Megalocytic Interstitial Nephritis Following Acute Pyelonephritis with *Escherichia coli* Bacteremia: A Case Report

Hee Jin Kwon, Kwai Han Yoo, In Young Kim, Seulkee Lee, Hye Ryoun Jang, and Ghee Young Kwon

1Department of Medicine, 2Division of Nephrology, Department of Medicine, and 3Department of Pathology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

Received: 24 April 2014
Accepted: 27 August 2014

Address for Correspondence:
Hye Ryoun Jang, MD
Division of Nephrology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 135-710, Korea
Tel: +82.2-3410-0782, Fax: +82.2-3410-3849
E-mail: shinehr@gmail.com

INTRODUCTION

Megalocytic interstitial nephritis is a rare form of renal inflammatory disease associated with defect in intracellular destruction of invading foreign organisms by macrophages (1). These unusual inflammatory disorders are often associated with chronic urinary tract infection by Gram-negative bacteria (2). Although the pathogenesis of these diseases is unclear, macrophage bactericidal dysfunction has been presumed as a possible pathogenic mechanism (3). We report an extraordinary case of a 45-yr-old woman who had oliguric acute kidney injury (AKI) and acute pyelonephritis with *Escherichia coli* (*E. coli*) bacteremia, accompanied by megalocytic interstitial nephritis.

CASE DESCRIPTION

A 45-yr-old woman was hospitalized for abdominal pain, watery diarrhea, and jaundice of one-week duration on October 28, 2013. One day before admission, she noticed a marked reduction in her urine output. Her past medical history was unremarkable except for a two-year history of alcoholism.

At the time of admission, her blood pressure was 134/84 mmHg, and heart rate was 93 beats per minute. Her respiratory rate and body temperature were 20 breaths/min and 36.5°C, respectively. The patient was icteric and confused. She was unable to state her precise complaints. Physical examination was unremarkable except for a distended abdomen.

Laboratory findings included leukocytosis of 24,300/μL, high serum creatinine level of 6.80 mg/dL, high C-reactive protein level of 24.61 mg/dL, and high procalcitonin level of 39.05 ng/mL. Liver function test showed abnormalities including low albumin level of 2.9 g/dL, high aspartate aminotransferase level of 139 U/L, but alanine aminotransferase of 31 U/L. Coagulation time was prolonged to a PT INR of 1.46. Urinary findings suggestive of acute pyelonephritis. Additionally, hepatic nodularity and atrophic change as features of liver cirrhosis were observed.

The patient was diagnosed with acute pyelonephritis (APN) accompanied by oliguric AKI. Antibiotic treatment using cefotaxime (third-generation cephalosporin) and azithromycin was administered for a presumed diagnosis of APN, Weil’s disease, and rickettsial infection. Continuous renal replacement therapy (CRRT) was initiated for septic shock with oliguric AKI. After recovering from septic shock, the patient was switched to conventional hemodialysis for the treatment of AKI. Later, *E. coli* susceptible to all feasible antibiotics were isolated from initial urine and blood cultures. Azithromycin administration was discontinued because there was no evidence of elevation of tsutsugamushi and leptospira antibodies.

Although there was no microorganism in subsequent blood and urine cultures with improving parameters of infection such
as fever, CRP, and procalcitonin, there were persistent severe leukocytosis with atypical lymphocytes and high level of lactate dehydrogenase over 1,000 IU/L. Serum protein electrophoresis (PEP) revealed increased gamma-globulin (34.5%), and serum immunofixation (IF) showed an abnormal band against anti-immunoglobulin G (IgG) and anti-lambda. To evaluate hepatosplenomegaly and blood cell abnormalities including leukocytosis, thrombocytopenia, and monoclonal gammopathy (< 3 g/dL), bone marrow examination was performed. Bone marrow examination showed hemophagocytic histiocytes and increased plasma cells (below 10%). These results suggested the possibility of monoclonal gammopathy of undetermined significance because there was no evidence of bone lesion and hypercalcemia. After one month, kidney biopsy was performed to clarify the cause of persistent oliguric AKI despite adequate conservative treatment. Light microscopic examination showed extensive interstitial inflammation with a massive infiltration of histiocytic cells without Michaelis-Gutmann bodies. Special staining showed CD68 positivity in infiltrated histiocytes, Von Kossa (for calcium) negativity, and Prussian blue (for iron) negativity. Additionally, C1q staining and electron dense deposits were shown in mesangial matrix without clinical and serological evidence of systemic lupus erythematosus. The final pathologic diagnosis was megalocytic interstitial nephritis accompanied by C1q nephropathy (Fig. 1).

