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Diagnostic Value of Cytology of Voided Urine

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A B S T R A C T

There are 961 new cases and approximately 366 deaths from urothelial carcinoma registered annually in Croatia. Exfoliative urinary cytology has important role in detection of high grade urinary tumors, invasive and in situ lesions respectively. In contrast to cystoscopy and biopsy, cytology is a noninvasive method which is easily repeated. The aim of this retrospective study was to assess value of urinary cytology in our institution. For this purpose only patients with histological diagnosis and clinical follow up were considered. There were 138 urine specimens with cytological diagnosis of dyskaryosis, suspicious for malignancy or malignant and histology and follow up data examined at our Department of Clinical Cytology between 2004 and 2011. Cytological diagnosis suspicious for malignancy and malignant were considered positive and the results were correlated with histological diagnosis according to the WHO histological classification of tumors of the urinary tract. Patients with negative histological findings were followed for the next two years. The positive predictive value of cytological detection of malignant urothelial lesions was 91.8%. In 10 cases cytological diagnosis of malignancy was not confirmed histologically or clinically which makes the total of 8.2% of false positive reports. Of the total of detected malignant urothelial lesions 90.9% are high grade lesions and only 9.1% low-grade lesions; 67.3% are invasive lesions and 32.7% non-invasive lesions. Cytological findings of dyskariotyc cells requires further urological investigation because such findings in further processing prove the presence of tumor in 93.8% of cases. In conclusion: cytology is very good diagnostic tool for detection of high grade invasive and noninvasive carcinomas of the urinary tract. In order to make it more efficient we need to study its limits carefully, define diagnostic criteria and reach consensus in nomenclature.

Key words: *urothelial tumor, urinary cytology, CIS, atypical cells, dyskaryotic cells, urothelial neoplasia, transitional cell carcinoma, high grade urothelial carcinoma, papilloma, low grade, cytology, histology, bladder cancer, positive predictive value*

Introduction

The cancer statistics clearly demonstrate a rising incidence of urothelial tumors, especially in the industrialized and urban areas[1,2]. In Croatia, 961 new cases of urothelial carcinoma are estimated annually, with approximately 366 deaths[3]. Most urothelial tumors have long survival due to indolent nature of the neoplasms and the possibility of effective therapy if discovered early. Although 70% of bladder tumors are superficial or only minimally invasive, 50–70% of these patients will have recurrent or new tumors, up to a third of which are of higher grade and stage[1,4]. The remaining 30% initially present with muscle invasion or distant metastases (lymph nodes, liver, lung, bone, but also adrenal gland, orbit)[1,5].

Concurrent tumors different in histological grade and stage may develop in the urothelium of the urinary tract. Detecting and treating one at a certain location does not deny the existence of another one which might be of a higher grade.

It is the early diagnosis of both the primary tumor and of recurrent disease that ensure an effective treatment. 95% of all urothelial cancers develop on the mu-

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cosal surface[6–8] and malignant, as well as normal urothelial cells can be found in the voided urine sample. This is especially important in the diagnosis of dysplasias and flat tumors, which can escape detection by endoscopy, uroradiology and biopsy. Moreover, urinary cytology is a noninvasive method of examination and can easily be repeated.

In the process of frequent monitoring of the patient, who is likely to become a lifetime candidate for recurrent or new urothelial lesions, long term cooperation between the cytopathologist and the urologist is created. For the patient's benefit, it is important that the communication between the two specialists is a constructive one.

Materials and Methods

A retrospective study was conducted to correlate urinary cytology and pathology findings in Department of Clinical Cytology, KBC Osijek between 2004 and 2011. For the purpose of this study only specimens with cytological diagnosis of dyskaryosis, suspicious or malignant with available histological confirmation and clinical follow up for two years were considered. The cases described as cytological atypia of urothelial cells were excluded from the study because they relate to reactive changes of urothelium. Cytological specimens of the second voided urine of the day taken in three consecutive days were analyzed. Samples were centrifugated at 1500 rpm for 3 minutes (Shandon Cytospin Cytocentrifuge) the same day and stained with MGG stain. Cytological findings were compared to pathohistological results; histological diagnosis was made according to the WHO histological classification of tumors[9] of the urinary tract. Patients with negative histological findings were followed for the next two years.

Results

When cases with cytologic diagnosis of dyskaryosis and suspicious for malignancy were excluded from analysis, malignant cytological diagnosis was confirmed in 92 cases, which rises to 112 cases (91.8%) when suspicious cases were included (Table 1). In two of these cases we have recognized malignancy, but not the type of the tumor. These were the cases of a poorly differentiated adenocarcinoma. Malignancy was not cytologically recognized in 15 histologically confirmed cases, but dyskaryotic cells were noticed and further investigation was recommended. The positive predictive value of cytological detection of malignant urothelial lesions was 91.8%. In 10 cases false positive report was made – 6 malignant and 4 suspicious lesions, which was not confirmed at histopathological analysis or with clinical follow up and makes the total of 8.2% of false positive reports.

