The association of urinary tract infection with urothelial carcinoma

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Abstract:

Background: In Iraq bladder carcinoma is a major problem according to the results of the Iraqi cancer registry between the years (1991-2006). Cancer of the urinary bladder was the 2nd on the table of the commonest ten cancers in male and it was the 8th commonest cancer in females (1).

According to the same registry the main histological types were: Transitional cell carcinoma: 43.82%.

Sequamous cell carcinoma: 4.49%. Undifferentiated cell carcinoma: 0.31 %. Adenocarcinoma: 0.92%.

Male to female ratio was 3.39:1 the peak age incidence was found in the 70+ years (1). Bilharzial ovals were found in about 7%-29% of bladder cancers, which is lower than that in Egypt; 82-90% (2). On the other hand urinary tract infections are among the most common bacterial infections that lead patients to seek medical care. It had been estimated that more than 6 million outpatient visits and 300,000 hospital stays every year are due to urinary tract infections (3). The aim of this study is to find the association or disassociation between bacterial infection of the urothelium and urothelial carcinoma and if it was **associated which type is it:** causative or associative.

Material and Method: This study was carried out on 105 patients with carcinoma of the bladder (transitional, sequamous), whom were referred to the surgical specialties hospital, medical city for diagnostic transurethral endoscopy during the period between 5th of October 2007 till the 1st of September 2008. History of smoking, previous recurrent urinary tract infection and stone was taken, identification of the causative bacteria for their urinary tract infection was done from three samples collected; two urine samples (on admission and post-operatively) and one tissue sample (tumor biopsy).

Results: The results showed that: 85.65% of the patients had infections associated with their tumors, the rest 14.35% were negative. These infections were either Escherichia coli, Klebsiella, Proteus, Staphylococcus, Enterobacter, Citrobacter or Morganella spp. Escherichia coli was the most common 73.3% of all the cases. The results also showed that there was a significant association between positive urine culture on diagnosis for bacterial growth and urothelial carcinoma, also Escherichia coli was collected from the intracellular compartment by a mechanical approach.

Conclusion: Associations between urothelial carcinomas and bacterial growths were studied and showed that urothelial carcinomas were highly associated with bacterial growth especially Escherichia coli. Although Klebsiella, Proteus, Staphylococcus, Enterobacter, Citrobacter or Morganella spp., occured in a lower incidence, still had a role in urinary tract infection. Finding Escherichia coli intracellular and its high association with urothelial carcinoma could put these bacteria in the causative section of urothelial carcinoma through producing a recurrent acute infection.

Introduction:

Invasion by uropathogenic Escherichia coli

Uropathogenic Escherichia coli have not traditionally been considered an intracellular pathogen. Researches dating back to the 1970s and a number of more recent reports indicate that uropathogenic Escherichia coli can act as an opportunistic intracellular pathogen. (47)

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Standard gentamicin protection assays and microscopic studies of infected rats and mice bladder, along with studies using host cells grown in culture, have shown that bladder epithelial cells can internalize uropathogenic Escherichia coli both in vivo and in vitro (48) .

Similarly, investigations using cultured renal epithelial cells have demonstrated that these host cells can also internalize Escherichia coli (49).

The entry of uropathogenic Escherichia coli into the host's uroepithelial cells, rather being a deleterious event for uropathogenic Escherichia coli, can provide the bacteria with survival advantages (50).

Uropathogenic Escherichia coli invasion of the host cells within the urinary tract possibly enhances bacterial survival by providing protection from host immune defenses and allowing the pathogens greater access to deeper tissue (47).

The uroepithelial cells have innate ability to phagocytose adhered bacteria, this intimate contact with the host cells facilities the bacterial uptake (48).

More recently, some of the adhesive organelles (such as pilli, adhesins etc.) elaborated by uropathogenic Escherichia coli, along with few host factors have been shown to directly trigger and /or modulate bacterial entry into the host cells. Specifically both type 1 Pilli and Dr Family adhesions have been implicated as factors that can effectively promote bacterial invasion of host cells by activating distinct host signaling events (51, 52).

Once internalize, uropathogenic Escherichia coli could activate cytokine responses by stimulating intracellular Toll-like receptors independent pathway, such as the Lipopolysaccharide-dependent CARD4/NOD1 pathway that is triggered by invasive Shigella flexneri (53).

Pillus component may also engage Toll-like receptors and initiate inflammatory responses independent on Lipopolysaccharide or other bacterial factors (54, 55).

Within the bladder, the induced exfoliation of infected epithelial cells represents another hallmark of the host response to the interaction with Uropathogenic Escherichia coli (47). The bladder epithelium normally has an exceptionally slow turnover rate of approximately 40 weeks in both mice and human (56), large numbers of exfoliated bladder epithelial cells can often be found within the urine from human patients with urinary tract infections and from rodents with experimentally induced cystitis (57). In a mouse urinary tract infection model massive exfoliation of bladder epithelia is induced within 6 hours after transurethral inoculation with Escherichia coli expressing functional type 1 Pilli (58), also massive exfoliation in this system depends on Fim-H mediated bacterial interactions with the bladder surface epithelial cells, but does not require viable bacteria or functional Toll-like receptors this occurs by apoptosis (59).
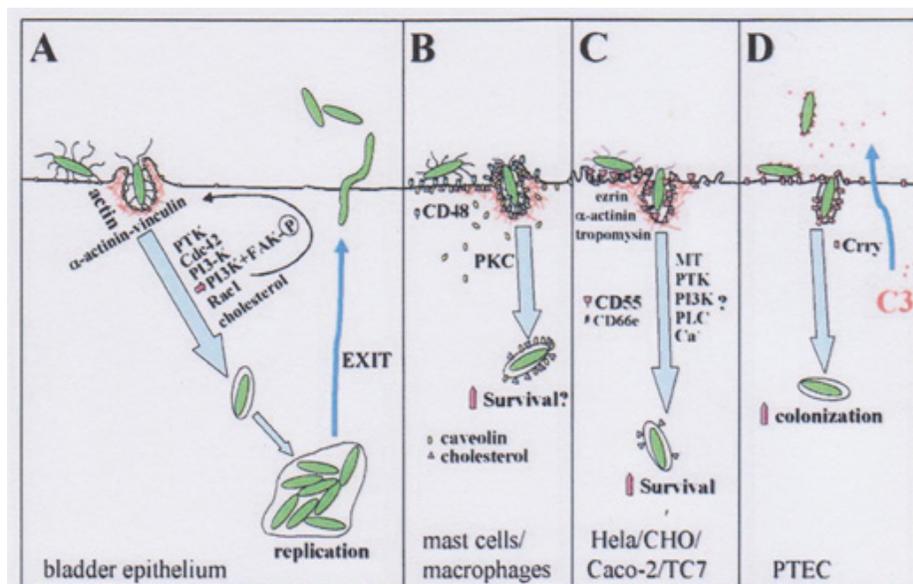
Fig. (4). Mechanisms and consequences of Uropathogenic Escherichia Coli invasion of host cells. Signaling molecules and other host components involved in the internalization of UPEC by various host cell types are outlined. Current data suggests that bacterial internalization via these pathways targets UPEC away from lysosomes and, in most cases, appears to enhance survival within the host cells.

