Efficacy of Urine Cytology in the Detection of Bladder Urothelial Carcinoma: A Retrospective Study in Medical City-Baghdad

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ABSTRACT

Objective: To make a cyto-histological correlation and to evaluate the diagnostic efficacy of urine cytology in routine practice.

Materials & methods: From January 2015 to June 2020, one hundred and thirty-nine cases have been included in this case series retrospective study. Subjects were collected from the Ghazi al-Hariri Surgical Specialties Hospital, Medical city, Baghdad, Iraq. Ranging in age from fourteen to eighty-six years, presented most frequently with hematuria, or diagnosed radiologically with bladder tumor, who underwent cytological examination with the histological examination at the same time or within one year.

Results: Patients were mostly between sixty-one and seventy years old (36.7%). The studied group was made of male (61.2%) and female (38.8 %).

Fifty-five patients who were diagnosed as negative/ benign in cytology examination, and histological examination at the same time, eight patients were diagnosed as high-grade urothelial carcinoma when they were diagnosed negative/ benign in cytological examination, four patients were diagnosed negative in histological examination when they were reported as high-grade urothelial carcinoma in cytological exam, thirty-four patients were reported as high-grade urothelial carcinoma, cytologically and histologically. The sensitivity of high grade urothelial carcinoma detection in suspicious or malignant cases in urine cytology was (80.95%), while the specificity (92.98%). positive predictive value was (89.47%) when negative predictive value was (86.88%).

Conclusion: It has always been known that urine cytology is a powerful and an effective method for the screening of urothelial carcinoma; specifically, for high-grade urothelial carcinoma, and in follow up of patients after surgery or cystoscopy.

Keywords: Urine, cytology, histology, cystoscopy, urothelial carcinoma screening.

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فاعلية الفحص الخلوي في الكشف عن سرطان المثانة : دراسة رجعية في مدينة الطب ـ بغداد

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الخلاصة

الاهداف : الهدف من هذه الدراسة هو ايجاد العلاقة بين الفحص النسيجى والخلوى وتقييم الفعالية التشخيصية للفحص الخلوى لخلايا المثانة فى الممارسة الروتينية.

المواد وطرق العمل : من كانون الثانى ٢٠١٥ إلى حزيران ٢٠٢٠ ، تم تضمين مائة وتسع وثلاثين حالة. تم جمع الحالات فى قسم الزرع النسيجى فى مستشفى غازى الحريرى التعليمى ، مدينة الطب ، بغداد ، العراق . تتراوح أعمار المرضى بين أربعة عشر إلى ستة وثمانين عامًا ، فى الغالب يعانون من بيلة دموية او تم تشخيصهم بورم فى المثانة باستخدام السونار ، وخضعوا للفحص الخلوى مع الفحص النسيجى فى نفس الوقت أو خلال عام واحد.

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النتائج: غالبية المرضى تتراوح أعمارهم بين (٦١-٧٠)عام (٣٦.٧٪). وتكونت العينة من الذكور (٦١.٢٪) والإناث (٣٨.٨٪) .

خمسة وخمسون مريضًا تم تشخيصهم على أنهم (سلبى / حميد) فى فحص الخلايا ، والفحص النسيجى فى نفس الوقت ،و تم تشخيص ثمانية مرضى على أنهم (لسرطان الظهارة البولية عالى الدرجة) فى حين تم تشخيصهم كـ (سلبى) فى الفحص الخلوى ، وتم تشخيص أربعة مرضى (سلبى) فى الفحص النسيجى عندما تم تشخيصهم كـ (سرطان الظهارة البولية عالى الدرجة) فى الفحص الخلوى، وتم تشخيص أربعة وثلاثين مريضًا كـ (سرطان الظهارة البولية عالى الدرجة) فى كل من الفحص الخلوى والنسيجى .

