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ORIGINAL ARTICLE

Cell block preparation in urine cytology: examination of utility and workflow in an academic practice

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Introduction Urine cytology is a common non-invasive test to screen for urothelial carcinoma. Urine cell blocks may sometimes be prepared as a diagnostic aid (eg, to characterize architecture or perform immunohistochemistry). The aim of this study was to determine whether routinely preparing cell blocks on urine specimens improves diagnostic sensitivity.

Materials and methods Three time periods were compared: time period 1 (prior to November 2009; 1437 consecutive selected cases), when cell blocks were rarely prepared; period 2 (November 2009 to May 2010; 1230 selected cases), when cell blocks were prepared on all cases; and period 3 (after May 2010; 1499 consecutive selected cases), when cell blocks were made only when indicated (for samples with substantial cellular pellets or when requested by a pathologist).

Results Patient demographics and the type of specimens received were relatively similar during the 3 time periods. Increased preparation of cell blocks was not accompanied by a notable improvement in specimen adequacy rate, given that <1%, 2%, and 1% of samples were unsatisfactory for the 3 periods. Only the proportion of atypical cases differed during the time periods, being highest in period 1 (23%), but lower in periods 2 and 3. Turnaround time was fastest for period 1 (mean: 47 hours, median: 33 hours), and slower for period 2 and period 3.

Conclusion These data show that routinely preparing cell blocks for urine samples did not improve our laboratory's specimen adequacy rate. Nonetheless, cell block preparation on urine samples did

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help lower the proportion of atypical diagnoses, when routinely or selectively prepared. Because preparation of cell blocks on all urine cases can be costly and only provides minimal added clinical benefit, our recommendation is to rather judiciously utilize cell blocks when screening urine cytology samples.

Introduction

Bladder cancer is the ninth most common cancer in the world, with 430,000 new cases diagnosed in 2012.[1] In the United States, the American Cancer Society's estimates for bladder cancer for 2016 were about 79,030 new cases and about 16,870 deaths.[2] Urine cytology plays an important role in the management of patients with urothelial abnormalities, and is often the first test utilized to evaluate patients with hematuria. Given that it is an inexpensive, quick, and non-invasive test, urinary cytology is also used in patients with a history of bladder cancer and as a screening test for high-risk patients. Although traditional urine cytology has a relatively high sensitivity at detecting high-grade lesions, its sensitivity for low-grade papillary tumors is very low.[3-5]

In cytology, cell block (CB) preparation is sometimes performed as an adjunct to help in rendering an accurate diagnosis by enhancing the ability to see histomorphologic architecture or to perform ancillary tests, like immunohistochemistry.[6-9] The use of CBs is relatively routine in most fine-needle aspirations and body fluid specimens if there is sufficient material,[10-12] but is less frequently utilized in exfoliative specimens with limited material, such as urine, Papanicolaou tests, and cerebrospinal fluids.[13-15] For these exfoliative specimens, CBs have previously been reported to be of use in gynecological cytopathology, whereby it can help in Papanicolaou test specimens with blood clot and in those with potential atypical glandular or squamous cells.[16-18] The diagnostic value of CBs as an aid to traditional urine cytology has been described in rare reports.[19-23] With the recent adoption of The Paris System for Reporting Urinary Cytology (TPSRUC), CBs may be of value to look for fibrovascular cores that can help in rendering a diagnosis of low grade urothelial neoplasm.[5] The goal of this study was to determine whether routine or selective preparation of CBs on urine cytology specimens improves adequacy or lowers indeterminate diagnoses in a cost-effective manner.