A. UPEC that enter bladder epithelial cells by a type 1 Pillus-mediated pathway are able to multiply within membrane-bound vacuoles and are eventually induced to exit the host cell.

B. Type -1 mediated entry of UPEC into mast cells and macrophages.

C. Dr adhesion-mediated entry in to host epithelial –like cells.

D. C3-mediated uptake of UPEC by PTEC. Bacterial or LPS alone can induce secretion of C3 by PTEC (proximal tubular epithelial cells in the kidney) and subsequent internalizations between C3, UPEC, and the complement receptor Crry can lead to bacterial internalization.

PTK, protein tyrosine kinase; P13-K, phosphoinostide-3-kinase; FAK, focal adhesion kinase; PKC, protein kinase C; PLC, phospholipase Cγ; MT, microtubules; Crry, CR1-related protein y; LPS, Lipopolysaccharide.

This figure was designed by Mathew A. Mulvey (Pathological department, University of Utah, USA) (2002).

This exfoliation and their clearance from the host with the flow of urine serve as a fairly effective anti-bacterial defense (60) it also facilitates bacterial spread outside the host, and leaves underlying epithelial cells exposed and more susceptible to infection (61).

This may not only promote bacterial dissemination within the urinary tract but also allow uropathogenic Escherichia coli to enter a sheltered environment within the bladder where bacteria can persist for long intervals. Mice studies support this possibility, indicating that uropathogenic Escherichia coli can survive at low levels within bladder tissue in a seemingly quiescent state for weeks to months undetected by immunosurveillance mechanisms and often protected from antibiotic treatment (62, 63).

Such low level infections in humans may go unnoticed by standard clinical assays and could be a significant source for recurrent acute urinary tract infections that plague many women throughout their lives (47).
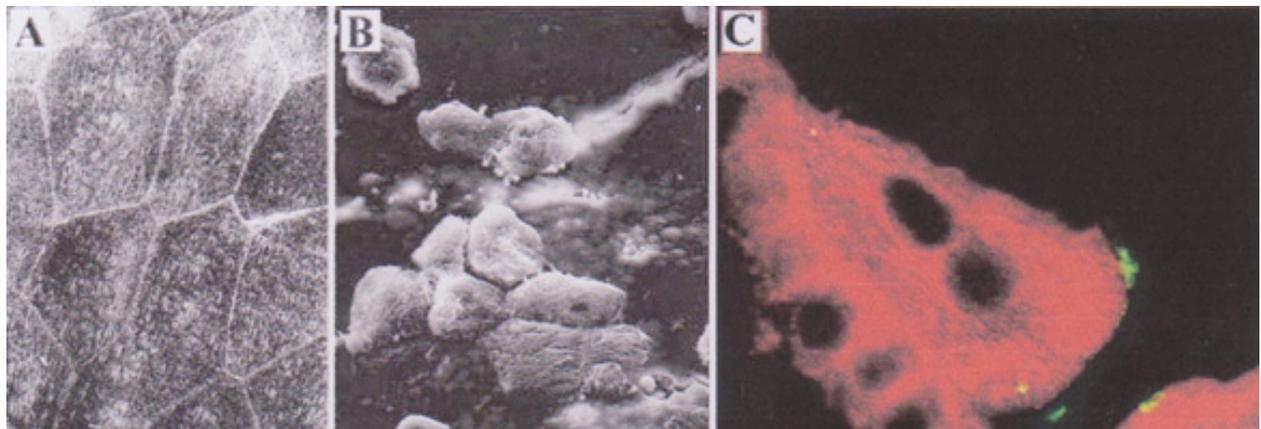

Fig. (5): Exfoliation of bladder superficial cells in response to infection with type 1-piliated E coli.
 Non- infected mouse bladder epithelial cells under electron microscope.
 Within 6 hours after inoculation of mouse bladder epithelial cells with ~ 10^8 colony-forming units of type 1-piliated E. coli showing exfoliation of the epithelial infected cells.
 Epifluorescent image showing an infected binucleate bladder epithelial cell starting to lift away from the bladder surface.
Figure 2 was taken from M. A. Mulvey (Adhesion and entry of UPEC) (2002).
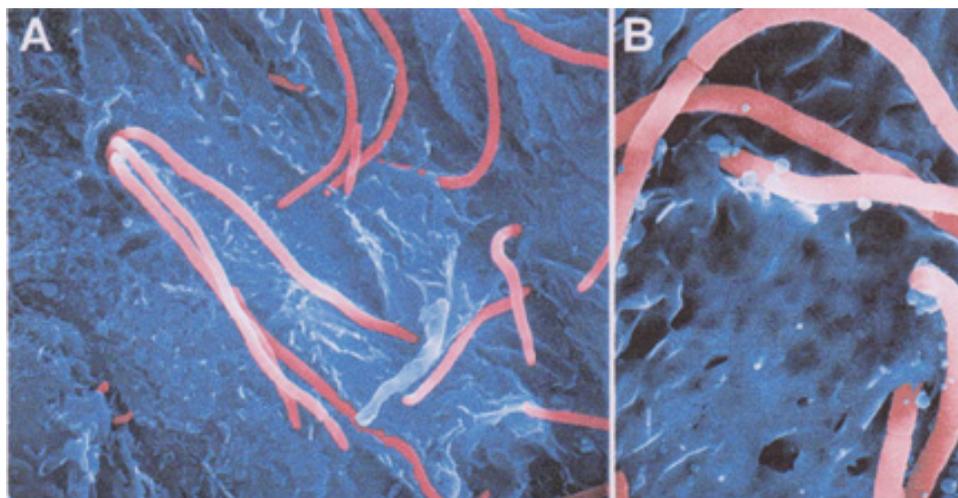
Figure (6): An electron microscopy view of efflux of filamentous UPEC from the bladder superficial epithelial cells.
It was taken from convert operations of Uropathogenic E.coli within the urinary tract by Jean M. Bower (pathologic department division of cell biology Utah, USA) (2005).

