

Case Report

Kawasaki disease with nephrotic syndrome: a case report

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Abstract: Kawasaki disease (KD) is systemic inflammatory disease that occurs predominantly in children younger than five years. In which multiple organ damage can be developed, renal manifestations are rare in KD, especially nephrotic syndrome (NS). Several cases of NS in KD have been reported with some kind of complications, and only one case of a patient with KD associated with steroid-resistant NS has been reported with a renal biopsy available to date, with the patient ultimately dying of chronic renal failure. We report a case of a 5-year-old boy who presented with typical KD symptoms (fever, nonpurulent conjunctivitis, fissured lips, strawberry tongue, peripheral edema, desquamation of fingers and crissum, and multiple lymphadenopathies) and developed NS without any other complication. A renal biopsy was available in this case performing as mesangioproliferative glomerulonephritis (MsPGN). The diagnosis of the case was KD presenting with NS. And the patient was treated with intravenous immunoglobulins, aspirin, dipyridamole, antibiotics, and steroid therapy. To date he has maintained long-term remission. The result shows that a common immune-mediated damage might be the possible mechanism for KD with NS.

Keywords: Kawasaki disease, nephrotic syndrome, renal biopsy, child

Introduction

Kawasaki disease (KD), or mucocutaneous lymph node syndrome, is systemic inflammatory disease that occurs predominantly in children younger than five years. It can develop multiple organ damage, while renal manifestations are uncommon in KD, especially nephrotic syndrome (NS), with the exception of sterile pyuria and trace proteinuria. The cases previously reported had some kind of complications. In 1989, Lee et al [1] firstly reported a case of a 3-month-old boy with KD and NS during the acute phase of illness, which improved under steroid therapy but ultimately died from acute myocardial infarction due to coronary aneurysm. Krug et al [2] reported three cases of KD, where one child developed acute renal failure and the other presented with features of hemodynamic shock. Their renal impairments all recovered spontaneously after treatment of KD showing a good prognosis of NS in KD. However the renal histology was not available. Here we report a case of KD, did not develop any other complication but NS during the acute phase

which the renal biopsy performed as mesangioproliferative glomerulonephritis (MsPGN).

Case report

A 5-year-old boy was admitted to our hospital due to fever for 6 days. He had no past medical history. Three days after onset of fever, the patient presented with nonpurulent conjunctivitis, fissured lips, strawberry tongue, multiple lymphadenopathies, desquamation of fingers and crissum, and without skin rash (**Figure 1**). On the fourth day, he developed edema of the acral of the limbs and oliguria with a poor general condition. He also had a 5 cm liver. The cardiopulmonary examination was normal. Blood pressure was 110/63 mmHg. Biological tests showed leukocytosis ($16000/\text{mm}^3$), thrombocytosis ($662000/\text{mm}^3$), raised erythrocyte sedimentation rate (ESR) (92 mm/h), elevated C-reactive protein (CRP) (9.2 mg/l). And NS with hypoalbuminaemia (12.40 g/l), proteinuria (1.58 g/day, albuminuria $>50 \text{ mg/kg/d}$), hyperlipidemia (7.80 mmol/l) without renal failure or haematuria were noted. Serum urea nitrogen



Figure 1. The clinical manifestation. A, B. The desquamation of finger tips. C. The desquamation of crissum. D. Fissured lips, strawberry tongue.

and creatinine were in normal range. Blood culture was sterile. The test for anti-streptolysin O antibodies was negative. Immunoglobulin M (IgM) of adenovirus was detected in blood by PCR. Serum IgG, IgA, complement component C3 and C4 were normal, IgE was increased significantly (10233.00 ng/ml, normal 0~691.40 ng/ml). Rheumatoid factor and anti-nuclear antibodies were negative. Chest X-ray was normal and the cardiac ultrasonography indicated non-dilated coronary arteries. The abdominal ultrasonography ruled out hepatomegaly with 58 mm, and echo enhancement was seen in renal parenchyma. There was no hydrocholecystitis.

The child was diagnosed with a case of KD with NS and received intravenous immunoglobulins (IVIG) (2 g/kg) immediately after admission, along with aspirin, dipyridamole, antibiotics (moxalactam). The patient's fever disappeared after IVIG. The edema of the limbs disappeared within 5 days after IVIG.

Based on the written consent of the child's guardian, the child underwent renal biopsy on

the 12th day after admission. Histological examination showed 7 glomeruli, one of which were glomerulotubular interlinked and necrotic. The glomeruli were with increased glomerular cells, mesangial cells (2-3/block), and matrix. Part of glomeruli had exudation and a small amount of inflammatory cellular infiltration. There was no duplication of basement membranes. Mesangial regions were with fuchsinophilic deposits. Some renal tubules showed vacuolar degeneration and interstitium was infiltrated with a few inflammatory cells. Inflammatory cells were also seen in blood vessels. The findings were suggestive of mesangioproliferative glomerulonephritis (MsPGN). Immunohistology showed positive mesangial staining for Fib; IgA, IgG, IgM, C1q, and

C3 were negative. The monoclonal antibodies against type IV collagen α chains (MAB α) 1, 3, 5 were positive. Electron microscope showed 2 glomeruli with mild-to-moderate proliferation of matrix and segmental matrical electron dense deposits. Some capillary endothelial cells proliferated (2-3/tubule), foot process of epithelial cells fused comprehensively and microvilli-formed, renal tubular epithelia were edematous and packed with red blood cell casts. These findings indicated mild-to-moderate mesangial proliferative glomerulonephritis with segmental endocapillary proliferation (**Figure 2**).

