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Case report

Genitourinary tuberculosis in children - a diagnostic challenge

Tuberculoza genitourinară la copii – o provocare diagnostică

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Abstract

Pediatricians frequently encounter hematuria in children. One of the tardy complication of pulmonary tuberculosis, which is most characteristic and common in teenagers and middle aged, is represented by genitourinary tuberculosis. Renal tuberculosis is rare during childhood. The authors present a series of cases where the presenting symptom was gross or microscopic persistent hematuria. The diagnosis of urogenital tuberculosis was established from early-morning urine culture in all cases. In a patient with symptoms of recurrent urinary tract infection or hematuria associated with sterile pyuria the suspicion of GUTB must be considered. A delayed diagnosis of renal tuberculosis led to kidney damage and sequels of GUTB, including renal failure. Our cases report emphasizes that in case of persistent hematuria GUTB may be considered as a differential diagnosis.

Keywords: *children, hematuria, genitourinary tuberculosis*

Rezumat

Pediatrii se confruntă frecvent în practică cu hematuria. Tuberculoza genito-urinară (GUTB) este una dintre complicațiile tardive ale tuberculozei pulmonare, mai frecventă fiind în rândul tinerilor şi a adulților. Tuberculoză renală este rară în copilărie. Autorii prezentă o serie de cazuri în care simptomul principal a fost hematuria macro sau microscopică persistentă. În toate cazurile diagnosticul de tuberculoză urogenitală a fost stabilit prin cultura realizată din prima urină de dimineață. Suspiciunea de GUTB trebuie avută în vedere, de fiecare dată când pacientul se prezintă cu infecții urinare recidivante sau hematurie asociată cu piurie sterilă. Diagnosticul precoce al tuberculozei renale poate preveni sechelele tardive, inclusiv insuficiența renală. Prezentarea de față subliniază faptul că GUTB trebuie considerată ca şi diagnostic diferențial al hematuriei persistente la copii.

Cuvinte cheie: *copii, hematurie, tuberculoză genito-urinară*

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Introduction

Tuberculosis persists to be an important public health problem in our country. Romania ranks first place in the European Union in the incidence of tuberculosis, although the number of cases is declining steadily since 2002. In 2011 Romania accounted for 19 212 (27%) of all cases in European region (notification rate: 89.7/100 000) and for 56% of the overall decrease from 2010 (1).

According to WHO and European Centre for Disease Prevention and Control in their report from 2013, total tuberculosis cases by site of disease in children in 2011 in Romania was 776 notified cases with the following distribution: pulmonary TB - 317 cases (40.8%), extrapulmonary TB - 459 cases (59.1%).

Average incidence rate for Romania (new cases) in children 0-14 years was 23.6%ooo in 2011. In our county the global TB incidence was 65.7%ooo, while in children it was of 34.1%ooo in 2011 (2).

One of the tardy reactivations or complications of pulmonary tuberculosis, which is most characteristic and common in teenagers and middle aged pesons, is genitourinary tuberculosis (GUTB). Less than 5% of cases of pediatric extra pulmonary disease are represented by renal tuberculosis, so it is an uncommon illness in children and juveniles. Renal tuberculosis has a large spectrum of presentation, varying from asymptomatic involvement to entire kidney destruction and renal failure. Early diagnosis of renal tuberculosis can prevent the sequelae of GUTB, including renal impairment.

Materials and methods

The authors report a series of three cases where the presenting symptoms were gross or microscopic persistent hematuria. All these cases were diagnosed and admitted at our clinic during 2011 and 2012 with genitourinary tuberculosis. Data of these cases were evaluated. Clinical aspects, organ implication, analysis, medication and effect of therapy were revised.

The study group consisted of three children, 1 boy and 2 girls, with age of 9 to 14 years (*Table 1*). Two of them had good life conditions while one child (case 2) had poor socioeconomical conditions, but all of them had good nutrition status. All of them underwent vaccination with BCG.

Two children complained of fever, lumbar pain and had macroscopic hematuria while one child reported no urological symptoms except of a chronic headache and had a microscopic hematuria.

No pathologic finding was detected during general examination except lumbar sensibility in two cases. Medical history of all these children was negative for tuberculosis and they didn't know anything about a close connection with someone suffering or receiving treatment for tuberculosis.

