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Abstract

In view of comparatively-high incidence of papillary, well or moderately-well differentiated, transitional cell carcinomas in urology, and of frequent recurrence of carcinomas after appropriate procedures, we have undertaken the correlative study on urinary cytology with cystoscopy, pathology and the amount of fibrinogen and degradation products of fibrinogen and fibrin (FDP). Cytopathologically, 191 cases were confirmed histologically for cancers out of 442 cases studied cytologically; among these 442 classes IV and V were found in 136 cases, and 99 of 136 cases (72.8%) had cancers. Admittedly, we were unable to suspect tumors cytologically in 24.5% of the cases. As to histological gradings and cytology, 48.7% of classes I and II in well differentiated were found against 52.9% and 57.1% of classes IV and V in moderately-well and poorly differentiated carcinomas, respectively. Urinary FDP assay was quite promising; out of 19 cases with both positive cytology and FDP, 18 (94.7% had carcinomas histologically, whereas 12 of 56 cases (21.4%) with both negative cytology and FDP bore cancers. Subsequently, several proposals for improving the diagnostic accuracy were discussed. We concluded the importance of accumulating more cases by combining several diagnostic procedures, especially among well and moderately-well differentiated carcinomas.

KEYWORDS: urinary cytology, FDP, bladder cancers

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A CORRELATIVE STUDY ON URINARY CYTOLOGY AND FDP WITH CYSTOSCOPY AND PATHOLOGY IN THE URINARY BLADDER CANCERS

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Abstracts. In view of comparatively-high incidence of papillary, well or moderately-well differentiated, transitional cell carcinomas in urology, and of frequent recurrence of carcinomas after appropriate procedures, we have undertaken the correlative study on urinary cytology with cystoscopy, pathology and the amount of fibrinogen and degradation products of fibrinogen and fibrin (FDP). Cytopathologically, 191 cases were confirmed histologically for cancers out of 442 cases studied cytologically; among these 442 classes IV and V were found in 136 cases, and 99 of 136 cases (72.8%) had cancers. Admittedly, we were unable to suspect tumors cytologically in 24.5% of the cases. As to histological gradings and cytology, 48.7% of classes I and II in well differentiated were found against 52.9% and 57.1% of classes IV and V in moderately-well and poorly differentiated carcinomas, respectively. Urinary FDP assay was quite promising; out of 19 cases with both positive cytology and FDP, 18 (94.7%) had carcinomas histologically, whereas 12 of 56 cases (21.4%) with both negative cytology and FDP bore cancers. Subsequently, several proposals for improving the diagnostic accuracy were discussed. We concluded the importance of accumulating more cases by combining several diagnostic procedures, especially among well and moderately-well differentiated carcinomas.

Key words: urinary cytology, FDP, bladder cancers.

Papanicolaou (1) in 1928 emphasized the usefulness of exfoliative cytology for detecting the patients bearing cancers. In spite of efforts made by Americans including Papanicolaou himself and also European investigators, the recognition of the exfoliative cytology as one of medical sciences has been rather neglected by pathologists and clinicians almost for two decades; this may be largely due to the fact that we are solely relying on cell(s) or cell clump(s) because of the lack of the structure of tissues or organs which we are familiar with in pathology. Likewise, in 1945, Papanicolaou and Marshal (2) proposed the use of urinary sediments for urinary tract cancers. The urinary cytology, however, has not

become popular as compared to in other fields such as in gynecology, except for among rather limited workers; Yamada *et al.* (3) have stressed the need of urinary cytology especially for nonpapillary bladder cancers which usually manifest rapidly invasive character with high incidence of mortality. Unpopularity of urinary cytology may have depended on routine feasibility of cystoscopy as daily clinical practice. As yet, cystoscopy itself has some burden on patients, especially males, as compared to collecting voided urine.

The aim of our present investigations is twofold. Firstly, papillary, well or moderately-well differentiated, transitional cell carcinomas are exceedingly frequent comparing to other types of malignancy in urology. Therefore, it will be worthwhile to investigate the correlation of final histological findings in these carcinomas with urinary cytology. Secondly, in view of frequent recurrence of tumors in these cancer-bearing patients after local excision or partial cystectomies, it will be necessary to look for other feasible procedures than cystoscopies as follow-up purposes on these patients. We would like to report our preliminary data which we have achieved in recent years, and also to make urologists as well as hospital pathologists more acquainted with the usefulness of urinary cytology for detecting urinary tract cancers. At the same time, we state briefly the relationship of bladder cancers and the amount of fibrinogen and degradation products of fibrinogen and fibrin (FDP) in urine.

