

=Abstract=

ASCUS, AGUS and Benign Endometrial Cells in Cervicovaginal Smears: Histologic Correlations and Clinical Significance

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Objective: The purpose of this study is to evaluate the histologic correlations and the clinical significance among patients with atypical squamous cells of undetermined significance (ASCUS), atypical glandular cells of undetermined significance (AGUS) and benign endometrial cells identified on cervical Pap smear screening.

Materials & Methods: The computerized files of the Department of Pathology at Samsung Cheil Hospital were searched from 1991 to 1997 to evaluate the annual statistics of cytologic diagnoses including normal/benign, ASCUS, AGUS, low-grade squamous intraepithelial lesion (LSIL), high-grade squamous intraepithelial lesion (HSIL) and cancer classified by the Bethesda System (TBS). Cytohistologic correlations on follow-up were separately analysed in ASCUS (190 cases), AGUS (268 cases) and benign endometrial cells (169 cases), respectively. Additionally, post-menopausal squamous atypia (83 cases) were also included in this study. TBS terminology was used in both cytologic and histologic diagnoses.

Results: During 7-year period (1991-1997), 447,049 cervicovaginal smears were evaluated. The median rate of abnormal cytology was 4.4%, with 2.1% of ASCUS, 2.06% of squamous intraepithelial lesion (SIL), and 0.08% of AGUS. The median ratio of ASCUS versus SIL was 1.24. Specimen adequacy was evaluated on 47,525 cases, of which categories of "satisfactory for evaluation but limited by" and "unsatisfactory for evaluation" were 28.3% and 0.03%, respectively. Follow-up of 190 patients with ASCUS cytology showed 30% (57 cases) with SIL on biopsy; 18% (35 cases) with LSIL, 11% (21 cases) with HSIL, and 1% (1 case) with microinvasive squamous cell carcinoma. On histologic examination, 77% (37/48 cases) with ASCUS favoring SIL

revealed SIL in contrast to 14%(20/142cases) with ASCUS favoring reactive change, which is statistically significant.(Chi-Square test, P<0.0001). Of 83 cases of post-menopausal squamous atypia(PSA), smears with LSIL showed 34.9%(15/43cases) with LSIL on biopsy. 268 patients with AGUS smears had 25%(67cases) with clinically significant cervical or endometrial lesions on histologic examinations. Among 17.9%(48cases) with cervical lesions, squamous abnormalities were 10.5%(28cases); including 1.5%(4cases) with LSIL and 9.0%(24cases) with HSIL. Glandular lesions in cervix were 7.5%(20cases); 3.0%(8cases) of glandular atypia or dysplasia, 1.9%(5cases) of adenocarcinoma in situ, 1.1%(3cases) of microinvasive adenocarcinoma and 1.5%(4cases) of adenocarcinoma. Of 7.1%(19cases) of endometrial lesions, 2.2%(6cases) was endometrial hyperplasia, 4.1%(11cases) endometrial carcinoma, 0.4%(1case) MMT and 0.4%(1case) metastatic adenocarcinoma from stomach were verified. The pathologies of 169 cases with benign endometrial cells shed in cervicovaginal smears were confirmed to be endometrial polyp(8.3%), endometrial hyperplasia(4.1%) and endometrial carcinoma(5.9%).

Conclusion: The results of this study indicates that clinicians should communicate with pathologists for proper management of abnormal cytology. Further evaluation and decision of management should be made based on input from pathologists as well as on clinical setting and professional guidelines.

Keywords: ASCUS, AGUS, Benign endometrial cells, Postmenopausal squamous atypia(PSA), Cervicovaginal smear, Histologic correlation, Specimen adequacy, The Bethesda System(TBS)

Pap smear (specimen adequacy) , ASCUS (Atypical Squamous Cells of Undetermined Significance) 가 , HPV (, low grade squamous intraepithelial lesion, LSIL) CIN II가 (, high grade squamous intraepithelial lesion, HSIL) , AGUS(Atypical Glandular Cells of Undetermined Significance)

.4) TBS 1988 1991 . 1991 TBS 1997 .5) TBS TBS TBS 가 ASCUS AGUS

(cytological correlation) TBS가 TBS (within normal limits), (benign cellular change, BCC), (benign endometrial cell) Normal/Benign

ASCUS LSIL (benign endometrial cell) cancer

ASCUS ASCUS-SIL (Ratio of ASCUS-SIL) 1990 1991 6 TBS IIb

ASCUS ASCUS-SIL 1991 1997 LSIL HSIL ASCUS TBS

(Pap smear) HPV (immature atypical metaplastic cell), (atrophic cellular atypia) (atypical parakeratosis) (atypical repair cell) ASCUS

