An Epidemiological Study of Urinary Tuberculosis in Iraq

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Abstract

Genitourinary tuberculosis is almost always secondary to symptomatic or asymptomatic primary lesion in the lung. After lymphadenopathy, the most common form of nonpulmonary tuberculosis is genitourinary disease. Most patients are between 20 to 40 years of age with a male to female ratio of 2:1. 4. However, a negative test does not exclude clinical disease. This is a cross sectional double centered study of patients with recurrent urinary tract infections attends the private and public outpatient's clinics in Basra teaching hospital and Imam Husain medical city-AlZahra teaching hospital in Kerbala holy. Patients who full fill two out of the following three diagnostic criteria were considered to have urinary tuberculosis. These criteria were: demonstration of mycobacterium tuberculosis in urine by microbiological ,histopathological methods ,and intravenous urography.We exclude patients who prove to have genital tuberculosis ,and those who had only positive findings in intravenous urography. Statistical analyses were performed using IBM-SPSS version 20. Among our 1500 patients enrolled in this study,35(2%) full fill the diagnostic criteria of urinary tuberculosis. The mean age was 50.7 ± 14.9 SD.The urine for acid fast bacili was positive in 1patient(4%) and urine culture for mycobacterium was positive in only 2patients(16%).The tuberculin skin test was positive in 26 patients(74%).The intravenous urography showed abnormalities in 29patients(84%).40% of patients had a positive findings in histopathology of kidney tissue. At a cut off value of 0.6 the sensitivity was 82% and specificity was 50% for the tuberculin skin test in the diagnosis of urinary tuberculosis. The low prevalence rate 2% of urinary tuberculosis in our study is because our diagnosis was hypothesized in the setting of non-specific bacterial cystitis associated with a therapeutic failure or a urinalysis with a persistent leukocyturia and absence of bacteriuria.The clinical characteristics of urinary tuberculosis in older adults can be unusual and may be confused with age-related illnesses. Generally in Iraq like many other Middle East countries, Women spent more time at home and are more likely to be infected within the home than outside it, with a corresponding higher infectious dose. Our patients were less likely to offered histological diagnoses, a situation that points to late diagnosis. In such instance,urinary tuberculosis is consequently more severe, with a higher frequency of renal failure. When kidney and bladder tuberculosis are concerned ,the kidneys are mute and the bladder plays the role of vocal cords. In the context of immunosuppression, urinary tuberculosis behaves as a severe bacterial infection, with bacteremia and visceral metastatic foci. Sterile pyuria was found in 80 % in this study. This could be explained by more liberal use of antibiotics that has anti-mycobacterial effects in our country which render the urine sterile even in the presence of secondary bacterial infection. A high index of suspicion should be made in cases of sterile pyuria who resist antibiotic therapy that have no antituberculous effects. We recommend further studies to detect the prevalence of urinary tuberculosis among immunocompramised patients including those on chronic dialysis program.

Key words: Tuberculosis, urinary.

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Introduction

Globally, tuberculosis is a common disease[1] , In 2012, there were an estimated 8.6 million incident cases of TB (range, 8.3–9.0 million), equivalent to 122 cases per 100 000 population annually and a rising incidence, particularly in regions with a high incidence of HIV infection[2].Most often the lung is affected, but, after lymphadenopathy, the most common form of nonpulmonary tuberculosis is genitourinary disease[3]..In developed countries, nonpulmonary tuberculosis is relatively more common in patients from ethnic minority groups, the exception being genitourinary tuberculosis (GUTB), which is uncommon in this groups.[1]

GUTB is almost always secondary to symptomatic or asymptomatic primary lesion in the lung[3]. It may also occur as a result of military tuberculosis, and may presents with constitutional symptoms or symptoms related to the lower urinary tract, abdomen or genitalia[3].A high index of suspicion enables early diagnosis. Most patients are between 20 to 40 years of age with a male to female ratio of 2:1[4]. Because active GUTB presents 5 to 15 years after primary infections, it is relatively rare in children[4].In most active cases of extra pulmonary disease, latent foci are reactivated after a decrease in immunity brought about by malnutrition, diabetes mellitus, steroid and, immuno-suppressant use, and immunodeficiency. The latent period between pulmonary infection and clinical GUTB is, on average, 22 years[1]. GUTB most frequently affects the kidneys as part of generalized disseminated infection or as localized genitourinary disease. The morphology of the lesions depends on the site of infection, the virulence of the organism, and the immune status of the patient[1, 3].

