New Concepts in the Evaluation of the Abnormal Papanicolaou Smear

Michel Roy, M.D., Duane E. Townsend, M.D., Philip J. DiSaia, M.D., and C. Paul Morrow, M.D.

Los Angeles, California

An abnormal cervical cytology ("Pap smear") should always arouse suspicion of cervical cancer. Two forms of investigation can be used to determine the degree of abnormality and to exclude invasive cancer. The first method is the widely employed conization of the cervix, following punch biopsy of the non-staining areas from the Schiller's test to confirm an abnormal cervical lesion. The second, more conservative method is colposcopy and colposcopically-directed punch biopsy. In 95 percent of the cases, a colposcopic examination will provide an accurate diagnosis, and will avoid hospitalization and the complications of cone biopsy. Colposcopy, when available, is becoming the method of choice in the evaluation of a patient with an abnormal Pap smear.

Whenever a physician is confronted with a patient who has an abnormal Papanicolaou stained cervical smear ("Pap smear") suggestive of dysplasia (Class III) or worse, his most important obligation is to establish the presence or absence of invasive cancer. Fortunately, the overwhelming majority of patients with an abnormal Pap test do not have invasive carcinoma but, rather, an intraepithelial form of malignant neoplasia, i.e., dysplasia or carcinoma-in-situ.[1] At Women's Hospital, Los Angeles County-University of Southern California Medical Center, almost 1,000 patients with abnormal Pap smears are evaluated yearly, but only five percent have invasive cervical cancer. This low incidence of invasive carcinoma should encourage the physician to conduct a systematic, careful, and unhurried evaluation of the individual whose cervical cytology is abnormal.

This article updates the approach to the patient with abnormal Pap test. Evaluation with and without colposcopy will be presented. It is particularly appropriate to review the problem of the abnormal cervical cytology at this time because the Pap test is being extended to a younger population in which dysplasia and carcinoma-in-situ are surprisingly prevalent and invasive carcinoma is rare.

From the Department of Obstetrics and Gynecology-Section of Gynecologic Oncology, Los Angeles County-University of Southern California Medical Center, Women's Hospital, Los Angeles, California. Requests for reprints should be addressed to Dr. Duane E. Townsend, Department of Obstetrics and Gynecology-Section of Gynecologic Oncology, Los Angeles County-University of Southern California Medical Center, Women's Hospital, Room 903 L, 1240 North Mission Road, Los Angeles, California 90033.

Pathophysiology of the Uterine Cervix

A review of the pathophysiology of the cervical epithelium is helpful to understand properly the origin and significance of an abnormal Pap smear. It has been believed for over a century that the junction between the squamous and columnar epithelium of the normal cervix is at the external os. Studies by Pixley and Coppleson,[2] Stafl,[3] and others, together with daily experience in our colposcopy clinic, contradict this concept. In the majority of patients during the reproductive years, the squamocolumnar junction is found on the ectocervix. The presence of columnar epithelium on the ectocervix is embryologically determined; it does not arrive there by eversion, nor does it grow out onto the cervix. Pixley's exhaustive studies on female fetuses and adolescents have shown that over 70 percent have columnar tissue laid down on the ectocervix during intrauterine life. Under hormonal influence and the acid secretions of the vagina, this columnar epithelium is transformed into squamous epithelium through a process referred to as metaplasia. The transformation of columnar into squamous epithelium occurs throughout an individual's life, but is most active during adolescence and first pregnancy. It is an orderly process occurring both as a peripheral ingrowth from the original squamous epithelium towards the endocervical canal, as well as focal or patchy transformation within the ectocervical columnar epithelium itself. Initially, the metaplastic squamous epithelium is composed of very immature cells, which gradually develop the features of mature squamous epithelium. It is postulated that these immature metaplastic squamous cells are particularly susceptible to genetic injury by environmental carcinogens. The earliest recognizable microscopic change that occurs in the neoplastic squamous epithelium is a nuclear anaplasia confined to the epithelium. This is referred to as dysplasia. It is important to detect and eradicate these intraepithelial malignant lesions, since some of them will progress to invasive cancer. [4,5]

