Quiz Case

Epithelioid cell granulomas in urine cytology smears: A diagnostic approach

Deepika Gupta, MD, DNB¹, Manju Kaushal, MD¹, Swasti Jain, MD¹

¹Department of Pathology, Atal Bihari Vajpayee Institute of Medical Sciences and Dr. Ram Manohar Lohia Hospital, New Delhi, India.

CLINICAL HISTORY

A 35-year-old female patient presented with painful gross hematuria associated with clots and burning micturition for a duration of 1 month. She also reported urgency, incontinence, and nocturia. She had a history of lower segment cesarean section done 8 months previously. There was no history of fever or other associated comorbidity. The general examination was unremarkable. Figure 1 shows the cytological features of three consecutive urine samples in Giemsa- and Pap-stained smears.

QUESTION

What is your interpretation?

- a. Tuberculosis of urinary tract
- b. Urothelial changes with treatment effect
- c. Malignancy
- d. Cystitis cystica glandularis

Figure 1: (a,b) Dense acute inflammation along with histiocytic aggregates (Urine smear, Giemsa, a ×100; b, ×400), (c) Epithelioid cell granuloma with inflammatory cells (Papanicolaou stain, ×400), (d) Positive for Acid fast bacilli (AFB) (arrow) (Ziehl–Neelsen stain, ×1000 oil immersion).
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Answer

The correct cytopathological interpretation is (a) Urinary tract tuberculosis.

Explanation

Three consecutive urine samples showed the presence of epithelioid cell granulomas and multinucleated giant cells along with reactive urothelial cells and inflammatory cells [Figure 1a-c]. Special stain for acid-fast bacilli (AFB) was positive [Figure 1d], thereby confirming the diagnosis of tuberculosis. The reverse transcription polymerase chain reaction and cartridge-based nucleic acid amplification test of the urine sample were also positive. The patient was immediately started on antitubercular therapy, to which she responded well.

Ultrasonography for kidney, ureter, and urinary bladder revealed a mid-pole, well-defined, cortical hyperechoic space-occupying lesion (SOL) measuring 7×8×4 mm suggestive of hemangioma. A focal concretion and right-sided mild-to-moderate hydroureteronephrosis were present. Urinary bladder showed circumferentially thickened wall. Contrast-enhanced computed tomography revealed similar findings [Figure 2a and b].

ADDITIONAL QUIZ QUESTIONS

Q2. What is the most common route of infection in renal tuberculosis?
   - a. Ascending spread
   - b. Hematogenous
   - c. Lymphatic spread
   - d. Direct invasion.

Q3. In genitourinary TB, which one of the following is true?
   - a. Sterile pyuria is a consistent finding
   - b. AFB in early morning sample is always positive.
   - c. Most common site is pelvis
   - d. It is the commonest cause of pyelonephritis.

Q4. Golf hole ureter is seen in:
   - a. Ureteric calculus
   - b. Ureteral polyp
   - c. Tuberculosis of ureter
   - d. Retroperitoneal fibrosis.

Q5. Which of the following considered as reliable diagnostic modalities for urinary tract tuberculosis?
   - a. ZN staining and cultures isolation for Mtb in urine,
   - b. PCR for Mtb,
   - c. Imaging studies,
   - d. Histopathological evidence for TB
   - e. All of the above.

ANSWERS TO THE ADDITIONAL QUIZ QUESTIONS

Q2. b; Q3. a; Q4. c; Q5. e

Q2. b Genitourinary tuberculosis (GUTB) is mostly secondary to pulmonary infection. Renal TB is a chronic process that can start many years after the initial lung infection.

Q3. a Sterile pyuria is the rule. Tubercle bacilli can be identified on AFB staining of 24 h urine specimen or the first morning urine sample collected on 3 successive days. AFB staining is positive in about 60% of the cases. The most common site of GUTB is kidney. The most common cause of pyelonephritis is E. coli.

Q4. c Fibrosis due to Mycobacterium tuberculosis (Mtb)
usually starts around the ureter and causes pull at the ureter leading to a strictured, dilated, and rigid mouthed ureter called as golf hole ureter.

Q5. The most common procedures used for diagnosis of urinary tract tuberculosis include: (1) Urine cytology smears examination, (2) Ziehl–Neelsen (ZN) staining and cultures isolation for Mtb in urine, (3) PCR for Mtb, (4) imaging studies, and (4) histopathological evidence for TB.