MATERIALS AND METHODS

Patients. In the Department of Urology we had worked on urinary cytology in a total of 900 patients during the period from April 1974 to March 1977. Out of these, 442 patients were selected for present study, as these patients visited to our clinic for suspected urinary bladder tumors.

Urine specimens. Urine was collected by spontaneous voiding or chatheterization. Time for sampling was not particularly fixed, although urine from the first urination in the early morning was avoided. In hospitalized patients urinary cytology was repeated for 3 consecutive days, whereas for ambulatory patients it was performed only once unless otherwise stated.

Stainings. Papanicolaou and May-Grunwald-Giemsa stainings were employed on smeared urinary sediment on glass slides.

Cytological classification. This was tentatively made according to the criteria proposed in 1954 (4). That is: Class I absence of atypical or abnormal cells; Class II atypical cytology but no evidence of malignancy; Class III cytology suggestive of but not conclusive for malignancy; Class IV cytology strongly suggestive of malignancy; and Class V cytology conclusive for malignancy.

Assay of urinary FDP. For this purpose we used FDPL test (Teikoku Hormone Manufacturing Co. Ltd., Tokyo); its principle has been reported previously (5). As stated before, FDP includes fibrinogen and degradation products of fibrinogen and fibrin in urine. The test is based on latex aggulutination

test; reagent consists of latex coated with rabbit anti-human-fibrinogen serum. The reagent does agglutinate not only human fibrinogen but its degradation products. When urinary FDP is sensitive enough in the amount to the reagent, FDP reacts to antibodies on the surface of latex resulting in agglutination. The following 3 solutions are required; latex reagent: latex coated with rabbit anti-human-fibrinogen serum, 3 ml in 1 vial (sensitivity: 0.5 μg/ml); antiplasmin solution: aprotinin 18,000 KIE and NaCl 27.0 mg added by water, 3 ml in 1 vial (pH: 5.0-7.0); and solution for diluting urine: bovine serum albumin 100.0 mg and NaCl 450.0 mg added by water, 50 ml in 1 vial (pH: 5.0-7.0). One ml of spontaneously-voided fresh urine and 1 drop (0.04 ml) of antiplasmin solution were mixed together, and centrifuged 3,000 rpm for 5 min. The resulting supernatant was diluted 4 times with the solution for diluting urine. Two drops (0.07 ml) each of nondiluted and diluted supernatant were added by 1 drop (0.04 ml) of latex reagent. After mixing together and allowing to stand for 2 min, the amount of FDP according to positive or negative agglutination was assessed as follows (normal ranges of FDP: 0-0.5 μg/ml);

Nondiluted	Diluted (×4)	Amout of FDP (μg/ml)
−	−	FDP$<$0.5
+	−	0.5$\leqslant$FDP$<$2
+	+	2 $\leqslant$FDP

RESULTS

Urine turbidity and sampling. The relationship between urine turbidity and cytological and cystoscopic findings were examined (Table 1). Clear urine and hematuria correlated well ($p<0.001$) in contrast to turbid urine, indicating that turbidity interfered with proper judgement on cytology. The relationship between diagnostic accuracy and the way of collecting urine, *i. e.*, either through catheterization or spontaneous voiding, was not significant (Table 2a). Neither

TABLE 1. URINE TURBIDITY, CYTOLOGY AND CYSTOSCOPY

Type of urine	Cytological classification	Cystoscopical findings (Percent incidence)		
		Tumor (+)	Tumor (±)	Tumor (−)
Clear urine	Class IV, V	83.0	17.0	0
	Class III	48.8	34.1	17.1
	Class I, II	31.5	41.1	27.4
Turbid urine	Class IV, V	50	50	0
	Class III	50	25	25
	Class I, II	20	52	28
Hematuria	Class IV, V	80.0	20.0	0
	Class III	72.2	27.3	0
	Class I, II	44.4	33.3	22.2

was the frequency of repeating urinary cytology on the same patient, although there was some tendency to obtain rather high diagnostic accuracy among the group in which cytology was repeated more than 3 times consecutively (Table 2b).

