The value of cytological examination of the urine in the staging of invasive carcinoma of the cervix

A prospective study

C. J. C. DEALE, P. B. WRANZ, J. P. DU TOIT

Summary

During the period July 1976 - December 1978 midstream urine specimens were collected from all new patients with invasive cervical carcinoma admitted to Tygerberg Hospital, Parowvallei, CP. All specimens were cytologically screened to try and establish any correlation between the cytological result and the clinical staging. A very high proportion (24.2%) of specimens unsuitable for screening and unacceptable false-negative and false-positive rates forced us to abandon this prospective study. From January 1979 to July 1980 the study was repeated on catheter specimens of urine. The final analysis of the second series revealed that a catheter specimen had definite advantages, but a detection rate of only 37.5% and a false-negative rate of 62.5% forced us to conclude that urinary cytological examination is at present too inaccurate to be of any value in the staging of invasive cervical carcinoma.

Patients and methods

During the period July 1976 - December 1978 a total of 369 new patients with invasive cervical carcinoma underwent clinical staging in the Department of Gynaecological Oncology, Tygerberg Hospital, and the existing methods of staging were re-evaluated. Concurrently, midstream urine specimens for cytological screening were collected from the patients by the nursing staff. From January 1979 to July 1980 a second series of 162 new patients with invasive cervical carcinoma underwent staging at the same hospital. In these cases the midstream urine specimen was replaced by a catheter specimen.

Midstream urine specimens

Midstream urine specimens were collected by the nursing staff in the early morning. The vulva and urethral opening were cleaned with a 1:1000 solution of chlorhexidine in water, and the specimen was collected directly in a sterile bottle containing heparin and 20 ml normal saline. The specimen was processed in the cytology laboratory within 30 minutes of collection by means of microfiltration, and two slides were prepared for cytological screening.

Catheter urine specimens

Catheter urine specimens were collected by the registrar under strict aseptic and antisepsic conditions before commencing with the bimanual examination required for clinical staging of the carcinoma. The object was to minimize the chances of secondary infection of the bladder and to avoid possible contamination of the specimen with vulval and vaginal cells. The urine was collected directly into a sterile bottle containing heparin and delivered to the cytology laboratory within 30 minutes. At the laboratory it was microfiltered and two slides were prepared for cytological screening.

A total of 426 midstream specimens were collected from the 369 patients in the first series. Because cystoscopic examination could only be performed on 356 patients, the remaining 13 had to be excluded from the final analysis. In the second series 162 catheter specimens from 162 patients were examined, but in the final analysis 1 patient had to be excluded because she died of renal failure before cystoscopy could be performed. Cytological examination of the urine in this case happened to be negative.

Criteria for cytological screening

Cytological evaluation was performed on the basis of four major subgroups: (i) unsatisfactory specimen; (ii) normal urothelial and squamous cells; (iii) inflammatory changes of urothelium, which may have shown a spectrum from minor to major abnormality; and (iv) the presence of malignant squamous cells.

A specimen was not considered suitable for cytological examination when amorphous debris together with polymorphonuclear leucocytes and severe degeneration of squamous cells and/or urothelial cells was present (Fig. 1).
Normal urothelial cells are usually isolated, few in number and vary from large, flat and polygonal cells measuring 50-60 \( \mu m \) in diameter to those which are small, round and 20 \( \mu m \) in diameter. The cells have thin, transparent cytoplasm with a vesicular nucleus and finely granular chromatin. Superficial cells with pyknotic nuclei and intermediate cells with vesicular nuclei are similar to those found in the vagina (Fig. 2).

Inflammatory changes were classified as ranging from mild inflammatory changes in the urothelial cells to atypia. When inflammatory change was present occasional polymorphonuclear leucocytes, lymphocytes and red blood cells were observed. Karyorrhexis of urothelial cells was present. Atypia was considered to be present when the urothelial cells occurred in greater numbers, being shed in small isolated clusters of papillary fragments. This could be due to severe inflammatory processes, papillomas, calculi or catheterization. Smooth cellular borders were considered to be representative of papillary fronds, while rounded borders were probably caused by the forcible removal of fragments which occurs during catheterization (Fig. 3). In general the cells show cellular and nuclear enlargement, hyperchromasia of the nucleus may be observed, and there is vacuolation in the cytoplasm.

The malignant squamous cells are generally similar to those found in cervical preparations. The cells are mostly spindle-shaped and vary in size. There is extreme pleomorphism of the nuclei and the cytoplasm may show keratinization varying in relation to the degree of differentiation of the neoplastic process (Fig. 4).

Results

The diagnosis arrived at after cytological examination of the 426 specimens from the 369 patients screened in the first series are compared with those for the 162 catheter specimens from the 162 patients in the second series (Table I). The proportion of specimens showing inflammatory changes was equal in the two series (16,2\% v. 16,7\%). In the catheter specimens there was a marked drop in the proportion of those unsuitable for screening (7,4\% v. 24,2\%), while there was a sharp rise in the proportion of specimens demonstrating atypia (55,6\% v. 12\%). It is interesting to note that there were almost twice as many negative results in the midstream specimens and that in this series the proportion of positive results indicating squamous carcinoma was much higher (16,9\% v. 4,3\%).