Materials and methods

Following approval by the institutional review board, 4166 urine cytology cases were selected from the University of Pittsburgh Medical Center. The cases were classified into 3 eras: time period 1 (prior to November 2009; 1437 consecutive cases), when cell blocks were rarely prepared; period 2 (November 2009 to May 2010; 1230 selected cases), when cell blocks were prepared on all cases; and period 3 (after May 2010; 1499 consecutive cases), during which cell blocks were made only when indicated. The different time periods reflect different laboratory protocols for determining when CBs would be prepared, and a quality assurance analysis to see which is the most cost-effective and reasonable workflow in our setting. The indications for making CB preparations for time period 3 were: presence of good pellets in patients with a history of carcinoma and no history of urinary diversion; presence of good pellets from patients in the operating room or in the cystoscopy suite from an instrumented urine; presence of good pellets in patients with hematuria; and when requested by the pathologist. The reasons for requests by pathologists for a urine CB included: examination of clusters for fibrovascular cores, potential interest in doing immunohistochemical stains, and cases with ambiguous findings due to clotting or other obscuring factors.

Urine specimens were received fresh or in fixative (typically a ratio of 3:1 for urine:CytoLyt or a ratio of 2:1 for urine:PreservCyt as described in the "Quick Reference Guide" for ThinPrep urine specimens [Hologic, Marlborough, MA]), and processed to prepare a Papanicolaou-stained ThinPrep slide (Hologic). When a CB was made, the CB preparation was made utilizing the HistoGel (Thermo Fisher Scientific, Pittsburgh, PA) technique and sections stained with hematoxylin and eosin, as previously described.[7,9] The HistoGel technique is one of the more common CB preparation techniques utilized by cytopathology laboratories, as shown in a survey performed in 2014.[6] The ThinPrep and CB slides (if available) were then reviewed together by a cytopathologist, and signed out with a final diagnosis in the pathology laboratory information system. Immunostains were performed in select CB cases, as shown later in Fig. 4. Given that the study incorporated time periods prior to the implementation of TPSRUC at our institution, the diagnoses were rendered using a 5-tier diagnostic algorithm for the primary interpretation, similar to that used in other areas of nongynecologic cytopathology, and included: nondiagnostic, negative for malignant cells, atypical cells present, suspicious for malignant cells, and positive for malignant cells. In the analysis, indeterminate cases were defined as those with a diagnosis of atypical cells present or suspicious for malignant cells.

Results

There were a total of 4166 urine specimens included in the study, including 1437 urine specimens in period 1 (average

patient age: 64.6 years), 1230 urine specimens in period 2 (average patient age: 64.2 years), and 1499 urine specimens in period 3 (average patient age: 64.4 years). Patient demographics and the urine collection methods were relatively similar during the 3 time periods, as shown in Table 1. In period 2, there were slightly fewer total urine specimens, and a greater percent of voided urines, but the difference was not statistically significant. The increased preparation of CBs was not accompanied by a notable improvement in specimen adequacy rate given that 0.42%, 1.55%, and 0.93% of samples were unsatisfactory for the 3 periods, respectively. Turnaround time (TAT) was investigated in the 3 time periods, and was fastest (shorter time for TAT) for time period 1 (mean: 47 hours, median: 33 hours), and slower (longer time for TAT) for time period 2 (mean: 55 hours, median: 34 hours) and time period 3 (mean: 55 hours, median: 49 hours). When comparing time periods 2 and 3, the average TAT was similar, but the median TAT was longer. The proportion of atypical cases differed during the time periods, being the highest in time period 1 (23%), lower (16%) in period 3, and lowest (14%) in period 2.

Among cases in which CBs were obtained, the percentage of cases with a diagnosis of negative for malignant cells was higher for periods 2 and 3 (80% and 78%, respectively), and lower for period 1 (63%); nevertheless, there is a smaller sample size for period 1 given the nature of the time period where CBs were rarely prepared (161 versus 1230 and 864; Table 2). In conjunction with a lower proportion of negative cases in time period 1, there was a higher proportion of indeterminate diagnoses (33%) compared with the indeterminate diagnoses in time periods 2 (16%) and 3 (19%) when CBs were prepared routinely or selectively, respectively.

CBs appeared to have the greatest utility when ThinPrep slides appeared unsatisfactory or were less than optimal in

Table 1 Summary of clinicopathologic findings in different time periods (all cases).