CervexBrush® Ayre spatula cytobrush Papanicolaou IAC 1997 Neo-Path AutoPap 300 QC System® TBS 67) file system (AS 400 Host System) AGUS

1. (Specimen adequacy) 1997 5 1997 12 47,525 TBS (satisfactory for evaluation), (satisfactory for evaluation but limited by) (unsatisfactory for evaluation) 가 가 (tubal metaplasia), (microglandular hyperplasia) / (adenocarcinoma in situ) (adenocarcinoma)

2. 1991 1 1997 12 447,049 TBS

3. (Cytohistological correlation) , 가

TBS .8-12) 가 TBS AGUS

CIN I (mild dysplasia) , CIN II CIN III (moderate dysplasia) , AGUS

(severe dysplasia) (carcinoma in situ) .

1996 1 1996 12

(cytohistologic correlation) . 415

ASCUS . TBS 169

ASCUS LSIL HSIL 가 7,14

1993 5 1994 12 가

ASCUS 190 , LSIL Z-sampler[®] Pipelle[®]

120 , HSIL 112 422 가

ASCUS 가

LSIL HSIL 가

HPV-DNA (reco- mmendation) 1. 1997 5 1997 12 47,525

TBS 가 71.7%, 28.3% 0.03%

(Post-menopausal squamous atypia, PSA) 가 (20.5%) 가

1995 1 1996 12 ASCUS 가 (7.58%)

LSIL 50

Jovanovic 13) koilocytotic atypia PSA criteria . (poor fixation) (obscuring factor)

가 83 . 0.22%

HSIL 16 (0.03%) 가

ASCUS 32 LSIL 43 가 (scanty cellularity) (Table 1).

AGUS

1991 5 1996 12 AGUS 2.

326 1991 1 1997 12 447,049

가 268 TBS

(ASCUS, AGUS, LSIL, HSIL & cancer) 3.93%
 5.07% 4.4%
 1995
 1994 SIL
 ASCUS
 가 (Table 2, 3)

2.1% TBS 1991 1992
 1.24% 1.25% TBS 1990
 1993 2
 가 2.14% 2.88%
 1993
 (Table 2). LSIL HSIL SIL
 가 가
 1991 1992 1993

Table 1. Frequency distribution of adequacy categories

Categories	No.	%
Satisfactory for evaluation	34085	71.72
SBLB*	13424	28.25
due to		
drying artifact	6	0.01
obscuring inflammation	71	0.15
cytolysis	2	0.01
no EC**	3603	7.58
insufficient clinical information	9742	20.49
Unsatisfactory for evaluation	16	0.03
Total	47525	100

SIL
 1991 1992 2.07% 2.12%
 1993 1.94% 1.25%
 ASCUS/SIL ratio TBS
 1991 1992 0.6 1993
 1.1 2.0 1.2 SIL
 ASCUS가 가
 1992 NCI workshop17) 2 3
 (Table 3).
 AGUS
 ASCUS가 2.1% AGUS
 0.07 0.10% 0.08%
 AGUS ASCUS 26
 ASCUS 가
 (Table 2).

SBLB*: Satisfactory for evaluation but limited by
 EC**: Endocervical component

ASCUS ASCUS-SIL (Ratio of
 ASCUS-SIL)
 ASCUS 1.24% 2.88%

3. (Cytohistological corre-
 lation)
 ASCUS

Table 2. Annual statistics of cervicovaginal cytologic diagnoses pre-Bethesda(1990) and post-Bethesda(1991-1997)

	1990. 6 12		1991		1992		1993		1994		1995		1996		1997	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Normal	26363	96.45%	48984	96.07%	53874	96.07%	58518	95.40%	62846	95.46%	63997	94.93%	67374	95.75%	71927	95.87%
/Benign																
ASCUS	311	1.14%	631	1.24%	700	1.25%	1337	2.18%	1410	2.14%	1944	2.88%	1661	2.36%	1892	2.52%
AGUS			43	0.08%	53	0.09%	43	0.07%	53	0.08%	69	0.10%	53	0.08%	68	0.09%
LSIL	194	0.71%	507	0.99%	546	0.97%	509	0.83%	572	0.87%	480	0.71%	431	0.61%	383	0.51%
HSIL	341	1.25%	551	1.08%	645	1.15%	601	0.98%	702	1.07%	665	0.99%	666	0.95%	555	0.74%
Cancer	125	0.46%	273	0.54%	260	0.46%	329	0.54%	255	0.39%	261	0.39%	183	0.26%	198	0.26%
Total	27334	100%	50989	100%	56078	100%	61337	100%	65838	100%	67416	100%	70368	100%	75023	100%

