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ORIGINAL ARTICLE

Renal tubular epithelial clusters in voided urine: a potential diagnostic pitfall in renal transplant patients

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Introduction Urine cytology is often used to screen for polyomavirus in renal transplant patients. There are qualitative cytologic differences between urine from transplant and nontransplant patients, particularly the presence of epithelial cell clusters, that can pose diagnostic difficulty.

Materials and methods Voided urine cytology specimens from 100 renal transplant patients and 100 nontransplant patients were reviewed for cell clusters. Immunocytochemistry for renal cell carcinoma marker (RCC) and cytokeratin 7 was performed on 10 recent specimens. Clinical data was reviewed with a focus on evidence of graft dysfunction or malignancy.

Results Eighteen patients (18%) in the renal transplant group and no nontransplanted patients (0%) exhibited cell clusters with characteristic morphology: 3-dimensional cohesive groups; high nucleus-to-cytoplasm ratio; round, eccentrically placed nuclei with a prominent central nucleolus; and granular or vacuolated cytoplasm. Some had significant nuclear atypia. The groups were RCC–positive in 8 of 10 cases, and cytokeratin 7–positive in 6 of 10 cases, which is consistent with renal tubular epithelial clusters (RTECs). Clinical follow-up revealed that 88% (15 of 17) of those with RTECs developed graft dysfunction in a median of 65 days, compared with 6% (4 of 64) without RTECs (sensitivity 79%, specificity 97%, positive predictive value 88%, negative predictive value 94%). No patient developed a urinary tract malignancy.

Conclusions RTECs are relatively common in urine cytology from transplant patients, but are rare in other urine specimens. Recognition is important as they can be mistaken for urothelial carcinoma or

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adenocarcinoma. There appears to be a strong association with later development of graft dysfunction. These cells are most likely evidence of renal tubular injury secondary to a variety of factors, including rejection.

Introduction

Cytologic evaluation of urine specimens is performed primarily to assess for recurrence of urothelial carcinoma, as well as to screen for urothelial carcinoma in patients with hematuria. Additionally, urine cytology can be useful as a screening test for polyomavirus infection in patients who have undergone renal transplant.[1] These patients are at increased risk of clinically significant renal polyomavirus infection due to immunosuppression. Early detection of polyomavirus and subsequent reduction of immunosuppression prior to renal injury has been shown to reduce the incidence of graft loss.[2] The current recommended intervals for urine cytology in the renal allograft population is every 3 months during the first 2 years after transplantation and annually thereafter until the fifth year after transplantation, as well as when allograft dysfunction is suspected and when allograft biopsy is performed.[1] Cytopathologists are therefore likely to encounter urine cytology specimens in transplant patients.

Since 1997, urine cytology evaluation has been the primary screening tool to identify polyomavirus replication in our renal transplant population.[3] Anecdotally, we have observed numerous qualitative differences between urines from renal transplant and nontransplant patients. In particular, clusters of cells of uncertain origin, sometimes with features that were cytologically atypical, were noted to occur in numerous transplant urine cytology cases and appeared to be unique to transplant patients. Herein, we characterize the prevalence, cytologic features, and origin of these clusters, and the potential clinical significance of this finding.

Materials and methods

Incidence and cytologic features

Voided urine specimens of 100 consecutive patients with renal allografts and no evidence of polyomavirus collected over a 2-month period from February to March 2004 were examined. A group of 100 urine cytology cases excluding those with renal allografts and genitourinary malignancies collected from 2004 to 2009 were selected as a comparison group. Urine cytology slides were prepared according to the laboratory's routine urine concentration method. Briefly, the voided urine specimens were processed by concentrating a 45-ml aliquot of urine using conventional centrifugation. The supernatant was discarded and a small amount of BD Cytorich Red Preservative Fluid (BD Diagnostics, Franklin Lakes, N.J.) was added to form an even cell suspension. A few drops were placed in a Shandon Cytospin (Thermo Fisher Scientific, Waltham, Mass.) chamber and the samples were set for at least 30 minutes before centrifugation at 800 revolutions/minute. The slides were placed in 95% ethyl alcohol and subsequently Papanicolaou stained. The cytologic preparations were examined by at least 2 of the authors. The presence or absence of morphologically distinct cell clusters was noted. In addition, the cytologic features of the cells in the clusters were noted.

Immunocytochemical characterization

Ten urine cytology specimens from current cases that exhibited cell clusters identical to those seen in the 2004 cohort were selected for immunocytochemical evaluation. Additional Cytospin preparations were prepared, but without Papanicolaou staining. Immunocytochemical staining for renal cell carcinoma marker (RCC) and cytokeratin 7 (CK7) were performed, following the laboratory's routine immunohistochemical staining procedures. Staining was performed on an automated Ventana Benchmark XT immunostainer using prediluted mouse monoclonal antibodies to RCC (PN-15, Cell Marque, Rocklin, Calif.) and CK7 (OV-TL 12/30, Cell Marque).

Clinical correlation and follow-up

The clinical history was reviewed for all 100 renal transplant patients for findings that could be related to the cell clusters, using the hospital's electronic medical records. We evaluated for biopsy-proven acute graft rejection and/or significantly increased creatinine levels, as defined by an increase of serum creatinine of 0.4 mg/dL, in accordance with the Efficacy Endpoints Conference on Acute Rejection.[4,5] These parameters were evaluated over a period of 2 years; from 1 year prior to the index urine cytology to 1 year after it. Additionally, any other urine cytology specimens collected for a period of 1 year following the index urine cytology were reviewed. Finally, the clinical record was examined for evidence of development of any genitourinary malignancies up to the most recent available follow-up (up to 6 years). Clinical follow-up was available for 81 of the 100 renal transplant patients.

Results

Incidence and cytologic features

Of the 100 renal allograft patients, 18 (18%) exhibited cell clusters with the particular morphologic features demonstrated in Fig. 1. None (0%) of the 100 patients in the