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TOPIC PAPER

Male genital tuberculosis: epidemiology and diagnostic

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Abstract
Introduction Urogenital TB (UGTB) is the second most common form of extrapulmonary TB (EPTB) in countries with severe epidemic situation and the third most common form in regions with low incidence of TB. Male genital TB (MGTB) seems to be a rare disease. Nevertheless, 77% of men who died from TB of all localizations had prostate TB that had mostly been overlooked during their life time.
Materials and methods A Medline/PubMed research with key words "*male genital tuberculosis*" was conducted. Estimates of incidence and spectrum of EPTB in Siberia are presented on the basis of statistical reports for 1999–2010. Additionally, the clinical features and laboratory findings of 310 patients with UGTB are reported.
Results A Medline/PubMed research with key words "*male genital tuberculosis*" resulted in a total of 861 titles only. During the last decade, the incidence rate of TB in Siberia increased up to 20%. Every year in Siberia, there are about 1000 new EPTB patients; the proportion of UGTB decreased from 42.9 to 33.9%. Late diagnosed complicated forms predominated.
Conclusion In Siberia, there is still a severe epidemic situation now. Low living standard, poverty, as well as poor knowledge lead to late diagnosis of EPTB with complicated multi-organ forms.

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Keywords Male genital tuberculosis · Epidemiology · Diagnosis · Urogenital

Introduction

According to the World Health Organization (WHO) report 2008, the worldwide estimated incidence of new cases of tuberculosis (TB) increased in 2006 to 9.2 million (139 per 1,00,000 on average). Large proportions of cases occur in Asia and Africa; 55 and 31%, respectively [1]. One-third of the world's population is currently infected with Mycobacterium tuberculosis (MBT).TB kills more youths and adults than any other infectious disease.

Every four seconds someone falls ill with TB and every 10 s someone dies from TB.

Left untreated, a person with active TB can infect between 10 and 15 people every year. TB accounts for 9% of deaths among women between 15 and 44 years of ages compared with wars, which accounts for 4%, HIV for 3%, and heart diseases for 3% of deaths. Of all causes of death, TB holds the eighth place, of all infectious diseases the fourth place, and of infectious diseases in adults the first place [2].

Pulmonary TB is more dangerous and obvious, but extrapulmonary TB (EPTB) is also contagious and potentially lethal and it affects the quality of life much more than pulmonary TB [3]. Bacillum calmette guerin (BCG) vaccine is used for the therapy of bladder cancer and kidney transplantation and may also play a role in the incidence of urogenital tuberculosis [4]. UGTB is the second most common form of TB in countries with a severe epidemic situation and the third most common form in regions with low incidence of TB [5].

Male genital TB (MGTB) includes tuberculous epididymorchitis (uni- and bilateral), TB of the prostate, TB of a seminal vesicle (only in combination with other forms of UGTB),

unilaterally or bilaterally, and TB of the penis (very rarely). MGTB seems to be a rare disease. Nevertheless, 77% of men who died from tuberculosis of all localizations had prostate tuberculosis that had mostly been overlooked during their life time [6]. In actual figures, this means about 19,000 men yearly in Russia. MGTB presents with nonspecific symptoms and laboratory findings, except for positive Mycobacteria tuberculosis (MBT) culture, but only about 36% cases are culture positive [7]. This is one of the main reasons for late and poor diagnosis of MGTB. The significance of genital TB may be considerable when the high prevalence of overall TB and the asymptomatic nature of genital TB are taken into account.

Materials and methods

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A Medline/PubMed research with key words "*male genital tuberculosis*" was conducted. Estimates of incidence and spectrum of EPTB in Siberia have been made on the basis of the data available in the official reporting forms No 8 (approved by Resolution No 175 of the Russian Statistics Agency November 11, 2005). Statistical reports from 21 regions in Siberia were reviewed annually from 1999 till 2010 to gather new information from surveillance (case notifications) and other studies.

Also, 310 patients with UGTB were under our surveillance; clinical features and laboratory findings were investigated. The age range was 22–71 years. Two hundred and eight of them had kidney TB, and 102 patients had MGTB.