Intravenous administration of methylprednisolone 1 mg/kg was initiated for megalocytic interstitial nephritis and severe infection-related hemophagocytic lymphohistiocytosis that was seen in the histological examination of the patient’s kidney and bone marrow, respectively. High-dose steroid treatment was performed for one week, and steroid was halved every 3 days for 2 weeks. Both oliguric AKI and severe leukocytosis were dramatically improved after steroid treatment (Fig. 2).

After using steroids for 12 days, her kidney function had improved enough to stop dialysis. On the day of discharge, her serum creatinine level was 2.48 mg/dL. Her renal function had improved further by her first visit to the outpatient clinic; the serum creatinine level was 1.95 mg/dL.

Fig. 1. Features of the renal biopsy. (A) Under light microscopy (× 200), the mesangial matrix was mildly increased and the interstitium was multifocally infiltrated by histiocytic collection. (B) Tubules revealed diffuse acute damage and minimal atrophy accompanied by mild interstitial fibrosis. Immunohistochemistry studies showed CD68 positivity in infiltrated histiocytes. But stain for iron and calcium were negative. (C) Using immunofluorescence microscopy (× 400), mesangial staining was positive for C1q (2+). (D) Electron microscopy showed moderate effacement of epithelial foot processes. The mesangial matrix is moderately increased with a few electron dense deposits.
Megalocytic interstitial nephritis is an uncommon form of interstitial nephritis affecting mainly the renal cortex in an otherwise normal kidney. This disease was first described by Zollinger in 1945 (4). The diagnosis of megalocytic interstitial nephritis must be histologically distinguished from two other inflammatory conditions: renal parenchymal malakoplakia and xanthogranulomatous pyelonephritis (5). All of these conditions represent histological variant expression of chronic inflammation and are associated with Gram-negative bacterial infection (4, 6). Although inflammation is caused by infiltration by various inflammatory cells, histiocytes (a type of immune cell that eliminates foreign materials as a part of the host defense) were reported to play a key role in the pathogenesis of megalocytic interstitial nephritis (6). The pathogenic mechanism is suspected to be associated with impairment of bacterial clearance by neutrophils and macrophages, especially in immunodeficient patients (7). Alcohol abuse, as in our patient, was reported as another risk factor of this disease. Göttz et al. (8) previously reported an alcoholic patient with E. coli bacteremia and biopsy-proven megalocytic interstitial nephritis. In that paper, chronic alcohol consumption was reported to cause immune system damage and subsequently facilitate the development of the disease.

DISCUSSION

Megalocytic interstitial nephritis is an uncommon form of interstitial nephritis affecting mainly the renal cortex in an otherwise normal kidney. This disease was first described by Zollinger in 1945 (4). The diagnosis of megalocytic interstitial nephritis must be histologically distinguished from two other inflammatory conditions: renal parenchymal malakoplakia and xanthogranulomatous pyelonephritis (5). All of these conditions represent histological variant expression of chronic inflammation and are associated with Gram-negative bacterial infection (4, 6). Although inflammation is caused by infiltration by various inflammatory cells, histiocytes (a type of immune cell that eliminates foreign materials as a part of the host defense) were reported to play a key role in the pathogenesis of megalocytic interstitial nephritis (6). The pathogenic mechanism is suspected to be associated with impairment of bacterial clearance by neutrophils and macrophages, especially in immunodeficient patients (7). Alcohol abuse, as in our patient, was reported as another risk factor of this disease. Göttz et al. (8) previously reported an alcoholic patient with E. coli bacteremia and biopsy-proven megalocytic interstitial nephritis. In that paper, chronic alcohol consumption was reported to cause immune system damage and subsequently facilitate the development of the disease.

There is no clear clinical distinction between megalocytic interstitial nephritis and malakoplakia (9). Megalocytic interstitial nephritis might be an early stage or a morphologic variation of malakoplakia. Malakoplakia is an uncommon form of chronic inflammatory granulomatous disease that most frequently affects the urinary tract. Various organs such as the genitourinary tract, skin, retroperitoneum, lung, gastrointestinal tract, testis, thyroid, and bone also can be involved (10). Kidney parenchymal involvement was reported in only 15% of patients with malakoplakia (3). The typical histologic finding of renal malakoplakia shows many histiocytes with Michaelis-Gutmann (MG) bodies, a distinctive basophilic inclusion containing calcium, phosphate, and often iron. These MG bodies are indicative of malakoplakia and will stain with von Kossa stain (for calcium).
Our patient required hemodialysis for one month and had poor renal function recovery despite clearing the bacteria. The reason for the delayed recovery of renal function was probably a systemic infection so severe that hemophagocytic histiocytes were seen in the bone marrow. Despite appropriate use of antibiotics, serious systemic inflammation as shown by hemophagocytic histiocytosis and megalocytic interstitial nephritis could not be controlled, and thus steroids were used. However, there are no established steroid treatment regimens in megalocytic interstitial nephritis or renal malakoplakia. Jo et al. (15) used methylprednisolone 500 mg/day from the second hospital day, and Al-Sulaiman et al. (5) prescribed pulse methylprednisolone 500 mg/day. Our patient also was given high-dose steroid was administered early in the disease course, and the prognosis was excellent. Our patient also was given high-dose steroids late in the disease course and she eventually achieved renal functional improvement. Prompt and sufficient use of appropriate antibiotics is the most important treatment for megalocytic interstitial nephritis. Also, steroid administration is worthwhile with regard to prevention of interstitial inflammation progression (16).