The various reasons for considering a specimen unsuitable for screening are analysed in Table II. In the catheter specimen series only two reasons were given, namely overwhelming infection and too few transitional cells. These reasons were of minimal importance in the midstream series. Here the main reason was that only squamous cells were present in the specimen, with the result that no opinion could be given.
The correlation between the cystoscopic findings and the cytological diagnoses in the two series is summarized in Tables III and IV. In the first series there were 39 proven cases of squamous carcinomatous infiltration of the bladder mucosa. Urinary cytological examination was positive in 26 (66.6%) of these cases and negative in 13 (33%) (Table III). Of the 16 patients in the second series in whom cystoscopy revealed invasion of the bladder mucosa 6 (37.5%) had a positive cytological result and 10 (62.5%) a negative one (Table IV).

The cytological reports for the patients in whom cytological examination was negative but cystoscopy was positive are analysed in more detail in Table V. The commonest cause for the negative reports was few or absent transitional cells in the urinary specimens, while inflammatory changes and atypia were additional factors.

The final diagnoses on cytological examination of the urine in patients found to have bullous oedema of the mucous membrane and a normal mucous membrane on cystoscopy are compared in Tables III and IV. It is obvious that the correlation between urinary cytological examination and cystoscopy is much better in the catheter specimen series. In 46 (63.9%) patients in the midstream specimen series in whom cytological examination of the urine was positive, cystoscopy was negative (Table VI). In 12 (26.1%) of these cases bullous oedema was noted and in 34 (73.9%) cystoscopy revealed no abnormality of the bladder mucosa. In 1 patient (14.3%) in the catheter specimen series in whom cytological examination of the urine was positive and cystoscopy negative, bullous oedema of the mucous membrane was visible on cystoscopy. Table VI also reveals that the diagnosis of infiltration was confirmed on cystoscopy in only 26 (36.1%) of 72 patients with cytologically positive midstream specimens, compared with 6 out of 7 (85.7%) of those with positive catheter specimens.

Discussion

Once the results of the midstream series were analysed it was obvious that cytological examination of urine specimens collected in this manner was not accurate enough to be of value in
Pregnancy after oocyte and sperm transfer to the uterus

In vitro fertilization of ova for the relief of infertility has obvious drawbacks. It is costly and tedious and presents moral and ethical problems. There may be a more acceptable alternative if the preliminary results of a technique used by Craft et al. (Lancet 1982; i: 1031) stand the test of time. What Craft et al. have done is to induce ovulation in 31 infertile women with clomiphene citrate and then capture oocytes by laparoscopy 36 hours after giving an injection of choricionic gonadotrophin. They then incubated the oocyte in a tissue culture medium for 6 hours, added sperm, continued culture for a further hour and then transferred the oocyte and sperm directly into the uterus. Measurements of choricionic gonadotrophin levels in the urine indicated that there was some trophoblastic activity in 14 of the patients; 2 of the patients at the time of reporting have a continuing intra-uterine pregnancy. Further information will be eagerly awaited, since there are no moral or ethical problems associated with this technique and it might well be used in an ordinary infertility clinic attached to a general hospital.

Orale voorbehoedmiddels en serviks-karsinoom

Baie navorsers wil 'n verband sien tussen die gebruik van orale voorbehoedmiddels en die ontstaan van displasie van die cervix uteri. Ander is weer oortuig dat dieselfde verband tussen seksuele aktiwiteit en die ontstaan van maligne en premaligne serviksaandoeninge bestaan.

Swan et al. (Am J Obstet Gynecol 1981; 139: 52) het hierdie faktore by 69 vrouens met karsinoom in situ van die serviks ondersoek en die resultate vergelyk met die van 243 gesonde vrouens van dieselfde ouderdom, huwelikstaat, geloof, sosiale status en pariteit. Hulle het 'n seksuele aanduiding gebruik wat bereken word uit die gegevens van die ouderdom ten tyde van die eerste huwelik, eerste koitus, aantal huwelike, koitusfrekwensie en die aantal veneriese infeksies.

Van die vrouens met 'n karsinoom in situ blyk 86% nooit orale voorbehoedmiddels te gebruik het nie teenoor 58% uit die kontrolegroep. Hier moet onthou word dat nie net die pilgebruikers minder sotologies ondersoek is nie, maar ook dat vrouens uit die kontrolegroep selde 'n ginekologiese ondersoek ondergaan het. Sover dit die seksuele aanduiding betref, blyk dit dat die vrouens met karsinoom in situ gemiddeld twee maal soveel seksgeselle gehad het as die kontroles. Die gemiddelde aanvangsouderdom van gereelde geslegsverkeer was laer en die trou-ouderdom sowel as die eerste aanvangsouderdom van gereelde geslegsverkeer is op 'n nooder stadium plaasgevind. Die aantal veneriese infeksies en terapeutiese aborsies het min verskil tussen die groepe. Die risiko van karsinoom in situ het toegeneem namate orale voorbehoedmiddels gebruik is vir langer as 4 - 6 jaar. Daarna het die frekwensie weer afgenem.

Wanneer die genoemde seksuele faktore in ag geneem word, is die verhoogde risiko as gevolg van pilgebruik egter nie langer statisties beduidend nie.

REFERENCES