

Pyuria in patients with Kawasaki disease

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Abstract

Kawasaki disease (KD) is an acute, febrile vasculitis that predominantly develops in children ≤ 5 years of age and can lead to multiple organ injuries including the kidneys. Of these injuries, pyuria is a common feature of patients with KD, occurring in 30%-80% of patients. Sterile pyuria is most common in KD patients ≤ 1 year of age. KD patients with sterile pyuria exhibit more severe inflammatory reactions and may have sub-clinical renal injuries. Sterile pyuria in KD is associated with mononuclear cells (not neutrophils) in the urine. Although sterile pyuria in KD was at one time thought to be due to urethritis caused by a non-specific vasculitis of the urethra, recent studies suggest that sterile pyuria in KD originates from the urethra, the kidney as a result

of mild and sub-clinical renal injuries, and/or the bladder due to cystitis. Pyuria is not always sterile in KD, but can result from a urinary tract infection (UTI). As causative pathogens, *Escherichia coli* and *Klebsiella oxytoca* have been reported. The clinical phenotypes do not differ between those with or without UTI. Because some KD patients with UTIs have urinary tract abnormalities such as vesicoureteral reflux, a complete UTI workup including renal ultrasound, voiding cystourethrogram and/or dimercaptosuccinic acid renal scan recommended in KD patients with UTIs.

Key words: Sterile pyuria; Kidney involvement; Urinary tract infection; Kawasaki disease; Vasculitis

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Core tip: Pyuria is a common feature of patients with Kawasaki disease (KD), occurring in 30%-80% of patients. KD patients with pyuria exhibit more severe inflammatory reactions and may have sub-clinical renal injuries. Pyuria in KD originates from the urethra, the kidney as a result of mild and sub-clinical renal injuries, and/or the bladder due to cystitis. Pyuria is not always sterile in KD, but can result from a urinary tract infection (UTI). Because some KD patients with UTIs have urinary tract abnormalities, a complete UTI workup including renal ultrasound, voiding cystourethrogram and/or dimercaptosuccinic acid renal scan is recommended in KD patients with UTIs.

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INTRODUCTION

Kawasaki disease (KD) is an acute, febrile vasculitis that predominantly develops in children ≤ 5 years

of age^[1]. KD affects medium-sized arteries, with a striking predilection for the coronary arteries^[1,2]. Children with KD have an acute onset of fever, followed by signs of mucosal inflammation and vasodilation that evolve during the first week of the illness^[1]. Laboratory examinations revealed a marked systemic inflammatory response^[3]. The cause of KD remains unknown, but it is thought that the immune system is activated by infectious or environmental triggers in genetically-susceptible hosts^[2,3].

Because KD is a systemic vasculitis, KD can involve multiple organs and tissues^[2], including the coronary arteries, heart, joints, liver, central nervous system^[4], muscle^[5], and kidney^[6,7].

Renal manifestations in KD includes pyuria, pre-renal acute kidney injury (AKI), renal AKI caused by tubulointerstitial nephritis, hemolytic uremic syndrome, immune-complex-mediated nephropathy, renal AKI-associated with KD shock syndrome, acute nephritic syndrome, nephrotic syndrome, and renal tubular abnormalities^[7]. Of these renal manifestations of KD, pyuria is the most common abnormal finding^[7]. Some KD patients with pyuria have been misdiagnosed with acute pyelonephritis^[8], especially in cases of patients with incomplete KD^[9,10], defined as patients with fever \geq 5 d but only 2 or 3 of the other KD criteria^[2]. The following is a review of the prevalence, clinical and laboratory characteristics, and origin of pyuria in patients with KD.

PREVALENCE OF STERILE PYURIA IN PATIENTS WITH KD

No patients had pyuria according to the first report of KD, as described by Kawasaki^[11] in 1967. Yamamoto *et al*^[12] first described sterile pyuria in Japanese patients with KD in 1968. Yamamoto *et al*^[12] reported that 8 of 23 (34.8%) patients with KD exhibited pyuria. Subsequently, Kawasaki *et al*^[13] reported an increase in urine sediment leukocytes as a significant finding of KD in 1974. Thereafter, several studies regarding pyuria in KD have been reported. Melish *et al*^[14] reported that 10 of 16 (62.5%) American patients with KD exhibited sterile pyuria. Barone *et al*^[15] indicated that 13 of 27 (48.1%) American patients with classic KD and 4 of 11 (36.4%) patients with atypical KD had pyuria. Wirojanan *et al*^[16] found that 23 of 70 (33%) Thai patients with KD had sterile pyuria. We also reported that 10 of 23 (43.5%) Japanese patients with KD had sterile pyuria^[17]. Perrin *et al*^[18] showed that pyuria was present in 45.3% of French patients with complete KD and in 30.8% of patients with incomplete KD. Recent studies by Shike *et al*^[19], Sepahi *et al*^[20], Liu *et al*^[21], Choi *et al*^[22], and Soleimani *et al*^[23] have described sterile pyuria in 106 of 135 (79.8%), 32 of 47 (68%), 44 of 145 (30.3%), 40 of 133 (30%), and 17 of 47 (36.2%) patients with KD, respectively. Taken together,

