Mycobacterial Diseases
ISSN: 2161-1068

Kulchavenya et al., Mycobac Dis 2012, 2:3
DOI: 10.4172/2161-1068.1000110

Case Report Open Access

Natural and Iatrogenic Bladder Tuberculosis: Two Cases

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Introduction

Urogenital Tuberculosis (UGTB) is complicated by bladder tuberculosis (TB) in more than half of cases [1]; late diagnosis and/or absence of pathogenetic therapy leads to the development of shrinked bladder up to full its obliteration. It is known, that tuberculosis is antropozoonotic disease. Reciprocal contamination of humans and animals, mainly cattle, is with M. bovis. In 80th years of past century 16% of all nephrotuberculosis in Siberia were caused by M. bovis; now same forms of UGTB are revealed sporadically [1].

In 70th of past century Zbar B et al. [2] discovered, that intradermal inoculation of mixtures containing living tumor cells and living *Mycobacterium bovis* (strain BCG) into unimmunized syngeneic guinea pigs results in an inflammatory reaction to the BCG, and there is no progressive tumor growth.

In 1976 first patients with recurrent superficial bladder tumors have been treated by vesical and intradermal administration of Bacillus Calmette-Guerin (BCG). The pattern of recurrence in 9 patients has been altered favorably [3], These preliminary results lied in the base of concept on BCG therapy for bladder cancer. A systematic review of intravesical bacillus Calmette-Guerin plus transurethral resection vs. transurethral resection alone in Ta and T1 bladder cancer was conducted. 26 publications comparing transurethral resection (TUR) with TUR + BCG showed that TUR with intravesical BCG provides a significantly better prophylaxis of tumour recurrence in Ta and T1 bladder cancer than TUR alone. Randomized trials are still needed to address the issues of BCG strain, dose and schedule, and to better quantify the effect on progression to invasive disease [4].

A formal meta-analysis of comparative studies on recurrence and toxicity of intravesical bacillus Calmette-Guerin versus mitomycin C for superficial bladder cancer estimated 1,421 patients who were treated with BCG and 1,328 who were treated with mitomycin C (MMC). The results suggest superiority of BCG over mitomycin C for prevention of tumor recurrences in the combined data and particularly in the BCG maintenance treatment subgroup, irrespective of the actual (intermediate or high) tumor risk status. The toxicity with BCG is higher but does not differ between BCG maintenance and nonmaintenance groups [5].

Two another meta-analyses demonstrated statistically significant superiority for BCG compared with MMC for the prevention of tumor progression only if BCG maintenance therapy was provided. Intravesical BCG significantly reduces the risk of progression after transurethral resection in patients with superficial bladder cancer who receive maintenance treatment. Thus, it is the agent of choice for patients with intermediate and high risk papillary tumors and those with carcinoma in situ [6,7].

Nevertheless alongside with positive results many complications of BCG therapy, including lethal, were noted [8-16]. We have no met a comparison of outcomes of bladder TB, caused by *M. tuberculosis u M. bovis*. Typical scenario of development of natural bladder TB grade 4 (classification of E. Kulchavenya [1]), caused by M. tuberculosis, is demonstrated by case 1, and a case 2 demonstrates the iatrogenic bladder TB as a complication of BCG therapy.

Case 1

Patient BLM, 62 years, inhabitant of Altay. For many years he complained of flank pain, which was interpreted by his doctors as radiculitis. He was treated with non-steroid anti-inflammatory drugs with short and incomplete efficiency. In 2008 he found the increasing of the size of right testis, scrotal pain, frequency urination, and pyuria. The patient received some courses of antibiotics for "urogenital infection" without any effect. When intervals between micturitions got 30 min., his urine was investigated for *Mycobacterium tuberculosis* (MBT) with positive result. The urinalyses, biochemical blood analyses, culture and microscopy of urine, X-ray and ultrasound examination revealed generalized UGTB: policavernous TB of left kidney, afuntion of left kidney, tuberculous papillitis of right kidney, bilateral TB of ureters, bladder TB grade 4 (microcystis), right-side vesico-renal reflux. Renal failure. TB orchiepididymitis on the right, TB of the prostate, MBT+.

Complex chemotherapy with four drugs (isoniazid, rifampicin, pyrazinamid, streptomycin) was begun. In two months none effect was noted, so the patient underwent nephrectomy on the left, epididymectomy on the right. Chemotherapy was continued till 14 months. Severe disturbance of urination, low bladder volume were indication for hydrodistension, but it resulted in deterioration of his condition.