In summary, megalocytic interstitial nephritis is difficult to diagnose without histologic examination. Therefore, megalocytic interstitial nephritis should be considered in patients with poor recovery from acute kidney injury following urinary tract infection.

DISCLOSURE

The authors have no conflicts of interest to disclose.

AUTHOR CONTRIBUTIONS

Conception and coordination of the study: HR Jang. Design of ethical issues: JE Lee, WS Huh, YG Kim, DJ Kim, HY Oh. Acquisition of data: GY Kwon. Manuscript approval: all authors.

REFERENCES

1. Rubin RH, Contran RS, Tollkoff-Rubin NE. Urinary tract infection, pyelonephritis, and reflux nephropathy. In: Brenner BM, Levine SA. editors. Brenner and Rector’s the kidney. 8th ed. Philadelphia: Saunders, 2008, p313-31.
2. Kobayashi A, Utsunomiya Y, Kono M, Ito Y, Yamamoto I, Osaka N, Hasegawa T, Hoshina S, Yamaguchi Y, Kawaguchi Y, et al. Malakoplakia of the kidney. Am J Kidney Dis 2008; 51: 326-30.
3. Vijijter M, Ilčić D, Celik M, Arda IS, Hicşönmez A. Renal parenchymal malakoplakia: a different stage of xanthogranulomatous pyelonephritis? J Pediatr Surg 2007; 42: E35-8.
4. Mittal BV, Badhe BP. Xanthogranulomatous pyelonephritis: a clinicopathological study of 15 cases. J Postgrad Med 1989; 35: 209-14.
5. al-Sulaiman MH, al-Khader AA, Mousa DH, al-Swailem RY, Dhar J, Haleem A. Renal parenchymal malakoplakia and megalocytic interstitial nephritis: clinical and histological features. Report of two cases and review of the literature. Am J Nephrol 1993; 13: 483-8.
6. Esperza AR, McKay DB, Cronan JJ, Chazan JA. Renal parenchymal malakoplakia. Histologic spectrum and its relationship to megalocytic interstitial nephritis and xanthogranulomatous pyelonephritis. Am J Surg Pathol 1989; 13: 225-36.
7. Bae GE, Yoon N, Park HY, Ha SY, Cho J, Lee Y, Kim KM, Park CK. Silent colonic malakoplakia in a living-donor kidney transplant recipient diagnosed during annual medical examination. Korean J Pathol 2013; 47: 163-6.
8. Krupp G, Schneider W, Gobel U, Müller V, Haller H, Luft FC. Tumefactive megalocytic interstitial nephritis in a patient with Escherichia coli bacteremia. Am J Kidney Dis 1995; 25: 928-33.
9. Jennette JC, Olson JL, Schwartz MM, Silva FG. Hepinstall’s pathology of the kidney. 6th ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2006, p1546-61.
10. Hamvas A, Detre Z, Szinnyag G. Malakoplakia of kidney and urinary tract. Report of a case of fatal outcome. Int Urol Nephrol 1981; 13: 55-63.
11. Dasgupta P, Womack C, Turner AG, Blackford HN. Malakoplakia: von Hansemann’s disease. BJU Int 1999; 84: 464-9.
12. Kelly DR, Murad TM. Megalocytic interstitial nephritis, xanthogranulomatous pyelonephritis, and malakoplakia. An ultrastructural comparison. Am J Clin Pathol 1981; 75: 333-44.
13. Mii A, Shimizu A, Masuda Y, Fujita E, Aki K, Ishizaki M, Sato S, Griesemer A, Fukuda Y. Current status and issues of C1q nephropathy. Clin Exp Nephrol 2009; 13: 263-74.
14. Colvin RB. Diagnostic pathology: kidney diseases. [Salt Lake City, Utah]: Amirsys, 2011, p84-86.
15. Jo SK, Yun JW, Cha DR, Cho WY, Kim HK, Won NH. Anuric acute renal failure secondary to megalocytic interstitial nephritis in a patient with Behcet’s disease. Clin Nephrol 2000; 54: 498-500.

16. Tam VK, Kung WH, Li R, Chan KW. Renal parenchymal malacoplakia: a rare cause of ARF with a review of recent literature. Am J Kidney Dis 2003; 41: E13-7.