Of the total of detected malignant urothelial lesions 90.9% (100/110) are high grade lesions and only 9.1% (10/110) low-grade lesions; 67.3% (74/110) are invasive lesions and 32.7% (36/110) non-invasive lesions. In 6.2% of cytological findings of dyskaryotic cells, histological analysis did not reveal any abnormality of the urothelium. In 37.5% of cytological findings of dyskaryotic cells histological analysis proved low-grade tumors and in 56.3% of cases it proved high grade tumors.

Discussion

As well as in any other part of the body, cytological samples from the urinary tract are not always easily placed into distinct categories – malignant – benign. Also, inconsistencies in the nomenclature make it difficult for a cytopathologist to interpret the urine findings. Different terms often denote meanings that are understood differently by different cytopathologist and physicians.

At our Institution the term atypia is used when morphologic changes exceed those described as benign cellular changes, but lack clear signs of neoplasia or dyskaryosis. This is usually found in the presence of severe inflammation, calculus disease, or following chemotherapy or catheterization. The term dyskaryosis is applied to early urothelial changes accompanied by nuclear enlargement with a slight to moderate change in the nucleocytoplasmic ratio and slight to moderate increase in nuclear hyperchromasia, usually below the level of hyperchromasia and granularity of chromatin associated with obvious cancer. The finding of dyskaryotic cells in urine sediment requires further investigation. The term suspicious for malignancy was used when some but not

TABLE 1
CORRELATION OF CYTOLOGICAL AND HYSTOLOGICAL FINDINGS (N=138)

Cytologycal diagnosis	Histological diagnosis								
	Benign	PHGNI	PHGI	PLGNI	PLGI	CIS	HGI	ADENOCA	Total
Dyskaryosis	1	4	4	5	1		1		16
Suspicious	4	5	5	3	1	1	4	1	24
Malignant	6	16	34	4	2	7	28	1	98
Total	11	25	43	12	4	8	33	2	138

PHGNI – papillary non-invasive high grade urothelial carcinoma, PHGI – papillary invasive high grade urothelial carcinoma, PLGNI – papillary non-invasive low grade urothelial carcinoma, PLGI – papillary invasive low grade urothelial carcinoma, CIS – carcinoma in situ, HGI – invasive high grade urothelial carcinoma, ADENOCA – metastatic adenocarcinoma

all criteria for malignancy were met or specimen was poorly preserved or sparsely cellular.

Different authors suggest and use different terminology. In our country there is no consensus, so at some institutions the term of dyskaryosis is used for reactive or inflammatory changes, while the term atypical describes severe changes which suggest neoplasia.

Rosenthal and Raab[4] do not include »dysplasia« or »dyskaryosis« as a diagnostic choice. In their experience, cytological samples rarely contain cells from a dysplasia unless they have been mechanically dislodged. If they are present, authors suggest that they should be placed in a low or high grade category depending upon individual cell morphology. They suggest cytological equivalents for histologic grading systems for urothelial carcinoma, which seem very convenient in everyday use. They find that cytology can only recognize reactive/inflammatory changes, atypical cells (with flat lesions atypia indeterminate for neoplasia or with papillar lesions low grade carcinoma) and high grade urothelial carcinoma.

Our research confirmed already established cytological possibilities, which proved useful when a high grade malignancy or carcinoma in situ is present. Of the total of detected malignant urothelial lesions 90.9% were high grade lesions, which means that the number of false negative low grade lesions is high, but the exact proportion could not be determined because of the study design which did not include benign cytological findings.

The positive predictive value of cytological detection of malignant urothelial lesions (invasive and in situ) was 91.8%. This corresponds to quotations in literature[10–17]. In 10 cases cytological diagnosis of malignancy was not confirmed histologically or clinically which makes the total of 8.2% of false positive reports. Revision of these findings showed that these samples had a strong inflammation or severe hematuria or presence of very pronounced degenerative changes on the cells.

Cytology detected 93.4% (71/76) histologically confirmed high grade invasive carcinoma; only 5 cases (6.6%) described dyskaryotic cells. It also detected 87.9% (29/33) histologically confirmed noninvasive high grade carcinoma. In four cases (12.1%), the diagnosis described dyskaryosis. Since both in situ and invasive urothelial carcinoma have essentially identical cytological criteria and invasion cannot be reliably predicted cytologists at our Department refer to all of the above cases as carcinoma.