The patient was admitted in Urogenital Clinic of Novosibirsk Research TB Institute on 29.09.2009. Laboratory examination presented pyuria, haematuria, bacteriuria (Klebsiella pneumoniae $5x10^4$; Pseudomonas aeruginosa 10^5). White blood cells – $7.9x10^9$/l, urea – 13 mmol/l, creatinin – 270 mkmol/l, PSA - 1,9 ng/ml. The prostate biopsy was performed 14.12.09; pathomorphologically – chronic non-specific prostatitis with intensive sclerosis of the stroma were found.

Microcystis complicated by vesico-renal reflux was considered as a reason for a progression of renal failure, so for urine derivation on 19.11.2009 troakar cystostomy was performed. A level of a urea soon decreased, and on 15.01.2010 cystprostatectomy, ileocystoplastic by Studer technique was conducted. The right ureter was dilated, but its wall was elastic, with peristaltic waves. The bladder was reduced in size, the surrounding fatty tissue was sclerotic. Histological findings: prostate – focuses of caseous necrosis surrounded by irregular layer of

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Received March 12, 2012; **Accepted** April 19, 2012; **Published** April 22, 2012

Citation: Kulchavenya E, Kholtobin D, Filimonov P (2012) Natural and Iatrogenic Bladder Tuberculosis: Two Cases. Mycobac Dis 2:110. doi:10.4172/2161-1068.1000110

granulomatous tissue with multinucleated giant cells (Langhans'); small granulomas, massive fibrosis, chronic inflammatory cell infiltrates and nonular glandular hyperplasia with cyst formation around. Seminal vesicles – cystic atrophia and pericanalicular fibrosis. Bladder – chronic nonspecific inflammatory infiltrate, massive fibromatous transformation of stroma. Diagnosis: active tuberculosis of prostate, progression phase. Chronic fibrosing cystitis.

Just after the operation some improving of renal function was noted. Volume of artificial bladder was 480 ml. Episodes of incontinence, mostly at night, were rarely. Pyuria and bacteriuria were the same despite of complex antibacterial therapy.

Spiral computer tomogram of a urinary system of the patient BLM is presented on Figure 1; Figures 2, 3 and 4 demonstrate his bladder macro and micro.

Case 2

Iatrogenic bladder TB, caused by M. bovis. Patient B.A.I., 50 years. In 2003 superficial urothelial carcinoma of a bladder was diagnosed, transurethral resection was performed without any adjuvant therapy. Control cystoscopy in 2004 presented relapse of the tumor in 4 sites.

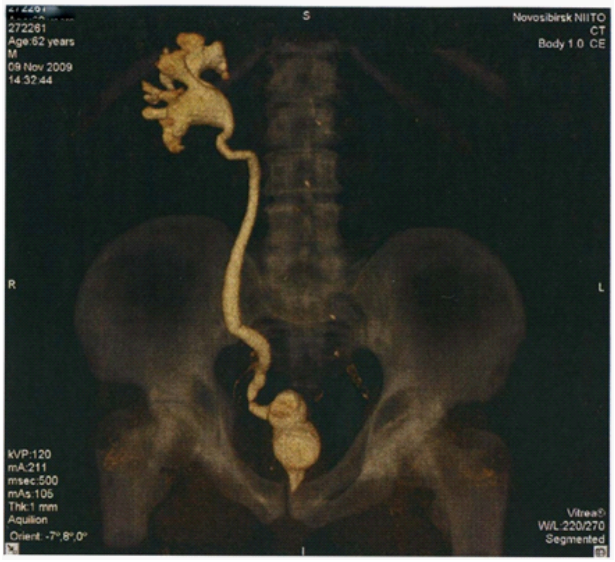

Figure 1: Spiral computer tomogram: tuberculous papillitis of single right kidney, bladder tuberculosis grade 4, microcystis.

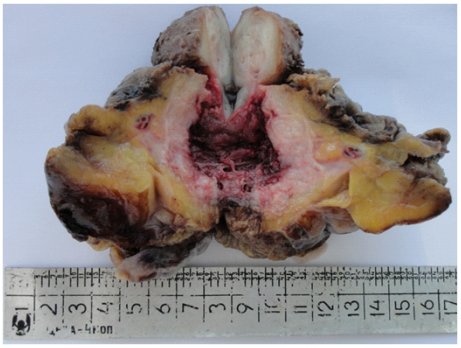

Figure 2: Removed bladder and prostate – longitudinal section. Bladder capacity very low, walls are thickened, fibrotic.

