RESEARCH ARTICLE

Clinicopathologic Importance of Women with Squamous Cell Carcinoma Cytology on Siriraj Liquid-Based Cervical Cytology

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Abstract

Objectives: The purposes of this study were to determine the prevalence and predictive value to detect significant neoplasia and invasive lesions, and to evaluate the correlation between clinical and histopathology of women with squamous cell carcinoma (SCCA) on Siriraj liquid-based cervical cytology (Siriraj-LBC). Methods: The computerized database of women who underwent Siriraj-LBC at Siriraj Hospital, Mahidol University from January 2007 to December 2010 were retrieved. The hospital records of women with SCCA cytology were reviewed. Results: The prevalence of SCCA cytology was 0.07%. A total of 86 women, mean age was 58.1 years. Sixty-one women (70.9%) were post-menopausal. Overall significant pathology and invasive gynecologic cancer were detected in 84 women (97.7%) and 71 women (82.5%), respectively. The positive predictive values for detection of significant neoplasia and invasive lesion were 97.7% and 82.6%, respectively. The cervical cancer was diagnosed in 69 women and among these 58 women were SCCA. Thirteen women (15.1%) had cervical intraepithelial neoplasia (CIN) 3 and two women (2.3%) had cervicitis. The sensitivity and specificity of colposcopy for cervical cancer detection in SCCA cytology were 83.3% and 75%, respectively. Median follow up period was 17.6 months and 64 patients were alive without cytologic abnormality. Conclusions: The final histopathology of SCCA cytology in our populations demonstrated a wide variety, from cervicitis to invasive cancer and the most common diagnosis was invasive cervical cancer. Colposcopy with biopsy and/or endocervical curettage and loop electrosurgical excision procedure should be undertaken to achieve histologic diagnosis.

Keywords: Squamous cell carcinoma - cervix - liquid-based cytology - colposcopy - pathology

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Introduction

Cervical cytology is accepted worldwide for early detection of cervical neoplasia since the inception of the conventional Pap smear. The 2001 Bethesda Terminology System implemented the criteria for determining the squamous cell cytologic abnormalities as atypical squamous cells (ASC), low-grade squamous intraepithelial lesion (LSIL), high-grade squamous intraepithelial lesion (HSIL) and squamous cell carcinoma (SCCA) (Solomon et al., 2002). The previous publications reported the rate of serious pathology and invasive lesions in women with SCCA cytology on conventional smears were 26-97.9% and 15-33.3%, respectively (Massad et al., 2001; Charoenkwan et al., 2006). The study of correlation between cancer cytology on repeat Pap smear and colposcopic biopsies in 8 patients presented the rate of cancer as 38%. Benign or cervical intraepithelial neoplasia (CIN) 2-3 pathologies were detected in 13% and 51% of patients, respectively (Massad et al., 2001). A retrospective study in 48 patients with SCCA abnormality on their conventional Pap smear found cervical cancer and high grade squamous intraepithelial lesions in 16 and 24 patients, respectively (Charoenkwan et al., 2006). Nowadays, the management of squamous cell carcinoma abnormality type has no unique guidelines, and using the strategies as recommended for HSIL cytology by the American Society for Colposcopy and Cervical Pathology (ASCCP) (Wright et al., 2007).

Liquid-based cytology (LBC) has been proven of higher cost-effectiveness than conventional Pap method (Karnon et al., 2004; Strander et al., 2007). Additionally, the risk of serious histopathology for SCCA cytologic abnormality not only helps clinicians who counsel women but also leads to additional development of management strategies. To the best of our knowledge, no data of correlation between SCCA cytology on LBC and histopathologic results.

The objectives of the present study were (i) to investigate the prevalence of SCCA cytologic abnormality on Siriraj liquid-based cytology (Siriraj-LBC), (ii) its predictive value to detect significant neoplasia and

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invasive lesions, and (iii) the correlation between clinical, colposcopic findings, and final histopathology of SCCA cytology detected by Siriraj-LBC of women in an area of high incidence of cervical cancer.