Table 3. Ratio of ASCUS-SIL (ASCUS/SIL)

	1990. 6	12	1991	1992	1993	1994	1995	1996	1997
Annual Pap volume (No.)	27,334		50,989	56,078	61,337	65,838	67,416	70,368	75,023
Abnormal Pap (%)	3.55		3.93	3.93	4.6	4.54	5.07	4.25	4.13
ASCUS(%)	1.14		1.24	1.25	2.18	2.14	2.88	2.36	2.52
SIL(%)	1.96		2.07	2.12	1.81	1.94	1.70	1.56	1.25
ASCUS/SIL	0.6		0.6	0.6	1.2	1.1	1.7	1.5	2.0

1993 5 1994 12

(Chi-Square test, P < 0.0001)

가
 ASCUS 190 57 (30%)
 35 (18%), 21 (11%)
 1 (1%)

(Table 4).

Table 4. Rate of SIL on biopsy

Cytology	Histology			Total
	LSIL*	HSIL**	SCC***	
ASCUS (n=190)	35(18%)	21(11%)	1(1%)	57(30%)
LSIL (n=120)	67(56%)	2(2%)	0(0%)	69(58%)
HSIL (n=112)	2(2%)	103(92%)	2(2%)	107(96%)

* LSIL: Flat condyloma & CIN I
 ** HSIL: CIN II & III
 *** SCC: Squamous cell carcinoma

ASCUS 142 (75%)
 ASCUS 190 (25%)
 48 (25%)
 20 (14%)
 48 37 (77%)
 ASCUS

SIL

(Table 5).

Table 5. ASCUS-RC vs ASCUS-SIL in rate of SIL on biopsy

Cytology	Histology (SIL-positive)	
	No.	%
ASCUS favoring RC* (n=142)	20	14a
ASCUS favoring SIL**(n=48)	37	77b

* RC: Reactive change

** SIL: Squamous intraepithelial lesion

a vs b Chi-Square test, P < 0.0001

LSIL 58% HSIL 96%
 LSIL ASCUS
 HSIL (Table 4).
 LSIL, HSIL
 LSIL HSIL
 LSIL HSIL 58% 56% 96%
 92%
 Jovanovic PSA criteria
 ASCUS 8, LSIL ASCUS
 32, LSIL 43 가
 ASCUS 8 2 (25%), ASCUS,
 R/O LSIL 32 5 (15.6%) LSIL 43
 15 (34.9%) LSIL

(Table 6).

Table 6. Cytohistologic correlation of postmenopausal squamous atypia (PSA)

Cytology	Histology (LSIL-positive)	
	No.	%
ASCUS (n=8)	2	25
ASCUS R/O LSIL (n=32)	5	15.6
LSIL (n=43)	15	34.9

AGUS
 1991 5 1996 12 AGUS
 326
 가 268
 (17.9%)
 67 (25%)
 (Table 7).
 LSIL 4 (1.5%), HSIL

Table 7. Histologic diagnoses in AGUS Paps on follow-up

	Histology	No.	%
Cervix (n=48)	Squamous lesions		
	LSIL	4	1.5
	HSIL	24	9.0
	Glandular lesions		
	Glandular atypia/dysplasia	8	3.0
	Adenocarcinoma in situ	5	1.9
	Microinvasive adeno ca.	3	1.1
Endometrium (n=19)	Adenocarcinoma	4	1.5
	Hyperplasia	6	2.2
	Adenocarcinoma	11	4.1
	MMMT*	1	0.4
	Metastatic adeno ca.	1	0.4
Total		67/268	25

MMMT*: Mixed Müllerian mesodermal tumor

24 (9.0%) 28 (10.5%)
 (glandular atypia)
 (3.0%), 5 (1.9%), 8
 (1.1%) 4 (1.5%) 3
 7.5% AGUS
 54 (20.1%)
 6
 (2.27%), 11 (4.1%), MMT 1 (0.4%)
 1 (0.4%)
 , AGUS가
 1996 1 1996 12
 415
 169 75 (44%)
 14 (8.3%), 7 (4.1%), 10
 (5.9%) 31 (18.3%)
 (Table 8). 46 (27%),
 10 (5.9%), IUD 4 (2.4%)
 3 (1.8%)

Table 8. Histologic diagnoses of benign endometrial cells in Paps

Histology	No.	%
Normal endometrium	75	44.4
Endometrial polyp	14	8.3
Endometrial hyperplasia	7	4.1
Adenocarcinoma	10	5.9
Others*	63	37.3
Total	169	100.0