Diagnostic specimens should be collected before starting treatment. Confirmation of the diagnosis is important as treatment for TB is long and drug side effects are possible[5].Specimens should be transported to the laboratory without delay in leak-proof sterile containers. To prevent general bacterial overgrowth (as many specimens will contain normal bacterial flora), specimens should be refrigerated if transport to the laboratory is likely to take longer than 1 hour[5]. Diagnosis of extra-pulmonary TB often requires biopsy or fine needle aspiration of the infected site to obtain material for culture and for histopathological/cytological confirmation and should not be delayed[5].Biopsy specimens should be submitted to the laboratory in a dry container or with a maximum of 5 mL normal saline but never in formalin as this will kill viable MTB organisms[3,5].

Mantoux test -also referred to as a tuberculin skin test (TST) may be an aid to the diagnosis of active TB especially in children. However, a negative Mantoux test does not exclude clinical disease. Up to 20-30% of patients with active TB will be Mantoux test negative and a positive Mantoux test may be indicative of asymptomatic infection without disease[5,6]. Advanced HIV ,and kava abuse may be associated with Mantoux test anergy (false negativity)[6]. The use of specialized laboratory tests (including nucleic acid amplification testing techniques, such as polymerase chain reaction for the diagnosis of TB are not routinely carried out currently and require approval by a specialist[5]. These tests can be used to rapidly determine whether a patient's specimen contains Mycobacterium tuberculosis (MTB)[5]. False positive and false negative result do occur and depend on the quality of the specimen submitted as well as the nucleic acid copy numbers present in the specimen. Nucleic acid amplification testing is a supplemental test and does not replace smear microscopy or culture[5,6].

Nearly 25 % of patients with GUTB have no clinical or laboratory evidence of abnormality and the diagnosis is made on investigations for other diseases, during

surgery or at autopsy[7]. Another 25 % have asymptomatic urinary abnormalities, usually acid sterile pyuria or hematuria[6].Of the patients who are symptomatic, lower urinary tract symptoms occur in more than 75 %.Constitutional symptoms such as fever, night sweat and weight loss occur in less than 20 % of patients and indicate active infections in other organs or secondary bacterial infections of the urinary tract [5,6]Investigations that assist in the diagnosis of urinary tract tuberculosis include high erythrocyte sedimentation rate, acid sterile pyuria which presents in 50 % of patients, hematuria, positive TST which is useful for proving infections but not necessarily active disease[6].Although the urine acid fast bacilli (AFB) test is simple, economical, and rapid, it has low sensitivity and specificity for MTB[7]. Isolation of MTB by urine culture is the definitive diagnostic test. It has a higher specificity compared with the urine AFB test but requires at least 8 weeks before the results are obtained[7,8]. Urine for polymerase chain reaction can be used for early diagnosis but it is expensive and not available in some centers [9].Imaging studies are used to assess the extent, severity of involvement and complications of the disease e.g. intravenous urography (IVU), computerized tomographic scan and magnetic resonance immaging[10].