Materials and Methods

The study protocol was approved by the Siriraj Institutional Review Board. Data was retrieved from the computerized database of women who received cervical cytologic examinations using Siriraj-LBC at the outpatient unit of the Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital, Mahidol University between January 2007 and December 2010. The medical records of women with SCCA cytology undergoing completed evaluation at our institute were reviewed.

Since 2005, our institute has been use the Siriraj-LBC and the high quality with the beneficial cost were approved (Laiwejpithaya et al., 2008: 2009). Cervical cytology was collected from women who came for cervical cancer screening and patients who presented with vaginal discharge, abnormal bleeding, dysmenorrhea, pelvic mass, or lower abdominal pain. The specimens for cervical cytology were collected by residents, fellows and staff of our department. In cases of suspicious cervical lesions, punch biopsies was taken after the collected cervical cytology. Women with abnormal uterine bleeding received fractional curettage or endometrial sampling as indicated despite the result of cervical cytology. Colposcopy was performed by gynecologic oncologists, the severity and impression was based on the white epithelium, abnormal vessels pattern and texture of the surface. In addition, the colposcopically directed biopsy (CDB) and/or endocervical curettage (ECC) were performed to confirm the diagnosis. Diagnostic loop electrosurgical excision procedure (LEEP) was carried out in cases of normal colposcopic findings, unsatisfactory colposcopies, and when the pathology of the CDB and/or ECC were less than invasive cancer. The final histopathologic results were determined by gynecologic pathologists. The significant neoplasia include the following; vaginal intraepithelial neoplasia (VAIN) 2+, CIN 2+, endometrial hyperplasia, and endometrial cancer. The staging of invasive cancer was defined by gynecologic and radiation oncologists. All patients were appointed for examination every three months in first two years and then every six months thereafter.

Statistical analyses were performed using SPSS version 14.0 for Windows (IBM, Armonk, NY, USA). Descriptive statistics were used for demographic data. The data was presented in mean, median, range, number and percentage (%) as appropriate. All tests were two sided and a p-value of less than 0.05 was statistical significance.

Results

During the study period, 125,839 records were retrieved and 86 women had SCCA cytologic abnormality, signifying the prevalence of 0.07% SCCA cytology. The mean age±SD was 58.1±12.3 years (median 58, range 30-85). The mean body mass index (BMI) was 23.9 kg/

Table 1. Demographic Data and Final Histopathology of 86 Women with Squamous Cell Carcinoma Cytologic Abnormality on Siriraj Liquid-Based Cervical Cytology

Variables		No. (%)
Age (years)	≤50	28 (67.4)
	>50	58 (32.6)
BMI (kg/m^2, n=61)	≤30	56 (91.8)
	>30	5 (8.2)
Parity	Nulliparous	6 (7)
	Parous	80 (93)
Menopausal status	Premenopause	25 (29.1)
	Postmenopause	61 (70.9)
Presenting symptoms	Checkup	40 (46.5)
	Bleeding per vagina	29 (33.7)
	Vaginal discharge	8 (9.3)
	Pelvic pain	4 (4.7)
	Other	5 (5.8)
Provisional diagnoses	Normal	27 (31.4)
	Cervicitis or cervical erosion	7 (8.1)
	Suspected cervical cancer	37 (43)
	Abnormal uterine bleeding	9 (10.5)
	Pelvic mass	1 (1.2)
	Other	5 (5.8)
Final histopathologies	Cervicitis	2 (2.3)
	CIN3	13 (15.1)
	Cervical carcinoma	
	Squamous cell carcinoma	58 (67.4)
	Mucinous carcinoma	4 (4.7)
	Adenosquamous carcinoma	6 (7.0)
	Serous carcinoma	1 (1.2)
	Vaginal squamous cell carcinoma	1 (1.2)
	Endometrial carcinoma, serous type	1 (1.2)

Table 2. Correlation between Clinical and Significant Neoplasia of Tissues from Genital Organs