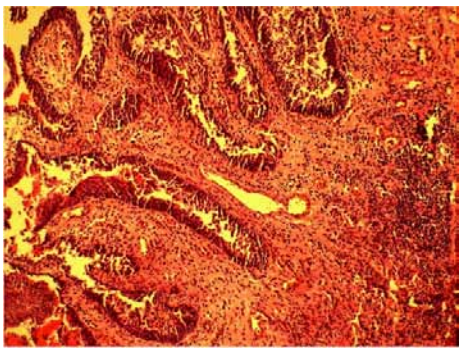

Figure 3: Bladder - papillary cystitis, mononuclear infiltration and stromal fibrosis. Hematoxylin and eosin. x150.

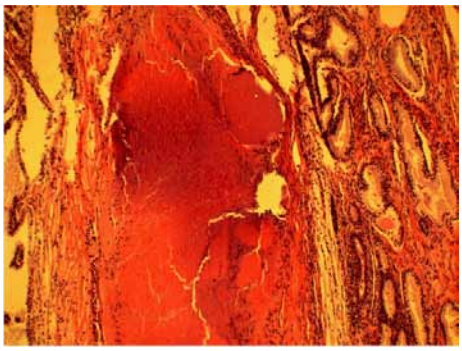

Figure 4: Prostate - granuloma-like eosinophilic amorphous mass, contacting (top right) with rounded deposition (corpus amylaceum). The mass is surrounded by mature fibrous capsule. Stromal fibrosis and mononuclear interstitial infiltrate. Hematoxylin and eosin. x150.

Transurethral resection was repeated and pathomorphologically urothelial carcinoma without invasion of lamina propria was found. After this operation the patient left the city and didn't address to a doctor during 6 years. In March 2010 he was admitted in urological clinic because of gross-haematuria. Cystoscopy presented multitude (more than 10) tumors of 5–20 mm in diameter. Transurethral resection was repeated again; pathomorphologically – low grade urothelial carcinoma T1 was found. In one month BCG-therapy in dose 100 mg weekly was started. After 3rd instillation dysuria, fever appeared. Levofloxacin 500 mg was prescribed, and in one week temperature became normal, but dysuria was the same, bladder capacity decreased till 50 ml intervals between urination were about 30 minutes. In august, 2010 control cystoscopy revealed a solitary ulcer, tubercles. This figure was estimated as bladder TB and anti-TB therapy was recommended. But the patient got sick in myocardial infarction, underwent cardio-surgery and only 07.09.2010 he was admitted in urogenital clinic of TB Institute.

The patient complained of frequent painful urination both at day and at night. Complex examination revealed pyuria, haematuria, soft anemia. Functions of kidneys and a liver were normal, PSA - 0,3 ng/ml. X-ray examination showed a stone 15 x 10 mm in the right kidney with hydronephrosis. Left kidney was normal. Retrograde cystogramm showed left vesico-uretral reflux, bladder capacity was 50 ml. Mycobacteriuria was not found by any method (microscopy, PCR, culture). Atypical cells in urine were not found too.

Diagnosis was: bladder cancer T1N0M0G1, urolithiasis, the

stone in the right kidney. Hydronephrosis of right kidney. Bladder tuberculosis grade 4. Vesico-uretral reflux on right. MBT-.

The patients took rifampicin, isoniazid, pyrazinamid and cicloserin for 4 months that resulted in disappearance of the pain but frequency was the same, bladder volume was 50 ml. He was operated on 24.01.2011. Simultaneously pyelolithototomy, cystprostatectomy, appendectomy and ileocystoplastic by Studer were performed. Figures 5-8 demonstrate operation material and hystology.

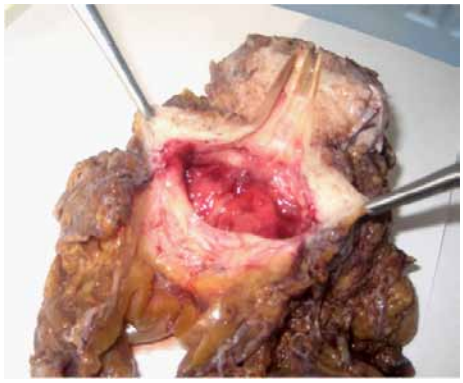

Figure 5: Removed bladder and prostate of B.A.I. on sagittal section. The diameter 4.5 cm, thick walls. Mucous membrane is reddish with hemorrhages. Prostate is grey, dense, at a glance without pathology

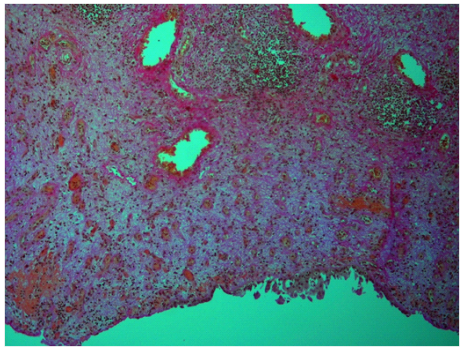

Figure 6: Chronic erosive cystitis. Wide erosion of bladder epithelium (bottom). Lamina propria shows neoangiogenesis (granulation tissue), edema and early collagenic fibrosis. Focal mononuclear inflammatory infiltration, formation of lymphoid follicles, and more mature fibrosis (top). van Gieson, x120.