Table 1 The prevalence of pyuria in patients with Kawasaki disease

Ref.	No. of patients with pyuria /No. of total patients	The percent of patients with pyuria
Yamamoto <i>et al</i> ^[12]	8/23	34.8
Melish <i>et al</i> ^[14]	10/16	62.5
Barone <i>et al</i> ^[15]	13/27	48.1
Wirojanan <i>et al</i> ^[16]	23/70	33
Watanabe <i>et al</i> ^[17]	10/23	43.5
Perrin <i>et al</i> ^[18]		45.4
Shike <i>et al</i> ^[19]	106/135	79.8
Sepahi <i>et al</i> ^[20]	32/47	68.1
Liu <i>et al</i> ^[21]	44/145	30.3
Choi <i>et al</i> ^[22]	40/133	30
Soleimani <i>et al</i> ^[23]	17/47	36.2

30%-80% of patients with KD had pyuria (Table 1).

In contrast, Turner *et al*^[24] reported that 43% of febrile children without urinary tract infection had moderate pyuria (10-100 cells/high-power field) with only 9% of febrile children having definite pyuria (> 100 cells/high-power field). This finding indicated that pyuria might be a non-specific feature of fever in acute childhood illness. Shike *et al*^[19] also reported that 79% of KD patients and 54% of febrile control subjects had sterile pyuria; however, they showed that the median urine white blood cell count was significantly higher in patients with KD than in febrile control subjects. Our study also showed that one-third of patients with KD exhibited definite pyuria^[17]; thus, pyuria is a common feature of KD.

CLINICAL AND LABORATORY CHARACTERISTICS OF KD PATIENTS WITH STERILE PYURIA

Pyuria is defined as > 5 leukocytes/high-power field^[25] or > 10 leukocytes/ μ L^[26]. Sterile pyuria is defined as pyuria with a negative urine culture^[26]. Sterile pyuria can occur in various infectious or noninfectious disorders (Table 2)^[25,27]. Although pyuria can occur in patients with KD of all ages, pyuria is more common in patients \leq 1 year of age. Wirojanan *et al*^[16] reported that 10 of 13 (77%) KD patients \leq 1 year of age had pyuria, although only 13 of 57 (22%) KD patients \geq 1 year exhibited pyuria. Liu *et al*^[21] also reported that pyuria was present in 28 of 75 (40%) and 16 of 80 (20%) KD patients \leq 1 and \geq 1 year of age, respectively.

We studied the laboratory data of patients with KD divided into three groups: patients without pyuria, patients with pyuria in both voided urine and bladder urine obtained by transurethral catheterization (bladder pyuria), and patients with pyuria only in voided urine (urethral pyuria) and reported that the urinary protein level was higher in patients with pyuria than patients without pyuria, and the urinary β 2-

Table 2 Causes of sterile pyuria in children

Causes
Infectious causes
Partially treated bacterial UTI
UTI in the presence of urinary obstruction
Renal tuberculosis
Renal abscess
Renal tuberculosis
Inflammation near the ureter or bladder (appendicitis, Crohn disease)
Febrile disorders other than UTI
Noninfectious causes
Nephrolithiasis
Kidney and urinary tract anomalies
Glomerulonephritis
Interstitial nephritis
Systemic lupus erythematosus
Interstitial cystitis
Kawasaki disease

UTI: Urinary tract infection.

microglobulin (β 2MG), serum blood urea nitrogen (BUN) and creatinine levels were higher in patients with bladder pyuria than in patients with urethral pyuria or in patients without pyuria^[17]. Choi *et al*^[22] reported that the erythrocyte sedimentation rate, C-reactive protein level and serum concentrations of alanine aminotransferase and BUN were significantly higher in patients with pyuria than in patients without pyuria. These studies suggest that KD patients with pyuria exhibit more severe inflammatory reactions and may have sub-clinical renal injuries.