Variables		Histopathologic results (N)		P value
		Cervicitis & CIN 3	Invasive cancer	
Age (years)	≤50	7	21	0.199
	>50	8	50	
Menopausal status	Premenopause	7	18	0.099
	Postmenopause	8	53	
Presenting symptoms	Non-bleeding	13	44	0.066
	Bleeding	2	27	
BMI (kg/m^2, n=61)	≤30	10	46	0.233
	>30	2	3	
Colposcopic impression (n=40)	Non-cancer	9	56	0.122
	Cancer	6	15	

* BMI, body mass index; CIN, cervical intraepithelial neoplasia

Table 3. Correlation between Colposcopic Impression and Final Histopathology of 40 Women Who Underwent Colposcopy

Colposcopic impression	Histopathologic results (%)								Total
	Cervicitis	CIN 3	FIGO stage of invasive cervical cancer						
			IA1	IA2	IB1	IIA1	IIB	IIIB	
Normal	1	1	0	0	2	0	0	0	4
CIN 1	0	1	0	0	0	0	0	0	1
CIN 3	0	3	1	0	0	0	0	0	4
MIC	0	1	0	0	1	0	0	0	2
Invasive	0	5	1	0	4	2	3	4	19
Indecisive	0	2	3	1	2	1	1	0	10
Total	1	13	5	1	9	3	4	4	40

*CIN, cervical intraepithelial neoplasia; FIGO, the International Federation of Gynecologic Oncology; MIC, microinvasive cancer

m^2 (range 17.2-43.3). Data on BMI were not available in 25 women (29.1%)." into "Data on BMI were not available in 25 women (29.1%). The mean body mass index (BMI) was 23.9 kg/m^2 (range 17.2-43.3). Punch biopsy and fractional curettage were carried out in 42 and 9 the women presenting SCCA, respectively. Forty of the original 86 women were investigated by colposcopy, of which, 30 women (75%) were unsatisfactory colposcopy due to 14 incompletely seen the transformation zone, 15 lesions with an unidentifiable extent, and 1 contact bleeding. CDB and/or ECC and diagnostic conization were performed for 26 and 25 women, respectively. Table 1 shows demographic data and final histopathologic results of 86 women with SCCA cytology.

The positive predictive value (PPV) for detected significant neoplastic lesions and invasive lesions were 97.7% (84/86) and 82.6% (71/86), respectively. Out of 86 women, 15 (17.4%) were false positive, showing only cervicitis or CIN 3. The correlation between clinical characteristics and invasive cancer of genital organs were summarized in Table 2.

Table 3 showed the correlation between colposcopic findings and significant neoplasia of 40 women with SCCA cytology. Ten cases yielded indecisive colposcopic examinations. In 30 cases of the colposcopic impression that were received, the sensitivity and specificity for cervical cancer detection were 83.3% and 75%, respectively.

Overall, 69 invasive cervical cancer patients were clinically staged and 5, 1, 14, 2, 4, 19, 22, and 2 patients were in stages IA1, IA2, IB1, IB2, IIA1, IIB, IIIB, and IVB, respectively. Of these, the primary treatment plan of 29 patients was hysterectomy appropriate with the stage of disease and patient status. After surgery, 4 patients received adjuvant radiation therapy (1 abandoned hysterectomy, 1 inadvertent hysterectomy, 1 pelvic lymph node metastasis, and 1 disease at vaginal surgical margin). The median follow-up period of 86 patients was 17.6 months and 64 patients were alive without disease or abnormal cervical cytology. Recurrence and persistent of diseases were found in 22 patients, of which one patient was dead from disease.

Discussion

The criteria for diagnosis of SCCA cytologic abnormalities include pleomorphic dysplastic feature, anisonucleosis, high nuclear/cytoplasm ratio, and clumped chromatin (Nguyen et al., 1984; Clark et al., 2002). The cytologic diagnosis of SCCA is uncommon with the prevalence of 0.01% of cervical cytology evaluations (Jones et al., 2000). The 0.07% rate in our study was substantial because it is higher than most other nations.