The clinical workup of the patients included digital rectal examination, urinalysis, plain X-ray of the renal areas, and the pelvic area to detect calcifications, intravenous urography, retrograde urethrography, ultrasound investigation of the urinary tract, transrectal ultrasound investigation of the prostate, prostate biopsies, and uroflowmetry. Bacteriological investigation included 3–5 consecutive early morning specimens of urine. Ejaculate, prostate biopsies, and expressed prostate secretion obtained through massage were investigated with PCR and culture both for MBT and nonspecific microbes. Bacteriological investigation conducted primary and in time of provocative test.

Results

A Medline/PubMed research with key words "*male genital tuberculosis*" resulted in a total of 861 titles, 162 within the last 10 years (since 2001). Among the articles of the last 10 years, 63 (39.6%) were case reports, including cases of tuberculous epididymorchitis and prostatitis following intravesical BCG for superficial bladder cancer, 16 (10.1%) were associated with AIDS, 32 (20.1%) mentioned MGTB in the context of other diseases, and only 48 were specifically dedicated to MGTB, describing the experience of single centers. To estimate the real prevalence of MGTB worldwide is almost impossible, since genital tuberculosis accounts for relatively small fractions of tuberculosis. Only one meta-analysis was found and two guidelines (one in Russian), also seven monographs in Russian, but all of them were dedicated to urogenital TB or extrapulmonary TB, but none to MGTB exactly.

In MGTB, the epididymis and the prostate are the most common sites, followed by the seminal vesicles and the testicles [8, 9]. Tuberculous foci in the epididymis are caused by metastatic spread of MBT via the blood stream. TB of the testis is almost always secondary to infection of the epididymis, which in most cases is blood borne because of the extensive blood supply of the epididymis, particularly the lobus minor. Isolated tuberculous orchitis is extremely rare [10]; we have found two cases in the literature, and actually both had epididymal lesion, too. The route of infection is through the hematogenous spread of organisms, as in infection of the kidney.

Prostate TB seems to be rare, it is usually asymptomatic and found after a transurethral resection. Nevertheless, 77% men died from tuberculosis of all localizations had prostate tuberculosis, mostly overlooked during life time [6]. In patients with AIDS, large tuberculous abscesses of the prostate have been reported [10, 11].

Recent data showed that TB is also a sexually transmitted disease. Patients with pulmonary TB presented MBT in ejaculate in 0.08%, in case of comorbidity of TB and hepatitis in 18.8%. Patients suffering from TB, hepatitis, and syphilis simultaneously have shown growth of MBT in ejaculate in 48.5% [12].

Penile TB is very rare but can occur after sexual coitus with infected women [13] or via a direct infection through a penile wound during ritual circumcision. Penile lesions present as ulcers on the glans or penile skin [14].

Epidemiology of UGTB in this study was evaluated in Siberia—66% of the area of the Russian Federation between Ural and Pacific Ocean, population of about 90 million people. Perhaps, low living standard and cold climate are predisposition for TB epidemic in Siberia. In 1999, the incidence rate of TB in Siberia was 116 per 1,00,000 inhabitants; in 2009, it increased up to 139 (plus 20%). Every year in Siberia, there are about 1,000 new revealed EPTB patients (Diagram 1). The number of isolated EPTB patients decreased from 973 to 878, but the number of combined forms (comorbidity pulmonary and