Two weeks after admission, proteinuria still existed (8 mg/kg/d), while improved markedly. So the patient was not put on steroids and kept on observation. He was discharged after 17 days of hospital admission. Two months after discharge, asymptomatic proteinuria had not disappeared yet, so we added prednisone (1 mg/kg/d) and mycophenolate mofetil (MMF). Four months after discharge, urinalysis, ESR and cardiac ultrasonography were normal. We gradually discontinued the steroid therapy, and there was no relapse of NS in next 1 year.

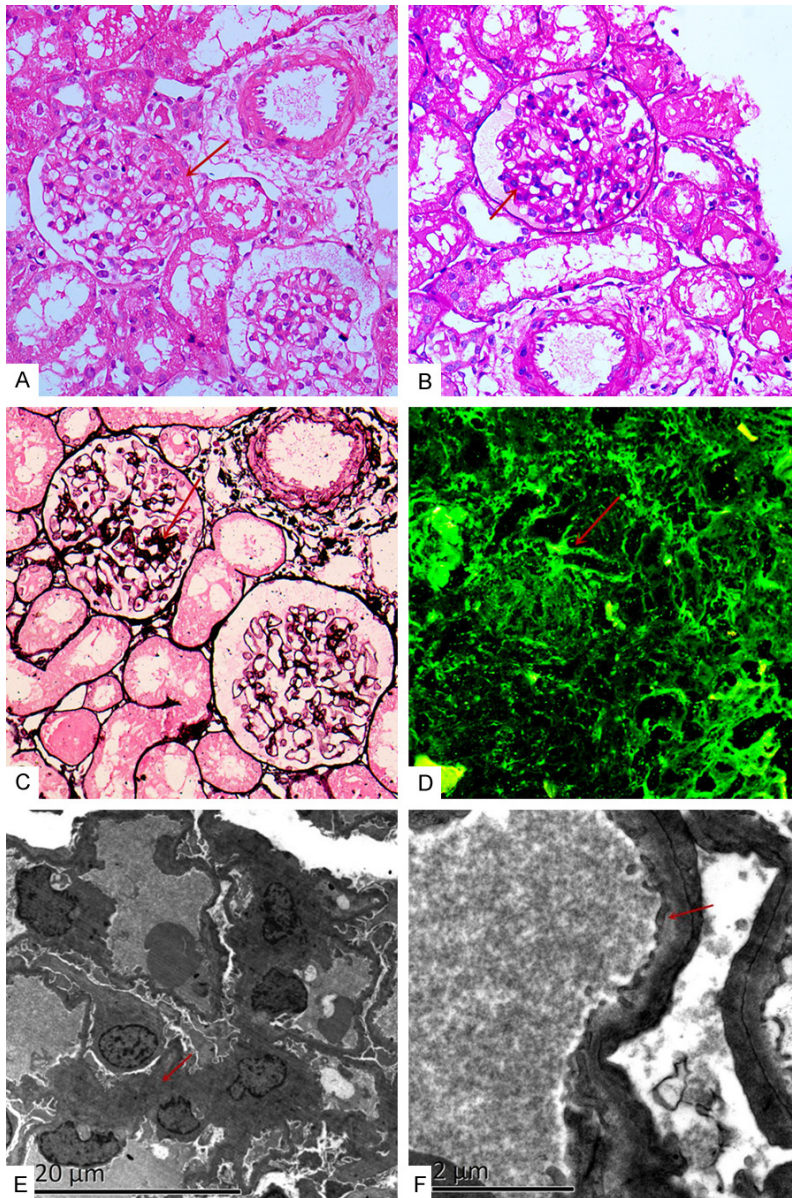


Figure 2. Light and electron microscopes in renal pathology: mild glomerular mesangial proliferation. A-D. Light microscopes. E-F. Electron microscopes. A. Hematoxylin and eosin (HE, ×400). B. Periodic acid Schiff (PAS, ×400). C. Periodic acid-silver methenamine (PASM, ×400). D. Fib (Fibrinogen): (Immunofluorescence, ×200). E. Mild to moderate glomerular mesangial matrix hyperplasia (×1000). F. Epithelial cell foot process fused comprehensively and formed microvilli (×6800).

Discussion

KD, or mucocutaneous lymph node syndrome, is systemic inflammatory disease that occurs predominantly in children younger than 5 years. It can develop multiple organ damage including coronary artery lesions, carditis, arthritis, hepatitis, central nervous system diseases, muscle involvement, and kidney and urinary tract involvement [3]. Here we report a case of KD with

NS during the acute phase which the renal biopsy performed as MsPGN.