In this moment we considered all cases as a urinary tract infection (UTI) and we started antibiotic treatment as soon as we collected biological samples for lab tests.

Usual hematological analysis illustrated a highly elevated erythrocyte sedimentation rate with normal hemogram in all cases. The lab tests for assessing renal function were in normal range.

Urinary examination revealed macroscopic hematuria in two patients and microscopic hematuria (more than five red blood cells per high power field) in one child as well as isomorphic hematuria in all cases. Urine culture didn't confirm our first supposition of UTI, as it was sterile. The chest radiograph was normal.

Ultrasound examination of the urinary tract revealed an enlarged kidney, mild renal pyelocalyceal dilatation and echogenity changes in two cases (in those with frank symptoms). In the other case the ultrasound examination didn't bring out any abnormality.

The first case was reevaluated and the ultrasound 2D mode examination demonstrated a heterogeneous picture of the right kidney, with a hypoechogen central area of ~ 23/30 mm

Table 1. Clinical aspects and investigations of studied cases

Case 1	Case 2	Case 3
Female. 14 y.o. Weight: 46 kg Height: 152 cm	Male, 12 y.o Weight: 32 kg Height: 135 cm	Female, 9 y.o Weight: 29 kg Height: 133 cm
Right loin pain, gross hematuria, low grade fever, recent onset	left loin pain, gross hematuria, fever, frequent urination; Recent onset	Headache, Microscopic hematuria
Labs: urine culture- sterile, ESR: 76mm/h, Isomorphic hematuria	Labs: urine culture- sterile, ESR: 86mm/h, Isomorphic hematuria	Labs: urine culture- sterile, ESR: 56mm/h, Isomorphic hematuria
US: right nefromegalia, hypere-choic renal sinus	US: left nephromegalia, hypoechoic areas, left ureterohydronephrosis	US: no anomalies
CT scan: polycyclic, inomogen/scratchy tumor in right sinus Urothelial carcinoma?	CT scan: left nephromegalia with an acute pyelonephritis appearance	CT scan: not done
Urological consult: renal sinus lipo-matosis	Urological consult: renal abscesses	Urological consult: -
Dg: right kidney tumor	Dg: left renal abscesses	Dg: Microscopic hematuria
Persistent microscopic hematuria	Persistent microscopic hematuria	Persistent microscopic hematuria

and normal Doppler signal at the upper pole, aspect that raised the suspicion of a renal tumor or papillary necrosis (*Figure 1*).

In the first case was also performed an ultrasonography with contrast agent which revealed a homogeneous opacification of the entire renal parenchyma; with a similar aspect of renal parenchyma at 23 seconds, fact that excluded a tumor (*Figure 2*).

One week later the second case was re-examined by ultrasonography which revealed an increased renal cortical echogenicity and hypoechoic areas about 20 mm diameter within the renal parenchyma.

Intravenous urography showed unaffected and functioning kidneys with normal and prompt excretion of the contrast without parenchymal calcification. The ureters and bladder were normal.

The PPD test was negative in all cases in accordance with the CDC criteria (3).

Despite empirical treatment with a therapeutic dosage of antibiotics over one-month duration in the first two cases (an initial 7 days course of i.v. cefuroxime, followed by i.v. ceftriaxone or meronem for 10 days, and then oral ciprofloxacin or levofloxacin), the patients had further elevated erythrocyte sedimentation rate and refractory to treatment hematuria.

We repeated renal ultrasonography one month later but we didn't notice improvement in the low grade hydronephrosis, except the kidney size which came to normal size. Also the kidney's echostructure had change, but the changes weren't recognized by the entire team who analyzed these cases.