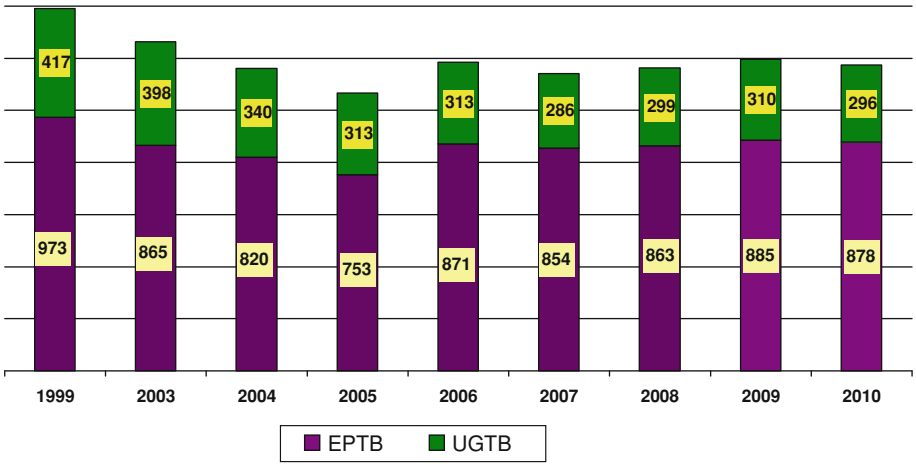


Diagram 1 Numbers of extrapulmonary TB patients diagnosed in Siberia in the years 1999–2010

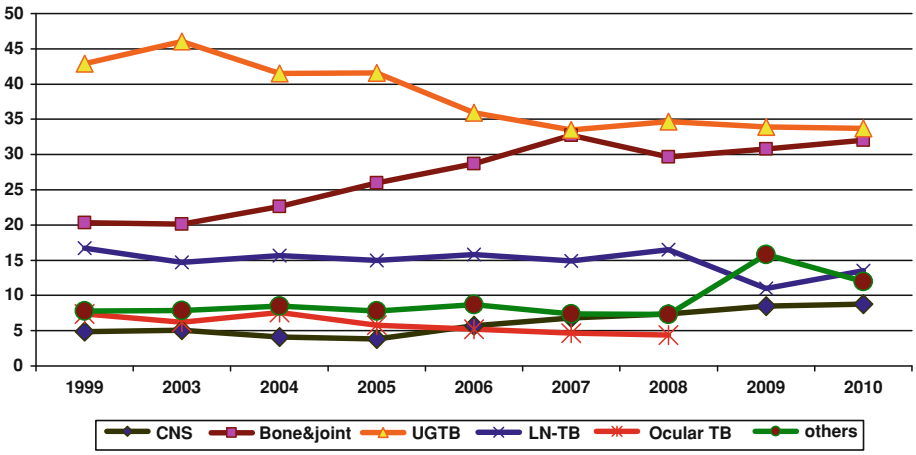


Diagram 2 Spectrum of EPTB in Siberia (percentage of distinct EPTB forms)

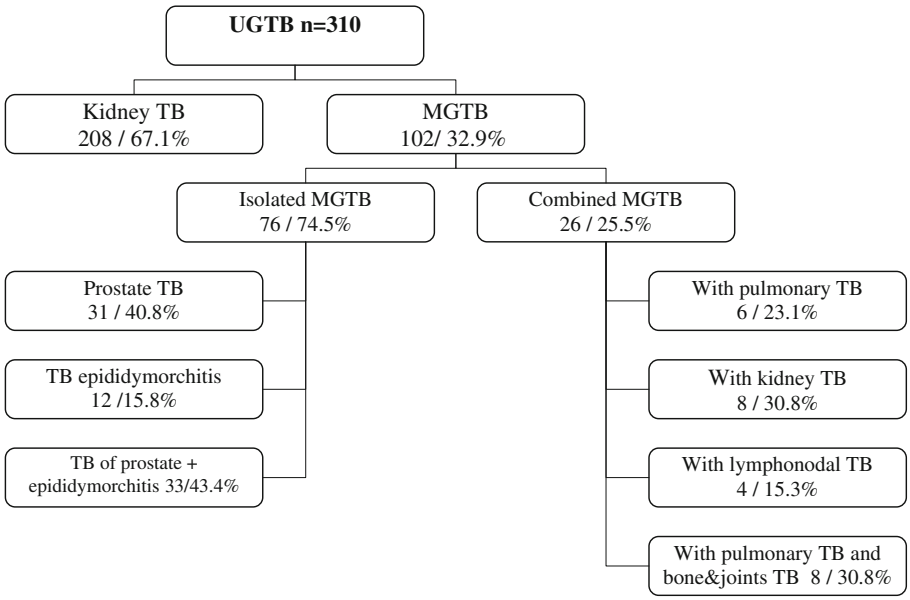
EPTB) increased dramatically (not shown here) up to currently 25.9%. UGTB and other EPTB forms were often overlooked for a long time and were diagnosed too late, when complications have already developed.

