Review Article

Sterile Pyuria: Causes and Evaluation

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Pyuria, the presence of polymorpho-nuclear neutrophils (PMNs) in urine, is the hallmark of inflammation.[1] Pyuria is defined as the presence of 10 or more PMNs / mm^3 in an uncentrifuged urine specimen[2] or > 2 PMN /HPF in male and > 5 PMN /HPF in female in centrifuged deposit of fresh urine.[3] Sterile pyuria is the persistent finding of PMNs in urine specimen, in the absence of bacteria, as determined by means of aerobic laboratory techniques (on a 5% sheep blood agar plate and MacConkey agar plate).[2] Sterile pyuria is a highly prevalent condition. It is more common among women than men because of pelvic infection.[4] Population-based studies show that 13.9% of women and 2.6% of men are affected.[5]

'Significant Bacteriurea' - greater than 10^5 CFU/ ml in a suitablely collected and well-transported mid-stream sample of urine (MSU) is the usual diagnostic criterion for a urinary tract infection. Originally, this term was used by Kass to distinguish between infected and contaminated urine samples in patients without symptoms but now a days it has become widely used to define the presence of urinary infection in symptomatic patients.[6] However, occasionally in sympomatic patients the count may fall to 10^4 CFU/ ml or even lower in absence of antibiotics.[7] Some recent studies indicate that a colony count of 10^5 CFU/ ml would differentiate clinically significant from clinically non-significant infections and thus reduce the number of positive cultures by 38% relative to the number of cultures that would be considered positive with the 10^3 CFU/ ml cutoff point.[7]

Table-I: Causes of sterile pyuria[8,9]

Causes related to infection

Current use of antibiotics

Recently treated urinary tract infection (within past 2 wk)
Genito-urinary tuberculosis
Partially treated pyelonephritis or cystitis
Urethritis due to Chlamydia, Neisseria gonorrhoeae, Mycoplasma, or Ureaplasma
Viral infection of the lower genitourinary tract
Fungal infection of kidneys and bladder
Parasitic disease such as Trichomoniasis or Schistosomiasis
Balanitis
Prostatitis
Appendicitis (if the appendix lies close to ureter or the bladder)

Causes not related to infection

Presence of or recent use of a urinary catheter
Recent cystoscopy or urologic endoscopy
Urinary tract stones
Foreign body such as surgical mesh in the urethra or a retained stent
Urinary tract neoplasm
Pelvic irradiation
Urinary fistula
Post-menopausal atrophic vaginitis
Bladder cancer
Polycystic kidney
Rejection of a renal transplant
Renal-vein thrombosis
Interstitial nephritis or analgesic nephropathy
Papillary necrosis
Interstitial cystitis
Inflammatory disease such as systemic lupus erythematosus or Kawasaki's disease

Discussion

Infectious cause

The name sterile pyuria is often misleading, as the patients undoubtedly has some sort of infections. This may be a partially treated urinary tract infection (even a single dose of antibiotic before urine collection) or a recently treated UTI, a UTI with fastidious or slow growing atypical organism that fail to grow during routine laboratory culture or a sexually transmitted infection.[10]

Genito-urinary tuberculosis

Genitourinary tuberculosis is the most common form of non-pulmonary tuberculosis after lymphadenopathy.[11] Bangladesh ranks 5th among the 22 countries with high incidence of tuberculosis globally but genito-urinary tuberculosis (GUTB) are diagnosed relatively infrequently[12] Mycobacterium tuberculosis reaches the urinary tract via blood stream from a primary focus in the lung or bowel, occasionally as tertiary spread from a lesion in the bone. In the urinary bladder granulomatous lesion develops in the form of tumor-like mass or ulcer.[4]

