



Servikal Patolojiler ve Kolposkopi Derneđi
TURKISH SOCIETY FOR COLPOSCOPY AND CERVICAL PATHOLOGY

V Ulusal Kolposkopi ve
Servikal Patolojiler
Kongresi

7 - 10 Aralık 2017
Wyndham Grand, İzmir



SMILE – Adenokarsinoma in situ: Farkları ve yaklaşım



Prof Dr M Anıl Onan

Adenocarcinoma in situ

Definition

An intraepithelial lesion containing malignant-appearing glandular epithelium that carries a significant risk of invasive adenocarcinoma if not treated.

ICD-O code

8140/2

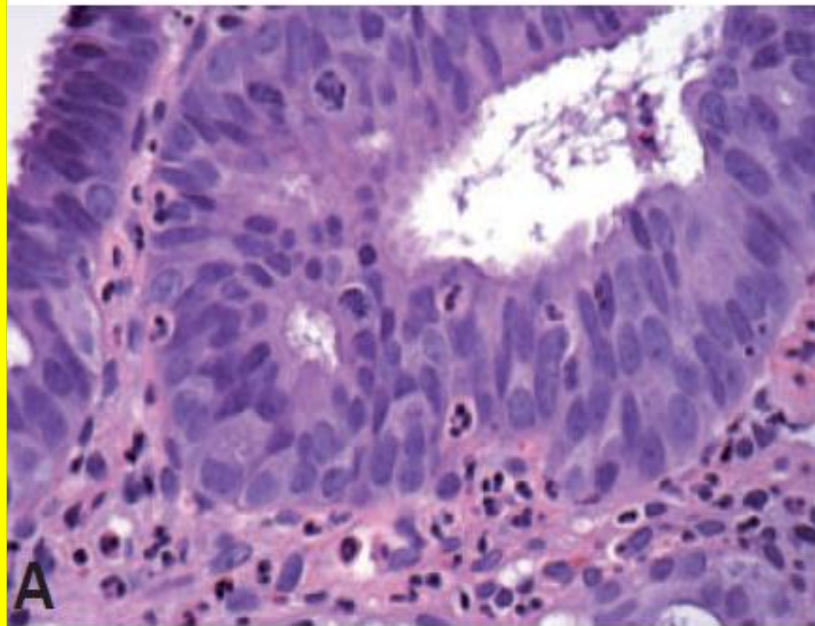
Synonym

High-grade cervical glandular intraepithelial neoplasia (HG-CGIN)

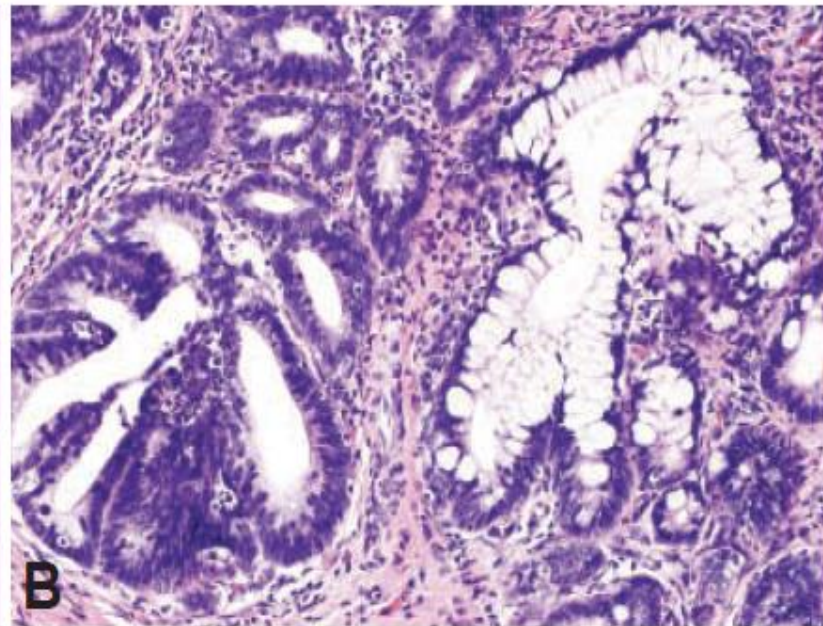
WHO/IARC Classification of
Tumours of Female
Reproductive Organs 2014