Within the last decade, the spectrum of EPTB has changed significantly. TB of the central nervous system almost doubled from 4.9 to 8.5%, mostly due to comorbidity with HIV. Bone and joints TB increased by one-third from 20.3 to 32.0%, and among this group especially TB spondylitis with neurological disorders, the most debilitating form of the disease. The proportion of UGTB decreased from 42.9 to 33.7% with change in gender distribution from male-to-female of 1:2 in 1999 to 1:1 in 2009. In contrary, there was a decrease in peripheral lymph nodes TB from 16.7% to 11.0%, with fistulous disease still frequent. At the end of the last century, ocular TB in Siberia accounted for 7.4% and in 2008 (from 2009 listed in "others") for 4.4% of the patients with EPTB. Accordingly, in 1999, other form of TB accounted for 7.8% and in 2010 for 12.0%. The increase is partly due to inclusion of patients with ocular TB in this group and partly due to better diagnosis of TB of the skin, abdominal organs, breast etc. The dynamic change of spectrum of newly revealed EPTB is presented in (Diagram 2). In all groups, late diagnosed complicated forms predominated.

Three hundred and ten patients with UGTB revealed in 2009–2010 were enrolled in this study for detailed analysis of clinical features and laboratory findings of MGTB. Two hundred and eight patients (67.1%) had kidney TB, and in the rest 102 (32.9%), MGTB was diagnosed. Mean age of male patients with genital TB was 36.4 ± 5.7 years (22–69 years). Seventy-six patients had isolated MGTB, but in 26 of them alongside with this form TB of other organs was diagnosed. Among 76 patients with isolated MGTB, 31 had prostate TB, including 9 with simultaneous TB of seminal vesicles, 33 had prostate TB in combination with TB epididymorchitis, and 12 suffered from TB epididymorchitis alone. The spectrum of UGTB patients is shown in the (Diagram 3).

Thus, the number of patient with kidney TB was twice higher than the number of patients with MGTB; among MGTB, isolated forms predominated (74.5%). Nevertheless, a quarter of patients had MGTB, combined with pulmonary TB, kidney TB, lymphonodal TB, and bone and joints TB. In MGTB, prostate TB prevailed, including in 43.4%—combined with TB epididymorchitis. Fistulous

Diagram 3 Characteristic of UGTB patients ($n = 310$)



forms of prostate TB were diagnosed in 8.2%, of TB epididymorchitis—in 12.4%.

The usual presentation of tuberculous epididymorchitis is a painful, inflamed scrotal swelling. Occasionally, a discharging sinus may be found posteriorly; fistulous forms were seen in 12.4%. In these patients, only the diagnosis may be made by culture of MTB from a discharging sinus, in other cases by pathomorphology after epididymectomy. In case of a testicular mass, genital TB is difficult to differentiate from malignancy [15].

Frequency and nocturia are the most common symptoms of prostate TB. Other urinary tract symptoms such as dysuria, hematuria, and haematospermia are also present in prostate TB. Urgency is usually present if the bladder is involved [15, 16].

The physical findings suggesting genital TB are the following: an enlarged, hard, and non-tender epididymis; thickened or beaded vas deferens; prostatic indurations or nodules on rectal examination; or a non-tender testicular mass. As inflammation progresses, fistula formation on the scrotum or perineum may also be seen in 11–50% of patients [6, 17] (Fig. 1). Hydrocele and inguinal lymphadenopathy may be present infrequently [8, 18].

Analysis of MGTB in West Sibiria in 2004 has shown other results. [7, 16]. In 61.9% of cases besides epididymorchitis, nephrotuberculosis was diagnosed. In 30.9%, bilateral lesion of the epididymis was marked. Comorbidity of scrotal organs and prostate was diagnosed in 35.7% [7]. The culture of MTB in urine was positive in 36.2% of patients with tuberculous epididymorchitis. All of them had also kidney TB, none had a growth of MBT in ejaculate or prostate secretion [16]. Every fifth patient (21.4%) was diagnosed after orchidectomy, performed while misdiagnosed as nonspecific acute epididymorchitis in general urological clinics [7].