The association of chronic inflammation with a variety of epithelial malignant tumors has been recognized for many years, for example sequamous carcinoma may develop along the draining sinus in chronic osteomyelitis (64) and the development of adenocarcinoma is a significant risk in patients with chronic inflammatory bowel disease (65, 66).

Several epidemiological and experimental animal studies have suggested that infection of the urinary tract is a significant risk factor for the development of bladder carcinoma (67, 68). Based on the causes of bladder cancer it could be divided into two types: One produced by chemicals and tobacco smoking which is most common in the western world, the majority of which is transitional cell carcinoma. The second type of bladder carcinoma occurs as a complication for long standing urinary tract infection, which is mostly deeply invasive sequamous cell carcinoma, which has a more aggressive and a more fatal outcome. In the western world this type of cancer typically occurs in patients with spinal cord injury because such patients invariably develop chronic bacterial cystitis (69, 70), which could be due to urine stagnation.

In North Africa and the Middle East where Schistosoma heamatobium is endemic, there is a high risk factor for deep invasive sequamous cell carcinoma. It is the leading cause of cancer death in Egypt (71).

Several recent reports indicate that urinary tract infection promotes carcinogenesis in the urinary bladder of rats (72, 73).

In order to elucidate this mechanism of infection associated enhancement of the urinary bladder cancer they used a hetero-tropically transplanted rat urinary bladder system in an attempt to develop a reproducible animal model of bacterial cystitis-associated urothelial hyperplasia (74).

Instillation into the hetero-tropically transplanted rat urinary bladder of live Escherichia coli results in persistent infection, acute or chronic inflammation and also in a diffuse urothelial hyperplasia (75). Instillation into the hetero-tropically transplanted rat urinary bladder of killed Escherichia coli also induced hyperplasia which regressed after withdrawal of the killed Escherichia coli treatment; furthermore urothelial hyperplasia was induced by repeated instillation of protein-rich Lipopolysaccharide, the endotoxin derived from a cell wall component of bacteria. A finding common to bladders showing hyperplasia was the infiltration of neutrophils into the intracellular space of the urothelium and also into the lumen of the bladder (75).

The inflammatory response was associated with an increase in the hydrogen peroxide (H2O2) concentration and several cytokines (IL1 α, IL6 and TNF) in the bladder lumen .These observations in vivo suggested the possibility that reactive oxygen intermediates (ROI) and/or cytokines released during the inflammatory response might contribute to carcinogenesis (76). When stimulated by Lipopolysaccharide, polymorph nucleated cells generate a large quantity of hydrogen peroxide (H2O2) and reactive oxygen intermediates (ROI) (77). H□O□ as a source of ROI causes DNA damage and inducing the formation of 8-hydroxydeoxyguanosine (8-OHdG) an indicator of oxidative DNA damage (78). 8-hydroxydeoxyguanosine (8-OHdG) has been shown to increase in the DNA of target tissue and increased oxidative stress is directly related to increase tumor development (79, 80).

Chronic (on-going) bladder irritation and infections: Urinary infections, kidney stones, bladder stones, and bladder catheters left in for a long time have been linked with bladder cancer, but it is not clear if they actually cause bladder cancer. (120,121).

Urinary tract stones might induce chronic irritation that may lead to proliferative urothelial changes, or mechanical effect of stones on the epithelium might increase absorption and/or exposure to carcinogens in the urine, or they may be markers of chronic infections or conditions, which may, in turn, enhance bladder cancer risk (122).

Materials & Method:

Patient specimens

A total of 105 patients' specimens were selected from a population whom attended the surgical specialties hospital, medical city from the period 5th of October 2007 till 1st of September 2008 (12 month) for trans-urethral endoscopy due to the suspicion of bladder tumor and biopsy taking. Their ages ranged from 22-71 years. The male to female ratio is 1.763:1.

Examination and Clinical manifestations

The patients were interviewed using a data sheet (appendix). They were specially questioned about their age, chief complaint; their symptoms, passed history (recurrent urinary tract infection, smoking and history of renal stone) and they were also asked whether or not they took antibiotics.

All the patients had a history of painless hematuria and by ultrasound were diagnosed having thickening in the wall of the bladder.

All cases were thoroughly studied from bacteriological aspect. Each case was carefully assisted regarding isolation and identification of the causative agents as will be discussed with details later.

Materials

Reagents and chemicals: Blood agar base (oxoid), MacConkeys agar (oxoid), Manitol salt agar (oxoid), IMViC test reagent (Indole, methyl red, voges-Proskauer test, Simmons citrate), API rapid 20E (bioMerieux,Inc), Oxidase test reagents, Catalase test reagents, Coagulase test reagents, Microscope, Sterile urine cups, Platinum wire loop, Incubator, Petri dishes (disposable), Markers, Spirit lamp, Surgical blades, Formalin solution 10% & Normal saline.