There is a variant pattern of AIS referred to as “stratified mucin-producing intraepithelial lesion (SMILE)”. This lesion consists of stratified epithelium with cells containing mucin in the form of discrete vacuoles or as cytoplasmic clearing throughout all cell layers. Nuclear atypia, hyperchromasia, mitoses and apoptotic bodies are usually present. p16 immunohistochemistry is positive and there is a high Ki-67 proliferation index. SMILE often occurs in association with HSIL and/or AIS/HG-CGIN but may rarely appear as an isolated finding {1459}.

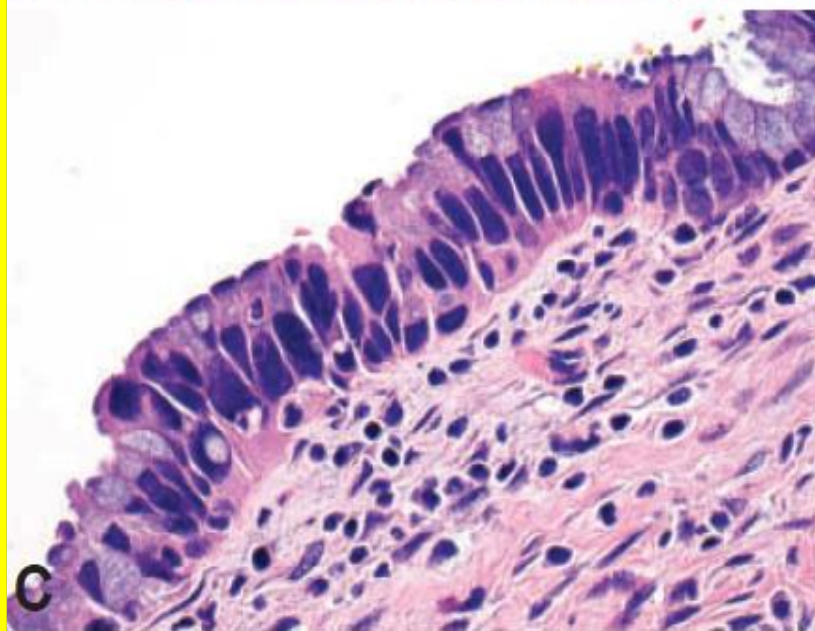
ACIS



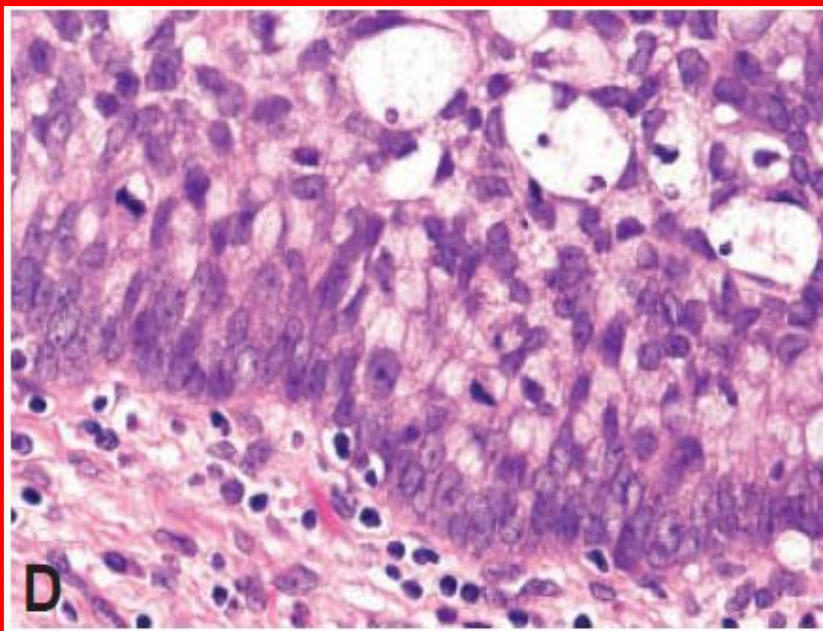
ACIS



ACIS



SMILE





SMILE

(Stratified Mucin-Producing Intraepithelial Lesions)