Study period	Period 1 (Rare CB obtained)	Period 2 (CB on all cases)	Period 3 (CB on selected cases)
Time frame	Prior to Nov 2009	Nov 2009-May 2010	After May 2010
Average patient age, years	64.6	64.2	64.4
Patient sex, M:F	1.5:1	1.5:1	1.4:1
Total urine samples	1437	1230	1499
Number (%) of cell blocks	161 (11)	1230 (100)	864 (58)
Unsatisfactory rate	0.42	1.55	0.93
Mean turnaround time, hours[a]	47.0	55.0	55.0
Median turnaround time, hours[a]	33.0	34.0	49.0
Turnaround time range, hours[a]	4-311	21-286	23-149
Urine collection method, n (%)			
Voided urine	1118 (78)	1029 (83)	978 (65)
Catheterized urine	222 (15)	145 (12)	162 (11)
Bladder washing	63 (4)	33 (3)	10 (1)
Upper tract sample	29 (2)	21 (1)	10 (1)
Urinary diversion	1 (<1)	2 (<1)	5 (<1)
Not specified	4 (<1)	0 (0)	334 (22)
Sample adequacy, n (%)			
Unsatisfactory	6 (<1)	19 (2)	14 (1)
Less than optimal	84 (6)	185 (15)	214 (14)
Satisfactory	1347 (93)	1026 (83)	1271 (85)
Cytology diagnosis, n (%)			
Negative	1031 (72)	987 (80)	1200 (80)
Atypical	333 (23)	176 (14)	228 (16)
Suspicious for malignant cells	35 (2)	22 (2)	35 (2)
Positive for malignant cells	32 (2)	26 (2)	22 (1)
Nondiagnostic	6 (<1)	19 (2)	14 (1)

Abbreviation: CB, cell block.
[a]Turnaround time is defined as hours from accessioning of a case to sign-out of that case by the pathologist.

Table 2 Summary of clinicopathologic findings in different time periods (only CB cases).

Study period	Period 1 (Rare CB obtained)	Period 2 (CB on all cases)	Period 3 (CB on selected cases)
Number of cell blocks	161	1230	864
Urine collection method, n (%)			
Voided urine	112 (70)	1029 (83)	583 (67)
Catheterized urine	42 (26)	145 (12)	114 (13)
Bladder washing	7 (4)	33 (3)	7 (1)
Upper tract sample	0 (0)	21 (1)	5 (1)
Urinary diversion	0 (0)	2 (<1)	0 (0)
Not specified	0 (0)	0 (0)	155 (18)
Sample adequacy, n (%)			
Unsatisfactory	1 (1)	19 (2)	9 (1)
Less than optimal	19 (12)	185 (15)	126 (15)
Satisfactory	141 (88)	1026 (83)	729 (84)
Cytology diagnosis, n (%)			
Negative	101 (63)	987 (80)	673 (78)
Atypical	49 (30)	176 (14)	147 (17)
Suspicious for malignant cells	5 (3)	22 (2)	21 (2)
Positive for malignant cells	5 (3)	26 (2)	14 (2)
Non-diagnostic	1 (1)	19 (2)	9 (1)

Abbreviation: CB, cell block.

Table 3 Potential situations when CB preparation can be helpful.

Cytospin/ThinPrep diagnosis	Cell block diagnosis
Unsatisfactory/less than optimal	Many cells or tumor trapped in blood clot, tissue fragments identified
Cell groups: atypical versus reactive versus LGUN	Low-grade urothelial carcinoma (papillary groups with a fibrovascular core)
Unknown neoplastic cells: LGUN versus HGUC versus metastasis/other	Groups with mitoses/high-grade features and supportive ancillary tests (immunohistochemical stains)

Abbreviations: CB, cell block; LGUN, low-grade urothelial neoplasia; HGUC, high-grade urothelial carcinoma.

cellularity, or when there were indeterminate groups of urothelial cells (reactive versus low grade urothelial neoplasm), or an adequately cellular specimen with limited neoplastic cells, as summarized in Table 3. Figs. 1-3 illustrate selected cases in all 3 time periods where CB preparation impacted the diagnosis. In addition, Figs. 4 and 5 illustrate the utility of cell blocks for the evaluation of immunostains and for the evaluation of architecture when tissue fragments with fibrovascular cores are seen.