79.3% (23/29) of histologically confirmed high grade noninvasive carcinoma were cytologically described as carcinoma, and 20.7% (6/29) as suspicious for carcinoma. With histologically confirmed invasive carcinoma, 12.7% (9/71) cytology findings were described as suspicious. There is no significant discrepancy in the number of cytologically suspicious findings in these two categories ($z=-1.018$ $p=0.1543$). We can conclude that a cytologist, when establishing a high grade carcinoma diagnosis, can rely on morphological cell indicators without a specific tumor diathesis in the background.

Clean background, which confirms the lack of invasion and cytological details of the cells which raise suspicion of a high grade carcinoma, diagnosis of carcinoma in situ has to be considered, but biopsy is necessary to determine presence or absence of muscle invasion that cannot be predicted by any cytomorphologic criteria.

Our research did not answered the question and it remains uncertain which histological changes are corresponding to cytological findings of dyskaryotic cells, in which we histologically found low grade tumors (37.5%), high grade tumors (56.3%), but also benign findings (6.2%). However, such findings showed great significance and require further urological investigation, because in further processing in 93.8% of the cases the presence of low grade or high grade tumors was found.

There was only one case where histologically confirmed papilloma was cytologically described as malignant lesion. According to a number of studies exfoliative cytology shows low sensitivity in detection of highly differentiated carcinomas because of their paucity of nuclear abnormalities, but it proved to be highly successful in diagnosing atypical flat lesions, including carcinoma in situ. At the same time cytology cannot detect whether the individual cells with atypias originate from an overt tumor or a flat atypical lesion or carcinoma in situ. It can be concluded that severely atypical cells found in a bladder specimen with a coexisting papilloma do not originate from the tumor itself but from accompanying foci of dysplasia or even carcinoma in situ.

Conclusion

The rising incidence of urothelial tumors is an epidemiologic phenomenon which is based on a variety of established and probable causes. The effective treatment for urothelial cancer can only be achieved by early tumor detection in the setting of the primary diagnostic workup and follow-up. Exfoliative urinary cytology represents an essential tool in establishing diagnosis with high positive predictive value. In order to make it more efficient we need to study its limits carefully, define diagnostic criteria and reach consensus in nomenclature.

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DIJAGNOSTIČKA VRIJEDNOST CITOLOGIJE URINA

S A Ž E T A K

Prosječna incidencija urotelijalnog karcinoma u Hrvatskoj u posljednjih pet godina iznosi 961 novi slučaj, a smrtnost 366. Eksfolijativna citologija ima važnu ulogu u otkrivanju high-grade lezija (ne samo invazivnih već i in situ promjena) zbog svoje mogućnosti detekcije tumora na kompletnom urotelu, od pelvisa do uretre, koji mogu ostati nezamijećeni pri endoskopskom i radiološkom pregledu te na biopsiji. Osim toga urinarna citologija je neinvazivna metoda prihvatljive cijene, koja se lako može ponavljati. U retrospektivnoj su studiji korelirana 138 citološka nalaza urina (s dijagnozom diskarioza, suspektno ili maligno) iz razdoblja od 2004. do 2011. godine, koji su imali patohistološku verifikaciju postavljenu na bioptičkom ili resekcijskom materijalu. Točno se pozitivnim citološkim nalazom smatrao suspektan ili maligan citološki nalaz koji je potvrđen patohistološki kao invazivna ili in situ lezija u skladu s WHO klasifikacijom iz 2004. godine. Pacijenti s negativnim patohistološkim nalazom praćeni su naredne dvije godine. Pozitivna prediktivna vrijednost citologije u detekciji maligne promjene urotrakta iznosila je 91,8%. Nađeno je 8,2% lažno pozitivnih nalaza – šest uzoraka urina citološki su okarakterizirani malignim, a četiri suspektinim, što niti histološki, niti kliničkim praćenjem nije potvrđeno. Od ukupnog broja detektiranih malignih urotelijalnih lezija 90,9% čine high grade lezije, a 9,1% low grade lezije, te 67,3% invazivne, a 32,7% neinvazivne lezije. Citološki nalaz diskariotičnih stanica zahtjeva daljnju urološku obradu jer se kod takvog nalaza u daljnjoj obradi dokaže prisustvo tumora u 93.8% slučajeva. U zaključku: citologija je efikasna dijagnostička metoda za otkrivanje bilo primarnih, bilo rekurentnih urotelijalnih karcinoma. Za njenu veću efikasnost potrebno je podrobno istražiti njene dosege i definirati dijagnostičke kriterije, donijeti konsenzus u nomenklaturi i raditi na edukaciji pacijenata u smislu davanja kvalitetnog materijala za citološku pretragu.