كانت حساسية وخصوصية الفحص الخلوى فى الكشف عن سرطان الظهارة البولية عالى الجودة فى الحالات المشتبه بها أو الخبيثة (٨٠.٩٥٪) ، (٩٢.٩٨٪) على التوالى. كانت القيمة التنبؤية الإيجابية والقيمة التنبؤية السلبية (٨٩.٤٧٪) و (٨٦.٨٨٪) على التوالى .

الاستنتاجات : يعتبر الفحص الخلوى لخلايا المثانة طريقة معروفة وقوية وفعالة للكشف عن سرطان الظهارة البولية. على وجه التحديد ، سرطان الظهارة البولية عالى الدرجة كما ويتم استخدام الفحص الخلوى لمتابعة المرضى بعد الجراحة او ناظور المثانة.

الكلمات المفتاحية : بول ، فحص خلوي ، فحص نسيجي ، ناظور المثانة ، الكشف عن سرطان المثانة .

INTRODUCTION

Bladder cancer is the tenth most common type of cancer worldwide, with approximately five hundred and fifty thousand new cases and two hundred thousand deaths [1]. It is the ninth most common cause of cancer death in Iraq. It is more prevalent in males than in females [2-4]. The majority of cases occurs in patients over 55 years old. despite its rarity, bladder cancer can be found in young adults and in children [5]. transitional cell carcinomas (TCC) is considered the most prevalent neoplasm of the urinary tract, more than ninety percent of urinary tract neoplasm are TCC [6], other rarer types include squamous cell carcinoma, small cell carcinoma, and adenocarcinoma [7].

Cystoscopy with tissue biopsy usually render the standard diagnosis; however, in routine clinical practice, such diagnostic technique is intrusive and inconvenient, therefore; urine cytology becomes a highly useful method in the detection of urothelial cancer in individuals who are at risk [8]. Recurrent bladder tumors early detection after preliminary diagnosis is still the greatest consideration in the disease treatment, as a result , repeated cystoscopy examination and exfoliative cytology is the main way to make early detection of recurrence feasible [9-11].

Urine cytology is the straight forward microscopic examination of the exfoliated urothelial cells. In 1945, this technique was first reported by Papanicolaou and Marshall, which was continually used for urinary neoplastic cell detection [12]. In spite of the convenience and non-invasiveness of this technique with its well-known (exceeding 95%) high specificity for bladder cancer detection; it exhibits humble sensitivity mainly for low-grade urothelial neoplasm (LGUN) ; therefore, the presence of a LGUN will not be excluded by a negative result, as such; urine cytology (along with cystoscopy) is the most specific adjunct tool for the monitoring of bladder tumors [13].

If a comparison is made between urothelial cells exfoliated in urine and biopsy , the exfoliated urothelial cells depict a far greater surface area of the urinary tract while biopsy samples a specific restricted small area, making the detection of urinary tract tumors much easier, furthermore cytology allows a 3D study of urothelial cells [14].

Considerable number of parameters play a serious influence on the result and reliability of examination of urine cytology, including an accurate and adequate sampling of urine, a variation that may occur during processing of the sample in the same laboratory, subjective explanation and interpretation of results and absence of obvious criteria of reporting results, besides, many obstacles may arise when the patient has inflammatory state, synchronous presence of indwelling catheters, stones or infection of the urinary tract. Furthermore; several parameters can decide the accuracy of urine cytology including; the grade of the tumor , the type of sample and the technique which was used to take samples [15].

The aim of this study is to evaluate the effectiveness of cytological studies in the detection of bladder cancer compared to histopathological studies, in order to facilitate evolvement of a protocol that ameliorates the overall specificity and sensitivity of new cases detection and recurrence in patients with TCC.

MATERIALS AND METHODS

We conducted this case series retrospective study at the Department of Pathology, Ghazi al-Hariri Surgical Specialties Hospital, Medical city, Baghdad, Iraq. The included subjects were all urine cytological samples (either voided urine or catheterized specimens) of patients their age ranges from 14-86 years, presented with hematuria or diagnosed radiologically with bladder tumors, collected from January ٢٠١٥ to June 2020, who have had histological tissue samples went along with them, collected at the same time or within one year after cytological diagnosis had been made. Histological sections were stained with Hemotoxillin & Eosin stain, while cytological specimens were stained with Papanicolaou and Gimsa stain .

