RESEARCH COMMUNICATION

Can Adenocarcinoma *in situ* of the Uterine Cervix be Predicted before Cervical Conization?

Chumnan Kietpeerakool[1]*, Jatupol Srisomboon[1], Wiboonwan Prompittayarat[1], Panida Kanjanavaha[2], Ream Peuwsai[2], Chudsuda Dheerakul[2]

Abstract

   This study was undertaken to determine the effectiveness of the Papanicolaou (Pap) smear, colposcopically-directed biopsy (CDB), and endocervical curettage (ECC) in preconization detection of adenocarcinoma *in situ* (AIS) of the uterine cervix. Women, whose cervical conization specimens contained adenocarcinoma *in situ* without any associated invasive lesion at Chiang Mai University Hospital between March 1998 and March 2006, were reviewed. During the study period, fifty-one women who matched the study inclusion were identified. Glandular abnormality was detected by Pap smears in 22 women (43.1%). Among 29 women with squamous lesions on Pap smears, 9 additional glandular abnormalities were detected on CDB and/or ECC. In total, glandular abnormality was suspected in 31 women (60.8%) preoperatively. According to the histological type of AIS, glandular abnormality suspected from preoperative evaluation was noted in 20 women (70.4%) who had pure AIS. Among women with mixed AIS/ HSIL, only 12 women (50.0%) had preoperative evaluation suggesting glandular abnormality. These data demonstrate that the sensitivity of combining Pap smear, CDB and/or ECC in detecting glandular lesions before conization containing AIS appears to be suboptimal. Further study concerning the improvement of detecting AIS before conization is warranted to select the most appropriate diagnostic conization method for such lesions.

Key Words: Adenocarcinoma in situ - cytology - biopsy - cervical conization

Introduction

   Adenocarcinoma in situ (AIS) of the uterine cervix is a relatively uncommon disease. Current evidence supports the existence of AIS as a precursor lesion of cervical adenocarcinoma (Duggan et al., 1994, Zaino, 2002). Therefore, the appropriate management of AIS is mandatory. A definite diagnosis of AIS is generally made on conization specimens. Although loop electrosurgical excision procedure (LEEP) is currently the most common procedure for management of women with cervical intraepithelial lesions, cold-knife conization (CKC) is strongly recommended rather than LEEP for AIS that is usually endocervical in location because such procedure provides a greater depth and larger volume of cone specimens, resulting in a lower incidence of cone margin involvement. Additionally, there is no thermal artifact that interfers with the margin status determination, as observed in LEEP specimens (Mathevet et al., 1994, Wildrich et al., 1996). Therefore, the identification of women who possibly have occult AIS would imply that the surgeon select the most appropriate conization technique. Accordingly, this retrospective study was conducted to determine the effectiveness of cervical cytology, colposcopically directed biopsy (CDB), and endocervical curettage (ECC) in detecting glandular abnormality in women whose conization specimens contained AIS without associated invasive carcinoma.

Materials and Methods

   After approval from the Research Ethics Committee, the medical records of women with abnormal Papanicolaou (Pap) smear, who had AIS without associated invasive carcinoma on cervical conization specimens at Chiang Mai University Hospital between March 1998 and March 2006, were reviewed. All women underwent colposcopy before conization. The subsequent cervical conization was generally performed within 8 weeks after colposcopy. All enrolled women had their histological materials initially reported or reviewed by the gynecological pathologist in our institute at the time of treatment. The detailed histological diagnosis was made according to the World Health Organization (WHO) criteria, which were updated in 2003 (Tavassoli et al., 2003). The women who had mixed lesions of AIS and squamous intraepithelial lesion (SIL) of any grade were also recruited. The ECC specimens were histologically

[1]*Department of Obstetrics and Gynecology,* [2]*Obstetrics and Gynecologic Emergency Room Unit Faculty of Medicine, Chiang Mai University, Chiang Mai 50200, Thailand *For Correspondence: E-mail: kiet_ji@hotmail.com*

interpretaed as negative, positive, or inadequate. The results were negative when normal endocervical cells were presented. Positive results were those in which neoplastic cells were noted. Inadequate results were those without cells for interpretation. The demographic characteristics, Pap smear results, results of ECC and CDB, and cone histology were analyzed.

