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URINE CYTOLOGY OUTCOMES IN A TERTIARY HEALTH INSTITUTION IN NIGERIA

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ABSTRACT

Background: There is paucity of information on the significance of urine cytology in the management of the concerned patients in African literature. Objectives: To review the diagnoses and ascertain the overall diagnostic yield of urine cytology in a Nigerian tertiary health care centre. Materials and methods: Information on: age, sex, clinical presentation, pathologic diagnoses, specialty of the referring doctor and type of specimen were sought from duplicate urine cytology reports and request forms in pathology laboratory. The cytologic diagnoses were classified into two categories - diagnostic and non-diagnostic depending on the usefulness of the diagnoses to the requesting clinician/surgeon. Diagnostic smears included: inflammatory, negative for malignancy, suspicious for malignancy and positive for malignancy while non-diagnostic included: acellular, hypocellular, haemorrhagic smears and those composed of cellular debris/degenerating cells. Data was analysed with SPSS version 20 and presented as tables and figures. Results: There were 96 cases, 57 males and 39 females of which 53.1% were diagnostic while 46.9% were non-diagnostic. Hematuria was the commonest indication for urine cytology request (54.2%) out of which, 59.7% were diagnostic. Lower urinary tract symptoms constituted 20.8% of the requests, with 50% diagnostic yield. Overall, benign diagnoses were most prevalent (62.7%), with inflammatory lesions constituting 84.4%. Malignant diagnoses and cases suspicious for malignancy constituted 9.8% and 27.5% respectively. Conclusion: These findings tally with previous research findings. The poor diagnostic yield which could partly be from the poor handling of specimen prior to submission needs to be improved upon by more advocacies on proper handling and preservation of urine specimen.

KEYWORD: urine, cytology, hemorrhagic, diagnostic, malignancy, smear.

INTRODUCTION

Urine cytology is the microscopic evaluation of the morphologic features of shed urothelial cells. It is a simple, cost effective and non-invasive test; yet useful in screening for urothelial malignancies. Since the description of the presence of neoplastic cells in urine in 1864 by Sanders, urine cytology has remained relevant in the work-up of patients suspected of having urothelial tract malignancy.[1]

The accuracy of urine cytology is dependent on factors such as the tumor grade, nature of specimen, sampling technique, experience of the pathologist and the indication for the cytology request. Increased volume, multiple voids, voided urine, increase the sensitivity.[2,3,4]

While the sensitivity is as high as 98% in high grade urothelial carcinoma, it is as low as 8.5% in low grade.[5,6,7,8]

However, the paradox in urine cytology is that pleomorphic cells with enlarged hyperchromatic nuclei containing prominent nucleoli can be benign while malignant cells may appear less abnormal. Reactive changes due to bladder stones, infection, inflammation, intravesical therapy and instrumentation, as well as papillary clusters, are responsible for most such false diagnoses.[9]

The reporting system for urine cytology is prone to interobserver variability with the attendant avalanche of proposals on urine cytology reporting, ranging from the Papanicolaou system of 1947 to the most recent Paris consensus reporting system of 2013. The Papanicolaou Society of Cytopathology in 2004 recommended a diagnostic scheme that included "atypical urothelial cells" category which is further subclassified into reactive or neoplastic.[10] However, the morphologic criteria for separating atypia secondary to reactive lesion from that arising from neoplasia are not clearly defined. This lack of consensus on atypia, poses a major limitation to urine cytology.[2]

Although urine cytology requests are made by clinicians and urologists in most tertiary health facilities in Nigeria, there is paucity of information on the significance of these tests in the management of the concerned patients. This study was therefore undertaken to ascertain the overall diagnostic yield of urine cytology in the University of Port Harcourt Teaching Hospital.

MATERIALS AND METHODS

Urine samples which were cytologically evaluated and reported in Anatomical pathology department of the University of Port Harcourt Teaching Hospital, Port Harcourt, Nigeria were identified from the cytology register. The duplicate copies of the issued reports and case notes of the patients were retrieved from the archives of anatomical pathology and medical records departments respectively. The following information were retrieved and formed the basis for data analysis: age, sex, clinical presentation, specialty of the doctor referring the patient for urine cytology, and pathologic diagnosis. In order to avoid the potential problem of cellular degeneration inherent with stale samples, clinicians/surgeons are routinely advised to educate bedside nurses who interphase with patients more closely to prevail on patients or their relatives to send urine sample to the lab as soon they were collected or to fix same with an equal volume of absolute alcohol at the point of collection, if delays in submission is anticipated. The urine specimens were processed by smear preparation following centrifugation. All slides were stained with H & E and Papanicolaou stains and originally reported by any of the four histopathologists consulting in the department after detailed microscopic assessment of the cytomorphologic features of the shed cells. Further retrospective review of slides was at the discretion of the researchers and included cases originally diagnosed as insufficient. The cytologic diagnoses were classified into two major categories - diagnostic and non-diagnostic according to the potential usefulness of the diagnoses to the requesting clinician. While the diagnostic cases yielded information enough that the clinician makes informed judgement on the patients