The etiology of KD is still controversial, but it is thought that immune system is activated by an infectious trigger in genetically susceptible hosts. The patient was positive serology results for adenovirus. Chang et al found that common respiratory viruses, such as enteroviruses, adenoviruses, human rhinoviruses, and coronaviruses, were associated with KD. Heterogeneous infectious etiologies may be responsible for KD in different countries as well as during different seasons [4]. Jaqqi et al also found that adenovirus detection was not uncommon in KD [5]. These suggest a possible link between the onset of KD and adenovirus infection in our case.

The pathogenesis of KD with NS has not been fully understood yet. There is an obvious immunoregulatory abnormality in acute phase of KD, inducing T cell activation to produce interleukin, tumor necrosis factor, γ -interferon, et al. NS is associated with the activation of the immune system, including expansion of T and B cells and production of growth factors and cytokines, especially T cells. Since circulating immune complexes are detected frequently in KD, glomerular immune complex deposition may cause renal injury. It is possible to hypothesize that the immune mechanism leading to these two entities are similar, which could explain their association.

Joh et al [6] reported a 4-month-old girl presenting with KD had steroid-resistant NS at week 10 of the illness. Her renal biopsy showed

a diffuse mesangial proliferative glomerulonephritis with microcystic tubular dilatation. She ultimately died of chronic renal failure at age of 11 months and autopsy revealed as diffuse mesangial sclerosis of kidney. In our case, the renal biopsy was suggestive of mild-to-moderate MsPGN. Among the children with primary glomerular disease in China, MsPGN was the most frequent type (44.7%) [7]. It is important to determine the optimal treatment protocol according to the pathological type, meanwhile its prognosis is correlated with pathological type and treatment received. Tubulointerstitial changes may act as a major determinant in the progression of renal damage [8]. β -2 microglobulin examination is a sensitive indicator of tubulointerstitial function. If β -2 microglobulin decrease combined with proteinuria improvement, tubulointerstitial function is possible to recover. Proteinuria is a common presentation of MsPGN, and the treatment of MsPGN usually need combine with immunosuppressor which is not sensitive to simple steroid therapy. So in our case, the boy received steroid and MMF therapy and had a good prognosis.

In addition, the level of IgE was significantly elevated in this case, while the total eosinophil count was normal. This may be due to the highly activation of the immune system in acute KD. The over activation of T cells induces B cells polyclonal response and proliferation, resulting in the production of large quantities of immunoglobulin and cytokines. Particularly elevated IL-4, IL-5, IL-21 levels can increase the production of IgE by plasma cells. This phenomenon implies that there may be some correlation between KD and allergic diseases [9].

In conclusion, we describe a case of KD associated with NS which may be recognized as a possible renal manifestation of KD. KD with NS has been rarely described and few of them had renal biopsy. The boy in our case underwent renal biopsy performing as MsPGN. The common immune-mediated damage might be the possible mechanism for KD with NS.

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Disclosure of conflict of interest

None.

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References

- [1] Lee BW, Yap HK, Yip WC, Giam YC and Tay JS. Nephrotic syndrome in Kawasaki disease. *Aust Paediatr J* 1989; 25: 241-242.
- [2] Krug P, Boyer O, Balzamo E, Sidi D, Lehnert A and Niaudet P. Nephrotic syndrome in Kawasaki disease: a report of three cases. *Pediatr Nephrol* 2012; 27: 1547-1550.
- [3] Watanabe T. Kidney and urinary tract involvement in Kawasaki disease. *Int J Pediatr* 2013; 2013: 831834.
- [4] Chang LY, Lu CY, Shao PL, Lee PI, Lin MT, Fan TY, Cheng AL, Lee WL, Hu JJ, Yeh SJ, Chang CC, Chiang BL, Wu MH and Huang LM. Viral infections associated with Kawasaki disease. *J Formos Med Assoc* 2014; 113: 148-154.
- [5] Jaggi P, Kajon AE, Mejias A, Ramilo O and Leber A. Human adenovirus infection in Kawasaki disease: a confounding bystander? *Clin Infect Dis* 2013; 56: 58-64.
- [6] Joh K, Kanetsuna Y, Ishikawa Y, Aizawa S, Naito I and Sado Y. Diffuse mesangial sclerosis associated with Kawasaki disease: an analysis of alpha chains (alpha 1-alpha 6) of human type IV collagen in the renal basement membrane. *Virchows Arch* 1997; 430: 489-494.
- [7] He ZJ, Zhou ZL, Ma L, Pan T and Yang Q. Pathological analysis of 3090 cases in childhood glomerular disease. *J Clin Pediatr* 2013; 31: 157-158,161.
- [8] Xiao HJ, Liu JC and Chen H. Clinical pathologic significance and the appraisal of prognoses in children with primary nephrotic syndrome. *J Appl Clin Pediatr* 2002; 17: 14-15.
- [9] Bae YJ, Kim MH, Lee HY, Uh Y, Namgoong MK, Cha BH and Chun JK. Elevated serum levels of IL-21 in Kawasaki disease. *Allergy Asthma Immunol Res* 2012; 4: 351-356.