Serial urinary and cervical cytological studies in women undergoing renal transplantation

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SUMMARY  Cervical dysplasia has been reported to occur more frequently in female renal transplant patients. The incidence of pre-existing dysplasia is unknown. A prospective study of several urinary and cervical cytological screenings of 50 transplant patients was undertaken. Two of 38 patients studied before transplantation had pre-existing dysplasia. No new cases of dysplasia were found during the study (mean surveillance 3 years). A high incidence of urinary viral infection was found, but a relation to cervical dysplasia was not noted. The frequency of cervical abnormalities previously reported might have been due to different immunosuppressive regimes or to failure to exclude pre-existing disease. Despite the low incidence of abnormalities the use of cytological screening provided valuable reassurance to our patients, and its use is recommended.

It is well known that recipients of organ allografts have an increased incidence of malignancy. In one series, 6% of renal graft recipients developed malignant tumours, an incidence 100 times greater than in a normal population. Tumour appearance is an early event, occurring on average 38 months after transplantation.

Carcinoma of the cervix is one of the commonest tumours occurring in female transplant recipients, being reported to be 13 times greater than in an age-matched population. It has been suggested that cervical cytological surveillance is an essential part of the routine management of female post-transplant patients.

Asymptomatic primary or activated latent virus infections occur frequently in immunosuppressed patients, and these may be related to the development of malignancy.

Cytological examination of freshly voided urine is a simple test for urinary viral infection and often a practical method of early diagnosis. Routine urinary cytology has been used after transplantation to discover asymptomatic renal tract infections.

It is, however, an unfortunate fact that the number of investigations already performed in post-transplantation clinics places a burden on both patients and hospital resources. The addition of any further investigations demands clear justification.

The value of routine cytological screening has not been established by a prospective study, and it is not clear whether the increased prevalence of cervical tumours is due to dysplasia arising de novo after transplantation or to pre-existing disease. The incidence of cervical dysplasia in patients before transplantation is unknown. We have therefore undertaken a prospective study of a cytological screening programme to establish:

1. the incidence of cervical dysplasia before transplant surgery;
2. the incidence of cervical and urinary cytological abnormalities after transplantation; and
3. the practicality and effectiveness of cytological screening.

Methods

Fifty women who had received a kidney graft were studied repeatedly over a three-year period. Each patient received immunosuppression treatment for at least six months (range 0.5-10 years). The patients studied had received 201.3 woman years of immunosuppression, of which 105.9 woman years was during the period of the study. Their mean age was 42.5 (range 25-70) years. All received immunosuppression therapy, namely, azathioprine, 2.0-2.5 mg/kg body weight per day, and prednisolone, 0.1-0.25 mg/kg body weight per day. Sixteen patients had received renal grafts before the period of investigation. Three patients died within the study period, and their results up to death are included.

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Urinary and cervical specimens for cytological examination were obtained before transplantation, three months post-transplantation, and then at annual intervals. Further specimens were examined when abnormal results had been obtained. The 16 patients already transplanted had only post-transplant cytology studies.

Cervical specimens were obtained using an Ayre's spatula after good visualisation of the cervix uteri with a Cusco's speculum. Smears were taken immediately and fixed in ethanol. They were stained by the Papanicolaou technique and examined under the light microscope.

Urine specimens were obtained at the same consultation. After cytocentrifugation, smears were made of the urinary sediment, Pap stained, and examined by light microscopy.

Results

One case of mild dyskaryosis and one case of carcinoma-in-situ were found before transplantation. The cervical dyskaryosis did not progress during the three-year period of observation. The carcinoma-in-situ lesion was treated by cone biopsy, and cervical cytology has remained normal for a further three years.

No new case of dysplasia or frank malignancy developed during the period of the study.

Twenty-six patients had mild cervicitis on at least one smear. The patients were asymptomatic throughout. One case of severe cervicitis was noted on a single occasion, a mild cervicitis persisting thereafter for 18 months. At this time monilia was isolated (see below).

Eight patients' smears demonstrated moniliasis. Trichomonas vaginalis, candida, and herpes infection were observed on a single occasion in three patients.

Urinary cytological examination of 218 specimens revealed a single episode of moniliasis, three episodes of yeast infection, and two papovavirus infections. Asymptomatic cytomegalovirus was detected in two patients, and in one it was persistent.

The relationship of the urinary findings to cervical cytology is shown in the Table.