Clinical condition and treatment modality, the non-diagnostic cases yielded diagnoses which were not informative enough to contribute to the clinician's decisions. Among the diagnostic categories were: inflammatory, negative for malignancy, suspicious for malignancy and positive for malignancy while the non-diagnostic included: acellular, hypocellular and haemorrhagic smears, as well as smears composed of cellular debris and degenerating cells. According to the 2013 Paris System for reporting urinary tract cytology, specimen is considered adequate if it is negative for malignancy (unobscured urothelial cells show benign nuclear features), atypical or suspicious for malignancy (non-degenerated urothelial cells show a N:C ratio of > 0.5 with either hyperchromasia or irregular coarse, clumped chromatin or irregular nuclear membrane). Out rightly positive for malignancy indicate that all the above listed nuclear features are present. Inadequate samples are those in which non-urothelial factors obscure urothelial cells or cases with absence of appropriate benign urothelial cells in instrumented specimen.

RESULTS

The urine of 96 patients were processed and reported within the study period. There were 57 males and 39 females giving a gender ratio of 1.5:1. (FIGURE 1) Out of the 96, 51 smears (53.1%) were categorised as diagnostic while 45 (46.9%) were non-diagnostic. Figure 2 Hematuria constituted the most common indication for urine cytology with 52/96 smears (54.2%) out of which, 31/52 (59.7%) were diagnostic. Lower urinary tract symptoms accounted for 20/96 (20.8%), with 50% diagnostic yield. The rest of the indications were relatively uncommon (Table 2) Majority of the patients – 59/96 (61.5%) belonged to the economically viable age range of 21-60 years, while the elderly (61-90 years) and the young (0-20 years) constituted 32/96 (33.4%) and 5/96 (5.1%) respectively. The single most involved age group was 31-40 years (4^{th} decade) with 21/96 cases (21.9%) while 0-10 (1^{st} decade) was the least involved. (Table 3) Hematuria contributed the most to the diagnostic category of the cases with 31/51 cases (60.8%), followed by LUTS with 10/51 cases (19.6%) while those with gynaecologic symptoms 1/51 case (1.9%) was the least. Table 4 Of the diagnostic category, benign cases were most prevalent with 32/51 (62.7%) out of which inflammatory lesions constituted 27/32 (84.4%). Suspicious for malignancy made up 14/51 (27.5%) while overtly malignant cases constituted only 5/51 (9.8%).Table 4. Acellular smears constituted the most frequent finding among the non-diagnostic category with 18/45 (40%), followed by cases with cellular debris devoid of characteristic cytologic details of the constituent cells with 11/45 (24.4%). Haemorrhagic cases constituted 3/45 (6.7%) of non-diagnostic category. Table 5.

Table 1: GENDER DISTRIBUTION.

DIAGNOSES	MALE	FEMALE	TOTAL
Acellular smear	9	9	18
Cell debris	7	4	11
Hypocellular	6	3	9
Degenerating cell	3	1	4
Haemorrhagic smear	3	0	3
Inflammatory	19	8	27
Negative for malignancy	3	2	5

Suspicious of malignancy	6	8	14
Positive for malignancy	1	4	5
Total	57	39	96

TABLE 2: INDICATIONS FOR URINE CYTOLOGY.

Indication	No	%	Diagnostic	Non-diagnostic
Hematuria	52	54.2	31	21
LUTS	20	20.8	10	10
Gynae Symptoms	7	7.3	1	6
Flank pain	4	4.2	4	0
Necroturia	4	4.2	2	2
Neurogenic bladder	2	2.1	0	2
Scrotal swelling	2	2.1	0	2
Groin mass	2	2.1	0	2
Bladder mass	3	3.1	3	0
Total	96	100%	51	45

TABLE 3: AGE DISTRIBUTION.

Age range	Diagnostic	Non-diagnostic	Total	%
0-10	0	2	2	2.0
11-20	1	2	3	3.1
21-30	4	6	10	10.4
31-40	11	10	21	21.9
41-50	8	6	14	14.6
51-60	9	5	14	14.6
61-70	11	6	17	17.7
71-80	5	4	9	9.4
81-90	2	4	6	6.3
Total	51	45	96	100

TABLE 4: ANALYSIS OF DIAGNOSTIC CATEGORY.