TABLE 2a. CORRELATION BETWEEN SAMPLING METHOD OF URINE AND DIAGNOSTIC ACCURACY

Diagnosis*	Percent of case	
	Sampling method	
	Catheterization	Spontaneous voiding
Correct	38.5 (25/65)**	56.3 (103/183)
Incorrect	20.0 (13/65)	28.4 (52/185)

* Based on cytology and cystoscopy.
** Fractional number in parentheses; number of the case/total.

TABLE 2b. CORRELATION BETWEEN FREQUENCY OF SAMPLING AND DIAGNOSTIC ACCURACY

Diagnosis*	Percent of case	
	Frequency of sampling	
	Less than twice	More than 3 times
Correct	36.0 (95/264)**	64.2 (70/109)
Incorrect	54.9 (145/264)	33.0 (36/109)

* Based on cytology and cystoscopy.
** Fractional number in parentheses; number of the case/total.

Pathological investigations. A total of 161 cases of carcinoma was diagnosed through biopsies out of 222 cases, which were diagnosed to be malignant cystoscopically due to tumorous outgrowth (Table 3a). False negative, *i. e.*, either class I or II, was found in 52 cases (32.3%), and 31 cases (31/52: 59.6%) were well differentiated, transitional cell carcinoma. On the other hand, classes IV and V were found in 82 cases (50.9%), and 40 cases (40/82: 48.8%) were proved to be nonpapillary transitional cell carcinoma. For various reasons (6), we have ignored the existence of so-called benign papilloma in urology. When we add class III to classes IV and V, it amounted to be 67.7% (109/161) in the cytological accuracy.

Table 3a. Cytology in the group definitely malignant by cystoscopy and histology

Class I, II	Class III	Class IV, V	Total
32.3% (52/161)	16.8% (27/161)	50.9% (82/161)	161

Table 3b. Cytology in the group suspected malignant by cystoscopy and definitely malignant by histology

Class I, II	Class III	Class IV, V	Total
26.7% (8/30)	16.7% (5/30)	56.7% (17/30)	30

Table 3c. Cytological accuracy in the two groups combined

Class I, II	Class III	Class IV, V	Total
24.5% (60/245)	52.5% (32/61)	72.8% (99/136)	191/442

A total of 30 cases of carcinoma was diagnosed through biopsies out of 155 cases, which showed only localized mucosal reddness or velvet-like lesion cystoscopically and were suspected to be malignant (Table 3b). False negative was found in 8 cases (26.7%), and 6 cases (6/8 : 75%) were well differentiated, transitional cell carcinoma. On the other hand, classes IV and V were found in 17 cases (56.7%), and 12 cases (12/17 : 70.6%) were proved to be nonpapillary transitional cell carcinoma. When we add class III to classes IV and V, it became 73.4% in the cytological accuracy. When we sum up the first group of 161 cases and the second 30 cases, which were diagnosed histologically, out of a total of 442 cases studied cytologically, classes IV and V had a significantly-high incidence ($p<0.001$) of the tumor (72.8%) as compared to classes I and II (Table 3c). We must, however, admit that 24.5% of the cases were proved to be false negative, *i. e.*, we were unable to suspect tumors cytologically.

The histological gradings concerning only outgrowing papillary tumors showed a statistically-significant correlation ($p<0.05$) with cytological classifications, *i. e.*, 48.7% of classes I and II in well differentiated against 52.9% and 57.1% of classes IV and V in moderately-well and poorly differentiated transitional cell carcinomas, respectively (Table 4). It was unable to draw any conclusive evidence regarding the correlation between cytology and the staging, *i. e.*, degree of downward tumor invasion through the submucosa into muscle layers, owing to a lack of enough cases with partial or total cystectomy.

TABLE 4. HISTOLOGICAL GRADING AND CYTOLOGY

	Well diff.	Moderately diff.	Poorly diff.	Total
Class I, II	48.7%	23.5%	19.0%	
	(37/76)	(4/17)	(4/21)	45/114
Class III	23.7%	23.5%	23.8%	
	(18/76)	(4/17)	(5/21)	27/114
Class IV, V	27.6%	52.9%	57.1%	
	(21/76)	(9/17)	(12/21)	42/114

Urinary FDP. This investigation was based on the report of Wajsman *et al.* (7) that "a high degree of accuracy (90%) was found in correlating cytology and urinary fibrinogen degradation products with the activity of the disease".