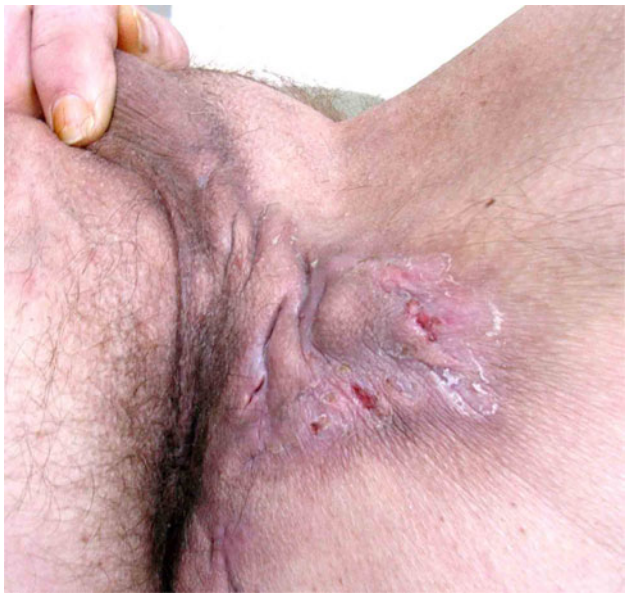


Fig. 1 Tuberculosis of a prostate gland with fistula. Duration of disease is 17 years

Half of the patients with prostate TB complained of dysuria, 39.6% had perineal pain, 58.6% had flank pain. Laboratory findings showed leucocyturia in 84.5% and leukocytes in prostate secretions or ejaculate in 77.6%. Erythrocytes in urine were present in 53.4% and in prostatic secretions in 29.3%. MBT was found only in 36.2%, but in 9.5% with drug resistance to ethambutol and streptomycin [16]. In 79.3%, tuberculous prostatitis was combined with nephrotuberculosis, in 31.0% with TB of a testicle and epididymis, in 17.2% with bladder TB [16].

The main reason for late diagnosis of UGTB is probably poor knowledge of the doctors and the population of this disease. Also, the clinical picture has changed over the last years, which makes an on time diagnosis difficult. For a correct diagnosis, a careful investigation of the epidemiological history (contact with tuberculous infection, TB in history, especially in childhood) and special diagnostic algorithms, including provocative tests, is necessary.

In patients with suspected genital TB, the clinical investigation should aim to detect concomitant urinary and pulmonary TB, since most genital TB cases are combined with renal or pulmonary TB. The Mantoux test is positive in more than 90% of patients, but it has no value in regions with a severe epidemic situation (China, Russia, India, Africa), where all adults are infected with MBT and thus all have positive skin tuberculin test [19–21]. Chest films reveal lung lesions in about 50% of patients [19–21]. All patients with suspected or confirmed genital TB should be screened for HIV.

Abnormal urinalysis can be seen in up to 90% of UGTB [17]. Sterile pyuria was the classic finding in kidney TB; but now up to 75%, patients with UGTB have associated nonspecific pyelonephritis. Thus, the growth of uropathogens in urine is not uncommon in TB patients [27]. Hematuria was present in about 50% of patients. MTB can be identified in urine in 64% of UGTB patients by urine acid-fast bacteria (AFB) cultures, AFB smears, or nucleic acid amplification tests (NAATs) [22], but actually bacteriological verification is significantly lower due to the widespread use of fluoroquinolones. Because TB is epidemic in Russia, the National Russian Urological Congress approved a resolution in 2007, that *all cases* of infections of the urogenital tract should be suspicious for TB, and first line therapy should exclude antibacterials affecting MBT (fluoroquinolones, rifampicin, streptomycin, or amikacin). All patients with an infection of the urogenital tract should be investigated for TB by culture and/or microscopy. Only, after TB is excluded, they may be treated with fluoroquinolones [23].

The detection rates of MGTB may be lower than that of renal TB, because the quantity of MBT in urine can be lower, the affected sites may not be in direct contact with urine, and the urine itself may not be infected [24]. Therefore, bacteriological investigations of prostate secretion and ejaculate are obligatory for patients with suspected MGTB.