In two cases computed tomography (CT) was performed and revealed abnormalities mainly in the renal system. In the first case the renal pelvic uroepithelum was thickened and showed contrast enhancement. No calcifications or abscesses were observed. In the second case

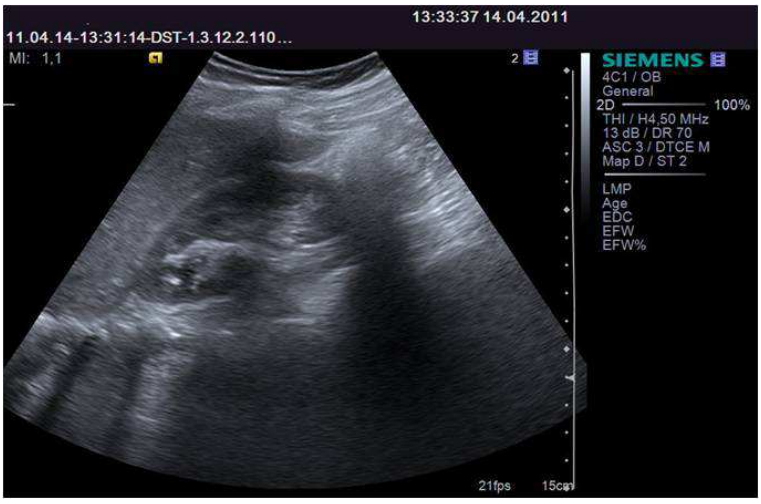

Figure 1. Ultrasound 2D mode (case 1): heterogeneous picture of the right kidney with a hypoechogen central area of ~ 23/30 mm at the upper pole, without Doppler signal

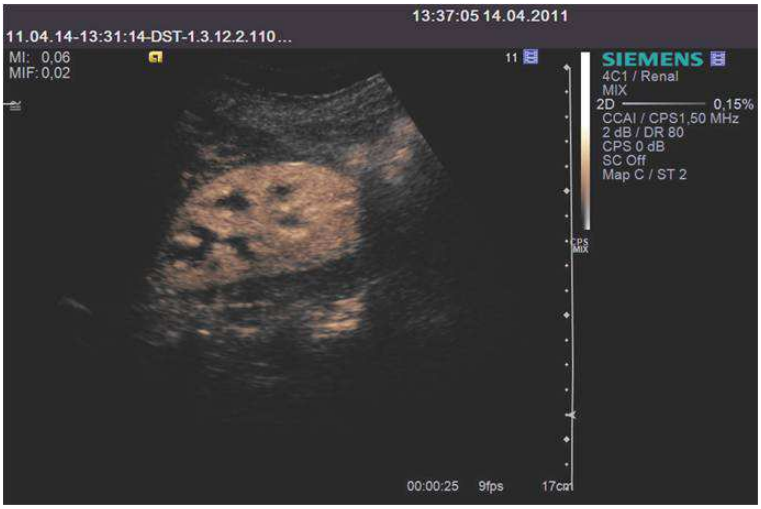

Figure 2. Ultrasound with contrast agent (the same case): homogeneous opacification of the entire renal parenchyma, without any changes in the hypoechogen area in 2D examination (exclude the renal tumor)

CT examination demonstrated a left enlarged kidney of 73 mm with a mild dilated left renal system with proximal left ureteric dilatation; within the renal parenchyma focal pyelonephritic areas were noted (*Figure 3*). Even though, radiological opinion suggested the possibility of renal tumor in the first case and a pyelonephritic process in the second case.

Based on their past history, clinical exam, lab tests and imagistic investigations we ruled out other causes of hematuria in children like: glomerular disease: an acute/chronic glomerulonephritis, nephrotic syndrome, Henoch-Schönlein purpura, immunoglobulin A nephropathy, Hemolytic-uremic syndrome; interstitial and tubular disease: UTI, acute pyelonephritis, coagulopathies; other causes: anatomic abnormalities (hydronephrosis, polycystic kidney disease, vascular malformations), nephrolithiasis or hypercalciuria, trauma, tumor, vigorous exercises, drugs/toxins, etc.

Results

The diagnosis of GUTB was established from early-morning urine specimens in all cases. Every case underwent initially three successive first morning urine samples for microscopic exam that were negative for acid-fast bacilli (AFB), but the urine culture was positive for *Mycobacterium tuberculosis.* Laboratory contamination was excluded. Number of isolated *Mycobacterium tuberculosis* colonies ranged among 1 to 11 in one to three samples. An explanation can be the previous treatment with second-line antituberculosis treatment, paucibacillar samples and lack of enrichment media. The susceptibility of *M. tuberculosis* to rifampicin, isoniazid and para-aminosalicylic acid was tested. Later, others urine samples were sent for microscopic exam for AFB that were also positive repeatedly.