The study was made on a total of 93 cases which had combined examination of urinary FDP with cytology. These 2 factors had a statistically-significant correlation ($p<0.001$) with the presence or absence of tumors (Table 5a). When we summarize this in one table (Table 5b), out of 19 cases with both positive cytology and FDP, 18 cases (94.7%) were found to have carcinoma histologioally; the remaining one case had cystitis glandularis. Among 56 cases with both negative cytology and FDP, 44 cases (78.6%) were free of malignancy. These data imply the significance of combined studies on both cytology and urinary FDP for diagnostic purpose. The cases with positive FDP but negative cytology had no

TABLE 5a. URINARY FDP*, CYTOLOGY AND HISTOLOGY

Tumor and FDP

	Tumor (+)	Tumor (−)
FDP (+)	71.0%	29.0%
	(22/31)	(9/31)
FDP (−)	24.5%	75.8%
	(15/62)	(47/62)

Tumor and cytology

	Tumor (+)	Tumor (−)
Cytology (+)	80.0%	20.0%
	(20/25)	(5/25)
Cytology (−)	25.0%	75.0%
	(17/68)	(51/68)

* Refer to the text.

TABLE 5b. URINARY FDP*, CYTOLOGY AND HISTOLOGY

	Cytology (+)		Cytology (−)	
	FDP (+)	FDP (−)	FDP (+)	FDP (−)
Tumor (+)	94.7%	33.3%	41.7%	21.4%
	(18/19)	(2/6)	(5/12)	(12/56)
Tumor (−)	5.3%	66.7%	58.3%	78.6%
	(1/19)	(4/6)	(7/12)	(44/56)

* Refer to the text.

tumors in 58.3% (7/12 cases), indicating that mere positivity of FDP alone is not reliable for the malignancy. Unfortunately, 12 of 56 cases (21.4%) with both negative cytology and FDP were proved to bear cancers histologically; the analysis on these cases are now in progress and will be reported elsewhere

DISCUSSION

In spite of high frequency of well or moderately-well differentiated carcinoma in urinary bladder cancers, our data indicate comparatively-high false negative cases especially among well differentiated transitional cell carcinomas. For early detection of cancers as well as surveillance of tumor recurrence, at least in urology, collection of spontaneously-voided urine is one of the simplest ways of diagnostic procedure. Therefore, we feel the urgency for improving the diagnostic accuracy in the cases of well and moderately-well differentiated carcinomas.

For this purpose, first of all, consecutive repetition of cytological examination or, like in sputum cytology (8), three-day pooled collections of voided urine would be worthwhile to be considered. The second point will be the appreciation of irrigating the urinary bladder using either alpha-chymotrypsin (9) or normal saline (10) through a catheter inserted into the bladder, although this procedure may have some burden on the patients.

Concerning cytological view point, as pointed out by others (11), papillary fronds can be frequently observed among the patients with well differentiated papillary transitional cell carcinoma. Although cytologically these fronds often have a lack of any nuclear atypism, we should caution these patients for further follow-up studies. Another cytological problem will be, as emphasized by Inada (9), the reevaluation of the classification hitherto employed. As far as the classification limited to urology is concerned, he has proposed the recognition of the class III to be more "active" than conventional classification, *i. e.*, "potentially malignant or low-grade malignant" instead of "suggestive of but not conclusive for malignancy". Thus, it is followed by class IV meaning high-grade malignancy. Based on this classification, he improved diagnostic accuracy up to 98%, *i. e.*, 78 out of 80 patients with urinary bladder cancers.

Lastly, analysis of urinary FDP will be quite promising. Fibrin clots deposited around tumor cells and around tumor itself could be dissolved by plasmin, of which precursor, namely, plasminogen may be derived from peripheral blood and also tumor tissue and be activated by urokinase (12); this might result in the increment of urinary FDP in bladder cancers. On the other hand, increased FDP may or may not be related to the amount of blood component discharged from the bladder. Since asymptomatic macrohematuria in elderly patients is highly suspected of malignancy in the urothelium, the FDP assay might possibly be one of indices to ascertain the degree of this hematuria in

quantitative aspect. The question as to whether or not hematuria and increased FDP in the bladder cancers are related with each other is being investigated; this will be published elsewhere.

Therefore, we do feel the paramount importance to accumulating more cases, in which cytology, FDP assay, cystoscopy and biopsy are combined, especially among the patients with well and moderately-well differentiated transitional cell carcinomas.

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