Indication	Inflammation	Negative for malignancy	Suspicious of malignancy	Positive for malignancy	Total	%
Hematuria	16	3	9	3	31	60.8
LUTS	6	1	3		10	19.6
Gynae Symptoms		1			1	1.9
Flank pain	2		2		4	7.8
Necroturia				2	2	3.9
Bladder mass	3				3	5.9
Total	27	5	14	5	51	99.9

TABLE 5: ANALYSIS OF NON- DIAGNOSTIC CATEGORY.

Diagnosis	Accellular smear	Cellular debris	Hypocellular smear	Haemorrhgic smear	Degenerating smear	Total	%
Hematuria	7	6	5	3		21	46.7
LUTS	3	5	0		2	10	22.2
Gynae Symptoms	2		2		2	6	13.3
Necroturia			2			2	4.4
Neurogenic bladder	2					2	4.4
Scrotal swelling	2					2	4.4
Groin mass	2					2	4.4
Total	18	11	9	3	4	45	99.8
	40%	24.4%	20%	6.7%	8.9%	100%	

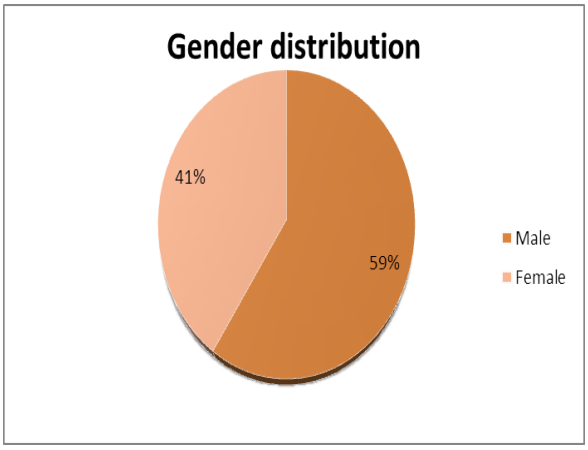

FIGURE 1: Gender Distribution.

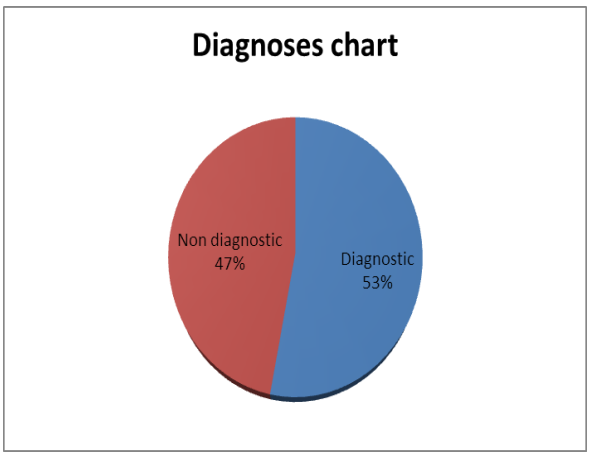

Figure 2: Diagnoses distribution.

DISCUSSION

As the controversy and uncertainty over the usefulness of urine cytology continue to rage, several researchers have worked on the significance and usefulness of urine cytology in suspected lower and upper tract urothelial malignancies especially from the developed countries but there remains a significant void in the literature of Africans, specifically Nigerians in this topic. This paper lends a contribution from the Niger Delta region of Nigeria.

The diagnostic yield of this study is relatively low - 51/96 (53.1%). This is consistent with the literature documentation that the sensitivity of urine cytology is low although the specificity is high.[7,8]

Our centre performs urine cytology routinely on hematuria patients. This explains why more than half (54.2%) of the processed urine were on account of hematuria. Similar practice obtains in other urology tertiary health care centres in developed countries, including UAE.[11,12] Also the American Urology Association (AUA) recommends voided urine cytology for all patients with asymptomatic hematuria.[13] Lower urinary tract symptoms were the next common indication for urine cytology in this study. This is consistent with reports by other reseachers that dysuria and other irritative urinary symptoms were common reasons for the performance of urine cytology.[14]

