKD and ESRD. Moreover, the patients with post-streptococcal GN achieved a higher percentage of CR (87.5%, 53.6%).

Kaplan-Meier survival curve for the time to ESRD, the time to proteinuria less than 500 mg/day and the time to creatinine less than 2 mg/dl are shown in Fig. 1 and 2; respectively. The median times to resolution of proteinuria and serum creatinine were 2 months and 8 months, respectively. None of those achieved

Table 1. Clinical features of patients with post-streptococcal and post-non-streptococcal GN

	Post-streptococcal GN (N = 8)	Post non-streptococcal GN (N = 28)
Age (years)	47 (15-76)	43 (19-80)
Clinical presentation		
- Edema (%)	87.5	76.9
- Hypertension (%)	75.0	59.3
- Gross hematuria (%)	12.5	7.7

Table 2. Laboratory features of patients with post-streptococcal and post-non-streptococcal GN

	PSGN (N = 8)	Post non-streptococcal GN (N = 28)	p-value
Blood chemistries			
- BUN (mg/dl)	54.0±28.5	54.9±48.9	NS
- Cr (mg/dl)	3.1±2.3	3.9±4.2	NS
Urinalysis			
- % Macroscopic hematuria (> 3cell/hpf)	71	100	0.005
- % Gross hematuria	25	8	NS
- Proteinuria			
- % of proteinuria > 500 mg/day	100	97.0	NS
- 24-hr urine protein(mg/day)	8.7±8.6	4.8±3.9	NS
- UPCR	4.7±2.7	7.1±7.0	NS
- % Pyuria (WBC > 5 cell/hpf)	71	68	NS
Complement level			
- Low C3 (%)	85.7	26.3	0.007
- Low C4 (%)	0	25	NS
- Low CH50 (%)	75	25	NS

Table 3. Renal pathologic finding of patients with post-streptococcal and post-non-streptococcal GN

	PSGN (N = 7)	Post non-streptococcal GN (N = 26)	p-value
- Mean percentage of glomerulosclerosis	0.1	0.7	0.02
- Mean percentage of crescent	0.2	0.1	NS
- Mean percentage of endocapillary proliferation	0.8	0.3	0.01
Interstitial scoring			
- Interstitial infiltration	1.6	1.3	NS
- Interstitial fibrosis	0.7	1.0	NS

Table 4. Intensity of IF was graded by the quantity of intensity

	IgG	IgA	IgM	C3	C1q	Fibrinogen	Albumin
Post-streptococcal GN	0.8	0.5	0.4	3.5	0.3	0.8	0.2
Post-non-streptococcal GN	0.8	0.5	1.0	2.4	0.5	0.5	0.4
p-value	NS	NS	NS	0.03	NS	NS	NS

Table 5. The clinical outcome of the patients

Final clinical outcome	PSGN (N = 8)	Post non-streptococcal GN (N = 28)	Total
Complete Remission (%)	7 (87.5)	15 (53.6)	22
Partial Remission (%)	0 (0)	2 (7.1)	2
Steroid Dependent (%)	1 (12.5)	1 (3.6)	2
Chronic Kidney Disease (%)	0 (0)	1 (3.6)	1
ESRD (%)	0 (0)	4 (14.3)	4
Lost to follow up (%)	0 (0)	5 (17.9)	5
Composite end point			
CR, PR, SD (%)	8 (100)	18 (64.3)	NS
CKD, ESRD (%)	0 (0)	4 (14.3)	NS

statistical difference, whether patients received steroid treatment, when both were compared.

Discussion

Infection has been known to cause GN since the mid-19th century. Samuel Wicks found abnormal urine findings in patients who died from scarlet fever[2]. The mean age of post-infectious GN in the present study was in the fifth decade. This is similar to the results from a previous study[2]. A similar result observed by Washio, et al[3] where the outcome of post-streptococcal GN was excellent. None of those developed ESRD.