Patients and methods

This is a cross sectional double centered study of patients with recurrent urinary tract infections attends the private and public outpatient's clinics in Basra teaching hospital and Imam Husain medical city teaching hospital in Kerbala holy. The study was conducted over a period of three years starting from September 2010 to September 2013. Patients who full fill two out of the following three diagnostic criteria were considered to have UTB[1-3,6] .These criteria were: demonstration of MTB in urine by microbiological (AFB or culture), histopathological methods (demonstration of granulomatous lesion in kidney biopsy), and IVU. We exclude patients who prove to have genital TB, and those who had only positive findings in IVU. History of non specific constitutional symptoms (fever, fatigue, night sweat, weight loss or anorexia),suggestive urinary symptom like hematuria, and history of past pulmonary tuberculosis were taken from all patients. The demography of patients like age, gender, smoking and risk factors which include diabetes, chronic kidney disease and immunosuppressive medications were covered in this study[1,3]. Investigations were done for all patients and include the following: hemoglobin (Hb) with anemia definition of Hb < 13 g/dl in men and post-menopausal women and Hb < 12 g/dl in pre-menopausal women[11], fasting blood sugar normal value 70-110 mg/dl[11],serum creatinine normal value 0.6-1.1 mg/dl[11], erythrocyte sedimentation rate normal value in male=age/2 and in female age+10/2[11], general urine exam (GUE), urine culture for bacteria using standard culture media, three to six first morning midstream centrifuged urine specimens for acid fast bacilli (AFB) using Ziehl-Neelsen stain, urine culture for mycobacterium in Lowenstein-Jensen medium[3]. Plain radiographs of chest and spine were done to detect any pulmonary (active or old healed granuloma) or spinal involvement. Abdominal ultrasound ,intravenous urography (IVU) and TST were done to all of our patients[1,3]. The findings on IVU which is suggestive for renal tuberculosis include erosion of the tips of the calyces, blunting of the calyces or overt papillary necrosis and parenchymal scarring and calcification[10]. kidney biopsy were done for those patients who presented with acute or progressive renal disease with an elusive clinical picture when pulmonary symptoms and signs were not typical for tuberculosis, and in cases, when no specific bacteriological confirmation was established in cultures and no acid-fast organism was demonstrated in the urine

staining while their IVUs were suggestive[12]. Statistical analyses were performed using IBM-SPSS version 20[13], the data expressed as number and percentage of frequencies. Prevalence, sensitivity and specificity of TST were estimated[14]. Mean, standard deviation and error, and Chi-square were used as a test of significance where appropriate value <0.05 was considered significant[13].

Results

Among our 1500 patients enrolled in this study, 35 (2%) full fill the diagnostic criteria of UTB, and were included in this study. The remaining patients were excluded. The age range of patients was 20 to 85 years and the mean was 50.7 ± 14.9 SD.Eleven patients (31.4%) were male and 24 patients (68.6%) were female with a male/ female ratio of 1:2.3.Table 1 showed demographic characteristics of the patients. One patient (2.9%) was less than 20 years,9 patients (25.7%) were between 21-40 years,16 patients (45.7%) were between 41-60 years and 9 patients (25.7%) were more than 61 years. Nine patients (25.7%) had normal body weight, 23 patients (65.7%) were overweight and 3 patients (8.6%) were obese. Nine patients (25.7%) were smokers and 26 patients (74.3%) were non smokers.

Table 1. Demographic characteristics of the patients.

Character		**No. (%)**
Mean age in years ± SD		50.7 ± 14.9
Age distribution in years	< 20	1 (2.9)
	21-40	9 (25.7)
	41-60	16 (45.7)
	> 61	9 (25.7)
BMI distribution	15.5-24.9	9 (25.7)
	25-29.9	23 (65.7)
	>30	3 (8.6)
Gender	Male	11 (31.4)
	Female	24 (68.6)
Smoking	Smokers	9 (25.7)
	Non smokers	26 (74.3)

Figure 1 showed the clinical presentations of patients with UTB. Seven (20%) with dysuria, Seven patients (20%) had urolithiasis,7 patients (20%) were asymptomatic, hematuria in 9 patients (25.7%), nine patients (25.7%) presented with loin pain,10 patients (28.6%) had anemia, 12 patients (34.3%) with frequency ,Twenty three patients(65.7%) had constitutional symptoms, and Sterile pyuria presented in 28 patients (80%).