Method

Specimens' collections: The first step in this research took place in the out- patient clinic of surgical specialties hospital, medical city after Uro-surgeon on call had completed the examination of the patient who was referred to him for the suspicions of having an intra-vesical mass in need for transurethral endoscopy.

As previously titled in the introduction urinary tract infection is defined from microbiological point of view as the existence of pathogenic micro-organisms in urine, urethra, bladder, kidney or prostate and since this research is mainly concerned with urothelial carcinoma, the approach should exclude any infection from the prostate since it isn't part of the urothelium. In

order to do so taking sample by normal mid-stream urine could be query, so the pre-operative sample was collected from the bladder itself through the trans-urothelial endoscope, in other words as soon as the tube reaches the bladder the urine flowing out was collected.

The advantages of this approach will specify the urine collected to be from the bladder not from any place below the bladder. While the main disadvantage is that the numbers of micro-organisms collected by the platinum loop are less than that obtained from mid-stream urine sample according to Bailey and Scott's diagnostic microbiology and so the loop must be a larger calibrated loop, this is because mid-stream urine will also contain bacteria collected from the prostate, urethra and the vagina (101).

The biopsy material was divided into two samples after taking the permission from the patient; one was sent to the histo-pathological department for diagnosis of malignant tumor, the second sample was put in a sterile container with ten percent formalin for five minutes to get rid of the attached microorganisms on the surface and then washed with sterile distilled water to get rid from the formalin. The specimen was then minced to small pieces with sterile normal saline to liberate any bacteria which might be present or embedded inside the tissue. The minced tissue was then inoculated on the surface of blood agar and MacConkey agar plates at (37C□ for 24 hrs.) if the culture was negative then it was re-incubated for a further 24hrs before it was regarded as negative. On the next day another urine sample was collected from the patient and culture and sensitivity test (post-operative sample) was done to examine if these bacteria were still persistent after exposing the bladder to more than 2000 ml of 1.5% w/v Glycine irrigation solution which has an osmolarity of 200mosmol and if the patient was still producing microorganisms, putting in mind that the operation is diagnostic rather than complete resection of the tumor.

The colony morphology was examined; Gram's stain slide preparation was done and examined under the microscope and then each bacterium was identified according to its biochemical character as will be discussed later.
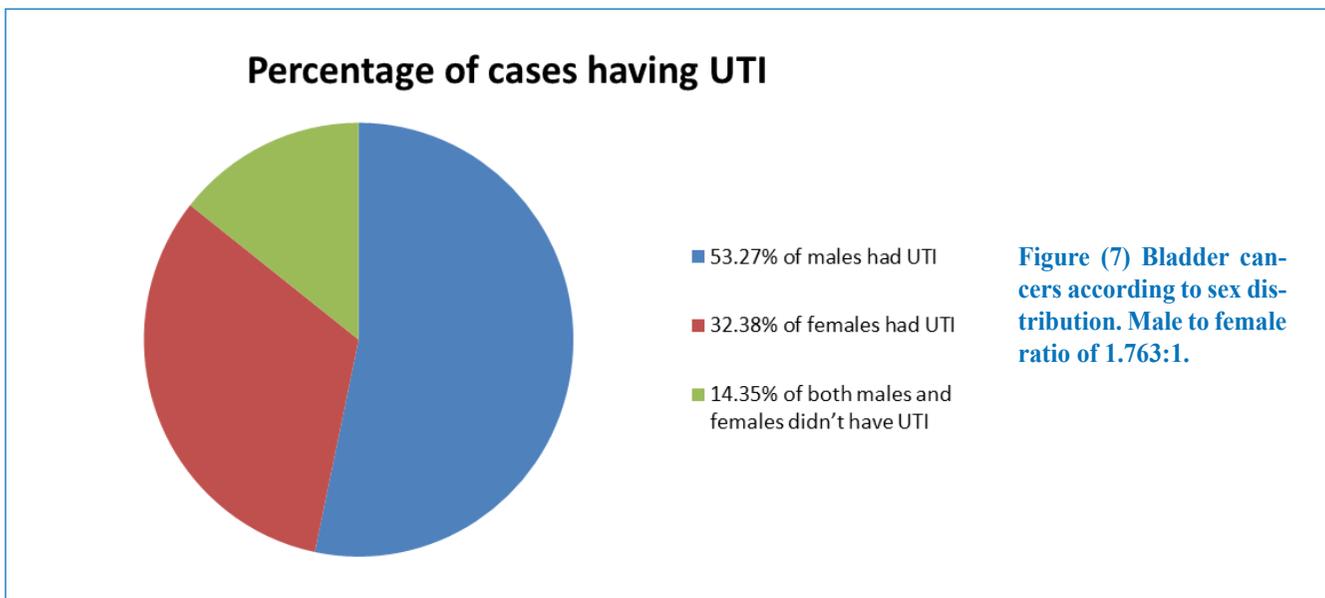
In molecular microbiology there are two ways to diagnose intracellular microorganisms. The first is by using specific antibodies labeled by fluorescine and the examining the tissue under florescent microscope (IFA) or by an electron microscope, it should be noted that in this case the serotype should be known which makes it useless for this research since the type of bacteria which has the ability to enter inside the urothelial cell is unknown. The other way is the mechanical way. In this way, first the surface of the cells must be sterilized by 10% formalin for five minutes then washing the tissue with sterile water to remove the formalin from the surface. After that, gentle cell wall damage is induced by adding 10% CaCl□ for another five minutes to evacuate the intracellular organelles to be examined (102).

