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Pyuria associated with acute Kawasaki disease and fever from other causes

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INTRODUCTION

Kawasaki disease (KD) is a self-limited, pediatric systemic vasculitis of unknown etiology (1). Sterile pyuria associated with acute KD was first reported by Yamamoto in Japanese children in 1968 (2). Despite the widespread recognition of this laboratory finding in acute KD patients (2-7), a systematic study of pyuria in KD and febrile control (FC) subjects has not been previously reported. While timely diagnosis and treatment with intravenous immunoglobulin (IVIG) are critical to reduce the incidence of coronary artery aneurysms (8), diagnosis of KD is still established based on clinical criteria supported by laboratory evidence of acute inflammation and there is no specific diagnostic test to aid the clinician. Pyuria, defined as >10 white blood cells/high-powered field (hpf), has been variously reported in 33-62% of acute KD patients (3,4,6,7) and was recognized in the recent American Heart Association guidelines as a laboratory finding supportive of the diagnosis of KD (9). Macrophages (10) with large cytoplasmic inclusions (11) have been reported in the urine of KD patients and a comparison of voided urine with urine obtained by cystocentesis concluded that the origin of these cells might be the urethra (3). We compared urinalysis data from 135 KD subjects and 87 FC subjects using an automated analyzer with flow cytometry and characterized the features of pyuria associated with KD.

METHODS

Subjects and clinical samples

KD and FC patients were recruited from the Emergency Department at Rady Children's Hospital San Diego. Subjects diagnosed as KD had fever and four or more of the five principal clinical criteria for KD (rash, conjunctival injection, cervical lymphadenopathy, changes in the oral mucosa, and changes in the extremities) or three criteria plus coronary artery abnormalities documented by echocardiography (8). Inclusion criteria for the FC children were age < 12 years, clinical condition warranting laboratory investigations, and documented fever (≥ 38.0° C) accompanied by any of the following signs: rash, conjunctival injection, cervical lymphadenopathy, oropharyngeal erythema, or peripheral edema, but not meeting the clinical criteria for KD. The final diagnosis for FC subjects was adjudicated by consensus of two

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investigators (JTK and JCB) based on details of the history and physical examination, results of nasopharyngeal (NP) and stool viral cultures, available microbiology, serology, and other clinical laboratory data, and illness course as recorded by the study nurse (JP) for the 3 days following study enrollment. Subjects diagnosed with a presumed viral syndrome were those with negative viral and bacterial cultures in whom fever resolved without specific treatment within 72 hours of subject evaluation. Diagnoses assigned to the FC subjects were as follows: *viral infection group*(n=60): adenovirus (n=16), Epstein-Barr virus (n=2), enterovirus (n=1), herpes simplex virus (n=3), influenza virus (n=1), parainfluenza virus (n=2), viral syndrome (n=35); *bacterial infection group* (n=20): staphylococcal toxin-mediated disease (n=3), methicillin-resistant *Staphylococcus aureus* infection (n=1), group A β-hemolytic streptococcal scarlet fever (n=4), cervical abscess (n=2), cellulitis (n=4), meningococcemia (n=1), sepsis (n=1), perforated appendicitis (n=1); *other febrile disease group* (n=7): Henoch-Schonlein purpura (n=3), systemic allergic reaction (n=1), juvenile inflammatory arthritis (n=1), autoimmune neutropenia (n=1), Stevens-Johnson syndrome (n=1). Urine cultures were performed in 53% of KD subjects and 64% of FC subjects and the results were sterile or yielded mixed flora in all subjects. UTI was not clinically suspected in the remaining subjects and so no urine culture was submitted. Patients with known renal disease or urinary tract infection (growth on urine culture of $>10^5$ of a single bacterial species/mL of urine) were excluded. Urine, plasma, and serum samples from KD patients were obtained before treatment with IVIG. The protocol for this study was approved by the institutional review board at the University of California San Diego and Rady Children's Hospital San Diego and written informed consent was given by the parents of all KD and FC subjects. Clinical data including sex, age, illness day (illness day 1= first calendar day of fever) of urine collection, results of laboratory testing (complete blood count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR)) were prospectively recorded for all subjects. Response to IVIG therapy and coronary artery status were recorded for all KD subjects.