That about 60% and 20% of hematuria and LUTS cases respectively were diagnostic indicates the higher tendency of pathologic conditions of the urogenital tract to be associated with hematuria than LUTS. This strengthens the practice of urine cytology in hematuria. However, only 3/31 (9.7%) and 9/31 (29%) of hematuria were diagnostic of malignancy and suspicious of malignancy respectively. Thus the rate of detection of malignancy is low. Although there was no correlation of the subsequent cystoscopy and biopsy findings of the patients because the subsequent cystoscopy and biopsy reports of the patients were very sparse, thus making the precise calculation of the sensitivity difficult. However, the sensitivity of urine cytology for the detection of malignancy remains generally low, thus prompting some researchers to make negative conclusive remarks on the need to routinely perform urine cytology in hematuria patients. For example, Mahmoud et al in their work in Saudi Arabia asserted that routine urine cytology does not affect the diagnostic strategy for urothelial cancer, and so, should not be carried out routinely on all patients but on selected patients[11]. However, these workers did not specify the category of hematuria patients to potentially benefit from urine cytology. Also Said et al concluded that urine cytology is not only of limited clinical value as a first line investigation for all hematuria patients but also costly, and therefore should not be a routine test.[12]

Cases designated as suspicious of malignancy/atypia represent a gray zone between the benign diagnoses (including reactive and instrumentation changes) and the malignant categories. Little wonder that it was designated a wastebasket that encompasses different processes (eg, cell clusters, poorly preserved cells, quantitatively low number of cytologically atypical cells) by Fadi et al.[2] Raab et al also alluded that it is used variably by individual cytopathologists in different institutions.[6] For example, some studies consider suspicious cases as negative for malignancy as long as the cystoscopy and upper tract imaging results are normal.[5,17] Also, Fadi et al reported that an atypical urothelial cell diagnosis does not have a significantly increased risk of urothelial neoplasia compared with the benign diagnostic category.[2]

Altogether, malignant cases constituted only 9.8% in this study while cases suspected of being malignant constituted 27.5%. Comparatively, Mahmoud et al in Saudi Arabia reported 0.3% positivity for cancer and 2% atypical cytology while Lotan et al reported 1% positivity.[7,11] Said et al in UK reported positivity of 5.4% and suspicious cases of 9.4%.[12] The observed discrepancy among the various researchers could be a reflection of the inter observer variability as well as differences in the burden of urogenital tract malignancy in the different working environments.

Low sensitivity is more common with low grade urogenital malignancies, unlike the high grade ones. This is attributable to the fact that urogenital tumours of low or even intermediate grades or small sizes are less likely to exfoliate cells spontaneously from the tumour mass due to the relatively preserved intercellular attachments.[7,8,15] In these categories of urogenital tumours, negative cytology would therefore not rule out carcinoma.

To improve the sensitivity, centrifugation of whole voided specimen or multiple samples should be adopted. [3] A fresh, uncontaminated specimen is required in order to maximize the usefulness.[9]

Besides, the specialty of the doctor making the request can also affect the outcome of urine cytology. In a study, there was significant difference in the rate of positivity of urine cytologies requested by urologists from those requested by non-urologists - 56% and 6%, respectively.[16] Thus urine cytology should be limited to proper clinical situation for an enhanced sensitivity. In our study, all the requests were made by urologists, hence the relatively high detection rate of malignancy.

Cellular degeneration could contribute to false positive diagnosis or cause an increase in the number of suspicious cases because, the associated process of nuclear disintegration may be misinterpreted as abnormal chromatin condensation. That is why the first morning sample of urine should be avoided in cytology due to the degenerating effects produced by overnight stagnation of urine. The second morning sample is preferred. However, because voided urine samples the entire urinary tract - from the pelvis to urethra - "funnel effect" there is the disadvantage of contamination by squamous cells especially in females.[6] Therefore, catheterized urine sample is preferred over voided one. Wash and brush samples which can be obtained from the bladder, ureter or pelvis during cystoscopy provide better cellularity, targeted sampling and lack of contamination, thus making it most suitable for cytologic evaluation. In our cases, there is paucity of information on the type of samples submitted.

Owing to these limitations with urine cytology, additional lab-based markers are needed in the evaluation of urine. A study by Cha et al found that immunocytology outperforms urine cytology and increases the accuracy of predictive models by a statistically and clinically significant margin for patients with painless hematuria.[18] Also, other biologic markers have been developed for the purpose of improving the cytologic diagnosis of bladder malignancies.[19]

This retrospective study is limited by the relatively small data available for analysis and the conclusion may not be tenable for the general population. This paper would have been further enriched by some data which were not analysed, like the type of urine.

CONCLUSION

The low rate of malignancy detection in this study tallies with findings from previous researches across different racial and geographic divides of the world. The poor diagnostic yield which could partly be from the poor handling of specimen prio to submission needs to be improved upon by more advocacies on proper handling and fixation of urine samples.

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Conflict of interest declaration

We declare no conflict of interest in this study.

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