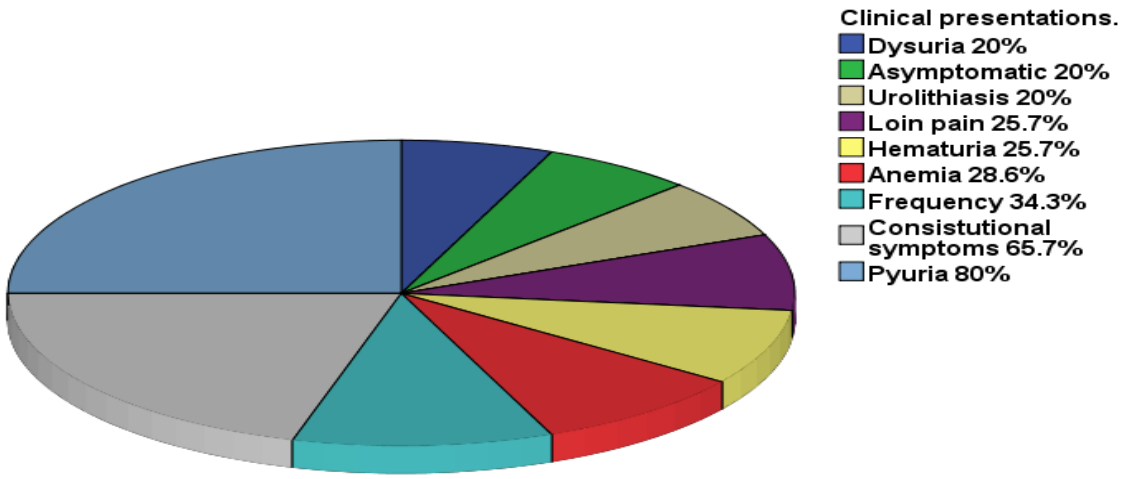

Figure 1:percentage of clinical presentations of patients with UTB,some patients had 2 or more symptoms .

Some of our patients had a comorbid illness that were considered a risk factors for UTB. These were immunosuppressive treatment in 1 patient (2.7%) with metastatic breast cancer, systemic lupus erythematosus in 1patient (2.7), diabetes mellitus in 8 patients (22.2%), both diabetes mellitus and chronic kidney diseases in 3 patients (8.3%), chronic kidney disease in 4 patients (11.1%) who were on haemodialysis program, and no underlying risk factors in 19 patients (52.7%), see figure 2.

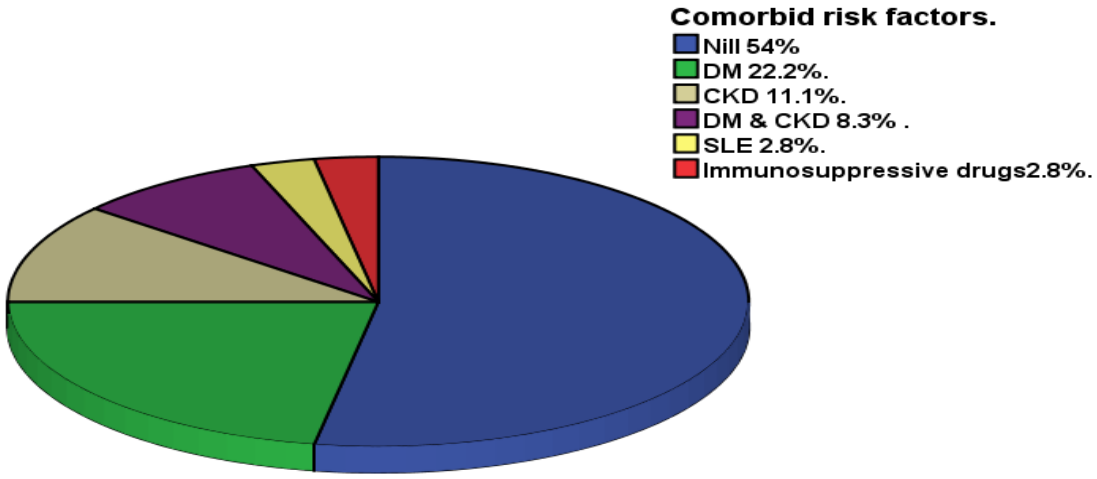

Figure 2:The percentage of UTB in association with other comorbid risk factors.