Discussion

Since its original description in 1945 by Papanicolaou and Marshall,[24] urine cytology has played an important role in early detection and surveillance of urothelial neoplasia.[25,26] In addition, it can be used in the investigation of patients with hematuria, lower urinary tract symptoms, and unexplained recurrent urinary tract infections.[27,28] Even though urine cytology is relatively sensitive in detecting high-grade urothelial carcinoma and carcinoma in situ,[4] the majority of urothelial carcinomas (60%) present at the low-grade stages,[28] which are associated with a low detection sensitivity.[3] This is the largest study looking at urine CB preparation; investigating the potential benefit of preparing CBs in addition to routine liquid-based preparation; and comparing the adequacy, diagnoses, and TAT during time periods with different triggers for CB preparation. Although CB preparation did not significantly impact adequacy, there was a decrease in atypical and overall indeterminate diagnoses when CBs were routinely or selectively performed, compared with when they were rarely performed. Cases that seemed to benefit most from CB preparation were those with a higher yield of obtaining a CB (ie, those from cystoscopy or collected in the operating room or with a visible sediment). Selectively triaging urine for CB based on these parameters can limit excess work and cost associated with preparing a CB on all urine cases without a dramatic effect on the overall average TAT of cases.

CB preparation in diagnostic cytopathology has become an integral part of routine examination, especially given the dramatic increase in ancillary studies that can be applied to CBs.[6-12] CB preparations are known to be very useful in the diagnosis of many lesions in nongynecologic cytology because they allow the opportunity to assess tissue architecture and to apply immunohistochemistry and molecular studies.[10-12] CB preparation is relatively underutilized in urine cytology, however, and there are only rare papers investigating CB preparation in these specimens.[19-23] In the studies looking at the application of CBs in urine cytology, some have seen highest utility in the indeterminate categories of The Paris System (eg, atypical urothelial cells and suspicious for high-grade urothelial carcinoma in TPSRUC) to help in upgrading or downgrading a diagnosis to a more definitive diagnostic category,[22,23] with one study showing that CBs led to a definitive diagnosis in 63% of challenging cases.[22] Our results showed similar findings, with a decrease in the percent of atypical diagnoses from 23% when CBs were rarely made to approximately 15% when CBs were

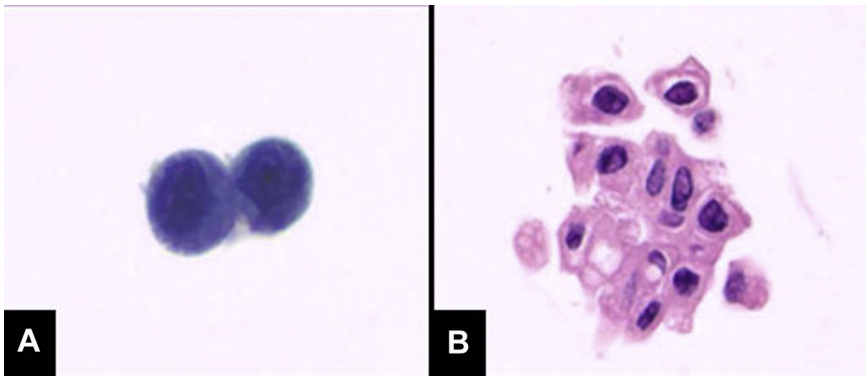

Figure 1 A voided urine cytology specimen from period 1. The ThinPrep slide shows only rare atypical cells (A), which were seen in a larger proportion on the corresponding cell block (B) to support a diagnosis of atypical cells present. A, Papanicolaou stain, high power; B, hematoxylin and eosin stain, high power.