The collected data was assorted as the following: age, sex, types of histological samples; which were either biopsy, trans-urothelial resection of bladder tumor (TURBT), and cystectomy. Cytological diagnosis was classified into 3 categories: negative for malignancy/ benign, atypia or LGUN, and the last category is, high-grade urothelial carcinoma (HGUC), the original slides were diagnosed depending on N/C ratio, nuclear chromatin, features of nuclear membrane, and the presence of papillary architectures with fibro-vascular cores in case of LGUN.

While Histological diagnosis was categorized as; first: Negative/ Benign, second category: Atypia/LGUN, and lastly third category: HGUC. (Original slides were diagnosed according to the scheme proposed by the World Health Organization/ International Society of Urological Pathology in 2016).

Glass slides or paraffin blocks could not be retrieved for second reviews and unsatisfactory cytological or histological materials were not included in this study .

Statistical Analysis

Various clinic-pathological variables were analyzed using SPSS statistic program version 26.0.0.0, A probability of 5% was used to assign significant end results. (The correlation is considered statistically significant when p value =<0.05), and Chi square was used to calculate p value.

RESULTS

A total of one hundred and thirty-nine cases from 2015 – 2020 were included. Mean age was 59.87 (14-86 years). Patients were predominantly between sixty-one and seventy years old (36. 7%).The studied group consisted of male (61.2%) and female (38.8 %). Features of specimens were outlined in Table 1, Figure (1,2,3,4).

When a correlation between histological diagnosis and cytological diagnosis was done as shown in Table 2 , fifty-five patients who were diagnosed as negative / benign in cytology examination , and histological examination at the same time , eight patients were diagnosed as HGUC when they were reported negative in cytological examination , four patients were reported negative in histological examination when they were diagnosed as HGUC in cytological exam , thirty-four patients were reported as HGUC in both cytological and histological examination.

Five patients who reported as LGUN in cytological examination, were confirmed to have LGUN by histological examination, while five patients were reported as HGUC in histological examination, in the other hand four of them were diagnosed as negative or benign in histological examination.

According to Cytological diagnosis; Thirty-six male and thirty-eight female were diagnosed as negative or benign, fifteen male and three female were diagnosed with atypia or low-grade neoplasm, thirty-four male and thirteen female were diagnosed with HGUC, while according to histological diagnosis; thirty male and thirty-five female were diagnosed as negative or benign, twenty-two male and four female were diagnosed with atypia or low-grade neoplasm, thirty-two male and fifteen female were diagnosed with HGUC.

In histological specimens, the most common age group (between sixty-one and seventy years), twenty, nine, and another nine of them were diagnosed as negative or benign, atypia or LGUN, and HGUC, respectively. In cytological specimens, twenty-three of them were diagnosed as Negative/ Benign, six were reported as LGUN and twenty-two of them were diagnosed as HGUC.

The sensitivity of HGUC detection in suspicious or malignant cases in urine cytology was (80.95%), while the specificity (92.98%). Positive predictive value (PPV) was (89.47%) when negative predictive value (NPV) was (86.88%).

Table 1 : Features of the specimens

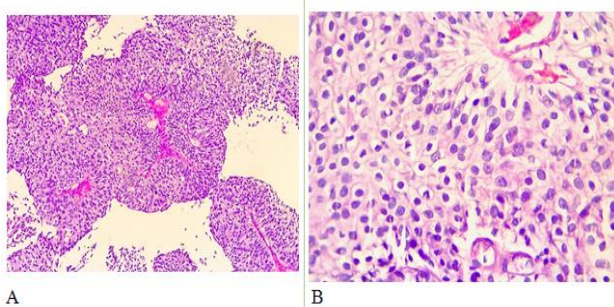| Features	Number of cases	Percentage
Types of histological specimen		
Endoscopic Biopsy	102	73.4%
TURBT	31	22.3%
Cystectomy	6	4.3%
Cytological Diagnosis		
Negative	74	53.2%
Atypia - low grade	18	12.9%
HGUC	47	33.8%
Histopathological Diagnosis		
Negative	65	46.8%
Atypia - low grade	26	19.4%
HGUC	47	33.8%