Although post-streptococcal GN tended to have more aggressive clinical manifestations, it had a better outcome. The aggressiveness of clinical manifestations was in accordance with the severe findings observed from renal histopathology such as cumulative crescent and endocapillary. These findings differ from the clinical spectrum and renal histopathology reported in children whose rising of serum creatinine and proteinuria more than 3 gm/day are rarely found[4]. Lien, et al[5] demonstrated a good correlation between clinical presentation and renal histopathology. He showed that patients with severe proliferative changes from renal histopathology had much occurrence of clinical features such as nephritis, hypertension, proteinuria level, hematuria, and heart failure. However, this conclusion should be interpreted with precaution since the worse clinical presentation might reflect the acuteness of disease that hastens the physician to do a renal biopsy and prescribe aggressive treatment.

Unfortunately, treatment with neither steroid nor immunosuppressive agents altered the outcome of post-infectious GN. The results were in accordance with a previous study[5]. The low C3 and normal C4 levels supporting that an alterative complement activation is the mainstay pathogenesis of post-infectious GN[6].

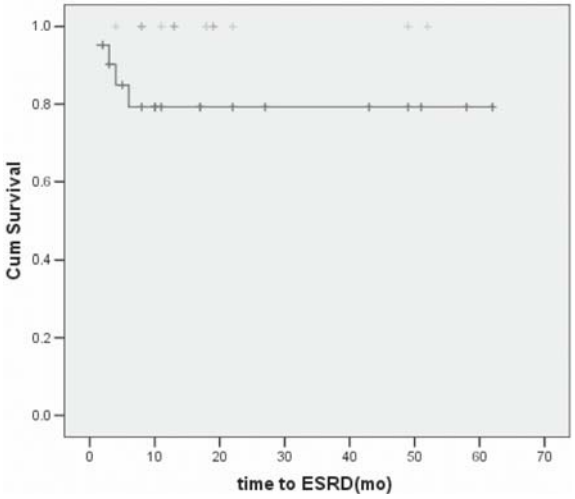

Fig. 1 Kaplan-Meier analysis of ESRD in post-infectious glomerulonephritis. Darker line: post non-streptococcal glomerulonephritis, Lighter line: post-streptococcal glomerulonephritis

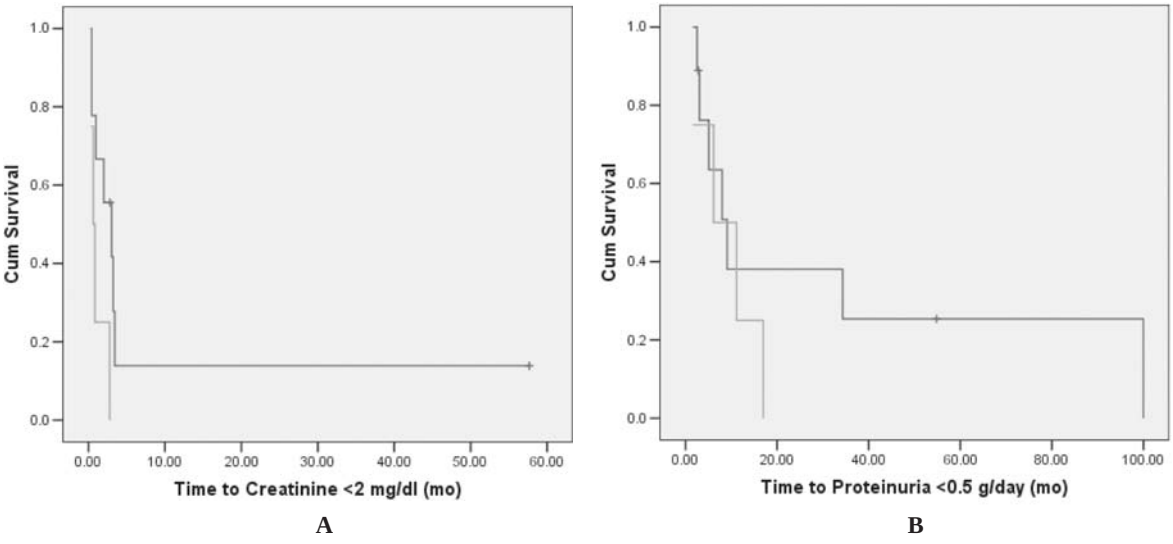

Fig. 2 A) Kaplan-Meier analysis of time to creatinine < 2mg/dl; B) Kaplan-Meier analysis of time to proteinuria < 500 mg/day. The darker line represents post non-streptococcal GN and the lighter represents post-streptococcal GN