- Nadir bir servikal intraepitelial lezyon – endoservikal kolumnar hücre neoplazisi varyantı
- HSIL'i anımsatan stratifiye epitel ile karakterlidir
- Sitoplazmik müsin ile birlikte bulunur
- Lezyonların çoğunda epitelial-stromal interfazda yuvarlak konturlar vardır
- Çoğu SIL, AIS veya invaziv karsinom ile birliktelik gösterir
- SMILE'in dağılımı ve immünfenotipi transformasyon zonundaki rezerve hücrelerden geliştiğini düşündürmektedir

Stratified Mucin-Producing Intraepithelial Lesions of the Cervix

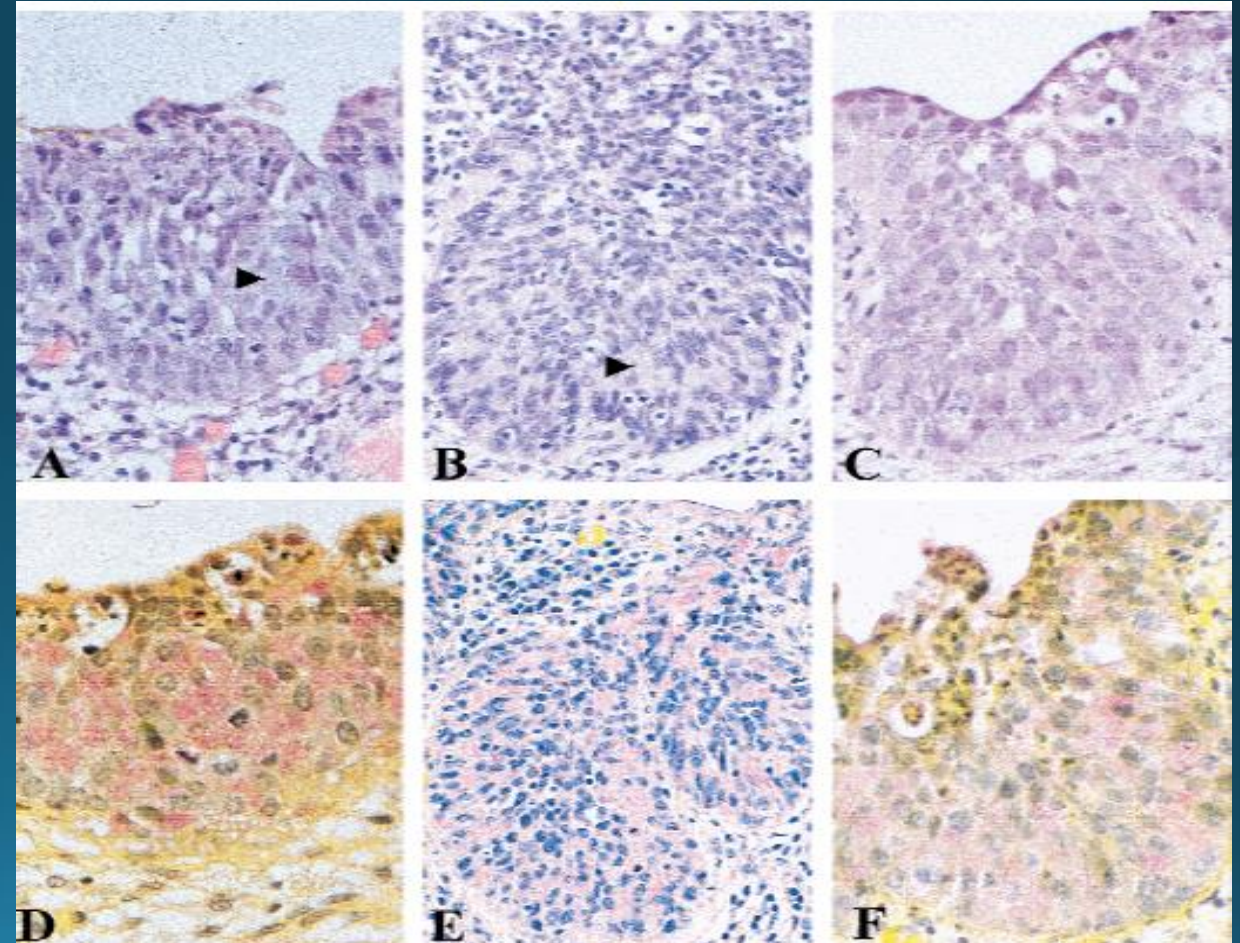
Adenosquamous or Columnar Cell Neoplasia?