Results

During the study period, 1,957 women underwent cervical conization at Chiang Mai University Hospital and only fifty-one women with abnormal Pap smear who had AIS without any associated invasive lesion on cervical conization specimens were identified, which accounted for 2.6% (95% confidence interval [CI] = 1.9 to 3.4). Among those 51 women, who enrolled in this study, 37 (72.5%) were premenopausal. The most common preceding abnormal Pap smear was high-grade squamous intraepithelial lesion (35.3%), followed by AIS (27.5%) and atypical glandular cells (13.7%). Thirty-six women (70.6%) had unsatisfactory colposcopy. Thirty-three women (64.7%) underwent LEEP, while the remaining 18 (35.3%) underwent CKC. The conization specimens contained AIS alone in 27 women (52.9%), while the remaining 24 (47.1%) had coexisting squamous cell abnormality consisting of high-grade squamous intraepithelial (HSIL) histology. Table 1 displays the baseline characteristics, results of CDB and/or ECC stratified by the type of preceding abnormal Pap smear. Glandular abnormality was detected by Pap smear in 22 women (43.1%). Among 29 women with abnormal squamous lesion on Pap smear, 9 additional glandular

Table 1. Demographic Characteristics and Outcomes According to Type of AIS Histology*

Variables	All (51)	Pure AIS (27)	Mixed AIS/HSIL (24)
Baseline characteristics			
Age, years	44.4±8.7	44.2±9.0	44.6±8.6
Premenopausal	37 (72.5)	19 (70.4)	18 (75.0)
Nulliparity	3 (5.9)	2 (7.4)	1 (4.2)
Pap smear and CDB/ECC			
Glandular lesion on Pap[a]	22 (43.1)	15 (55.6)	7 (29.2)
Glandular lesion on CDB/ECC[b]		3	0
Squamous lesion on CDB/ECC[c]		1	0
No CDB/ECC		11	7
Squamous lesion on Pap[d]	29 (56.9)	12 (44.4)	17 (70.8)
Glandular lesion on CDB/ECC[e]		4	5
Squamous lesion on CDB/ECC[f]		1	2
No CDB/ECC		7	10

AIS, adenocarcinoma in situ ; AGC, atypical glandular cell ; ASC, atypical squamous cell ; LSIL, low-grade squamous intraepithelial lesion ; HSIL, high-grade squamous intraepithelial lesion ; SCCA, squamous cell carcinoma ; CDB, colposcopically directed biopsy. [a]Including AIS (n = 14), AGC (N = 7), and adenocarcinoma (n = 1) [b]There were 3 AIS histologies [c]There was 1 LSIL histology [d]Including HSIL (n = 18), SCCA (n = 5), ASC (n = 4), and LSIL (n = 2) [e]Including mixed AIS/HSIL (n = 6), and AIS (n = 3) [f]All had HSIL histology *   Values are given as mean ± S.D or number (percentage) unless otherwise indicated

abnormalities were detected on CDB and/or ECC. By combining Pap smear, CDB and/or ECC, a glandular abnormality was suspected in 31 women (60.8%) before cervical conization. According to the histological type of AIS, a glandular abnormality suspected from Pap smear, CDB and/or ECC was noted in 20 women (70.4%) who had pure AIS. Among women with mixed AIS/HSIL on conization specimens, only 12 (50.0%) had Pap smear, CDB and/or ECC suggesting a glandular abnormality.