Since tuberculous prostatitis is mostly associated with renal and bladder TB, urinalysis should be performed primarily, before digital rectal examination or prostatic massage, to exclude renal and bladder lesions. If urinalysis shows any pathology, complete investigation of the urinary tract is indicated.

The urine should be examined for red blood cell and leukocytes in three consequent portions (three-glass test) during urine voiding without interruption. As the prostate is part of the external sphincter of the bladder, it contracts at the end of a micturition. Therefore, it is necessary that urination into the three glasses should be performed without interruption of the urine stream to avoid earlier contraction of the external sphincter including the prostate gland. Leucocyturia in the first portion means an inflammation in the urethra, in the second portion an inflammation in the urinary bladder or upper urinary tract, and in the third portion an inflammation in the prostate. Leucocyturia in all three portions mirrors a severe inflammation of the total urinary system. In our opinion, the classical four-glass test (initial urine, midstream urine, prostatic secretion obtained by prostatic massage, and urine after prostatic massage) is more difficult for the physician and more bothersome for the patient and also is of less informative value. Therefore, we consider it is difficult in daily practice. Moreover, in the case of prostate TB, the four-glass test may show false-positive results of midstream urine if micturition was interrupted after the first voided portion due to contamination of the urine with prostatic secretion.

Digital rectal examination (DRE) with soft massage of the prostate should be performed only after urinalysis, because DRE before urinalysis may lead to false positive leucocyturia. The prostatic secretion and/or ejaculate have to be investigated microscopically and by culture for both, uropathogens and MBT, as soon as possible after DRE or ejaculation, optimally not later than 40 min after. At least three to five consecutive early morning specimens of urine and prostatic secretion or ejaculate should be cultured by 2–3 slants (Lowenstein-Jensen, Finn-II, Middlebrook 7H9–12-a plain Lowenstein-Jensen culture medium to isolate M. tuberculosis and a pyruvic egg medium containing penicillin to identify M. bovis, which is partially anaerobic and grows below the surface of the culture medium) [23]. The antimicrobial susceptibility of the strain should be estimated. Prostatic secretion and ejaculate should also be investigated with PCR.

Ultrasound investigation of the urinary system should be performed in all patients with inflammation of the genitals. Epididymal or testicular TB has nonspecific findings. The presence of various pathologic components, including caseous necrosis, granulation tissues, and fibrosis is responsible for the diversity of findings. Tuberculous epididymitis and orchitis present as diffusely enlarged lesions, which may be homogeneous or heterogeneous and can also present as nodular enlarged heterogeneously hypoechoic lesions [24, 25].

Transrectal ultrasonogram findings of prostatic disease are irregular hypoechoic lesions in the peripheral zone [26]. On contrast-enhanced CT scan, TB of the prostate or seminal vesicles can be seen as low density or cavitation lesions due to necrosis and caseation with or without calcification.

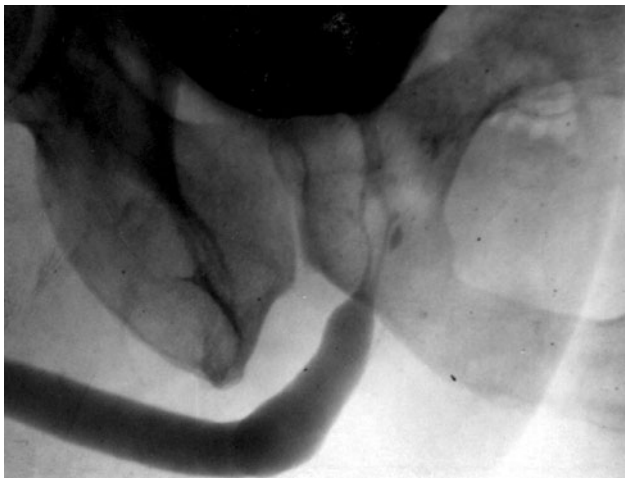


Fig. 2 Retrograde urethrogram: tuberculous caverns of a prostate

Without calcification, the findings may be similar to pyogenic prostatic abscess [27, 28]. Reports about MRI findings of prostatic TB are relatively rare. Diffuse radiating streaky low-signal intensity lesion in the prostate (watermelon skin sign) on T2-weighted images may be specific for tuberculosis of the prostate [29].