Culturing the intracellular bacteria was through a modified mechanical approach by allowing the cells to die and their cell wall gets damage forcing the bacteria extracellularly on the culture media.
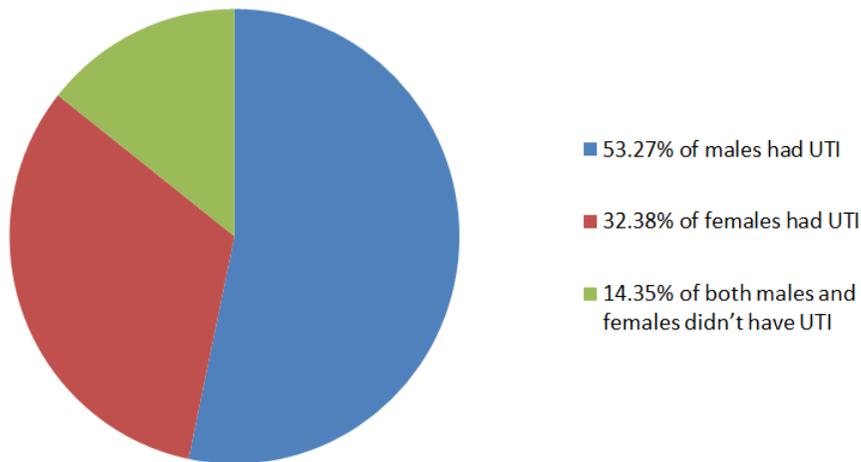
Biopsy sampling: During the operation the urologist uses transurethral endoscopy; a hypertonic fluid was pushed to expand the bladder, to visualize the internal bladder wall. Any fungating mass, papillary, flat, invasive, noninvasive, single to multiple will be either completely dissected or a biopsy taken from it for histological confirmation and grading.

A repeated internal wash of the bladder by the hypertonic solution to keep the internal surface of the blabber sterile during the operation had no effect on obtaining positive bacterial culturing post-operatively The instrumentations were completely sterile.

Results:

Percentage of cases having UTI

- 53.27% of males had UTI
- 32.38% of females had UTI
- 14.35% of both males and females didn't have UTI

Figure (7) Bladder cancers according to sex distribution. Male to female ratio of 1.763:1.

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Figure (8) Percentage of cases having UTI. Male to female ratio 1.65:1.

Table (3.1.1) Microorganisms isolated from the tested patients.

Bacteria	.No	%
Escherichia coli	77	73.3
.Klebsiella spp	6	5.7
Proteus	2	1.9
Staphylococcus	1	0.95
Enterobacter	1	0.95
Citrobacter	2	1.9
Morganella spp	1	0.95
Negative growth	15	14.35
Total	**105**	**100.0**

Table (3.1.2) The relationship between age and urothelial carcinoma.

	Transitional cell carcinoma		Sequamous cell carcinoma	
	Number	Mean+ Standard	Number	Mean+ Standard
Age	90	56.38±11.5	15	56.08±8.49

t=0.1, d.f=103, P=0.9

Table (3.1.3) The relationship between history of recurrent urinary tract infection and urothelial carcinoma.

History of Recurrent UTI	Transitional cell carcinoma		Sequamous cell carcinoma	
	Number	Percentage	Number	Percentage
Positive	67	74.4	13	86.7
Negative	23	25.6	2	14.3
Total	90	100.0	15	100.0

X_2=1.05, d.f=1, P=0.3

Table (3.1.4) The relationship between history of smoking and urothelial carcinoma.

History of smoking	Transitional cell carcinoma		Sequamous cell carcinoma	
	Number	Percentage	Number	Percentage
Positive	38	42.4	7	46.7
Negative	52	57.8	8	53.3
Total	90	100.0	15	100.0

$X_2=0.1$, d.f=1, P=0.7

Table (3.1.5) The relationship between history of renal stone and urothelial carcinoma.

History of stone	Transitional cell carcinoma		Sequamous cell carcinoma	
	Number	Percentage	Number	Percentage
Positive	31	34.4	5	33.3
Negative	59	56.6	10	66.7
Total	90	100.0	15	100.0

$X_2=0.007$, d.f=1, P=0.9

Table (3.1.6) The relationship between culture on diagnosis and urothelial carcinoma.

Culture on diagnosis	Transitional cell carcinoma		Sequamous cell carcinoma	
	Number	Percentage	Number	Percentage
Positive	56	62.2	14	93.3
Negative	34	37.8	1	6.7
Total	90	100.0	15	100.0

$X_2=5.6$, d.f=1, P=0.018 Fisher Exact Test= 0.018

Table (3.1.7) The relationship between culture from biopsy and urothelial carcinoma.

Culture from biopsy	Transitional cell carcinoma		Sequamous cell carcinoma	
	Number	Percentage	Number	Percentage
Positive	78	86.7	14	93.3
Negative	12	13.3	1	6.7
Total	90	100.0	15	100.0

$X_2=0.5$, d.f=1, P=0.4 Fisher Exact Test=0.6

Table (3.1.8) The relationship between culture of urine sample after surgery and urothelial carcinoma.

Culture after surgery	Transitional cell carcinoma		Sequamous cell carcinoma	
	Number	Percentage	Number	Percentage
Positive	67	74.4	11	73.3
Negative	23	25.6	4	26.7
Total	90	100.0	15	100.0

X_2=0.008, d.f=1, P=0.9 Fisher Exact Test=1

Patients

A total of 105 patients with urothelial carcinoma have met the following criteria. All the patients were on antibiotic for the previous four days, at least, before the operation, all were admitted for trans-urethral resection and diagnosis for a suspected bladder tumor with the exception of one patient whom came for a follow-up after BCG treatment for his already diagnosed transitional cell carcinoma of the bladder and all of them had had a previous abdominal ultrasound and were suspected of having a bladder tumor after finding a thickening of the bladder wall or a mass.

The age and sex distribution are shown in table (3.1.2) which reveals:

1- There are 69 males and 36 females.

2- The age range is between 22 years to 80 years.

3- The mean age of the patients is 56.38± 11.5 standard deviation.

Presentation

From the history which was taken from the patients, 57 (14%) of them had painless frank hematuria. While the rest ranged from pain during urination 33 (31.42%) cases, 11 cases of urgency, feeling the need to urinate without result, (10.74%) and one case of dysuria (0.95%).

In their past medical history 80 (72.2%) cases had previous recurrent urinary tract infection which was not confirmed by a single standard laboratory. 45 (42.9%) cases were smokers and 36 (34.3%) cases had a history of previous stone.