The most reliable and economical means to detect preinvasive neoplasia of the cervix is by exfolliative cytology. However, the Pap test is only a screening test and not a diagnostic tool. It has a false-negative rate of 10-30 percent.[6] One must never undertake treatment guided solely by the abnormal Pap test. Abnormal cervical cytology can be due to regeneration following inflammation, obstetrical injury, or some type of therapeutic procedure on the cervix, such as freezing, electrocauterization or biopsy. However, on occasion the most minimal epithelial changes on cytology will be associated with invasive cancer. In addition, patients can have cellular aberrations suggestive of invasive cancer, but due entirely to an intense inflammatory change. The best way to an accurate diagnosis and proper management of a patient with an abnormal Pap test is a thoughtful diagnostic evaluation scheme, methodically applied in every case.

Standard Evaluation Scheme

The first step in the evaluation of the patient with the abnormal cervical cytology is to repeat the Pap test. This should not be performed sooner than four weeks after the original cervical sampling because the false-negative rate is higher if taken sooner. The cervix is cleaned of mucus with a soft cotton ball prior to sampling. This must be a gentle wipe; vigorous rubbing causes bleeding which may obscure the presence of dysplastic cells. Once the cervix has been well exposed, a careful inspection should disclose the junction between the smooth, pink, squamous epithelium and a redder, often granular appearing, columnar epithelium. This is the squamocolumnar junction (SCJ) and it is the area of the cervix where nearly all neoplastic lesions arise because of the presence of immature tissue susceptible to carcinogens. The SCJ and one centimeter on each side should be firmly scraped using a spatula with two complete passes over the entire area. An additional sample from the endocervical canal should be taken either with a saline-moistened cotton tip applicator or an endocervical aspirator. The two samples can be mixed on a single slide but one slide for each sample is also satisfactory. In order to prevent drying of the cervical scrape specimen, the endocervical canal sample is taken first. In cases where the SCJ appears to be at the external cervical os or within the canal, it is imperative that the Pap test be taken from the endocervical canal. Cytology specimens obtained from the vaginal pool are frequently inadequate since they have a false-negative rate as high as 50 percent for cervical neoplasia.[7]

After the Pap smear is obtained, the cervix is thoroughly cleansed with saline or three percent acetic acid. The cervix is carefully inspected with a strong light and any grossly sus-

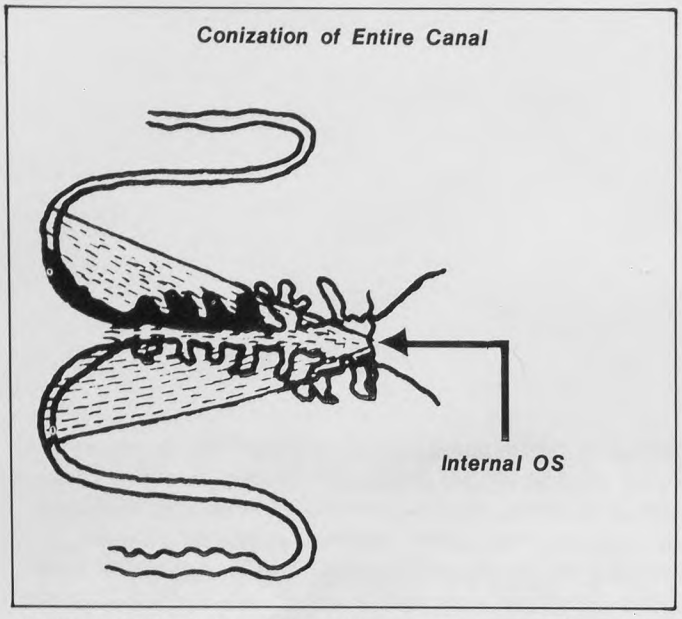

Figure 1. Following positive ECC, with lesion extending high in the canal.