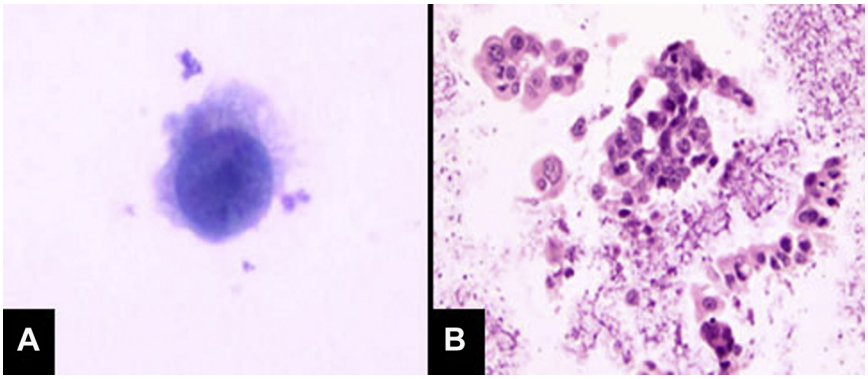

Figure 2 A voided urine cytology specimen from period 2. The ThinPrep slide only showed one atypical cell (A) that would have been characterized as suboptimal, but the corresponding cell block (B) had quantitatively more cells, confirming an adequate specimen sufficient for a diagnosis of positive for high-grade urothelial carcinoma. A, Papanicolaou stain, high power; B, hematoxylin and eosin stain, medium power.

routinely or selectively prepared (14% with CBs on all cases, 16% with selective CB preparation). In addition, in comparing CB preparation cases only, there was a decrease in indeterminate diagnoses from 33% in period 1 with rare CBs, to 16% and 19% when CBs were prepared routinely or selectively, respectively; but it is hard to make definitive conclusions given the low number of cases with CBs in time period 1. Another possible confounder is that the cytopathologists signing out urine cytology have changed over the time period and have had variable levels of experience, and this may have contributed to different atypia rates over time. In terms of TAT, in periods 2 and 3, the average TATs were longer, likely attributed to the fact that CB preparation required extra processing time, which can be challenging.

In the literature, four factors have been associated with adequate cellularity in urinary cell blocks: the presence of sediment, female sex, positive urinary cytology, and positive leukocyturia.[20] These factors, in addition to the factors guiding CB preparation in this study, such as the presence of good pellets in patients with a history of carcinoma, hematuria or an instrumented urine, or when requested by the pathologist for challenging cases with scant atypical cells or atypical clusters, could help in determining which cases could benefit most from CB preparation. In such cases, obtaining CBs could potentially help in making a more definitive diagnosis or diminished indeterminate diagnoses, which can help patient care by avoiding repeat or more-invasive biopsies. Furthermore, with new needles being introduced for small biopsies in the bladder, CB preparations may be helpful to avoid missing valuable mini-biopsy fragments. This was investigated recently by one institution using microbiopsy-type needles, where there tended to be greater recovery of cells and more definitive diagnoses from cytological processing of these biopsies using liquid-based cytology with CB preparation, as opposed to simply processing histology blocks alone, which highlights the utility of a combined approach using cytological processing with liquid based and CB techniques.[21] Given the limited cellularity of most urine specimens (particularly voided urines),

