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Short Communication

Tuberculous prostatitis is rare in prostate cancer patients in Bangladesh

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ABSTRACT: This study investigated whether tuberculous prostatitis is common among patients with different prostatic lesions including prostate cancer in Bangladesh. None of the 85 biopsy sample revealed acid fast bacilli on Ziehl-Neelsen (Z-N) microscopy or the presence of *Mycobacterium tuberculosis* on polymerase chain reaction (PCR). Moreover, eight samples of prostatic adenocarcinoma which were also tested by Xpert MTB/RIF assay did not show presence of *M. tuberculosis.* These findings indicate that tuberculous prostatitis is rare in the cross section Bangladeshi population investigated in this study.

KEYWORDS: Prostatic lesions, prostate cancer, *Mycobacterium tuberculosis,* polymerase chain reaction (PCR), Xpert MTB/RIF assay

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Tuberculosis (TB), caused by the bacterium *Mycobacterium tuberculosis* is a global health problem. According to the World Health Organization (WHO) one third of the world population is latently infected with M. tuberculosis. An estimated 9.6 million people developed TB and 1.5 million died from the disease in 2014[1]. Pulmonary TB is the most common form of the disease; however, 20-25% of cases are extra-pulmonary in nature[2,3]. Genitourinary TB accounts for 5-10% of extra-pulmonary cases in developed countries and 15-20% of cases in developing countries[4]. Tuberculosis of the prostate gland is seen in 2.6% of genitourinary system[5]. Studies have shown that approximately 20% of all human cancers in adults result from chronic infection and inflammatory states[6]. Chronic prostate inflammation accelerates initiation of prostate cancer originating from basal cells and accelerates prostate cancer progression[7,8]. There are reports describing TB of testis and prostate mimicking testicular cancer[9] and prostatitis caused by *M. tuberculosis* infection serving as a predisposing factor for prostate cancer[10].

Review of literature revealed two published cases of tuberculous prostatitis in Bangladesh[11,12]. As Bangladesh ranks 6th among 22 TB burden countries globally[13], we sought to investigate whether there is any association between TB of prostate and development of prostatic lesions especially cancer in a cross section of Bangladeshi population.

The study was a retrospective analyses working on 85 prostatic biopsy samples, each collected by trans-urethral resection of prostate (TURP) from 85 patients, admitted in different hospitals of Dhaka city, Bangladesh, namely BIRDEM hospital, Dhaka Community hospital, Uttara Crescent hospital and Gastroliver clinic between July 2013 and December, 2014. The male patients included in this study had symptoms of prostatic lesion such as frequency, urgency, dysuria, urinary incontinence, urinary tract infection, inadequate voiding and low back pain. They had an age range of 35-90 years with the average of 65.82. After collection, the tissue samples were fixed in 4% formalin, embedded in paraffin for its prolonged storage at room temperature. The samples were later

processed for routine Haematoxylin and Eosin (H&E) stain and Ziehl-Neelsen (Z-N) stain for acid fast bacteria as descried earlier[14] followed by histopathological diagnosis by light microscopy. The tissue samples were categorized into Granulomatous prostatitis (GnP), nodular hyperplasia with chronic prostatitis (NHCP), prostatic intraepithelial neoplasia (PIN) and prostatic adenocarcinoma (PA) following the criteria of Cancer staging manual of American Joint Committee on Cancer[15]. The histopathology of the 85 cases of suspected prostatitis revealed GnP in 3 (3.5%), NHCP in 48 (56.5%), PIN in 26 (30.6%) and PA in 8 (9.4%) cases (Table 1). Similar results were observed in another study involving 93 patients suspicious of prostatic TB[16]. It is normal to secrete small amount of Prostate Specific Antigen (PSA) into the bloodstream that measures 4 ng/ml or lower (http://www.cancer.gov/types/prostate/psa-fact-sheet). Large amount of PSA in the bloodstream usually signal that the prostate gland is enlarged, infected or malignant. Here, elevated levels of PSA were observed as the prostatic disorders complicated from GnP to PA, and the highest was recorded, as expected, in adenocarcinoma (9-119 ng/ml) with a mean value of 50.6 ng/ml (Table 1), consistent with previous reports[17,18].

Table 1: Histopathological analyses of prostatic tissues and corresponding PSA levels

Sample (Prostatic tissue)	Number of patients (%)	Age (yrs) Mean (±std. dev)	PSA mean (ng/ml) (±std. deviation)
Granulomatous prostatitis (GnP)	3 (3.5%)	50.7 (±14)	2.1 (±0.2)
Nodular hyperplasia with chronic prostatitis (NHCP)	48 (56.5%)	66.4 (±9.5)	14 (±18.1)
Prostatic intraepithelial neoplasia (PIN)	26 (30.6%)	65.9 (±11.8)	25.2 (±34.5)
Prostatic Adenocarcinoma (PA)	8 (9.4%)	67.8 (±6.3)	50.6 (±36.2)

The tissue samples along with two confirmed TB lymph node tissue samples were used as positive controls and were processed for molecular diagnosis of TB by conventional PCR[19], which detects a 123 bp fragment of insertion element IS6110 *Mycobacterium tuberculosis* and used for diagnosis of extra pulmonary tuberculosis. The PCR products, run on an 1.5% agarose gel, revealed that no amplicon was produced from all the sample tested (Figure 1) as a result of amplification from the primers[19] (Table 2).