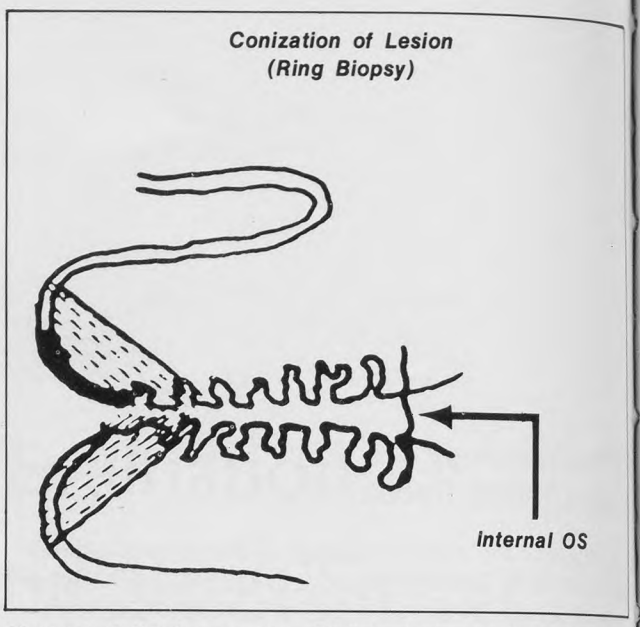

Figure 2. Following negative ECC for lesion on the ectocervix.

picious areas are biopsied. If there are no suspicious areas, a Schiller's test is performed by applying a two percent iodine solution (Lugol's) to the cervix. Normal glycogen-containing squamous epithelium stains a deep brown, whereas neoplastic squamous tissue is rather yellow or does not stain at all. The Schiller's test is non-specific for neoplasia. In addition to preinvasive and invasive neoplastic squamous tissue, neither normal columnar epithelium nor immature metaplastic epithelium (the tissue that replaces columnar epithelium in the transformation process) stains with iodine, since they also do not contain sufficient glycogen. The location of all areas that do not stain should be recorded for future reference.

Once the iodine staining has been carried out, every patient, except those who are pregnant, should have an endocervical canal curettage (ECC) to rule out the presence of abnormal epithelium in the canal. The curettage is a vigorous scrape of the canal from the internal to the external os. A Kevorkian endocervical curette is the recommended instrument for this procedure. All blood, mucus, and tissue debris is placed on a paper towel, molded into a small mound and placed in a fixative.

Cervical biopsies are then taken from all Schiller positive areas. The concept of random punch biopsies at the twelve, three, six and nine o'clock positions should be discarded. Cervical neoplasia is found predominantly on the anterior and posterior lips of the cervix. If four quadrant random punch biopsies are to be performed they should be taken at the ten, two, four and eight o'clock positions to sample the most likely location of cervical neoplasia. It is important, however, to thoroughly sample all iodine negative areas.

The next step depends on the results of the repeat cytology, the cervical biopsies and the ECC. If the biopsies or ECC show invasive cancer, conization of the cervix is unnecessary and contraindicated. The patient should be referred for management to a specialist in gynecologic cancer.

If the biopsies or endocervical curettage show dysplasia or carcinoma-in-situ, or if the repeat cytology is abnormal but the biopsies negative, the patient should have an excision biopsy of the endocervical canal and the iodine negative areas of the cervix, the so-called "cone biopsy" of the cervix (figure 1). If the endocervical curettings show no neoplastic tissue it is not necessary to excise all endocervical tissue, but only the distal portion ("shallow cone") along with iodine negative areas on the ectocervix (figure 2). If the repeat cytology, cervical biopsies and the curettage of the canal show no neoplastic epithelium, a repeat evaluation is carried out in three months. The physician and the patient can take comfort in the knowledge that the most serious disease suggested by the abnormal Pap test—invasive carcinoma of the cervix—has been properly excluded.

Colposcopic Evaluation

The colposcope is a steroscopic viewing instrument with a magnifying power ranging from 6X to 40X. Although developed in Europe more than a half century ago to detect cervical cancer, it received little attention in North America because of the efficacy and simplicity of detecting cervical malignancy by exfolliative cytology. During the past few years the colposcope has proven extraordinarily valuable, not in screening women for cervical cancer, but in evaluating the woman with an abnormal Pap smear. With a colposcope, the examining physician is able to locate and assess the quality of the cervical lesion responsible for the abnormal Pap test.