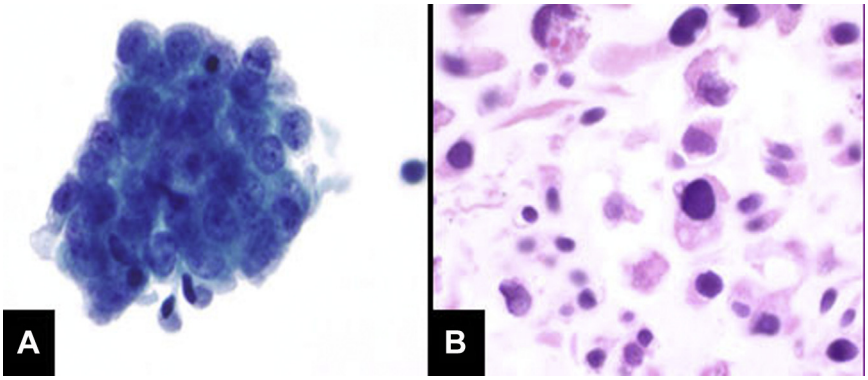

Figure 3 A voided urine cytology specimen from period 3. The ThinPrep slide shows rare crowded clusters of hyperchromatic cells with increased nuclear-to-cytoplasmic ratios (A). The corresponding cell block showed more discohesive cells with nuclear enlargement, nuclear membrane contour irregularities, and hyperchromasia, compatible with a diagnosis of high-grade urothelial carcinoma. A, Papanicolaou stain, high power; B, hematoxylin and eosin stain, high power.

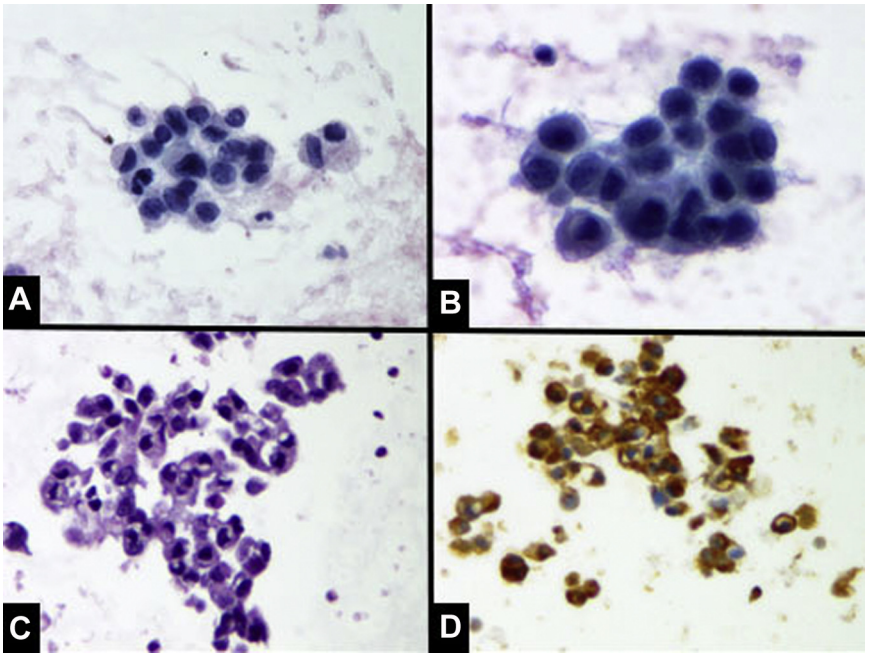

Figure 4 Urine cytology specimen with cell block preparation and immunostains. The urine ThinPrep specimen shows clusters of cells with nuclear irregularities, hyperchromasia, and pale cytoplasm present with vague glandular formation (A and B). A cell block was prepared to perform immunostains (C), given the patient's history of prostatic adenocarcinoma, and the lesional cells were confirmed to be positive for prostate specific antigen (D). A and B, Papanicolaou stain, medium and high power; C, hematoxylin and eosin stain, medium power; D, prostate specific antigen immunohistochemical stain, medium power.

however, the yield in universal CB preparation may be low, as shown in this study.