* endometriosis, anovulatory bleeding, IUD etc

(reproducibility) 가

TBS Pap smear 가 0.03% .16)

TBS 가 가

가 28.25%

가 20.5% 가 가 7.58%

nsultation) TBS (medical co- .1516) CervexBrush[®] cytobrush

가 가

.4) 1991 TBS7) ASCUS 가

가 (satisfactory for evaluation), 가 가 19) ASCUS (satisfactory for evaluation but limited by) 가 가 가 8.4% (satisfactory for evaluation) 3가 4가 가 가 가 가 (transformation zone) 가 가 가 1992 600 가 CAP survey 15) 가 0 20% 가 0.5 1% 40% 3.0 4.9% 가 ASCUS 1988 TBS 가 가 (un-determined) TBS ASCUS .46) 1991 . TBS 가

7) ASCUS

1992 NCI workshop HPV ASCUS ASCUS

ASCUS communication ASCUS HPV LSIL

communication HSIL ASCUS

ASCUS가 가 ASCUS

ASCUS LSIL HSIL ASCUS

ASCUS / ASCUS 가

ASCUS , Tricho- ASCUS

monas, Candida 가 ASCUS

(downgrade) 가 ASCUS

40 , , 가

Pap smear . 1992 NCI workshop) ASCUS

TBS 5% ASCUS가

5% ASCUS

SIL 가

ASCUS

가 ASCUS

가 ASCUS

(upgrade) (ASCUS "atypia", "inflammatory aty-
 ASCUS LSIL) pia" "class II" (

TBS BCC .)

가 ASCUS 가 ASCUS TBS

(severity) 가 가 가 CAP survey

가 0.7 9% 11-12) 1993 1600

1) ASCUS 2.8%

.1) TBS criteria) ASCUS University lab 6.0% , Hospital lab

2.5 3 2.4% ASCUS

N/C ratio 가가 가 5,000 2.1%

50,000

3.8%
 ASCUS TBS
 2 가 1.24% 2.88
 % 2.1%
 60,000 70,000

AGUS 가

SIL 1.25% 2.12% 2.06%
 survey 1.3 ASCUS/SIL ratio 1.24 CAP
 SIL ASCUS CAP survey
 가 University lab ASCUS,
 LSIL, HSIL 50,000
 lab lab 가
 ASCUS/SIL ratio ASCUS/SIL ratio
 90% 4 ASCUS
 ASCUS
 ASCUS/SIL ratio

가
 가 ASCUS
 가 SIL 12) ASCUS
 SIL ASCUS
 가 recommendation
 written guideline
 ASCUS

18) 30,488 1.6%, 19) 450 8.4%,
 20) 11,403 2.1% 21) 10,630
 5.7% ASCUS/SIL ratio
 22) 0.48 23) 2.13 CAP survey
 1.3 1.24

SIL 10 61%
 22) ASCUS 1/3 SIL
 TBS
 (squamous atypia)
 SIL 26%
 TBS 33% 가가
 가 TBS
 18) 30% 가 27.5%
 ASCUS SIL LSIL HSIL
 30% SIL
 18% LSIL, 11% HSIL, 1%
 Darnell Jones 30) 25% SIL 20%
 LSIL, 5% HSIL Davis 31)
 18% SIL LSIL 9.1%, HSIL 7.6%
 Abu-Javodeh 32) 31% SIL 18%
 LSIL, 13% HSIL

“(cytologic correlation: well correlated)”

(discrepancy)가
 recommend 가
 가

ASCUS
 ASCUS
 23) ASCUS
 24) 39.1%(36/92)
 45.8%(33/72)

) SIL HPV type
 30%(57/190)

ASCUS
 LSIL HSIL LSIL HSIL
 가
 2) 18.1%, 19.5% 9.7% 2) 21.7%,
 .34) TBS HPV
 14.2% 3.3% 18%, 11% 1%
 koilocytotic atypia LSIL
 가 ASCUS가
 SIL 가 koilocytosis
 1%
 ,2) 2) Lee 3) mild
 9.7%, 3.3%
 dysplasia koilocytosis
 1
 2mm SIL 가 koilocytosis
 mild dysplasia
 2) ASCUS 13.8
 % (9/65) 가
 ASCUS 29.4% (5/17) 가 CIN II (severity of abnormality)
 3) Lee 3)
 14% (20/142)
 77% (37/48)
 SIL .3)
 (Chi-Square test, P < 0.0001).
 TBS가 artifact,
 가
 communication ASCUS HPV DNA
 SIL
 .3) Jovanovic 13) koilocytotic atypia
 ASCUS SIL ,
 . ASCUS PSA
 Jovanovic
 .3) 가 ASCUS 8 8 가
 ASCUS PSA 2 SIL
 . HSIL LSIL ASCUS 32
 24 가 PSA 3 LSIL
 가 CIN II (mo- ASCUS 40 7 (17.5%) LSIL
 derate dysplasia) CIN III HSIL 30%
 . LSIL 43
 ASCUS 3 , PSA 26 , LSIL 14