The urine for AFB was positive in 1patient (4%) and urine culture for mycobacterium was positive in only 2 patients (16%). The TST was positive in 26 patients (74%). The IVU showed abnormalities in 29patients(84%).40% of patients had a positive findings in histopathology of kidney tissue, see figure 3.

The sensitivity of TST and specificity were 82%, 50% respectively as shown in table 2 .

Figure 4 show the ROC curve of TST in relation to UTB. It shows at any point on the curve (blue) the cut off value is the one of the same value for the sensitivity and specificity which here 0.6 that is in the y axis and it measure 0.4 in the x axis which is 1- 0.4= 0.6 for the specificity value. At this cut off value of 0.6 the sensitivity was 82% and specificity was 50% for the TST in the diagnosis of UTB.

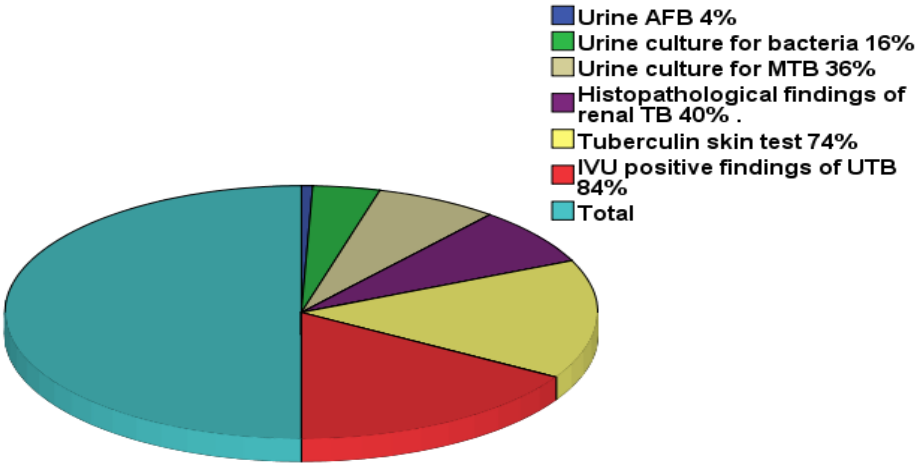

Figure 3:Percentages of positive investigations in patients with UTB.

Table2:The prevalence,seisitivity,specificity,95%confindence interval ,likelihood ratios, and positive, negative and false negative probability of TST in relation to UTB .

Prevalence	**Estimated Value**	**95%confidence interval**	
		Lower limit	**Upper limit**
	0.657143	0.47738	0.803156
Sensitivity	0.826087	0.604523	0.942762
Specificity	0.5	0.222868	0.777132
For any particular test result, the probability that it will be:			
Positive	0.714286	0.534754	0.847631
Negative	0.285714	0.152369	0.465246
For any particular positive test result, the probability that it is:			
For any particular positive test result, the probability that it is:	0.76	0.27367	0.863069
False Negative	0.4	0.136931	0.72633
likelihood Ratios: [C] = conventional, [W] = weighted by prevalence			
Positive©	1.652174	0.910316	2.998606
Negative©	0.347826	0.121228	0.997977
Positive(W)	3.166667	1.523743	6.581016
Negative(W)	0.666667	0.273838	1.623019