Complex radiography is indicated for patients suspected on UGT: plain X-ray films of the urinary tract detect calcification in the renal areas and in the lower urogenital tract; intravenous urography is indicated for patients with leucocyturia and/or abnormality on ultrasound investigations. Retrograde urethrography should be performed in all patients with genital tuberculosis to exclude caverns of the prostate. Some cases of cavernous tuberculosis of the prostate are demonstrated on Figs. 2, 3.

The correct diagnosis of the urogenital tuberculosis is difficult in general urological clinics; it is a prerogative of the urologist with a special skill in phthisiology. The diagnostic algorithm includes a subcutaneous tuberculin provocative test in modification Kulchavenya [23].

The indications for the provocative test are the following:

- Epidemiological history (contact with people or animal, suffering from tuberculosis);
- Recurrent pyelonephritis with simultaneous cystitis, chronic prostatitis, chronic epididymorchitis when standard medical treatment did not solve the symptoms.
- Suspicion of a destruction of calyces seen by intravenous urography; Contraindications are fever, gross hematuria.

Technique of the provocative test is as follows:

1. 48 h before the test, survey of body temperature.
2. Initial laboratory investigation includes analyses of urine and blood, microscopy of the prostatic secretion and ejaculate, culture of urine, prostate secretion, and ejaculate, including PCR investigation.

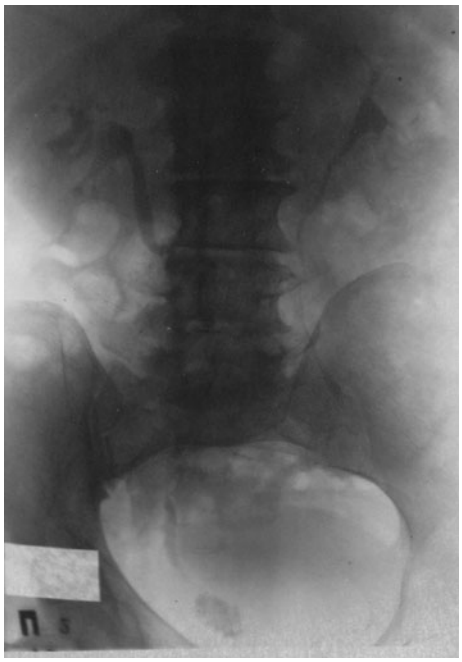


Fig. 3 Cavernous tuberculosis of a right kidney, TB of right seminal vesicle in stage of calcification

3. Injection of 50 units tuberculin subcutaneously.
4. All laboratory investigations including body temperature are repeated 24 and 48 h after tuberculin injection.

The following parameters are estimated: leucocytosis, lymphocytopenia, leucocyturia, and leucocytospermia and body temperature. The test is positive if at least three of them have increased by more than one degree (leucocytosis on 1,000 cells, body temperature on 1°, leucocyturia and leucocytospermia on 20%, lymphocytopenia on 500 cells concerning baseline. Also, local reaction (hyperemia, induration in place of injection tuberculin) is to be taken into account. After provocative subcutaneous tuberculin test, identification of MBT by culture or PCR increased by 16% [23]. On the whole, this test improved the diagnostics of UGTB, especially the hidden, latent forms, to 63.4% [23].

Conclusions

The incidence of MGTB is not high, but diagnosis is difficult because genital TB has no pathognomonic signs. We recommend following an algorithm to improve the management of patients with prostatitis or epididymitis:

I. Careful study of the history: if the patient had TB or contact with tuberculous infection earlier, he has a high risk of relapsing UGTB.
II. Complex examination is necessary: a three-glass test with uninterrupted urination before digital rectal examination, full investigation of the prostatic secretion,

provocative subcutaneous tuberculin test. In the case of relapse retrograde, urethrography is indicated. Comorbidity with pyelonephritis, prostatitis, and epididymitis, especially bilateral epididymitis or fistula is strongly suspicious for TB.

III. In regions with epidemic TB, the prescription of antibiotics with possible antituberculous effects (fluoroquinolones, streptomycin, and rifampicin) should be restricted unless TB can be excluded after full examination of the patient.

Conflict of interest None.

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