If not detected or treated early, it may cause obstructive uropathy. Genito-urinary tuberculosis may present with urinary symptoms like frequency, urgency, loin pain, hematuria and some constitutional symptoms.[9] History of pulmonary tuberculosis or co-existing pulmonary tuberculosis may be present in few cases.[13] Recurrent urinary tract infection with presence of plenty of pus cells in absence of positive urine culture for usual pathogens in acid urine always raise the suspicion of urinary tract tuberculosis.[14] Detection of AFB by culture or PCR[6] and histo-pathological examination confirms the diagnosis of tuberculosis.[13] In a study involving 42 patients in whom there was suspicion of GUTB on the basis of radiologic abnormalities, M. tuberculosis were isolated in the urine acid-fast bacilli culture in only 13 of 35 patients (37%) and bladder biopsy was positive in 11 of 24 patients (46%), whereas urinary PCR for M. tuberculosis was positive in 33 of 35 patients (94%).[15] Sterile pyuria may also be the only sign of prostatic TB. Prostate massage yields secretions which can be sent for AFB culture.[16]

Parasitic infections

Trichomoniasis or Schistosomiasis are common causes of pyuria worldwide.[9] Schistosoma hematobium infection (a tropical disease also known as bilharzia) may cause sterile pyuria as well as cystitis like symptoms or hematuria.[10] An estimated 119 million people in the world are infected with Schistosoma haematobium.[17] High risk areas are Africa and Mediterranean part of middle East.[10] Humans are infected by penetration of skin by the free-swimming fork-tailed cercariae present in water. After differentiation to adult worms, they reach the bladder veins.[9] The urogenital system is affected in 75% of infected persons.

Trichomonas vaginalis is one of the most common human parasitic and one of the most prevalent sexually transmitted infection. Infection can be diagnosed by identification of the motile parasite during microscopic examination of a wet-mount preparation of cervico-vaginal secretions in women and urethral discharge in men, but PCR is more sensitive. In one study, 46 of 205 male partners of women with confirmed Trichomonas infection (22%) had culture-detected infection, whereas 201 of 205 male partners (98%) had infection detected by means of PCR.[18]

STDs

One of the causes of sterile pyuria may be sexually transmitted diseases (STDs). In a study[19] in Bangladesh conducted to estimate the prevalence of STD showed 86.5% of participants were positive for STD pathogens studied. Among them the prevalence of N. gonorrhoeae, C trachomatis, T. pallidum and HSV type 2 were 39.1%, 47.8%, 12.2% and 38.2% respectively. None was positive for HIV. In men, the majority of sexually transmitted infections cause symptomatic urethritis. Many women may be asymptomatic initially, and pelvic inflammatory disease may develop without symptoms.[20] Commercially available nucleic acid hybridization tests provide rapid detection of N. gonorrhoeae and Chlamydia trachomatis.[21] Negative urine cultures can also be seen with infections such as Ureaplasma species.[22] In an Australian study, 1295 symptomatic men with nongonococcal urethritis and pyuria were evaluated for sexually transmitted diseases. C. trachomatis was detected in 401 (31%), and Mycoplasma genitalium was diagnosed in 134 men (10%).[23]

Genital vesicular eruption, which is characteristic of Herpes Simplex virus (HSV-2) infection, extrudes white cells into urine. Thus pyuria may be associated with HSV-2 associated urethritis and cervicitis.[24] In a 12-year study involving 423 patients with herpes zoster, twelve patients (3%) had pyuria.[25] A British survey tested 3123 urine samples obtained from male and female respondents who were 18 to 44 years of age. HPV DNA was detected in 29% of samples obtained from women and in 17.4% of samples obtained from men.[26] Pyuria may be associated with advanced human immunodeficiency virus (HIV) infection[27] and anti-retrovirals.[28]

Fungal infections

Fungal infections are a source of urosepsis in hospitalized patients, especially those who are immuno-compromised.[29] Patients with diabetes are prone to candida infections, patients who have received transplants are vulnerable to aspergillosis, and patients with HIV infection may be susceptible to cryptococcuria.[29]