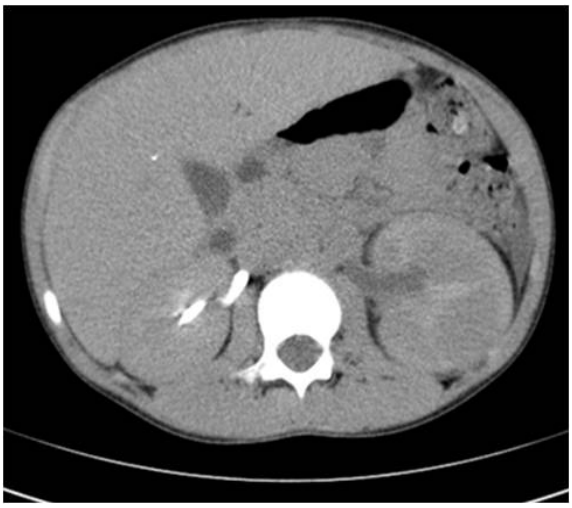

Figure 3. CT scan (case 2): left nephromegalia with hypodense areas

Mild pelvicalyceal dilatation and generalized thickening of the uroepithelium demonstrated on CT scan indicated a chronic inflammatory process and NO tumor as it had been suspected at beginning in the first case. In the second one the pyelonephritic aspect and the hypoechogenic lesion weren't renal abscesses.

An adequate treatment for tuberculosis was recommended for all children, for a period of 6 months. The therapy consisted from isoniazid, rifampicin, and pyrazinamide for 2 months, respectively isoniazid, and rifampicin for 4 months. For the first two months children were admitted in hospital and they received anti-TB treatment. Rest of the treatment was administrated at home as a directly observed therapy (DOT) by their parents who were instructed in this sense. They were followed-up at local Pneumophthisiology Department initially monthly and later at 3 or 6 month.

With antituberculosis therapy the evolution was good in all cases with disappearance of hematuria. After they finished the specific therapy, all cases underwent a QFT-GIT (QuantiFERON-TB Gold In-Tube), because this test wasn't available at the time of diagnosis. The QFT-GIT was performed according to the manufacturer's instructions (QuantiFERON-TB Gold In-Tube, Cellestis Ltd., Carnegie, Australia). The surprise was huge as we discovered 2 children with positive QFT-GIT test (*Table 2*).

Currently, they are being closely monitored and followed up.

Discussions

Urinary tract infections are one of the most common infections in humans. Most of these infections are caused by bacterial agents. Mycobacterial agents causing UTI are uncommon in immunocompetent individuals; they are more casual and with severe evolution in immunocompromised individuals. Unfortunately the incidence of tuberculosis is rising.

Tuberculosis is a worldwide disease with greater prevalence wherever the living conditions are abject: crowded, poor sanitation and improper socioeconomic status (4).

Almost 30% of non-pulmonary tuberculosis cases are attributed to genitourinary TB (5).

GUTB, a form of secondary tuberculosis accounts for less than 3% of all cases of tuberculosis during childhood. The symptoms and signs in GUTB are often vague and insidious (6).

A real challenge for clinicians is represented by the diagnosis of non-pulmonary TB, due to the variable forms and types in which the disease occur. The difficulty of the right diagnosis is a result of the fairly insensitive existing bacteriological methods for detecting *Mycobacterium tuberculosis* in our local labs. So, without lot of attention and a little bit of suspicion is not impossible to skip tuberculosis from the differential diagnosis of GUTB in patients with vague symptoms and obscure illnesses. All these difficulties stand for the complexity of the problem.

Although uncommon, GUTB continues to be a diagnostic and therapeutic challenge for the pediatrician. The diagnosis of tuberculosis is sustained by a positive skin test, but a negative one doesn't necessarily exclude an extra-pulmonary involvement. This finding is markedly constant in GUTB manifestation (7).

Table 2. Characteristics of specific investigation for UGTB

Method	Case 1	Case 2	Case 3
Urine microscopy for AFB (initially)	Negative	Negative	Negative
Urine microscopy for AFB (in evolution)	Positive (5 FAB)	Positive (10 FAB)	Positive (5 FAB)
QFT-GIT (after therapy)	Positive	Negative	Positive

Extra pulmonary tuberculosis (EPTB) represents a progressively greater proportion of new cases and the most frequent site of EPTB is represented by genitourinary tract (8). EPTB is not rare in children, but UGTB is (9, 10).