The rates of CIN 3+ and invasive cervical cancer were 15.1% and 80.2%, respectively. Interestingly, the invasive cervical cancer rate in the current study was higher than the previous studies, which were 15-68% (Grubb et al., 1967; Jones et al., 2000; Charoenkwan et al., 2006). The reason for this high rate may because nearly half of SCCA cytology women had cervical lesions like cervical cancer but the clinicians did not feel confident enough to make the diagnosis, so they usually undertook the cytology with biopsy simultaneously. Most of these cervical cancer patients were infiltrative type and after meticulous evaluation by oncologists, it was found that 80% of patients were categorized into advanced stages. Furthermore, 83.3% of patients had bleeding symptoms. Authors convinced clinicians and health providers to be more conscientious when pelvic and per-rectal examinations in women with SCCA cervical cytology, especially in cases of referral from other healthcare professionals or with those who have had bleeding symptoms. This care brings the benefit of avoiding unnecessary cervical cytology to patient, as well as preventing undesirable cost and extensive workload for the hospital.

This study showed, the SCCA cytology was strongly associated with invasive lesions not only the cervix but also the vagina origins. At the time of colposcopy, performing a LEEP as initial management for HSIL cytology ("see and treat") has been advocated (Numnum et al., 2005; Wright et al., 2007; ACOG, 2008). Overtreatment rate of the "see and treat" procedure in HSIL women was 5.8% (Kietpeerakool et al., 2007). In our SCCA cytology population, there are 21 women who had less than invasive lesions under colposcopic examinations. The "see and treat" approach for these 21 women, achieved a good yields 20/21 women (95.2%). The chance of having no cervical neoplasia is 4.8% (1/21 women was cervicitis). Nevertheless, clinicians should be careful when LEEP in cases of endophytic cervical cancer patients with high stages due to hemorrhagic risk.

Obviously, the PPV of SCCA cytology for detected significant histology was very impressive, both for significant neoplasia and invasive cancer of genital organs. However, the false-positive of SCCA cytology for invasive cancer detection was reported in range of 10-50% (Grubb et al., 1967; Levine et al., 2003; Uyar et al., 2003). This was consistent with the 17.4% found in this study. Cervical cytology is the only screening test. The false-positive may be affected by several factors such as similarity of cells from severe cervical dysplasia and invasive cancer, mistaking keratinizing carcinoma in situ for invasive carcinoma, and not strictly adhering to the criteria of the Bethesda system (Levine et al., 2003).

Unfortunately, this study did not found any clinical factors to predict the invasive cancer lesions in women with SCCA cervical cytology. Although, the bleeding symptom was the only clinical factor which closely correlated with invasive cancer of genital organs (p=0.066).

Colposcopy in this populations had highly sensitivity and specificity for detection both significant pathology and invasive cervical cancer. However, the accuracy rate did not reach 100% as stated by a previous study (Edeberi at al., 1990) could be from the unsatisfactory colposcopic evaluation consistent with a study population of 70% postmenopausal women. Colposcopy impressions are subjective; according to degree of white epithelium, contour of surfaces, margins, and vascular patterns. In cases of CIN 2-3, colposcopy missed to diagnose at the rate of underestimation was 57%, and the overestimation rate by Reid Index scoring was 70% (Massad et al.,

2009; Stoler et al., 2011). Recent systematic review and meta-analysis stated that colposcopic biopsies yielded a sensitivity of 81.4% and specificity of 63.3% for CIN2-3 detection (Underwood et al., 2012).

This research of SCCA cytologic abnormality on liquid-based cervical cytology of women is clinically beneficial because it occurred in an area of high incidence of cervical cancer. The limitation of the present study was retrospective design and a small sample size. The larger prospective study and cytopathologic review designs may provide more beneficial information to guide the unique appropriate management for the SCCA on cervical cytology. In conclusion, the underlying histopathology of women with SCCA cytology was widely variated. Physicians should be diligent and have accomplished skill for pelvic and per rectal examinations of women with SCCA cytology. Colposcopy, CDB and/or ECC and LEEP should be carried out as necessary for taking the histologic diagnosis.

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