Inflammatory and Autoimmune Conditions

The cause of the combination of interstitial cystitis and the painful bladder syndrome, which occurs primarily in women, is unclear. In an evaluation of 122 patients in whom this condition was suspected, 22 (18%) had detectable leukocyte esterase with a negative nitrite indicative of sterile pyuria and prodromal inflammatory changes in the bladder.[30] Sterile pyuria can be a manifestation of systemic lupus erythematosus (SLE)[31] or Kawasaki's disease (KD).[32]

Infection outside the Urinary Tract and Other Urologic Conditions

One study involving 210 patients who were hospitalized

for infections outside the urinary tract (e.g., pneumonia, bacterial septicemia, intra-abdominal infection, enteritis, and female genital tract infections) identified 31 patients (15%) with sterile pyuria.[4] In addition, radiation cystitis, renal calculi, foreign bodies, stents, transvaginal mesh, urinary fistulae, polycystic kidney disease, renal-transplant rejection, and intrinsic renal disease also may cause pyuria.[8]

Non- infectious cause

Tumors of kidney or bladder can be responsible for sterile pyuria. In addition, analgesic nephropathy can cause sterile pyuria in association with chronic interstitial nephritis and renal papillary necrosis.[33] In older female decreased estrogen level may lead to a degree of inflammation of vulva, vagina and bladder, making sterile pyuria.[10] Sterile pyuria is a common finding in pregnancy. This may occur due to contamination by physiological vaginal discharge. True clean-catch urine specimen should be collected and repeat culture should be done.[10]

Table-II: Possible approach of a Patient with Sterile Pyuria[9, 34].

Condition	Evaluation
Tuberculosis	Send urine for acid fast bacilli (AFB) staining. Perform MT interferon-ϒ release assay, urine cultures for tuberculosis; PCR assay also to be done.
STD	If sexually active with multiple partners, consider a genito- urinary (GU) screen including Gonococcus, Chlamydiae and send urethral smear for microscopy and urine for cytolog respectively. PCR for detection of Mycoplasma , ureaplasma and genital herpes in urine
Fungal infection	Perform M/E of urine to detect fungal elements, budding yeast, and hyphae. Perform fungal cultures of urine and obtain biopsy of the bladder & prostate. Evaluate for filling defects (fungal balls in renal collecting system and bladder) and the presence of a renal mass.
Parasitic infection	If Trichomoniasis is suspected, use wet-mount slide of discharge for microscopic visualization of motile trophozoites. Patient's sex partner should also beexamined. If schistosomiasis is suspected M/E of urine for ova with terminal spine of Schistosoma haematobium eggs
Pyuria without defined infection	bladder biopsy, antigen detection in blood by ELISA and serologic testing for antischistosomal antibody can be done. Consultations with nephrologist, infectious disease specialist, urologist gynaecologist or all of these specialist. Abdominal, renal, pelvic, and bladder imaging and renal biopsy to be done. Conduct a flexible cystoscopy-look for bladder tumor, bladder TB & CT intravenous urogram (CT IVU).

Conclusion

The differential diagnoses of sterile pyuria as stated above is broad. Though sterile pyuria has historically been considered to be suggestive of genitourinary tuberculosis and sexually transmitted diseases,[9] but a wide variety of other causes must be considered. A complete history and physical examination should be carried out to identify the potential causes of genitourinary inflammation. Evaluation to detect bacterial, fungal, and parasitic infections is indicated in patients with a clinical history that suggests specific infections.[9] Specific evaluation for sexually transmitted infections is also very important. Inflammatory conditions in the vicinity of the urinary tract as well as systemic diseases should be included in the differential diagnosis. In addition, abdominal, renal, and bladder imaging should be considered for evaluation of febrile or otherwise symptomatic patients.[10]

Abbreviations :

PMN- Polymorpho-Nuclear Neutrophil, HPF- High Power Field, CFU- Colony Forming Unit, MSU- Mid-Stream Urine, UTI- Urinary Tract Infection, AFB- Acid Fast Bacilli, PCR- Polymerase Chain Reaction, TB- Tuberculosis, HSV- Herpes Simplex Virus, HIV- Human Immunodeficiency Virus, HPV DNA- Human Papilloma Virus DNA

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