Findings

Out of the total there is 90 (85.7%) of the patients having transitional cell carcinoma and 15 (14.3%) patients having sequamous cell carcinoma, according to the slide examined from the biopsy taken during the operation which was examined in the pathological department of the central laboratories in the Medical City hospital Baghdad, these findings are shown in Figure (6).

Microbial findings

In Table (3.1.1) showed that 77 patients (73.3%) of the total had Escherichia coli while the rest types of Bacteria represented (12.35%) and (14.35%) showed no growth. Only one type of bacteria was cultured for each of the (85.65%) patients whom had infections associated with their tumors i.e. there wasn't any double growth on both blood and MacConkeys agar.

Escherichia coli were the only bacteria collected from the biopsy material which were cultured on both blood and Mac-Conkeys agar. Also Escherichia coli were cultured in (81.01%) of the patients whom said that they had previous more than two episodes of recurrent urinary tract infections and in (75%) of the patient whom said they had history of stone.

Table(3.1.3) shows that 67 (74.4%) of transitional cell carcinoma had a history of recurrent urinary tract infection and 13 cases (86.7%) of sequamous cell carcinoma also had the same history of recurrent urinary tract infection. No significant differences in the history of recurrent urinary tract infection between transitional cell carcinoma and sequamous cell carcinoma (P=0.3).

Smoking is reported in 38 cases (42.2%) of transitional cell carcinoma and 7 cases (46.7%) of sequamous cell carcinoma. No significant difference in reporting smoking between transitional cell carcinoma and sequamous cell carcinoma. (P=0.7) Table (3.1.4)

Thirty one patients (34.3%) of transitional cell carcinoma have a history of stone while only 5 patients (33.3%) of sequamous cell carcinoma. No significant difference in reporting history of stone between transitional cell carcinoma and sequamous cell carcinoma. (P=0.9) Table (3.1.5)

Positive urine culture on diagnosis for bacterial growth is present in 56 cases (62.2%) of transitional cell carcinoma and 14 cases (93.3%) of sequamous cell carcinoma. There is a significant association in culture on diagnosis. (P=0.018) Fisher exact test=o.o18 Table (3.1.6)

From Table (3.1.7) which concluded that positive bacterial cultures taken from the biopsy, during the operation which is 78 (86.7%) cases of transitional cell carcinoma and 14 (93.3%) cases of sequamous cell carcinoma. There is no significant association between urothelial carcinoma and bacterial culture from biopsy (P= 0.4).

In case of table (3.1.8) which represented the relationship between positive growth of bacteria on culture of urine sample after surgery and urothelial carcinoma there was also no significant association between them both.

Discussion:

Bladder carcinoma is a disease of worldwide distribution its incidence is raising in many countries, about 59 per cent of bladder cancer cases occurred in more developed countries. (123). They are among the most common human cancers in the USA, with approximately 50000 cases detected annually (94). It affects about 2000 people in Sweden every year (103) and has a peak incidence in the sixth decades of life .Ninety to

ninety five percent of bladder cancers derived from urothelium (96, 124).

According to the Iraqi cancer registry 1992-1994, urinary bladder cancer was the third of the ten most common cancers in Iraq, in 2006 the same registry classified it as the fourth (125), it was the second of the table of commonest male's cancer and it was the fourth commonest cancer in females. According to the latest WHO data published in April 2011 Bladder Cancer Deaths in Iraq reached 977 or 0.52% of total deaths (126). An etiological relationship to bladder Schistosomiasis which is wildly endemic in our country is thought to be related to such common occurrence of bladder cancer in Iraq (104,125).

In our country the first published reports of the association came from Shamma et al 1955(105), since then several other Iraqi investigators have supplied data supporting the association, like Shamma 1965(106), Talib 1970(107), Jasim 1983(109), Al Adnani and Saleh 1982(110), Al Ani and Al Waili 1984(108), Luay F. Tawfik 1985(111), Miqdad Al Ani 1985(112), T Al Saleem and N. Alash 1990(2), Nadham 2013

(127).