Laboratory assays

Urine WBC counts were performed using a Sysmex UF-100 automated urine analyzer (Siemens Health Care Diagnostics) that counts cells by flow cytometry. The institutional normal reference range for urine cell counts was <8 cells/μL for males and <20 cells/μL for females, which is approximately comparable to the semi-quantitative conventional urinalysis results of <2-4 cells/high-power field (hpf) for males and <5-10 cells/hpf for female(12). Urine leukocyte esterase, nitrite, and protein were detected by CLINITEK® 100 Urine Chemistry Analyzer (Siemens Health Care Diagnostics) that uses reflectance spectrophotometry to read the Bayer MULTISTIX® 10 SG Reagent strip.

Statistical methods

Descriptive statistics were used to summarize the data for each group, and the distributions of each variable were assessed. Comparisons between the KD and FC groups were performed using Chi-Square and Fisher's Exact tests for categorical variables as appropriate, and Wilcoxon Rank-Sum tests for differences in medians for continuous variables. Spearman Correlations and ANOVA tests were performed to define relationships between variables of interest. Statistical tests were two-sided, with a significance level of $\alpha=0.05$.

RESULTS

Urinalysis results were analyzed in 135 KD (59% male, median age 26 months, median illness Day 5 at urine collection) and 87 febrile controls (57% male, median age 26 months). Pyuria was defined as urine WBC count greater than the institutional reference range, and was detected in 106 of 135 KD subjects (79.8%) and 47 of 87 FC subjects (54.0%) ($p<0.0001$). Thus, the sensitivity and specificity of pyuria for differentiating KD from FC subjects was 79.8% and

46.0%, respectively. The median urine WBC count was elevated in both groups, but significantly higher in the KD group (42 cells/μL in KD vs.12 cells/μL in FC, p<0.0001). The urine WBC count exceeded the proposed cut-off level for screening for bacterial UTI using the Sysmex UF-100 analyzer (111 cells /μL) (13) in 25.4% of KD subjects and 9.2% of FC subjects. When the FC urine samples were stratified according to viral, bacterial, or other febrile diseases, only the viral infection group (median urine WBC count 10 cells/μL, p <0.0001) and the other febrile disease group (median urine WBC count 10 cells/μL, p =0.014) were lower compared to the KD group. Not all FC subjects had their urine cultured to conclusively rule out UTI. Of the 31 FC subjects whose urine was not cultured because UTI was not clinically suspected, 18 subjects had a specific diagnosis. The remaining 13 subjects with a non-specific diagnosis of viral syndrome had a median urine cell count of 8 cells/μL, which was similar to the FC subjects whose urine was cultured and sterile or in whom a specific diagnosis established.

All urine samples were negative for nitrite. No significant difference was seen between KD subjects and FC subjects in rate of positive leukocyte esterase reaction (trace or greater: 18.6% of KD subjects and 10.3% of FC subjects), median urine RBC counts (10 cells/μL in KD and 8 cells/μL in FC), hematuria rate (urine RBC count equal or greater than 12 cells/μL: 44.0% of KD subjects and 33.3% of FC subjects), proteinuria (protein trace or greater: 33.3% of KD subjects and 26.5% of FC subjects), and urine specific gravity (median 1.015 in KD and 1.017 in FC).

Proteinuria and leukocyte esterase were detected in the urines with relatively higher WBC counts in both KD and FC subjects. Specific gravity correlated positively with urine WBC counts in KD subjects (r=0.37), but urine RBC count, peripheral band percentage, serum CRP concentration, or ESR were only weakly correlated (data not shown). The presence or absence of pyuria and the number of urine WBC were not associated with illness day, age of onset, subsequent response to IVIG, or development of coronary artery abnormalities for KD subjects.