İLK TANIMLAMA

Jeong-Ja Park, M.D., Deqin Sun, M.S., Bradley J. Quade, M.D., Ph.D.,
Cythia Flynn, M.D., Ellen E. Sheets, M.D., Annie Yang, B.S.,
Frank McKeon, Ph.D., and Christopher P. Crum, M.D.

The American Journal of Surgical Pathology 24(10): 1414-1419, 2000

- 18 SMILE vakası
 - Nükleer hiperkromazi,
pleomorfizm
 - Yüksek Ki-67 indeksi
 - (-) keratin-14
 - (-) p63
 - TZ “Rezerve Hücre” orijinli
- Skvamoz Dif. markerları



Stratified Mucin-Producing Intraepithelial Lesions of the Cervix

Adenosquamous or Columnar Cell Neoplasia?

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TABLE 1. *Clinical pathologic profile of 18 SMILEs*

Mean age

Without associated invasion (n = 8) = 34.5 yrs (23–47)

With associated invasion (n = 19) = 41.8 yrs (25–57)

Associated lesions

CIN2–3 = 14

ACIS = 11

Adenocarcinoma and squamous carcinoma = 2

Adenocarcinoma = 2

Adenosquamous carcinoma = 5

Papillary neoplasia = 2

% 50 !!!

SMILEs, stratified mucin-producing intraepithelial lesions;
ACIS, adenocarcinoma in-situ.

Invasive Stratified Mucin-producing Carcinoma and
Stratified Mucin-producing Intraepithelial Lesion (SMILE)
*15 Cases Presenting a Spectrum of Cervical Neoplasia With Description
of a Distinctive Variant of Invasive Adenocarcinoma*

Ricardo R. Lastra, MD,† Kay J. Park, MD,‡ and J. Kenneth Schoolmeester, MD†§*

Am J Surg Pathol • Volume 40, Number 2, February 2016

- YR-HPV ilişkili karsinogenez için; **REZERV HÜCRE**
- TZ'da lokalize tek tabaka spesifik kolumnar hücre populas.
- HG intraepitelyal lezyon(HSIL, ACIS) ve Kanser
- SMILE: tüm lezyon kalınlığı boyunca müsin içeren hücreler
- ACIS'den farklı olarak iyi oluşmuş gland formasyonu ve glanduler lümen yokluğu