In this study it was found that the main histological type of bladder cancer was (85.7%) transitional cell carcinoma and (14.3%) sequamous cell carcinoma, these figures when compared with the previous Iraqi reports reveals a lower percentage of sequamous cell carcinoma in our study. Shamma et al 1965(106) found that sequamous cell carcinoma accounts for 55% and transitional cell carcinoma for 34% in his retrospective study, Luay F. Tawfik 1985(111) found that sequamous cell carcinoma accounts for 41% and transitional cell carcinoma for 47% and the corresponding results found by the Iraqi cancer registry 1992-1994 in which sequamous cell carcinoma accounts for 30.29% and transitional cell carcinoma for 60.5% explained this increase in the incidence of transitional cell carcinoma to the decrease in the incidence of sequamous cell carcinoma resulted from the decrease in the incidence of Bilharzial bladder cancer according to the Ministry of Health Iraq WHO Iraq report in 2005.
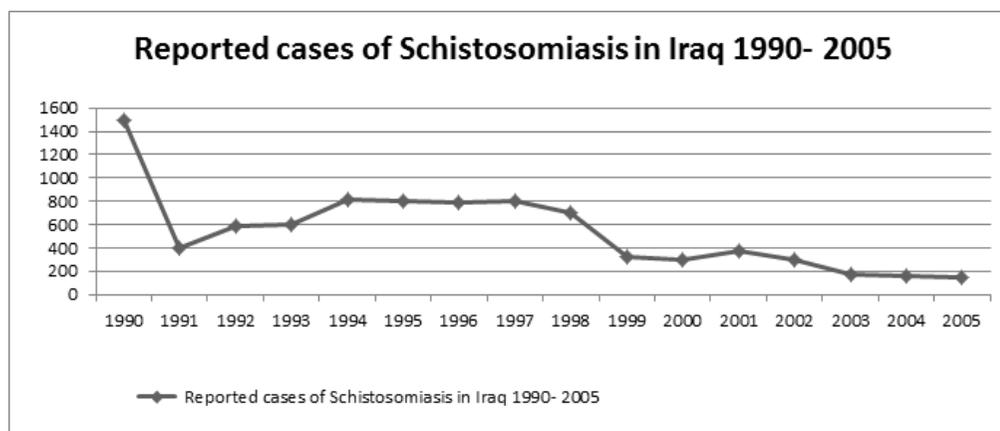
Figure (9). The incidence of Schistosomiasis in Iraq between 1990 - 2005. 2005 WHO report based on data taken from the Iraqi ministry of health.
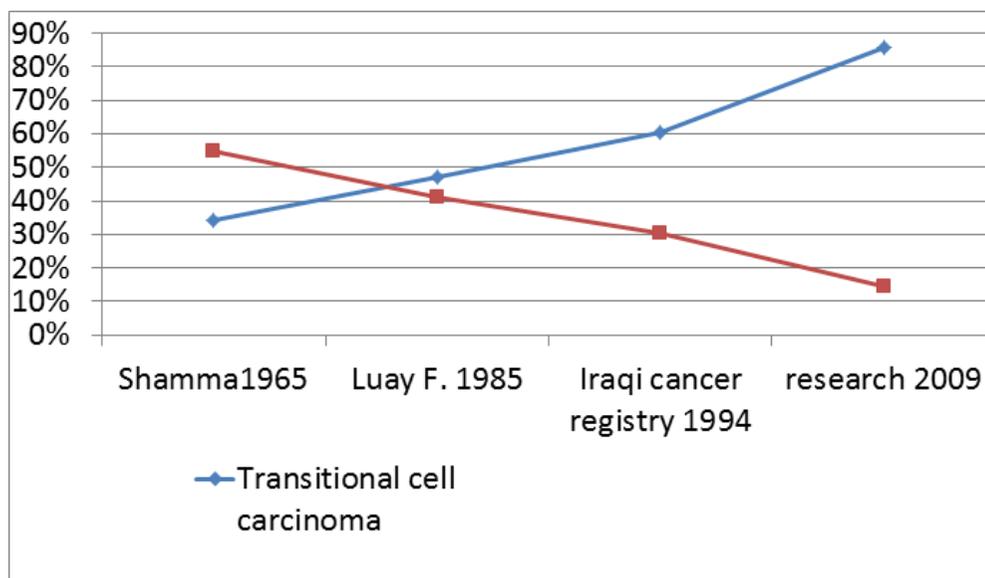
Figure (10) The change in the percentage of transitional cell carcinoma to sequamous cell carcinoma.

Still the increase in the incidence of transitional cell carcinoma and of urothelial carcinoma as a whole wasn't explained.

It was apparent from the above that the histological pattern of urothelial carcinoma in our country is taking a figure somehow similar to that of the western world were transitional cell carcinoma predominates forming 90.93% of bladder cancer cases in 1996 in the USA while the highest percentage of sequamous cell carcinoma 7%.

If so then the first cause for urothelial carcinoma in the western world is believed to be related to smoking tobacco (114).

Smoking cigarettes contributes in increases the risk of bladder cancer. The risk of smoking is up to six times that of a non smoker, with the highest risk for people who smoke heavily or have smoked for a long time (115). In Europe, two thirds of all bladder cancers in men and about a third in women are caused by smoking. Passive smoking also seems to increase the risk (116).

The chemicals in the smoke get into the bloodstream. They are then filtered out of the blood by the kidneys and end up in the urine. When the urine is stored in the bladder, these chemicals are in prolonged contact with the bladder lining. Chemicals called arylamines in cigarette smoke may be the cause of the increased bladder cancer risk in smokers (113). But still there was no significant association in our research between smoking and Urothelial carcinoma, this doesn't exclude smoking as a risk factor but in our country there is another cause for this high percentage of urothelial carcinoma.

Bladder stones are little lumps of calcium that can form in the urinary bladder. The risk of having urothelial carcinoma is higher in patients having a history of recurrent bladder calculi. This is because stones can cause chronic infection. Also the risk increases in patient having bladder stone for a long duration (117).

Although there isn't a significant association between urothelial carcinoma and stone in the bladder in this research, it doesn't exclude it from being a possible risk factor.

So until now we tested most of the possibilities which are known to cause most of the western world urothelial carcinoma (smoking, age, gender, stone) and proved there is no association between them and the Iraqi urothelial carcinoma statistically, still it is regarded the second leading cause of cancer death for the last six years its percentage is decreasing while still tobacco smoking is a national problem which is increasing year after year (118).

A history of urinary tract infection is currently accepted as an independent risk factor for the development of bladder carcinoma (94).

Also it was stated that recurrent acute urinary tract infection is an important risk factor for the development of carcinoma of the urinary bladder while testing on rats (74).

In Uganda a 62% of urothelial carcinoma were sequamous cell carcinoma which lacked Bilharzial ova in urine and histological sections and this high percentage to sequamous cell carcinoma was due to high incidence of urethral stricture complicated chronic gonorrhea which was highly prevalent in that country (97).

If we turn to the main issue for this research and ask the main question: are pathogenic bacteria associated with urothelial carcinoma in our country?

Statistically speaking then the answer will be yes, since the first sample collected of urine (urine sample on admission) proved that there was association with urothelial carcinoma both types transitional cell carcinoma and sequamous cell carcinoma (P=0.018) Fisher exact test=0.018 even if the patient was on antibiotic treatment before the admission which also proves that they are highly resistant bacteria.

It was noted that these bacteria where intracellular by collecting them from the malignant cells by inducing a gentle damage to the cell wall and evacuating the intracellular content and culturing them, although it proved to be non significant statistically but still it gave us positive culture of the same bacteria which was all Escherichia coli . The same bacteria which were collected in the first sample and the second sample were still collected post-operatively although the operation procedure included frequent washing the inside of the bladder by 1.5% w/v Glycine Irrigation solution BP which contained: Amino acetic acid 15.0 g normal saline 2.8g/L and theoretically its osmolarity =200mosm/L which should have made the procedure highly sterile!!! If there was any bacteria on the surface of the internal wall of the bladder then it would have been destroyed.