Figure (1): High grade Urothalilal Carcinoma in a bladder biopsy (Hemotoxillin and eosin stain) ,A: Papillary growth with disrordered architecture and with loss of polarity.   B: Enlarged nuclie with varation in size , pleomorphism , hyperchromasia , prominent nucleoli, (A:40X , B:400X).
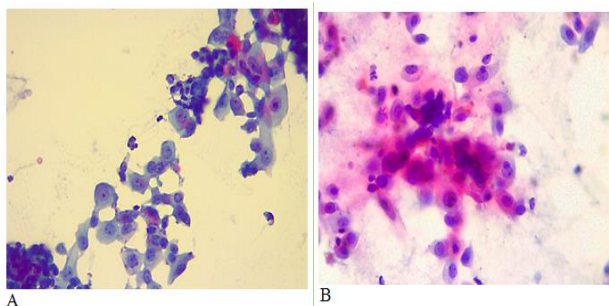

Figure (2): High-grade urothalilal carcinoma in a urine cytological specimen (Papanicolaou stain), A and B: Isolated malignant cells with increased neuclear to cytoplasmic ratio , coarse chromatin , large prominent nucleoli and hyperchromasia (A and B:400X) .
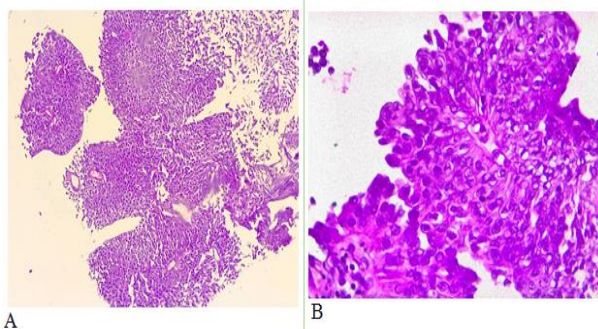

Figure (3): Low-grade urothelial carcinoma in a bladder biopsy (Hemotoxillin and Eosin stain), A: Papillary growth with predominantly ordered architecture minimal crowding, and minimal loss of polarity. B: Enlarged nuclei which are round-oval, slight variation in shape and contour, inconspicuous nucleoli (A:40X, B:400X).
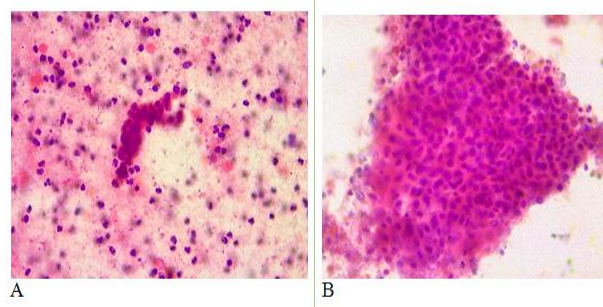

Figure (4): Low-grade urothalilal carcinoma a urine cytological specimen, (Papanicolaou stain) , A and B : Irregular cell clusters of cells with increased nuclear to cytoplasmic ratio , irrigular nuclear contours , with homogenous cytoplasm , inflamatory background can be seen in (a)   (A and B:100X) .

Table 2: Correlation between Histological and Cytological diagnosis

		Histological examination diagnosis			Total
		Negative , benign	Atypia , LGUN	HGUC	
Cytological examination diagnosis	Negative , benign	53	13	8	74
	Atypia , LGUN	8	5	5	18
	HGUC	4	9	34	47
Total		65	27	47	139

DISCUSSION

Urine cytology sensitivity in detecting Urothelial carcinoma of the bladder in this study was (80.95%), whereas specificity was (92.98%). The sensitivity of urine cytology and its specificity found in the compared studies were ranging from (29 – 94%), (26.3-95%) respectively as shown in Table 3.