Erythema of the urethral meatus(14), possibly indicating urethritis, has been reported in KD patients. To address the question of whether the urine WBCs in KD subjects originate from the urethra, as has been suggested by some investigators, subjects were stratified by the method of urine collection and sex (**Table**). No significant differences were seen in the urine WBC counts in either stratified analysis. Thus, urine collected directly from the bladder and urine voided through a shorter or longer urethra contained similar numbers of WBC. In one 4-month old male KD subject, a voided urine sample contained 185 WBC/μL and urine obtained by catheterization one hour later contained 150 WBC/μL. Thus, the method of urine collection did not appear to influence the cellularity of the sample and suggested that the cells were most likely to originate from the urinary tract at a level above the urethra.

DISCUSSION

We analyzed urine from acute Kawasaki disease and febrile control subjects using an automated analyzer with flow cytometry, which is a sensitive and reliable method to evaluate the urine cellularity (15) and has replaced manual cell counts in many clinical laboratories. The previously reported pyuria rate of 33-62% for acute KD subjects was based on relatively small cohorts using manual quantitation of cells in the sediment of centrifuged urine expressed as cells per high-power field (3-7). The new automated detection method increased the rate of pyuria in acute KD subjects to 79%. The American Heart Association (AHA) guidelines use a urine cell count greater than 10 cells per high-power field as a definition of pyuria (9) regardless of patient sex, which is equivalent to the definition of pyuria for females using flow cytometry. Thus, it is possible that more males would be classified as having pyuria using flow cytometry than using manual cell counts and the AHA definition for pyuria.

Pyuria detected on a single urinalysis was more common and urine white blood cells were more numerous in KD compared with FC subjects, but pyuria was also observed in 54% of these febrile controls. Whether pyuria is an intermittent or persistent laboratory finding during acute KD was not addressed by our study. A study of 16 untreated KD patients suggested that pyuria was persistent over a period of 2 to 5 days(3). The presence of pyuria in both spontaneously voided and catheterized urine suggests that these cells originate from the urinary tract at a level above the urethra. The urine WBC count was not higher in males, in whom the longer urethra might contribute to a higher urine cell count if urethritis was the cause of pyuria. Previously published observations of four KD subjects in whom pyuria was detected only in voided urine and not in the urine obtained by cystocentesis (3) may have been influenced by the supine position of the patients, which allowed the cells to sediment along the posterior bladder wall and thus be missed during sampling by aspiration through the anterior bladder wall. Erythema of the urethral meatus (14) also prompted clinicians to suspect urethritis as the source of urine WBC in acute KD. Our results, however, argue against the urethra as the source of the cells.

Renal involvement is rare in acute KD with only a few case reports of nephritis (16,17), acute renal failure (17-19), nephrotic syndrome (20), asymptomatic infiltration of the renal parenchyma with IgA-secreting plasma cells (21), and subsequent renal scarring detected by imaging (22). In our cohort, none of the KD subjects had renal dysfunction. Proteinuria was observed in a subset of both KD and FC subjects by CLINITEKR® analyzer. The method detects urine albumin at concentrations >10 mg/L (23) by sulfonephthalein dye, and lysed cells in urine are not a source of albumin. Albuminuria was mild and was similar between the KD and FC groups. Transient urinary albumin excretion is associated with fever, exercise, and UTI and the albumin value is positively correlated with urine concentration. The low level proteinuria observed in the KD subjects is likely related to fever and physiologic concentration of urine, rather than glomerular or tubular dysfunction.

In conclusion, pyuria was detected by automated flow cytometry in 79% of KD and 54% of FC subjects. These WBC in the urine originate from the urinary tract at a level above the urethra. Pyuria was more prominent in acute KD subjects regardless of illness day and age, but the finding of cells in the urine was neither a specific nor a sensitive indicator of KD.

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