ORIGIN OF PYURIA IN PATIENTS WITH KD

Sterile pyuria in KD is associated with mononuclear cells (not neutrophils) in the urine^[28,29]. A previous study demonstrated mononuclear cells with intracytoplasmic inclusions in the urinary sediment of a patient with KD, which might be derived from mononuclear phagocytic cells^[30].

Sterile pyuria in KD was thought to be due to urethritis caused by a non-specific vasculitis of the urethra^[29]. Melish *et al*^[14] performed bladder taps on 4 KD patients with pyuria in voided urine specimens and reported bladder urine to be free of white blood cells, suggesting that urethral inflammation was the source of pyuria in patients with KD; however, we reported that 5 of 10 KD patients with sterile pyuria in voided urine samples also had leukocytes in bladder urine, suggesting that some patients with KD develop sterile pyuria that originates from the urethra and/or the kidney as a result of mild and sub-clinical renal injuries^[17]. Renal injuries in patients with KD have been reported using imaging studies and/or urinary cytokines analysis. Ohta *et al*^[28] reported that increased levels

of urinary interleukin-6 (IL-6), β 2MG and N-acetyl- β -D-glucosaminidase in most patients with KD. Wang *et al*^[31] performed dimercaptosuccinic acid (DMSA) renal SPECT on 50 patients with KD, and reported that 26 of these patients (52%) had renal inflammatory foci. Wu *et al*^[32] performed DMSA renal SPECT and renal Doppler ultrasonography to measure the pulsatility index (PI), and analyzed urinary IL-6 levels in 50 patients with KD. They showed that 10 of 24 (42%) patients had renal inflammatory foci, that patients with renal inflammatory foci had significantly higher levels of urinary IL-6 and PI values than patients without renal inflammatory foci, and that there was a significant correlation between urinary IL-6 levels and PI values. These studies suggest the presence of renal parenchymal inflammatory lesions during the acute phase of KD, which can result in sterile pyuria.

In addition, we recently reported a case of acute cystitis in a patient with KD. This case suggested that sterile pyuria in KD may originate from the bladder due to cystitis^[33].

KD ASSOCIATED WITH URINARY TRACT INFECTION

Pyuria is not always sterile in KD. Ooto *et al*^[34] first reported a KD patient with urinary tract infection (UTI) due to *Klebsiella oxytoca* and left vesicoureteral reflux (VUR). Shiono *et al*^[35] reported a KD patient with acute pyelonephritis due to *Escherichia coli* (*E. coli*) and left VUR. Horikawa *et al*^[36] and Husain *et al*^[37] individually reported KD patients with UTIs caused by *E. coli* and without any urinary tract abnormalities.

Benseler *et al*^[38] reviewed the clinical, laboratory and microbiological data of 129 patients with KD and reported that 33% of patients with KD had concurrent infections at the time of KD diagnosis, 4 patients with KD developed UTIs due to *E. coli* (3 patients) or *Klebsiella* (1 patient), and concurrent infections at the time of diagnosis of KD did not affect the patient response to treatment with intravenous immunoglobulin. Wu *et al*^[39] retrospectively reviewed the clinical and laboratory data of 75 patients with KD who underwent urinalysis and urine bacterial cultures, and reported that 34 (45.3%) patients had sterile pyuria, 8 (10.7%) had bacterial pyuria and 2 (2.7%) had UTIs without pyuria, 6 of 10 (60%) patients with UTIs were \leq 12 mo of age, and there were no significant differences in clinical presentations, laboratory data, and response to treatment between those with and without UTI.

Taken together, pyuria is not always sterile. The clinical phenotypes do not differ between those with or without UTIs. Because some KD patients with UTIs have urinary tract abnormalities such as VUR, a complete UTI workup including renal ultrasound, voiding cystourethrogram and/or dimercaptosuccinic acid renal scan is recommended^[39].

CONCLUSION

Pyuria is a common feature of patients with KD, occurring in 30%-80% of patients. KD patients with pyuria are more likely to be \leq 1 year of age, exhibit more severe inflammatory reactions, and may have sub-clinical renal injuries. Sterile pyuria in KD patients originates from the urethra, the kidney as a result of mild and sub-clinical renal injuries, and/or the bladder due to cystitis. Pyuria is not always sterile in KD and results from UTI. Because some KD patients with UTIs have urinary tract abnormalities, a complete UTI workup is recommended.

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