The renal survival curve demonstrated that all ESRD patients turned to ESRD within the first few months. Time to resolution of proteinuria was faster than time to resolution of serum creatinine. One explanation is the different capacity to clear immune complexes which accumulate in different sites glomerular structures. Usually, inflammatory cells easier achieve the sub-endothelial immune deposits than subepithelial deposits due to the fact that subepithelial area was barrier and separated by glomerular basement membrane[7]. The more inflammatory cells there are, the faster the deposits will be removed. On the other hand, more extensive inflammatory response tightly correlates with more aggressive clinical manifestations. Sub-endothelial deposits commonly manifest with hematuria and compromise glomerular filtration while subepithelial deposits present with proteinuria. As such, proteinuria is slower to resolve compared to hematuria and rising GFR.

Finally, post non-Streptococcal GN had a tendency to have a worse outcome than post-Streptococcal GN did. Thus, rescue of the renal function of a patient with post-non-Streptococcal GN may need more aggressive and early treatment.

Conclusion

The present study demonstrates that post-Streptococcal GN has a different clinical manifestation, renal histopathology, and clinical outcome compared to post non-Streptococcal GN. This should urge clinicians to specify the causative pathogen as an additional diagnosis of post-infectious GN.

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ลักษณะอาการทางคลินิกพยาธิวิทยาและการดำเนินโรคในโรคไตอักเสบภายหลังการติดเชื้อ: ประสบการณ์จากผู้ป่วย 36 รายในโรงพยาบาลจุฬาลงกรณ์

ณัฐชัย ศรีสวัสดิ์, ลออ อรุณพูลทรัพย์, ทรงเกียรติ หลิวสุวรรณ, เถลิงศักดิ์ กาญจนบุษย์, ยิ่งยศ อวิหิงสานนท์, เกื้อเกียรติ ประดิษฐ์พรศิลป์, เกรียง ตั้งสง่า, เสาวลักษณ์ ชูศิลป์, สมชาย เอี่ยมอ่อง

โรคไตอักเสบตามหลังการติดเชื้อเป็นโรคที่พบได้บ่อยและมีความสำคัญ พบผู้ที่ป่วยเป็นโรคดังกล่าวสูงถึง 36 รายจากการสำรวจฐานข้อมูลผู้ป่วยที่ได้รับการวิเคราะห์ชิ้นเนื้อไตทั้งหมด 979 ราย ของโรงพยาบาลจุฬาลงกรณ์ ตั้งแต่เดือนมกราคม พ.ศ.2542 จนถึงเดือน ธันวาคม พ.ศ. 2548 ในจำนวนนี้พบผู้ป่วยจำนวน 8 รายเป็นโรคไตอักเสบภายหลังการติดเชื้อสเตรปโตคอคคัส และ 28 รายเป็นโรคไตอักเสบจากการติดเชื้อที่ไม่ใช่เชื้อสเตรปโตคอคคัส ผู้ป่วยส่วนใหญ่มาพบแพทย์ด้วยอาการบวม ความดันโลหิตสูง ปัสสาวะเป็นเลือด และมีโปรตีนรั่วออกมาในปัสสาวะ ร่วมกับตรวจพบระดับพลาสมา C3 และ CH 50 ลดต่ำลงกว่าปกติ โดยพบว่าไตอักเสบภายหลังการติดเชื้อ สเตรปโตคอคคัส มีลักษณะทางพยาธิวิทยารุนแรงกว่า แต่มีพยากรณ์โรคไม่แตกต่างจากการติดเชื้อที่ไม่ใช่เชื้อ สเตรปโตคอคคัส เป็นที่น่าสนใจว่ามีเพียงผู้ป่วยไตอักเสบภายหลังการติดเชื้อที่ไม่ใช้สเตรปโตคอคคัสเท่านั้นที่ เกิดภาวะไตวายเรื้อรัง และภาวะไตวายเรื้อรังระยะสุดท้าย สะท้อนให้เห็นถึงพยากรณ์โรคที่เรื้อรังและรุนแรงกว่าที่คาดไว้