The most common causative organism of kidney and urinary tract tuberculosis is the *Mycobacterium tuberculosis* and sporadically *Mycobacterium bovis* can also be responsible.

The demonstration of the presence of tubercle bacillus in clinical samples represents a certain criteria for a clear diagnosis of TB. An accurate diagnosis is based on traditional and conventional methods represented by Ziehl-Neelsen acid fast stain and laboratory culture of *Mycobacterium tuberculosis* on Lowenstein Jensen medium (11). Ziehl-Neelsen acid fast staining is deficient in specificity and sensitivity, therefore the confirmation by culture, which is absolutely necessary need several weeks, average 6 weeks.

Nowadays, in developed countries there are accessible rapid diagnostic methods that are based either on liquid culture techniques, such as BACTEC or molecular techniques, that permit detection of most mycobacterial growth in 4 to 14 days. These tests are expensive and require specialized staff and equipment that's why their use especially in developing countries is limited (12). In 2009, WHO recommended the use of the more sensitive fluorescent light-emitting diode (LED) microscopy instead of Ziehl-Neelsen (ZN) microscopy (13).

Another modern alternative to tuberculin skin test, also known as the Mantoux reaction, is represented by an immunological test using Interferon-gamma release assays (IGRAs) particularly QuantiFERON-TB Gold In-Tube test (QFT-GIT). This is a simple blood test that accurately detects people infected with *Mycobacterium tuberculosis,* used for the diagnosis of latent tuberculosis infection. QFT-GIT test uses tubes prefilled with antigens; this simplifies the laboratory procedures, making it more suitable for "on-field" usage in settings with limited resources (14, 15).

Young adults are generally affected by genitourinary tuberculosis, while it is exceptional in children since there is a silent period of 3 to 10 or more years after the primary infection. Only after this interval the signs and symptoms of GUTB will appear (16).

Because the high incidence of tuberculosis in our country we should have a high level of clinical awareness, fact that in some cases may represent the key to diagnosis.

According to Aaronson the most practical screening test is represented by the microscopic urinalysis for persistent pyuria, finding revealed in nearly 90% of cases. The same author recommends that, in such situation, at least 5 or 6 early morning urine samples should be investigated for AFB and cultured for mycobacteria (17). In every case 3 urine samples were sent for mycobacterium tuberculosis culture.

In our study the main symptom was hematuria. Hematuria is often encountered in children. The occurrence of frank hematuria in children is estimated to be 0.13%. According to

Ingelfinger et al in more than half of the cases (56%) hematuria is provoked by an uncomplicatedly and simply identifiable cause (18), so first we had to considered and exclude out other causes of hematuria and only then to think to a GUTB. In the study conducted by Nerli et al hematuria was encountered in 35% of cases of GUTB. According to reported data by Chattopadhyay et al almost 55% of the children have had one or more attacks of marked hematuria, which represented the most frequent presentation (9). Furthermore, in the specialty literature is described a rare case of gross painless hematuria which was the presenting symptom in male child aged 34 days with congenital renal TB (19).

Consistent with Cek et al findings, only 10% of patients have evident hematuria, but this percent is rising up to 50% when we speak of microscopic hematuria. In the same article a rare presenting symptom is represented by lower back pain and suprapubic pain that usually indicate an extensive involvement of the kidney and bladder. Hematuria was present in all our cases.

In our series, two cases presented mild urographic anomalies while in the reported data by Nerli et al X-ray signs of tuberculosis were found in 88% of studied children. Varied radiological anomalies were identified: calcification, cortical scarring, calyceal cavitations, non-functioning kidney, ureteral stenosis, a small-capacity bladder with an irregular wall.

In our group, no children had positive histopathological confirmation as they did not undergo a cystoscopic biopsy.

A rare presentation of the kidney tuberculosis involvement is suggested by a tubercular perirenal abscess, which may break outside with consequence of a persistent non- healing sinus as it is remarked by Dhandore et al (20).