The difference found in sensitivity and specificity are due to conflict found in considering the atypical category as positive or negative, discrepancy in the time interval between the cytological examination and obtaining the biopsy, and no dependable uniform criteria for atypical and for low grade category [16] .

The difference in results compared to Brimo et al [16] and Abdullah [17] , can be due to inter-institutional differences , considering difference   collecting specimen , dying methods, and other technical issues .

The cytological accuracy varies considerably among centers and there is lack of studies which can address this variation, so it is wise to use data specific for each institution when the effectiveness and advantage of urine cytology are assessed in the detection of TCC, furthermore, a great deal of variation among institutions can propose that the technique, beginning from the sample collection to the diagnosis, can be enhanced to correspond to the accuracy of laboratories with best results [18].

In order to yield an ideal diagnostic accuracy of urine cytology, several parameters can be relied on; most importantly the experience of cyto-pathologists and the sufficiency of specimens; therefore, in order to make a proper diagnosis, a combination of information including cytological, histopathological diagnosis and clinical history of the patient is needed [8].

Many studies suggested a theoretic limit concerning the ability of cytology in the diagnosis and detection of TCC. This limit is affected by the histologic classification used for the correlation with cytology, cyto-morphologic limitation, quality of specific patient specimen, and skill and experience of the cytologist. In spite of these limitations , many other cyto-histological studies have supported the efficacy of cytology when undergone under retrospective check-up by proficient experienced urinary cyto-pathologists [19].

This study has found that in daily practice, superior diagnostic yields can be achieved, as the sensitivity of urine cytology in detection of HGUC was (80.95%), specificity was (92.98%) and diagnostic accuracy (87.88%).

In our study four patients diagnosed as HGUC in cytology were diagnosed as negative in histology (false positive) , this finding can be due to small biopsy size , the method of obtaining samples in the first place possibly missed the pathological area ,or the sample was necrotic as a result of improper preservation with long time interval between obtaining sample and processing it in the lab .

while eight patients who histologically confirmed as HGUC were missed by cytology (false negative), this finding can be attributed to the lack of neoplastic shed cells in the urine or low cellularity, some of these cells in some samples have insufficient characteristic malignant features, overlapped with reactive conditions, poor preservation especially in voided urine samples or heavy inflammation obscuring the neoplastic cells .

Diagnostic discrepancy between cytological and histological examination concerning LGUN was due to poor inter-observer agreement for the cytological diagnosis of LGUN [20,21]. Insufficient association between cytological criteria of LGUN and HGUC [16].

The procedure in which the urine was collected also can affect the accuracy of cytological examination in reporting low-grade urothelial carcinoma, catheterization for example causes detachment of cells from deeper layers, these clusters of cells can form flat sheets or three-dimensional papillary configurations causing false-positive results reaching up to (11%), sometimes tissue fragments of basal cells and intermediate pyramidal cells are not uncommon in bladder washings. These fragments may show irregular borders [22].

Table 3: Comparing the sensitivity and specificity of this research with other studies

Similar studies	No. of cases	Sensitivity (%)	Specificity (%)
Plumworasawat et al. [8]	211	55.6	88.5
Abdullah [17]	191	94.1	26.3
Bastacky et al. [19]	1672	64	95
Brimo et al. [16]	2979	29.6	85

CONCLUSION

It has always been known that urine cytology is a powerful and an effective method for the screening of urothelial carcinoma; specifically, for HGUC.

Urine cytology specificity is high, while for LGUN; The diagnostic capability is humble, explaining the benign nature of these type of tumors .Great deal of false negative results explained by either inadequate or poorly preserved samples, close follow-up or further investigations are advised for urothelial carcinoma exclusion, while the false positive results occur due to reactive changes interpretation as LGUN.

In spite of lesser sensitivity of urine cytology compared to its specificity, it helps in the screening of patients who have high risk and for the patients who need follow up after surgery or cystoscopy.

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