In other areas of nongynecologic cytopathology, CBs and small biopsies can provide substrates for immunohistochemistry, fluorescence in situ hybridization, or molecular studies, in addition to being able to be easily archived for potential future research endeavors.[29-31] Given the recent interest in applying ancillary studies to urine

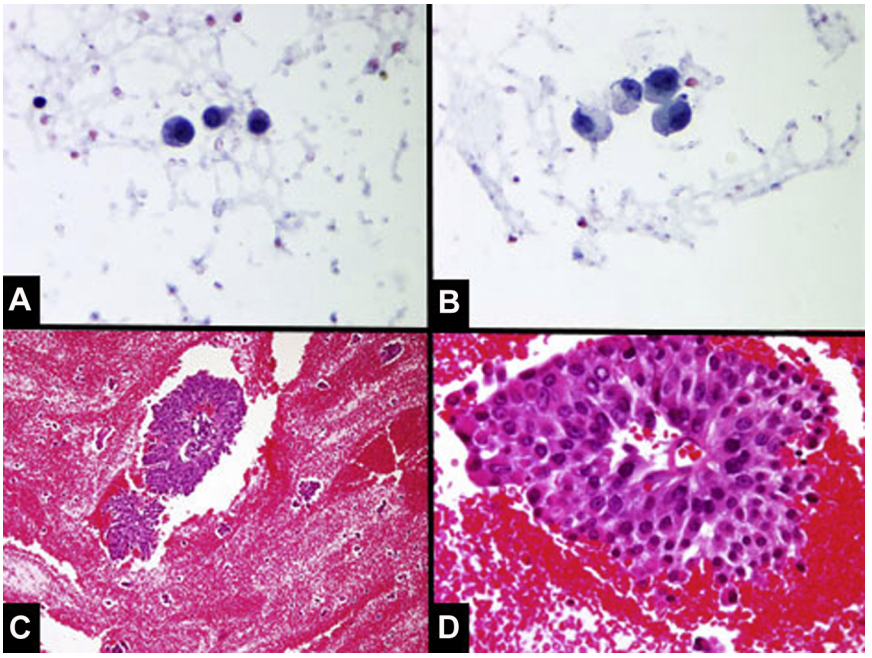

Figure 5 Urine cytology specimen with CB preparation containing papillary fragments. The ThinPrep slide shows only a few atypical urothelial cells in a bloody background (A and B), so a cell block was prepared that showed papillary tissue fragments with fibrovascular cores diagnostic of low-grade urothelial neoplasia (C and D). A and B; Papanicolaou stain, high power; C and D, hematoxylin and eosin stain, low and medium power.

cytology,[26-36] CBs may be helpful for these new tests entering the clinical realm. Because of the low cellularity of urine specimens, however, some of the tests are starting to be applied to cytospins or additional ThinPrep slides.[34,35] If these ancillary tests become more mainstream in the future on liquid-based or cytospin preparations, this could potentially decrease the remaining urine specimen available for CB preparation. In contrast, selective preparation of CBs, as performed in this study during period 3, leaves the decision-making in the hands of the sign-out cytopathologist in order to decide how best to allocate the remaining urine specimen. Perhaps in the future CBs will be prepared in cases worrisome for a possible low-grade urothelial neoplasm in TPSRUC, whereas cases worrisome for high-grade urothelial carcinoma will have additional liquid-based or cytospin preparations prepared for ancillary stains or molecular studies that enhance the detection of high-grade urothelial carcinoma. This algorithmic approach would allow the excess urine to be triaged based on morphology in a cost-effective way by avoiding testing in hypocellular specimens with low yield. This approach would likely delay TAT, however, as the preparation of the additional cytological slides and staining would take time and delay the final sign-out of the case.

In conclusion, our findings show that routinely preparing CBs for urine samples did not improve our laboratory's specimen adequacy rate. Nevertheless, CB preparation on urine samples did help lower the percentage of atypical diagnoses when compared with the period when CBs were rarely prepared. In addition, the preparation of CBs on all urine cases (similar to period 2 in this study) can be costly and provides minimal added clinical benefit compared to findings when CBs are selectively prepared. Thus, our recommendation is to rather judiciously utilize CBs when screening urine cytology samples, and to use predefined parameters to guide appropriate selection of cases that may benefit most from CB preparation.

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