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How Reliable Is Conventional Urinary Cytology in Post-Transplant Patients?

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Key Words
Cytology · Renal transplantation · Bladder cancer

Abstract
Introduction and Objectives: Factors like cold, flushing solutions, ischemia and reperfusion may alter the microscopic appearance of transitional cells leading to falsely positive results of urinary cytology in patients after kidney transplantation. After seeing 1 patient presenting with two consecutive highly suspicious cytology specimens 3 days after transplantation and no sign of urothelial tumor at retrograde urography, we analyzed the cytological picture of transitional cells in post-transplant patients. ***Material and Methods:*** We investigated 31 urine specimens of 11 patients undergoing kidney transplantation preoperatively (if possible) and on days 1, 3 and 9 postoperatively. Microscopic cytology was performed by using Papanicolaou's criteria: 0 – no cytology possible (no cells), I+II – negative cytology, III – doubtful, IV – suspicious for tumor, V – tumor cells. All microscopic examinations were performed by one experienced senior pathologist. ***Results:*** Mean patient age was 55.8 (± 17.5) years, mean residual diuresis 856 (± 636) ml, mean cold ischemia time 13.6 (± 6.4) h, mean creatinine level on day 1: 582 μmol/l, day 3: 533 μmol/l and day 9: 259 μmol/l. None of the urinary cytology results were suspicious for malignant transformation (Papanicolaou I+II). No patient presented signs of urothelial malignancy after a mean follow-up of 3 months. ***Conclusion:*** Although microscopic urinary cytology may be falsely positive in 1–12% of non-transplanted patients due to urothelia atypia, inflammation or radiation/chemotherapy, the present study suggests that conventional microscopic cytology examinations in post-transplant patients are not heavily altered and do not lead to an increased false-positive rate.

Introduction

Urinary cytology has been widely used as an adjunct in the diagnosis and follow-up of patients with bladder cancer. Malignant transformation can be detected microscopically within transitional cells (nuclei) of the urinary sediment or bladder washings. However, well-differentiated tumor cells may appear non-suspicious on microscopic examination and even high-grade bladder tumors are associated with a considerably high false-negative rate. That is why urologists need to rely on more invasive diagnostic tools to detect tumors of the urinary tract, such as urethrocystoscopy and intravenous pyelogram [1].

As clinically even more challenging appears to be managing patients presenting with clinically unconfirmed positive cytology. Schwalb et al. [2] reported that 77% of them eventually develop transitional cell carcinoma on follow-up. On the other hand, there is a falsely positive rate of conventional microscopic cytology of up to 12% that has been explained by inflammation or urothelial atypia [3].

Factors like cold, flushing solutions, ischemia and reperfusion injury may alter the microscopic appearance of transitional cells and possibly lead to an increased false-

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ly positive rate. Since post-transplant patients additionally carry an increased risk of developing cancer due to immunosuppression after renal transplantation, we investigated whether or not conventional microscopic cytology is associated with an increased false-positive rate in patients after renal transplantation.

Patients and Methods

We investigated 31 urine specimens of 11 patients undergoing kidney transplantation preoperatively (if possible) and on days 1, 3 and 9 postoperatively including creatinine levels, cold ischemia time and basic demographics. All data were collected prospectively.

Urine cytology was performed on a freshly voided specimen preoperatively and via a Foley catheter postoperatively. Following centrifugation, one or two smears were obtained. A negative cytology was reported if microscopic examination revealed no or normal transitional cells only as well as reactive changes. A positive cytology was documented when typical microscopic signs of malignancy were present, such as nuclear enlargement, increased nuclear/cytoplasmic ratio, hyperchromasia and irregular nuclear membrane thickness or contour. Any 'intermediate' findings that appeared not clearly indicative of malignancy were reported as suspicious. Microscopic cytology was performed by using Papanicolaou's criteria: 0 – no cytology possible (no cells), I+II – negative cytology, III – doubtful, IV – suspicious for tumor, V – tumor cells. All microscopic examinations were performed by one experienced senior pathologist.

Results

We investigated 31 urine specimens of 11 patients (5 women and 6 men) undergoing kidney transplantation preoperatively. Mean patient age was 55.8 (± 17.5) years, mean residual diuresis 856 (± 636) ml, mean cold ischemia time 13.6 (± 6.4) h, mean creatinine level on day 1: 582 μmol/l, day 3: 533 μmol/l and day 9: 259 μmol/l. None of the urine cytology results were suspicious for malignant transformation (Papanicolaou I+II). No patient presented signs of urothelial malignancy after a mean follow-up of 3 months including our first patient who originally had two consecutive positive cytology specimens. He underwent repeat cystoscopy, ureterography and ultrasound without any sign of malignancy.

Discussion

It has mainly been accepted that urine cytology is a diagnostic tool in patients presenting with clinical signs of transitional cell carcinoma of the urinary tract along with more invasive (and more reliable) diagnostic approaches such as IVP and cystoscopy. Unfortunately, negative cytology does not rule out malignancy and, furthermore, even at experienced centers considerable false-positive rates were found. Patients with positive cytology that remain clinically unconfirmed carry a considerable risk of developing malignancy on follow-up. In contrast to other reports, Chahal et al. [4] found in 285 patients on diagnostic follow-up for hematuria that no additional tumors were discovered solely by cytology. They concluded that 'routine cytology does not contribute to the evaluation of patients with hematuria'.

However, reviewing the pros and cons of urine cytology was not the objective of this study. There is no doubt of an supportive role of urine cytology (at least) in patients of higher risk of developing transitional cell carcinoma of the urinary tract. Patients under immunosuppression belong to this group. All of them live with the risk of a higher cancer incidence [5].

Kidney transplantation is not only associated with immunosuppression but also with organ perfusion by using preservation fluids, cold ischemia time and reperfusion (injury). During cold storage and early reperfusion, allografts are vulnerable to intracellular calcium overload, acidosis, cell swelling, injury mediated by reactive oxygen species, and the inflammatory response. These processes may give rise to alterations of transitional cells within the transplanted renal pelvis and ureter leading to cellular changes similar to that seen in positive urine cytology cases.

However, this hypothesis cannot be supported as shown in this study. 31 specimens of 11 consecutive patients presented no sign of positive or even suspicious urine cytology. Therefore, it appears highly unlikely to find a significant higher falsely positive rate compared to non-transplanted patients.

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