Invasive Stratified Mucin-producing Carcinoma and
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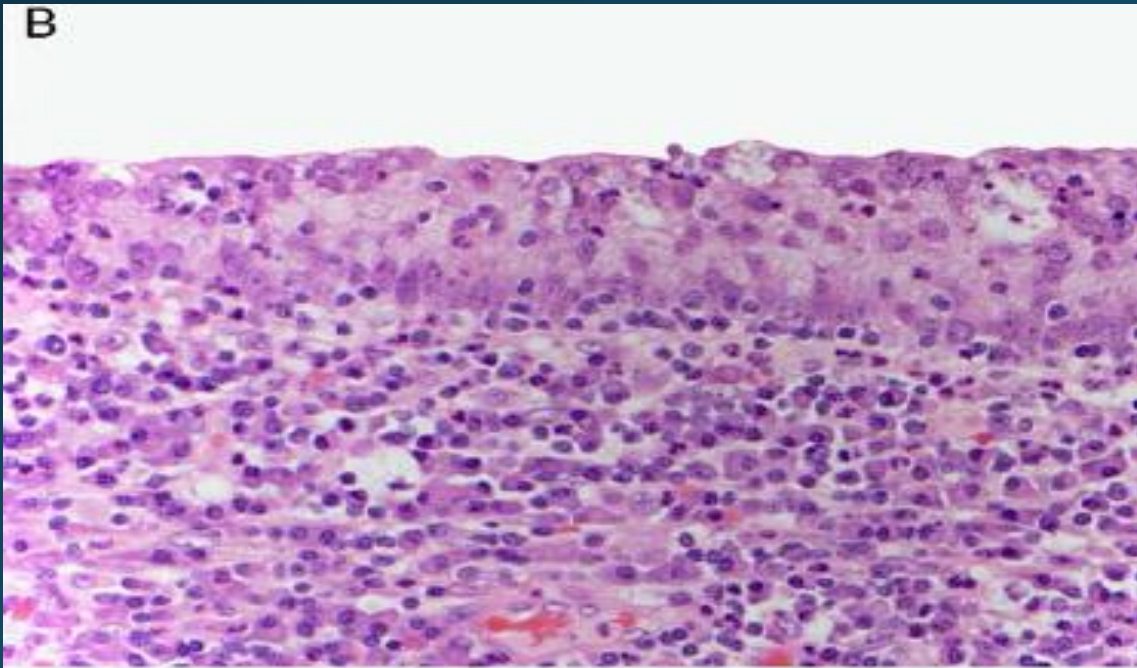
- p63 ve p40 ekspres. YOK – HSIL'dan farklı olarak
 - IMP3 ekspres. YOK- ACIS'dan farklı olarak
 - p16 ve Ki-67 ekspres. YÜKSEK – YR-HPV ilişkili lez. gibi
 - **HSIL** ve **ACIS** - SMILE birlikteliği **% 93** vs **% 42**
-
- 15 SMILE: 7 SMILE+ HSIL; 8 invaziv stratifiye müsin üreten
karsinom

Invasive Stratified Mucin-producing Carcinoma and Stratified Mucin-producing Intraepithelial Lesion (SMILE) *15 Cases Presenting a Spectrum of Cervical Neoplasia With Description of a Distinctive Variant of Invasive Adenocarcinoma*

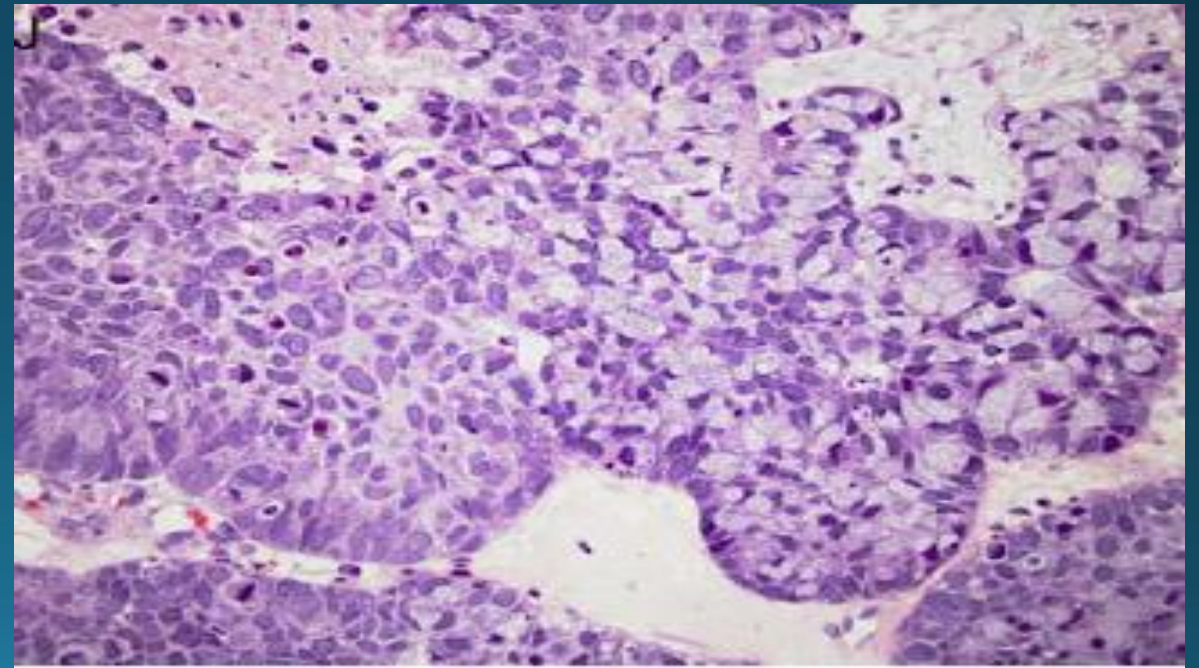
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SMILE