Table 2: Primers used for amplification of *IS6110* region

Primers	Sequences
Forward Primer	5'-CCTGCGAGCGTAGGCGTCGG-3'
Reverse Primer	5'-CTCGTCCAGCGCCGCTTCGG-3'

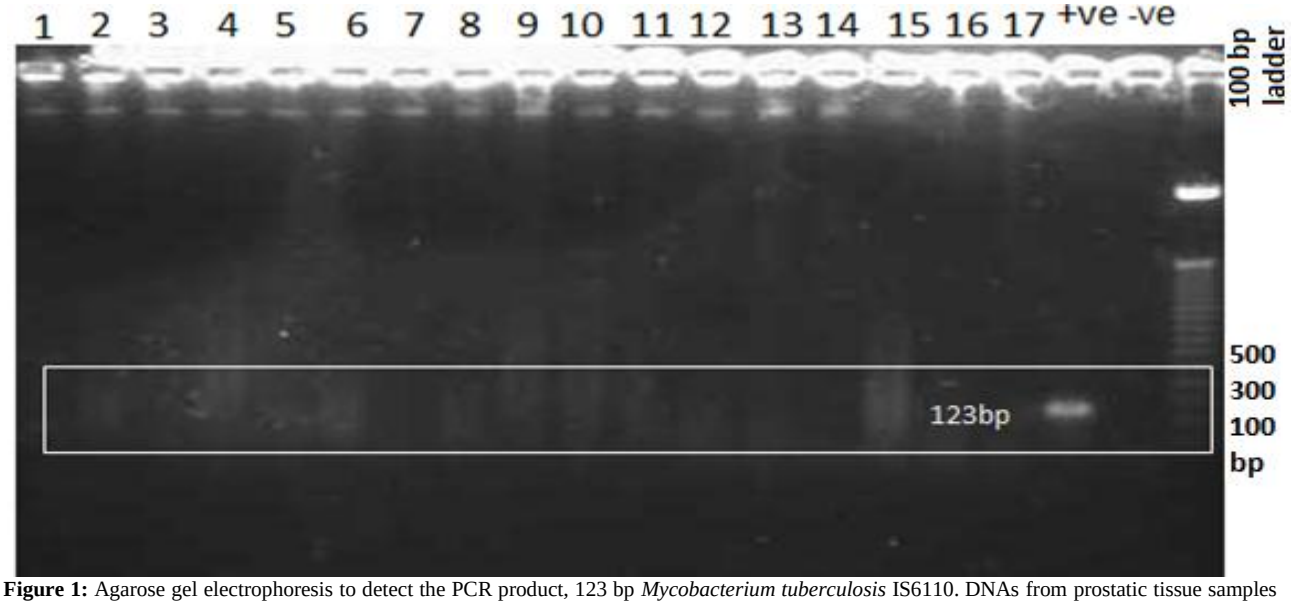

Figure 1: Agarose gel electrophoresis to detect the PCR product, 123 bp *Mycobacterium tuberculosis* IS6110. DNAs from prostatic tissue samples (lanes 1 to 15), two TB positive lymph node tissue samples (lanes 16 and 17), and *M. tuberculosis* H37RV (lane labeled +ve), template-free reaction (lane labeled –ve), and 100bp DNA ladder were loaded as indicated.

Moreover, the positive control from the lymph node tissue also failed to produce any amplicon in the same PCR (Table 3). However, the amplification of internal control, *M. tuberculosis* H37RV confirms that there was nothing wrong in the PCR experiment (Figure 1). This prompted us to use Gene Xpert MTB/ RIF (Cepheid, Sunnyvale, CA) which is a real-time heminested PCR test that simultaneously identifies *M. tuberculosis* and detects rifampicin resistance directly from clinical specimens. Two samples each from GnP, NHCP and PIN states, all 8

PA tissue sample were tested for presence of mycobacterial genomic DNA by the Gene Xpert MTB/ RIF. All these samples came out negative for mycobacterial DNA. However, the two positive control samples, which were lymph node tissues from confirmed TB cases, processed in formalin-fixed, paraffin-embedded squares in the same way as the test samples were prepared, appeared positive in the Gene Xpert MTB/RIF assay (Table 3). Our findings are in agreement with previous findings that Gene Xpert assay is more sensitive than conventional PCR in detecting mycobacteria directly from tissue samples[20,21]. Although only 85 prostate tissue samples have been analyzed in this study, the finding that none of the clinical samples harbored *M. tuberculosis* indicates that infection of prostate by this pathogen is not common in prostate cancer patients in Bangladesh

Table 3: Ziehl-Neelson staining, PCR and Gene Xpert MTB/RIF Real time PCR analyses of prostatic and lymph node tissue samples

Test	Tissue type	Result	Number
Ziehl-Neelson Smear	Prostatic	Positive	0
		Negative	85
		Total	85
	Lymph node	Positive	0
		Negative	2
		Total	2
PCR	Prostatic	Positive	0
		Negative	85
		Total	85
	Lymph node	Positive	0
		Negative	2
		Total	2
Gene Xpert MTB/RIF real time PCR	Prostatic	Positive	0
		Negative	14
		Total	14
	Lymph node	Positive	2
		Negative	0
		Total	2

Further study with larger number of subjects will be needed to come to a definite conclusion. Another important finding of this study is that positive control samples included in this study (lymph nodes tissues from confirmed TB cases) were negative in Z-N staining and conventional PCR in detection of mycobacterial infection in prostate tissues, but were in fact positive as detected by Gene Xpert. This finding highlights the need of performing sensitive molecular test such as Gene Xpert for formalin-fixed paraffin embedded tissues in ruling out whether a suspected patient is infected with *M. tuberculosis* or not.

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