Discussion

The first case of carcinoma of the cervix uteri in a renal transplant recipient was reported in 1969. Since then, Kay et al. have studied the cervical changes in 28 renal transplant patients and found three cases of dysplasia. One progressed from mild dysplasia to carcinoma-in-situ within a year, the patient having begun immunosuppression three years previously. Porreco et al. found the incidence of intraepithelial carcinoma of the cervix in renal allograft recipients to be 14 times greater than in age-matched controls. A possible association between cervical dysplasia and azathioprine therapy has been suggested by Gupta et al., but in their patient pre-existing cervical dysplasia was not excluded. Subsequently, other cases of cervical epithelial atypicity in patients treated with azathioprine after renal transplantation have been reported.

In this study, for the first time a group of renal transplant recipients has been examined repeatedly to determine the incidence of new cases of cervical dysplasia and carcinoma-in-situ. Using the incidence described by Porreco et al., we would have expected to find one to two cases of in situ carcinoma, but there were no new cases and no evidence of premalignant change. The duration of immunosuppression in our patients is similar to that in other series, but the therapeutic regime differs from that in other reported series. No patient in our group received antilymphocyte serum or irradiation of the donor kidney. If tumour induction is related to the degree of immunosuppression, our results may reflect the lower dose regime now in use.

The aetiological factors implicated in carcinoma of the cervix are unknown and probably multiple. There is increasing evidence that viruses may be implicated, especially herpes simplex virus type. A significant incidence of urinary viral infection in renal transplant patients is well documented, and we have confirmed this in the patients studied. Indeed, our results probably underestimate the true incidence as we used the simple light microscopy examination, whereas electron microscopy is more accurate in detecting and identifying urinary viruses. Electron microscopy is too complex a technique to be used as a routine investigation. Although we have failed to demonstrate a relation between urinary viral infection and cervical epithelial changes, the possibility requires further investigation.

Table: Urinary findings related to cervical cytological examination

<table>
<thead>
<tr>
<th>Patient</th>
<th>Immunosuppression (months)</th>
<th>Cervical cytology</th>
<th>Urine cytology</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 RA</td>
<td>14</td>
<td>Mild cervicitis</td>
<td>Monilia</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>Clear</td>
<td>Negative</td>
</tr>
<tr>
<td>2 PC</td>
<td>48</td>
<td>Normal</td>
<td>Candida</td>
</tr>
<tr>
<td></td>
<td>66</td>
<td>Normal</td>
<td>Negative</td>
</tr>
<tr>
<td>3 JH</td>
<td>108</td>
<td>Normal</td>
<td>Candida</td>
</tr>
<tr>
<td></td>
<td>120</td>
<td>Normal</td>
<td>Negative</td>
</tr>
<tr>
<td>4 AS</td>
<td>3</td>
<td>Monilia</td>
<td></td>
</tr>
<tr>
<td>5 IC</td>
<td>84</td>
<td>Normal</td>
<td>Cytomegalovirus</td>
</tr>
<tr>
<td>6 DH</td>
<td>18</td>
<td>Atrophic</td>
<td>Cytomegalovirus</td>
</tr>
<tr>
<td>7 EH</td>
<td>24</td>
<td>Mild cervicitis</td>
<td>Papovavirus</td>
</tr>
<tr>
<td>8 WS</td>
<td>3</td>
<td>Mild cervicitis</td>
<td>Papovavirus</td>
</tr>
</tbody>
</table>
The additional workload created by this study did not cause problems in either the clinic or the cytological laboratory. In the initial part of the study cervical specimens were taken by a nurse, but once the study was underway cytological specimens were obtained by the doctors in the clinic.

A central record of results enabled defaulters to be identified and recalled for examination. Once the investigation had been established as a routine measure, there were few difficulties.

The size of this series makes precise estimates of the incidence of disease impossible. It is nonetheless reassuring that no new cases of cervical dysplasia, or indeed of any other tumour, appeared during the period of the study. The importance of excluding pre-existing disease is emphasised by the fact that if these patients had not been excluded, our results would have wrongly suggested an abnormally high incidence of tumour development.

We found that cervical and urinary cytological screening of immunosuppressed women is simple and convenient and may be routinely performed in a clinic. Although we detected few abnormalities, we consider that the reassurance we were able to give the patient was sufficiently valuable to justify a continuing programme.

References

12 Reference deleted.

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