ISMPCancer



[The morphological and immunohistochemical characteristics of stratified mucin-producing intraepithelial lesion].

[Article in Russian; Abstract available in Russian from the publisher]

[Shamarakova MV](#)¹, [Asaturova AV](#)¹, [Ezhova LS](#)¹, [Dumanovskaya MR](#)¹, [Faizullina NM](#)¹, [Kozachenko AV](#)¹.

[Arkh Patol.](#) 2017;79(5):16-20. doi: 10.17116/patol201779516-20.

- 53 servikal kone spesmeni
- 2 CIN III + SMILE
- SMILE: (+) mucicarmine, zayıf p63, yüksek Ki-67, diffüz p16
- SMILE; morfolojik ve immunohistokimyasal olarak CIN II'e benzer
- CIN III genelde H&E ile değerlendirilmekte;
- SMILE tanısı sadece immunohistokimyasal olarak mümkün!

Cytologic Findings in Stratified Mucin-producing Intraepithelial Lesion of the Cervix: A Report of 34 Cases

Anastasia Backhouse, M.B.B.S., F.R.C.P.A.,^{1*}
Colin J. R. Stewart, M.B.B.S., F.R.C.P.A.,^{2,3}
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Ha Tran, B.Sc.,² Louise Farrell, M.B.B.S., F.R.A.N.Z.C.O.G.,⁴ and
Sukeerat Ruba, M.B.B.S., F.R.C.P.A.²

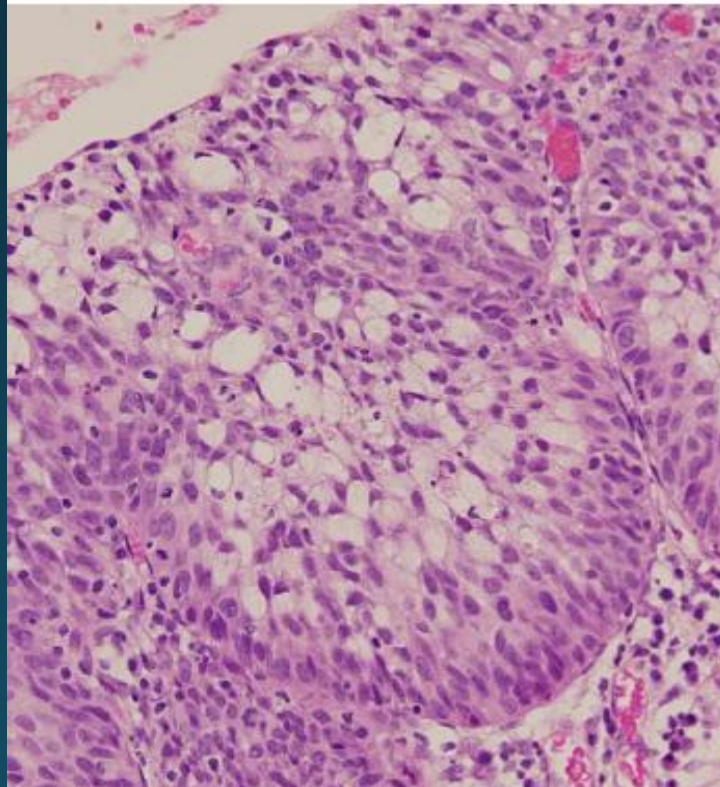
2016

Diagnostic Cytopathology, Vol. 44, No 1

Table I. Initial Cytology Diagnoses, Associated Neoplastic Lesions, and Mucosal Distribution of 34 SMILEs