ASCUS 3 1 , PSA 26 7 , LSIL 14
 7 LSIL 43 15 (34.9%) LSIL
 58%
 PSA 3) ASCUS .6
 LSIL 60 18 , , IUD,
 ASCUS, 27 LSIL 15
 . 18 ASCUS (endometrial meta-
 ASCUS가 5 , LSIL 5 VAIN I-II가 1 plasia) 가 AGUS
 . 27 LSIL 2
 ASCUS, 20 CIN, 1 VAIN 가 .4) cytobrush
 4 .

(koilocyte) 가 가 가 AGUS
 .44-4) Cytobrush

(parabasal cell) artifact AGUS brush
 .44-5)

(parakeratotic cell) .3) 가
 ASCUS 가 .4) 가

communication

(lower uterine segment) 가
 .47) ASCUS

HPV-DNA 가
 .3)

ASCUS
 AGUS

AGUS

ASCUS

가

.45) AGUS

(BCC)

가

ASCUS

0.15%

가

0.74%

0.5%

.485)

, , , , ,
 /

2) 0.31%

2) 0.12%

18) 0.32%,

0.08%

가

가

AGUS

TBS 1991 1992

18)

가

AGUS
가

.4)

AGUS HSIL
AGUS

Kennedy

4) 5

ASCUS

가 4.5%

AGUS

0.2%

가

AGUS

15%
LSIL 4%, HSIL 5%

9%가

가

AGUS

4%, 3%

7%

5)

Goff

5) AGUS

6 (2.2%),
(0.4%)

11 (4.1%), MMTT 1
(0.4%)

가

8%, 3%

11%

AGUS

50%

AGUS 268 67 (25%)

48 (17.9%) LSIL 4

(1.5%), HSIL 24 (9.0%)

.4)

8 (3.0%),

5 (1.9%),

AGUS

3 (1.1%)

4 (1.5%)

가

10.5%

7.5%

AGUS

가

HSIL

AGUS

AGUS

(undifferenti-

ated reserve cell)

(second opinion)

4) AGUS

.4)54)

가

(clus-

가

12

tering),

(feathered appearance),

(anisonucleosis)

.14)

가

.4)

(stromal cell)가

가

가

40

37%

26%

Cherkis 5)

1991 1997

ASCUS AGUS

179 23.9%

11.2%

169 75 (44.4%)

14 (8.3%)

10 (5.9%)

7 (4.1%)

1995

1994

ASCUS

1988 1992 13 26 20

1993 31 38 34.1 가

49 5)

2. ASCUS 2.1% SIL

2.06% ASCUS/SIL ratio 1.24

AGUS 0.08% ASCUS

가 ASCUS

가

60%(30/49) AGUS 16%(8/49)

23%(11/49)

ASCUS ratio

ASCUS/SIL ratio

3. 1997 5 1997 12 47,525

TBS 가

71.7%, 0.03%

28.3%

(20.5%) (7.58%)가 가

가

가

4. 1993 5 1994 12 가

ASCUS ASCUS-

SIL ratio ASCUS 190 57 (30%)

35 (18%), 21 (11%), 1 (1%)

ASCUS 31 (18.3%)
 ASCUS 190
 가 142 (75%),
 48 (25%)
 ASCUS 142 20 (14%)
 48 37 (77%)
 TBS
 TBS
 ASCUS
 ASCUS, AGUS
 SIL
 ASCUS
 recomme-
 ndation
 5. 1995 1 1995 12 ASCUS
 LSIL 50
 ASCUS 8
 LSIL 43
 83
 34.9%(15/43)
 LSIL
 LSIL
 6. 1991 5 1996 12 AGUS
 268 67 (25%)
 48 (17.9%)
 19 (7.1%)
 LSIL 4 (1.5%), HSIL 24 (9.0%)
 28 (10.5%)
 20 (7.5%)
 8 (3.0%), 5
 (1.9%), 3 (1.1%) 4
 (1.5%) AGUS
 6
 (2.2%), 11 (4.1%), MMT
 1 (0.4%)
 AGUS
 7. 1996 1 1996 12
 415
 169 14 (8.3%),
 7 (4.1%), 10 (5.9%)

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