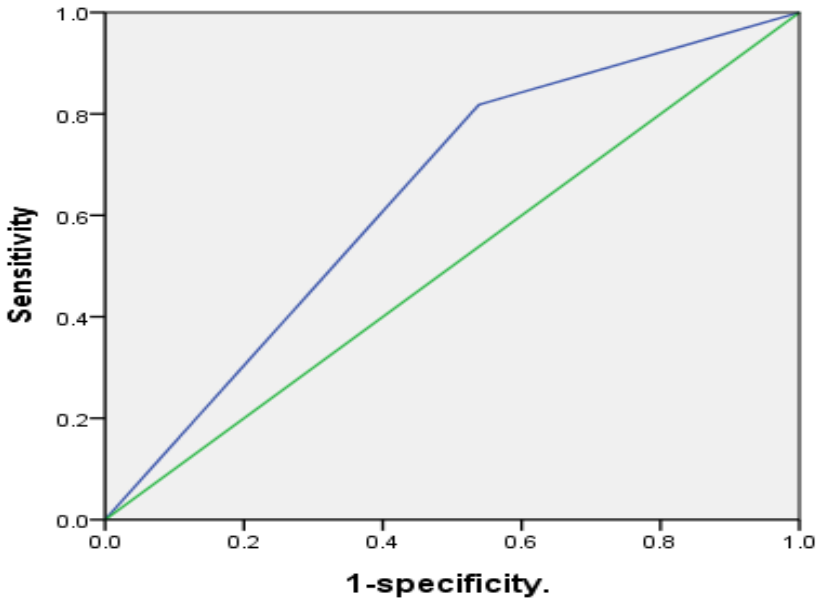

Figure 4:The sensitivity of TST in the diagnosis of UTB.Area under the curve = 0.64.Standard Error =0.1. 95% Confidnce Interval= 0.44 - 0.84.P value=0.17.

Comparing our results to that of developed and developing countries ,there were a statistically significant association between UTB and gender, past pulmonary tuberculosis, clinical presentations, and identification of MTB whether by direct urine staining or by culture. Tissue diagnosis was statistically significant in our results and that of developing countries, while not in developed countries. IVU was neither significant diagnostic test in Iraq, developing, nor in developed countries ,see table 3.

Discussion

The low prevalence rate 2% of UTB in our study is because our diagnosis was hypothesized in the setting of non-specific bacterial cystitis associated with a therapeutic failure or a urinalysis with a persistent leukocyturia and absence of bacteriuria. In addition we concentrated on the UTB and exclude cases of genital TB while other studies took both in the prevalence rate[3].

Table 3: Coparism of various patients variable between our results and that of developed and developing countries regarding UTB.

Variable		*Developed Countries	*Developing Countries	*Our Study	**P Value comparing developing countries to the developed countries	**P Value comparing Iraq to the developed countries	**P Value comparing Iraq to the developing countries
Total (N)		3036	5925	35			
Men(%)		62.9	65.4	11	P=0.02	P<0.001	P<0.001
Women(%)		37.1	34.6	24	P=0.02	P<0.001	P<0.001
Age median (range) in years.		42.6 (7-88)	39.2(5-83)	50.7(20-85)			
Previous TB.		37.9	38.4	20	P=0.66	P<0.001	P<0.001
Symptoms and signs.	Dysuria.	33.8	46.4	34.3	P<0.001	P<0.001	P<0.001
	Loin pain.	28.8	42.3	25.7	P<0.001	P<0.001	P<0.001
	Hematuria.	24.5	44.3	25.7	P<0.001	P<0.001	P<0.001
	Fever and malaise (constitutional)	23.2	19.9	65.7	P<0.001	P<0.001	P<0.001
	Asymptomatic.	8.4	0	20	P<0.001		P<0.001
Diagnosis by urine AFB and culture for MTB.		79.0	55.4	40***	P<0.001	P<0.001	P<0.001
Histopathology.		7.8	38.3	40	P<0.001	P=0.005	P<0.001
IVU		9.6	11.3	84	P=0.36	0.146	P=0.125

*Values are percentages unless otherwise noted.

Developed countries included the United States,Japan,and those in Europe. Other countries included Russia and those in Latin America. Asia and Africa.