	n	%
Initial cytology diagnoses:		
Negative	1	2.9
SIL/possible SIL	30	88.2
SIL and possible HGGL	2	5.9
AIS	1	2.9
Associated lesions on histology:		
CIN only	26	76.5
CIN and AIS	7	20.6
CIN, AIS, and adenocarcinoma	1	2.9
Distribution of SMILE:		
Surface epithelium only	6	17.6
Crypt epithelium only	2	5.9
Surface and crypts	26	76.5

SIL, squamous intraepithelial lesion; HGGL, high-grade glandular lesion; AIS, adenocarcinoma in situ.



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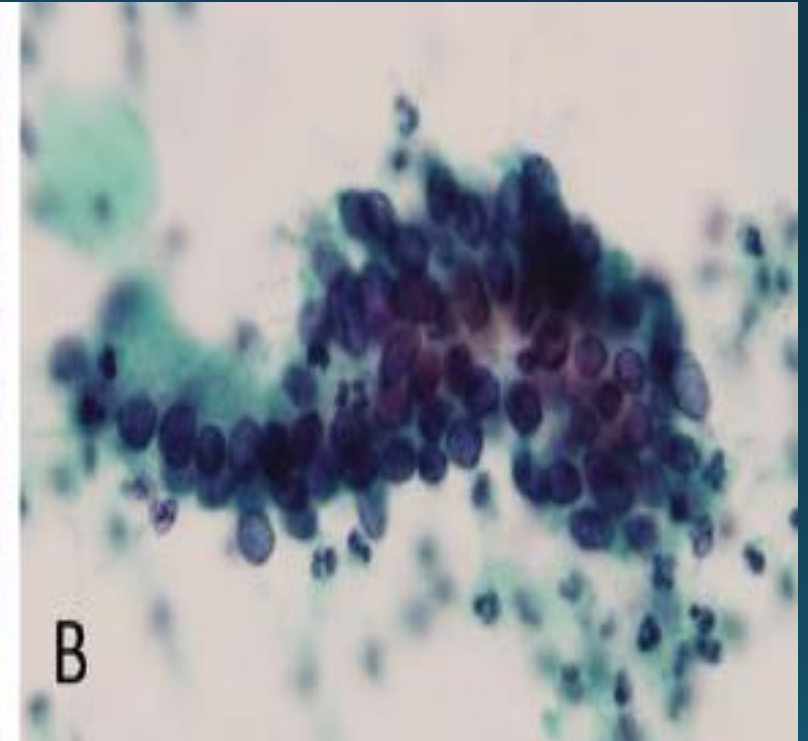
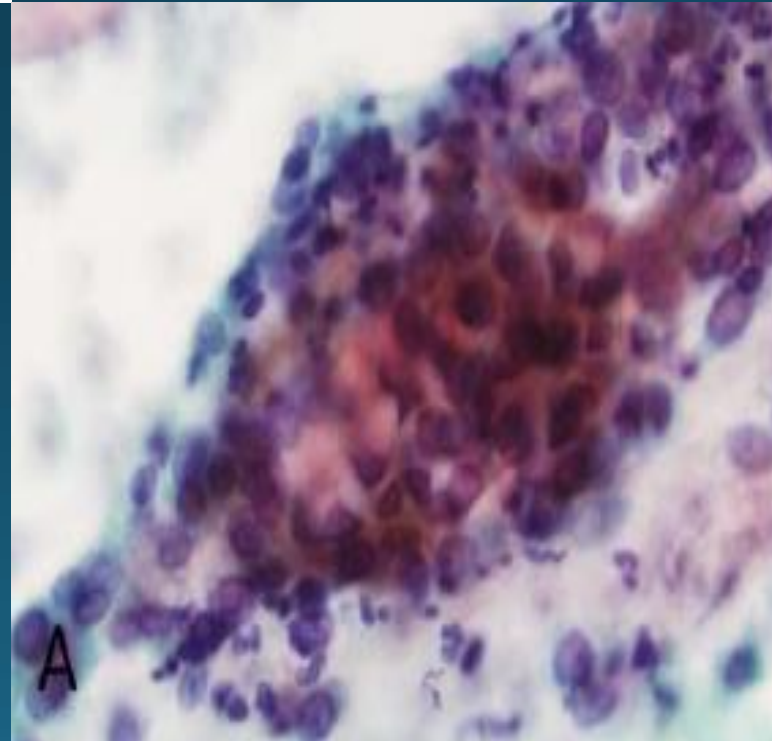
2016