Even if GUTB is rare, cases with kidney involvement with papillary injuries and cavitations are reported. Therefore the imaging studies are very important and they should include a detailed and meticulous ultrasound and an intravenous urography for enhanced calyceal visualization. Characteristic US signs we have to look for are: echogenic calyces and mixed or echo-free areas in the site of the pyramids, which suggest cavitations (21, 22). In the first two cases US revealed right nephromegalia with hyperechoic sinus and left nephromegalia with hypoechoic areas respectively.

According to Chiang et al a recently developed hydroureteronephrosis in a grown up child with sterile pyuria, is also indicative of GUTB (23) but we hadn't had any data about past medical history, respectively ultrasound exam in our cases.

The insidious progression, paucity and generality of symptoms during kidney disease in addition to the lack of physicians' awareness result in a delayed diagnosis.

Antituberculosis therapy is the mainstay of treatment for almost all patients with GUTB. In most of the patients a 6 months therapy is efficient. In accordance with Centers for Disease Control and Prevention and World Health Organization recommendations the antituberculosis therapy consists of two phase therapy. The initial 2 month or the intensive phase contains four drugs (rifampicin, isoniazid, pyrazinamide and ethambutol) administrated every day to destroy majority of mycobacterium. This phase is followed by a continuation phase 4 month length consisting of only two drugs usually rifampicin and isoniazid. In this last phase the medicines might be administrated twice or thrice a week (5, 24). This was the regimen recommended to all our cases. For a total adherence to antituberculosis therapy all our patients received directly observed treatment (DOT). Directly observed treatment, short-course (DOTS) is the recommended strategy to control TB, and DOT represents one of its five elements. This is one of the most effective ways of achieving cure in a patient with TB. The importance of this treatment type consists in reduction of TB incidence as well as the prevalence of primary drug-resistance in the community (13).

Because positive QFT-GIT test was found in 2 cases after they have finished treat-

ment according to standard protocol, we wonder if still there are sites of latent tuberculosis or the compliance to antituberculosis treatment wasn't 100% as they sustained. Also we had to consider the next possibilities: were treatment and dosage correct? Was the diagnosis of TB accurate? Were these drug-resistant TB? As all these possibilities have been excluded we have to look for others explanations.

According to Kadhiravan & Sharma an explanation can be represented by a tardy response to treatment which is a usual phenomenon in EPTB (25).

In a review of 8961 cases of GUTB from the world literature, Figueiredo and Lucon stated that after initial urine sterilization a microbiologic relapse of GUTB may occur, even a long-term treatment and sometimes nephrectomy of the affected kidney have been done. The same authors affirmed that in almost 6.3% of cases relapses, with bacilli that were sensitive to the drugs used occurred after an average treatment of 5.3 years. As a consequence of late relapse and the advantage of early treatment of initial lesions in the asymptomatic phase of relapse, a 10-year follow-up after pharmacologic treatment is recommended by most investigators (26).

Another explanation might be the fact that the reversion rate for QFT-GIT is low, as the reversion from positive to negative IGRA values occurs in a few of treated patients. There are two pediatric studies where the reported reversion rate was 14.28% and 20.33% respectively. According to Chiappini et al, the monitoring changes in IGRA response during antituberculosis treatment has an inadequate value in adults (27).

Because the late and severe complication we have to follow-up all cases for a long period.

Conclusions

Suspicion of GUTB must be considered if the patient has symptoms of recurrent urinary tract infection or hematuria associated with sterile pyuria or an atypical urinary tract infection.

The diagnosis of genitourinary tuberculosis stands on culture studies.

Our cases report emphasizes that in case of persistent hematuria, GUTB may be considered as a differential diagnosis and a long-term follow-up after pharmacologic treatment is essential.

Conflicts of interest disclosure

The authors declare no conflicts of interest.

Abbreviation list

AFB- acid fast bacilli
BCG- Bacillus Calmette–Guérin
CT- computed tomography
Dg- diagnosis
EPTB- extra-pulmonary tuberculosis
ESR- erythrocyte sedimentation rate
GUTB- genitourinary tuberculosis
IGRAs- Interferon-gamma release assays
QFT-GIT- QuantiFERON-TB Gold In-Tube test
TB- tuberculosis
US- ultrasound
UTI- urinary tract infection
y.o.-years old

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