Discussion

There is substantial evidence that a well organized prevention program of cervical carcinoma, including both early detection and adequate treatment of precancerous lesions, is an efficient means to reduce the incidence of invasive squamous cell carcinoma. However, the incidence of invasive cervical adenocarcinoma has relatively increased (Vizcaino et al., 1998, Vizcaino et al., 2000, Wang et al., 2004, Castellsague et al., 2006). These findings suggest that the current strategies for cervical cancer screening may not be sufficient for preventing invasive cervical adenocarcinoma.

AIS of the uterine cervix is now established as a precancerous lesion of invasive cervical adenocarcinoma. Convincing evidence includes: (1) AIS that is usually diagnosed in populations 10 to 20 years younger than those with invasive adenocarcinoma; (2) AIS that frequently coexists with invasive adenocarcinoma on excisional specimens; (3) similar human papillomavirus (HPV) types and ploidy status; and (4) cases of untreated AIS that precede invasive adenocarcinoma (Zaino 2002).

In this study, a coexistent SIL was noted in 47.1% of conization specimens containing AIS, which was in accordance with previous reports ranging from 30% to 60% (Wolf et al., 1996, Denehy et al., 1997, Azodi et al., 1999). No plausible explanation exists to address the mechanism that defines whether the site of neoplastic transformation involves glandular or squamous epithelium (Zaino 2002).

The sensitivity of the cervical smear in detecting AIS is lower than that of SIL. Mitchell and Higgins (1994) compared a proportion of previously negative cervical cytology for cases of histologically confirmed AIS with squamous cell carcinoma in situ (CIS) of the uterine cervix. They noted that 44 % and 60 % of women with AIS had a negative cervical smear within 2 years and 5 years, respectively. The analogous findings for CIS were 30% and 40%, respectively.

In this study, Pap smear had a sensitivity of only 43.1% in detecting a glandular abnormality preoperatively, while a combination of Pap smear and histological evaluation increased sensitivity to 60.8%. There are several reasons to explain why Pap smear screening for glandular lesions in our study appeared suboptimal. Firstly, it might be difficulty to approach on affected area of AIS which usually locates within the deep endocervical canal. Second reason might be inappropriate use of sampling device to detect glandular

neoplastic epithelium. An Ayre spatula is the only sampling device used in the majority of hospitals in Thailand. Generally, AIS is an irregular distribution of glandular neoplastic epithelium within the endocervical clef rather than at the surface as SIL. Therefore, sampling the affected area by such a device might be theoretically unachievable in some cases. The appropriate sampling devices for a cervical smear, including a combination of Ayre spatula and endocervical brush or a plastic broom are currently advocated because they are likely to produce results of improved endocervical sampling in cervical smear evaluation (Schoolland et al., 2002). Another reason why screening for glandular abnormality might not be satisfactory is the small size of some AIS, which might be a factor that limits sensitivity, particularly in cases of mixed AIS and HSIL, in which AIS is quite often incidental microscopic foci, as shown in a series from Schoolland et al (2002). The latter reason may have accounted, in part for the lower rate of cytologic diagnosis of a glandular abnormality in combined lesions which was also noted in our study.

Colposcopic assessment and biopsy for AIS cases are more difficult than that for SIL because AIS is more likely to locate within the deep endocervical canal, particularly in our study, where the majority of women (70.6%) had unsatisfactory colposcopy. Theoretically, ECC appears to be a sensitive evaluation for abnormal glandular epithelium. However, several reports demonstrated that it has been insensitive for detecting AIS (Denehy et al., 1997, Azodi et al., 1999).

As mentioned previously in the conization technique for AIS, CKC is strongly advocated rather than LEEP (Mathevet et al., 1994, Wildrich et al., 1996). Because of the low sensitivity of preoperative evaluation in detecting AIS in this study, it was not surprising that the majority of women still underwent LEEP.

In conclusion, the combining of Pap smear and preoperative histological evaluation including CDB and/or ECC had a sensitivity of only 60.8% in detecting glandular abnormality before conization in women who had AIS of the uterine cervix. Further study on predicting factors of occult AIS in women with cervical neoplasia is warranted to select the most appropriate diagnostic conization method for such lesions. .

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