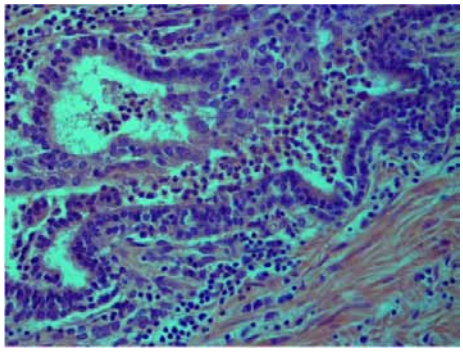

Figure 7: Prostate. Polymorphocellular interstitial infiltration, granulocytes fill dilated ductular lumens. Hematoxylin and eosin. x600.

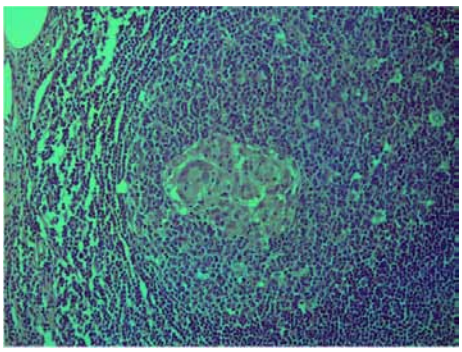

Figure 8: Appendix. Granuloma is located within germinal center of lymphoid follicle and consist of epithelioid and giant multinucleated Langhans cells. Hematoxylin and eosin. x300.

Pathologic examination. Bladder urothelium with focal thinning down to 1-2 epithelial cells. Lamina propria is obviously edematous, hyperemic, contains petechia. Diffuse lymphocytic and neutrophilic infiltrates in mucosa, some lymphoid follicles occur. Papillary lesion is identical of other mucosa by structure. Bladder wall is significantly desorganized by sclerotic expansion, smooth muscle fascicles are thin and fragmented. Prostate: nonspecific chronic inflammatory infiltrate with significant focal neutrofilic component, especially intra- and periductular. Stromal fibrosis in prostate, atrophic and cystic ductal changes. Appendix contain few epithelioid- and giant (Langhans') cell granulomas, including one within follicular germinal center. Thus, BCG therapy provoked local TB as well as generalized TB. Nevertheless histological signs of neither TB nor cancer were not found.

On control examination in 2 months the capacity of an artificial bladder was 400 ml, urination free, but sometimes there was night incontinence.

Discussion

Presented cases of bladder TB differ on etiology (in first case infectious agent is *M. tuberculosis*, in second case – *M. bovis*) and on pathogenesis (in first case – hematogenous dissemination with total involvement of organs of urogenital system, in second case –local TB inflammation caused by absorption of infectious agent). Nevertheless both outcomes were identical – formation of severe fibrosis, development shrank bladder, microcystis.

In case of urogenital TB bladder TB at normal kidneys is impossible, because bladder TB is a complication of kidney TB. Not all patients with natural bladder TB had mycobacteriuria, in 62% of patients diagnosis was verificated by clinical and radiological findings as well as results of provocative tuberculin test. Specific histology in bladder biopsies is rare. It is unknown the degree and duration of contact MBT with urothelium in case of natural bladder TB.

In case of iatrogenic bladder TB as result of BCG instillation there is certain contact of MBT with urothelium. In some conditions (co-morbidity, immunodeficiency, inflammation etc) infection agent may absorb and provoke local bladder TB – primary site of infection, which impossible in natural bladder TB. Low resistance of microorganism may lead to the spread of TB - especially in the prostate, the abdominal organs, regional lymph nodes, and in some cases it is possible generalization of infection with a fatal outcome.

Conclusion

These two cases of natural and iatrogenic bladder TB emphasize first, the actuality of UGTB. Flank pain with dysuria is indication for excluding UGTB, especially in the region with high incidence of TB. And second point – it is necessary to estimate all real and potential contraindications for BCG-therapy before first instillation, careful maintenance of technique and surveillance for the patients during the therapy.

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