The colposcopic evaluation is virtually identical to the standard evaluation scheme except that, in addition to using the naked eye, the physician examines the cervix through the colposcope. With the magnification that the colposcope provides, it is possible to locate the squamo-columnar junction, note the color and topography of the

epithelial surfaces and study the vascular architecture. Under colposcopy, normal squamous epithelium has a shiny, pink, smooth surface through which the tiny hairpin vessels of the stroma are apparent. Normal columnar epithelium appears like a collection of small grapes. The most important area to evaluate colposcopically is the transformation zone, which is that portion of the columnar epithelium which has been transformed by metaplasia to squamous epithelium. This is the region where dysplasia, carcinoma-in-situ, and invasive cancer of the cervix nearly always originate. The entire transformation zone must be thoroughly inspected. Dysplasia and carcinoma-in-situ invariably appear as white patches with sharp borders and minor alterations of the surface contour. In some cases the blood vessel pattern will be particularly prominent, and patterns referred to as mosaic and punctation are present. This is in contrast to the pattern of invasive squamous cell carcinoma, which has a highly irregular surface contour and heavy vessels. These abnormal surface vessels are responsible for the invasive lesion bleeding easily on contact.

Once a lesion has been located by colposcopy, it is important to determine its extent. Its border on the ectocervix is usually quite easy to delineate and the margin closest to the external os can also be readily defined in most cases. These lesions can be adequately evaluated by colposcopically-directed punch biopsies on an outpatient basis. Occasionally, a lesion will extend into the endocervical canal. If the lesion extends high in the canal, beyond the view of the colposcopist, the examination is unsatisfactory. It is mandatory in such cases that cervical conization be performed because the hidden part of the lesion may be invasive cancer. Fortunately, the need for diagnostic conization because the limit of the lesion cannot be seen occurs in no more than five to ten percent of patients with an abnormal Pap test. In more than 90 percent of the cases, the source of the abnormal Pap test is adequately assessed by a colposcopically directed biopsy of the worst lesion. In a study of 1,410 cases in Wisconsin, Stafl [8] showed that when the colposcopic examination is satisfactory (entire lesion seen), only 0.3 percent of the cases had a more advanced lesion on conization or hysterectomy than the colposcopically directed biopsy. No invasive cancer was missed by colposcopy.

Although colposcopy affords excellent visualization of the cervix and can provide a direct approach to localized biopsies, the procedure requires considerable experience on the part of the colposcopist and a substantial outlay for the necessary equipment. For these reasons, consultation with a specialist skilled in this procedure will usually be indicated when family physicians desire to utilize this diagnostic technique to follow up abnormal Pap smears.

Pregnancy

During pregnancy cervical cytology is reported to have a positive rate of 0.7 percent to 1.6 percent.[9] Because of the low yield of invasive cancer and the high maternal and fetal morbidity related to conization in pregnancy,[10] no patient should be managed without the benefit of colposcopy. Major fetal and maternal complications are reported to occur in 30-50 percent of cases coned during pregnancy, including abortion, premature labor, premature delivery and hemorrhage. With the aid of colposcopy, conization is rarely necessary.[11] Because the cervix is physiologically "everted" during pregnancy, the entire lesion is almost always visible and easy to evaluate by colposcopy. Only invasive carcinoma requires therapy during pregnancy and only invasive carcinoma contraindicates vaginal delivery.

Treatment

The management of the patient with a proven carcinoma-in-situ or severe dysplasia of the cervix is becoming more and more conservative. In the United States, hysterectomy is the most common treatment but it is seldom necessary in the management of carcinoma-in-situ or dysplasia. In the Scandinavian countries and Australia, clinical trials have demonstrated that conization which removes the entire lesion is a satisfactory treatment. Simple excision biopsy, electrocautery, and cryosurgery are currently under investigation in this country. Preliminary results are very encouraging and these methods will probably become a major course of treatment of preinvasive carcinoma of the cervix.

The physician should fully discuss the management with the patient, stressing the effect of the treatment on her childbearing capacity. If future pregnancy is desired, the most conservative approach should be taken and the patient followed up by cervical cytology and colposcopy twice a year after treatment. If the patient does not wish to have more children, or has other benign gynecologic disease, hysterectomy is a logical approach if she is otherwise a suitable candidate for major surgery.

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