**Comparison between developed countries and other countries (X^2 test).

***4% positive urine AFB and 36%positive urine culture for mycobacterium TB.

One fifth of our patients with UTB had a past history of pulmonary tuberculosis while in developed countries,2%-10% of them had pulmonary tuberculosis, and these figures rise to 15% - 20% in developing countries[3].The facts behind this difference in the percentages are; poor access of disseminated extra pulmonary lesions, the patients being usually paucibacillary (very often causing a negative smear), histopathologic findings are not pathognomonic(granulomatous reaction can be found in other diseases). The age in one half of our patients were 41-60 year-old which is the case in other studies in Korea and syberia[15,16]. On the other hand Raviglione and colleagues[17] found the most affected age group was 20-40 years. The clinical characteristics of UTB in older adults can be unusual and may be confused with age-related illnesses. Acute or chronic diseases, malnutrition, and the biological changes associated with aging can disrupt protective barriers, impair microbial clearance mechanisms, and contribute to the expected age-related diminution in cellular immune responses to microbes such as MTB[18]**.** The diagnosis of tuberculosis can be difficult, and this treatable infection is sometimes documented only on postmortem examination. Furthermore, institution-alized elderly persons are at especially high risk for reactivation of latent tuberculosis and are susceptible to new tuberculosis infection[18].The prevalence of UTB among females in our study was more than males[15-17]. We observe most of the females in this study of a child bearing age. This is due to the reproductive age group, and pregnancy increase the risk of reactivation of latent infections[19]. Population demography show increased numbers of women in relation to men in Iraq after the wars happened in this country. Generally in Iraq like many other middle east countries, Women spent more time at home and are more likely to be infected within the home than outside it, with a corresponding higher infectious dose, which could also contribute to the

young female excess in cases of disease [19].

Three quarters of our patients had a history of cigarette smoking which is a well known risk factor for tuberculosis. This may contribute to the excess of tuberculosis in older men. Other smoke exposure may also be important. Passive smoking has been shown to be a risk factor for tuberculosis in women and children[19].

Two thirds of our patients had constitutional symptoms like fever, weight loss, and anorexia. This is why our patients were less likely to offered histological diagnoses, a situation that points to late diagnosis. In such instance, UTB is consequently more severe, with a higher frequency of renal failure, these data underscore the relationship between the severity of UTB and the timing of the diagnosis[3].Recurrent or resistant urinary tract infection, sterile pyuria with or without hematuria were seen three quarters of our patients, while irritative voiding symptoms were seen in only one third of them. This was comparable with other studies [2,15,20].Renal tuberculosis was silent in one fifth of our patients, and progressed insidiousually that's why 11.1 % of our patients present with chronic kidney failure Furthermore, we observe in up to three quarters patients who present with tuberculous kidney infection were suffering cystitis as well. It was stated that when kidney and bladder TB is concerned ,the kidneys are mute and the bladder plays the role of vocal cords[21,22]. A cold perinephric psoas abscess was seen in one female in this study who responded to combined medical and surgical treatment[2] .

The presence of comorbid diseases increased the incidence of UTB in our results. This is consistent with Al asadi et al. [22] who found a rising number of people are contracting tuberculosis because their immune systems are compromised by immunosuppressive drugs & substance abuse, or AIDS. We found that UTB has a different clinicoradiological presentation in immunocompromised patients, with predominance of systemic symptoms, disseminated tuberculosis, multiple parenchymatous renal foci, and lower frequency of lesions of the collecting system. In the context of immune-suppression, UTB behaves as a severe bacterial infection, with bacteremia and visceral metastatic foci[24-25]. We recommend further studies to detect the prevalence rate of UTB among immunocompramised patients including those on chronic dialysis program.