This could explain the non association of both samples (from the biopsy and that from the post-operative) with urothelial carcinoma; also the biopsy material was very small.

So is there association between urinary tract infection and urothelial carcinoma? The answer could be yes but it isn't as simple as that since it is a chain of events that could lead to urothelial carcinoma.

Now is it causative or associative the answer to that question could be causative because the first sample (on admission sample) proved a significant association between the two (urinary tract infection and urothelial carcinoma) and the bacteria were found intracellular, which means that they have the ability to produce a recurrent acute infection with high neutrophil infiltration with the release of nitric oxide (NO) and the later is responsible for most of the causes of inflammatory induced DNA damage.

If it was associative all three samples would have shown a significant association because it would have been the result of decreased immunity and also we would have found Staphoccocal spp., Pseudomonas spp. and Klebsiella ssp. in a higher percentage than Escherichia coli because these bacteria are more opportunistic in patient taking corticosteroids for nephrotic syndrome (98) than the percentage in this research.

Steroids produce a sever loss of immunity and that this decrease in the immunity should have been local or mild. Still if so then the relation between the history of recurrent urinary tract infection and urothelial carcinoma in table 2 would have been significant. Let us suppose that another factor is present which has no relation to the urothelial carcinoma producing this high figure of bacterial infection only one thing could come in mind and that is a stone in the bladder or having at least a history of one.

First all cases where free from stones; because there weren't reported by the trans-urothelial endoscope were examination of the inner wall of the bladder was performed. While for the other suspicion table 4 showed there is no significant association between a history of stone and urothelial carcinoma.

Supposing that it was simply an infection that occurred and that both cases urinary tract infection and urothelial carcinoma where two separate diseases happening in one bladder, if so then the prevalence of urinary tract infection in the female cases would have been higher than the males. Also that all cases didn't have any signs and symptoms of mal nutrition or were on corticosteroid therapy and neither of them received any antineoplastic therapy (chemical, radiotherapy) because all were admitted for confirmation of the diagnosis by trans-urothelial endoscopy and even though it was taken in to consideration by asking them during the history.

Conclusion

In a study conducted in the united States; A culture of urinary tract infection significantly elevated the risk of bladder cancer, particularly in individuals who reported three or more infections (relative risk (RR) = 2.0) (128). Also a weak association between a history of other UTIs and slightly increased risk among men was also reported by X Jiang (2009). (129)

These and many other reports supported the association of a culture on diagnosis and Urothelial carcinoma, where the cases showed no response to preoperative antibiotic cover.

In experimental studies, antibiotics used to treat bladder infections have been found to inhibit bladder cancer growth (Seay et al, 1996; Ebisuno et al, 1997; Aranha et al, 2000, 2002; Kamat and Lamm, 2004).(129)

Trimethoprim -Sulfamethoxazole, cefazolin (cephalosporin), and nitrofurantoin significantly inhibited cell proliferation in human TCC cell lines (130), producing a proliferation inhibition rate as high as 95%. Inhibition occurred in a dose-dependent manner at concentrations attainable in the urine after oral administration (Kamat and Lamm, 2004). Similar dose–response anti-cancer effects were shown for ciprofloxacin or other fluoroquinolones (Seay et al, 1996; Ebisuno et al, 1997; Kamat and Lamm, 2004). The mechanism for the antibiotics' cytotoxicity against bladder cancer cells remains unclear. Ciprofloxacin has been shown to cause cell-cycle arrest, disruption of calcium homeostasis, mitochondrial swelling, and redistribution of Bax (a pro-apoptotic protein) to the mitochondrial membrane, eventually leading to apoptosis in human TCC lines (Aranha et al, 2000, 2002).

This study suggests the association of urinary tract infection with urothelial carcinoma.

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العلاقة بين التهاب المجاري البولية وسرطان النسيج البولي

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كلية الصيدلة/ جامعة الأنبار

الخلاصه:

تضمنت الدراسة 105 مريضا يعانون من اورام المثانة البولية والذين راجعوا العيادة الخارجية لمستشفى الجراحات التخصصية في مدينة الطب واحيلوا لاجراء الفحص التشخيصي للنسيج البولي بالناظور للفترة ما بين الخامس من تشرين الاول 2007 ولغاية الاول من ايلول 2008, وكانت اعمارهم تتراوح بين اثنان وعشرين وواحد وسبعين سنة. أخذت نبذة عن الحالة المرضية, كذلك أخذت ثلاث عينات من كل مريض : عينة من الادرار الموجود بالمثانة البولية من خلال الناظور, عينة من نسيج الورم السرطاني, وعينة من وسط مجرى الادرار ما بعد اجراء العملية الجراحية. أرسل نصف كمية النسيج السرطاني الى قسم تحليل النسيج المرضي لمعرفة نوع النسيج. استنبت باقي النسيج المرضي وعينتي الادرار التي أستحصل عليها من خلال الناظور التشخيصي و عينة وسط مجرى الادرار ما بعد العملية في اغار الدم والماكونكي. لوحظ نمو البكتيريا في (85.65%) من الحالات وكانت في الغالب سالبة الغرام. كانت نمو أشريكية القولون ((E. coli (73.3%)) من العينات, اما عن الباقي فتتراوح بين الكلبسيلا, البروتيوس, المكورات العنقودية, انتيروبكتر, ستروبكتر و الموركنلا, ولم نحصل على نمو بكتيريا في (14.35%). دراسة العلاقة بين التهاب المجاري البولية و سرطان النسيج البولي و وجد ان هنالك علاقة قوية بين الاثنان وخصوصا مع أشريكية القولون, على الرغم من ان باقي البكتيريا تلعب دورا ولكن بصورة اقل. جمع أشريكية القولون من داخل الخلايا السرطانية, يضاف الى ذلك العلاقة القوية المتلازمة مع النسيج السرطاني يجعلها من الممكن ان تكون من المسببات لذلك الورم السرطاني من خلال قابليتها على انتاج اصابات حادة متكررة والتي تؤدي الى التهابات حادة متكررة.