DISCUSSION

GUTB is a term coined by Wildbolz in 1937. GUTB is the second most common form of extrapulmonary tuberculosis after lymph node involvement and it usually affects adults between the second and fourth decades of life. Mtb bacilli are shed into the urine; they spread into the urinary tract, involving the renal pelvis, ureters, and bladder; the urinary tract mucosa may be ulcerated, thin, and without contractility. In most patients, acquired cellular immunity develops which inhibits multiplication of bacilli and contains the disease by forming microscopic granulomas, leading caseous necrosis with local tissue destruction. In addition, the tubercular granulomas are usually associated with Langhans' type multinucleated giant cells.

Urinary tract tuberculosis diagnosis is a challenge due to the insidious onset of UTTB with few non-specific symptoms and atypical presentations, technical difficulties to isolate Mtb, and the long time required to confirm the diagnosis by culture, lack of awareness of physicians, and poor care seeking behavior which lead to difficulty and delay the diagnosis.

The differential diagnosis of presence of granuloma in urine cytology includes tubercular, fungal, or protozoal infections, foreign body reactions after instrumentation, and bacillus of Calmette-Guerin (BCG)-induced cystitis.

Presence of epithelioid cell granuloma in urine specimen is a rare finding on urine cytology smears. Kapila and Verma described dispersed or loose clusters of epithelioid histiocytes that often have spindle or carrot shaped nuclei in urinary tuberculosis cases. It is necessary to differentiate between a case of tuberculosis and granulomatous reaction as a result of BCG therapy. In our case, there was no history of instrumentation or BCG therapy. There was no fungal or parasitic profile in the routine smears.

Multinucleated giant cells can display similar morphological features as umbrella cells, so must be differentiated. Umbrella cells are commonly seen in spontaneously voided urine of patients with renal colic, pronounced distention of the bladder, viral infections, previous radiation, or topical chemotherapy for superficial bladder cancers. Diamond shape of the cells, cytoplasmic vacuolation, and numerous nuclei (50 or more) usually indicate that the cells are of epithelial origin rather than histiocytic.

The presence of AFB in ZN stain or positive urine culture indicates a definitive diagnosis of urinary tuberculosis, however, the same is not excluded based on negativity of ZN staining.

A few studies have reported AFB in urine cytologic specimen previously. In one large series, the presence of bacilluria has been demonstrated in 5.2% of cases. In other studies, AFB positivity by ZN stain on urine smear has been reported variably from 25 to 42%. Urinary PCR is considered highly sensitive as it can detect 94.29% of cases. It is especially useful when AFB smears are false negative still suspected of having tuberculosis.

SUMMARY

The presence of epithelioid cell granulomas in urine along with Langhans’ type giant cells is highly suggestive of tuberculosis. The presence of AFB on ZN stain on the urine smears confirms the diagnosis, thereby obviating the need for invasive techniques such as cystoscopy and biopsy and allows immediate initiation of antitubercular therapy. Hence, AFB staining in urine smears is mandatory in all cases where tuberculosis is suspected clinically or cytomorphologically.

Tuberculosis continues to be a worldwide disease with predilection for immunocompromised patients and the lower socioeconomic populations. The kidney remains the primary target for disseminated disease. Untreated urinary tuberculosis can cause severe urinary symptoms, renal failure, and death. Effective treatment is dependent on awareness, early recognition, and prompt treatment.

COMPETING INTEREST STATEMENT BY ALL AUTHORS

The authors declare that they have no competing interest.

AUTHORSHIP STATEMENT BY ALL AUTHORS

Each author has participated sufficiently in the work and takes public responsibility for appropriate portions of the content of this article.

All authors read and approved the final manuscript.

Each author acknowledges that this final version was read and approved.

ETHICS STATEMENT BY ALL AUTHORS

As this is case without identifiers, our institution does not require approval from Institutional Review Board (or its equivalent).

LIST OF ABBREVIATIONS (In alphabetic order)

AFB – Acid-fast bacilli
BCG – Bacillus of Calmette-Guerin
CBNAAT – Cartridge-based nucleic acid amplification test
CECT – Contrast-enhanced computed tomography
GUTB – Genitourinary tuberculosis
MtB – Mycobacterium tuberculosis
RT PCR – Reverse transcription polymerase chain reaction
SOL – Space-occupying lesion
USG KUB – Ultrasonography for kidney, ureter, and urinary bladder
ZN – Ziehl–Neelsen.

EDITORIAL/PEER-REVIEW STATEMENT

To ensure the integrity and highest quality of CytoJournal publications, the review process of this manuscript was conducted under a double-blind model (authors are blinded for reviewers and vice versa) through automatic online system.

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