Urinalysis was abnormal in most of our patients which is the case in other studies[26]. Sterile pyuria was found in 80 % in this study while Wise and Shteynshlyuger in their study found that it occurred in 51 % of cases [26]. This could be explained by more liberal use of antibiotics that has anti-mycobacterial effects[17] in our country which render the urine sterile even in the presence of secondary bacterial infection. A high index of suspicion should be made in cases of sterile pyuria who resist antibiotic therapy that have no antituberculous effects. Generally speaking ;The yield of urine examination by smear and culture for detecting the tubercle bacillus was low in our study. This is probably because of the intermittent shedding of the bacilli and is also observer-dependent.

The IVU was abnormal in more than three quarters of the studied patients, which is comparable to the studies of Figuerido et al[8], and Burill et al[9]. The Plain film of IVU showed renal calcification or stone in one fifth of our patients, other studies found this abnormality in s 14-18% of their patients [1,9.10,27].Ultrasonography is a poor modality to show morphological changes. It was useful as an office procedure to monitor the degree of hydronephrosis and renal lesions during medical treatment. It also gives information regarding the bladder volume[1], renal calyceal dilation and more overt evidence of obstruction.

40% of our patients had a positive finding in kidney biopsies. Their histological findings consist of epithelioid

granulomata, with or without caseation, containing Langhans giant cells. Renal function was not compromised in these patients. Some patient who were immunosuppressed, the granulomas were less well formed and caseous necrosis was seen less frequently[1].In three of our patients, chronic tubulointerstitial nephritis with granuloma formation was found, and caseation was found in the rest of our patients. This pathological findings can be explained by a combination of both infection and immunologic renal damage causing the kidney malfunctions[1,29,30] secondary kidney amyloid involvement was observed in one adult male patient in this study who developed end stage kidney failure and diarrhea. Secondary amyloidosis is an important cause of end stage renal disease [1].There are a number of case reports of tuberculosis associated with various forms of glomerulonephritis, but no firm associations have been established. We didn't have such cases in this study.

The TST was positive in most of our patients, which was comparable with Jacob et al[31],who found a positive results in 60-90% of patients with UTB. This study found an 82% sensitivity and 50% specificity for TST as diagnostic method for UTB. This is reciprocal of the results of other studies in India that demonstrated a sensitivity of 55% and a specificity of 80% for TST[25,32,33].This differences depend on several factors, such as the immunological status of the patient, and history of previous vaccination. Six patients had a false-positive results of TST in our study due to infection with nontuberculous mycobacterium in 1 patient, previous BCG vaccination in 2, and incorrect administration of the test in 3.False negatives TST occur in 4 patients, in 1 immunocompromized patient,1 elderly man 90 year old,1 patient with recent overwhelming infection, and 1with incorrect administration of the test.

In most of our cases, at the time of presentation there is no evidence of active pulmonary disease, although there may be clinical or radiologic evidence of past infection, suggesting that renal involvement occurs as a result of reactivation after a period of dormancy[1]. Other studies showed approximately 25% of cases of UTB are caused by reactivation of pulmonary latent TB in older persons. The kidney usually is infected by hematogenous spread of bacilli from a focus of infection in the lung[1].

lower rates of bacteriological positivity[3] .

Conclusion and recommendations

The clinical characteristics of UTB in older adults can be unusual and may be confused with age-related illnesses. The reproductive age group, and pregnancy has been thought to increase the risk of reactivation of latent infections in women. Three quarters of tuberculous kidney infection were associated with tuberculous cystitis, who initially presented with cystitis symptoms. Rising number of people are contracting tuberculosis because their immune systems are compromised. UTB has a different clinicoradiological presentation in immunocompromised patients.

The yield of urine examination by smear and culture for detecting the tubercle bacillus was low because of the intermittent shedding of the bacilli. The Plain film of IVU showed renal calcification or stone in 20% of our patients. Histological findings of UTB consist of epithelioid granulomata, with or without caseation, containing Langhans giant cells.

A high index of suspicion should be made in cases of sterile pyuria who resist antibiotic therapy that have no antituberculous effects. We recommend further studies to detect the prevalence of UTB among immunocompramised patients including those on chronic dialysis program.

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