Diagnostic Cytopathology, Vol. 44, No 1

SMILE

ACIS

Tekrar incelenen
sitolojik örneklerde
SMILE
düşündüren
bulgular % 67.6

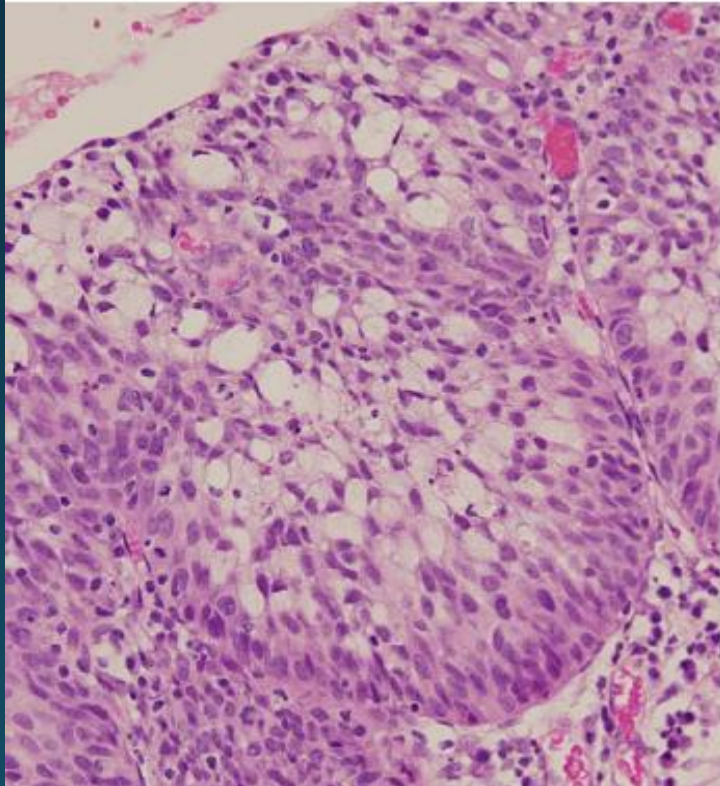


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2016

Diagnostic Cytopathology, Vol. 44, No 1



- İnvaziv kanser riski ~ % 10 (SC)
- ACIS'ya benzer tedavi
- LETZ yerine Konizasyon
- Fertilité sonrası Histerektomi
- Rezidüel multifokal neoplazi riski
- Sitolojik takip limitasyonu

Stratified mucin-producing intraepithelial lesion (SMILE): report of a case series with associated pathological findings

David P Boyle & W Glenn McCluggage

Department of Pathology, Belfast Health and Social Care Trust, Belfast, Northern Ireland

- 6 yıl boyunca 69 vaka, % 0.6
- Birliktelik: % 93 HGGIN, % 42 ACIS, % 10 Kanser
- Diffüz p16 pozitifliği, IMP3 negatifliği
- YD REZERV HÜCRE Displazisi (Stem-cell)
- ACIS gibi tedavi edilmeli

Stratified mucin-producing intraepithelial lesion (SMILE): report of a case series with associated pathological findings

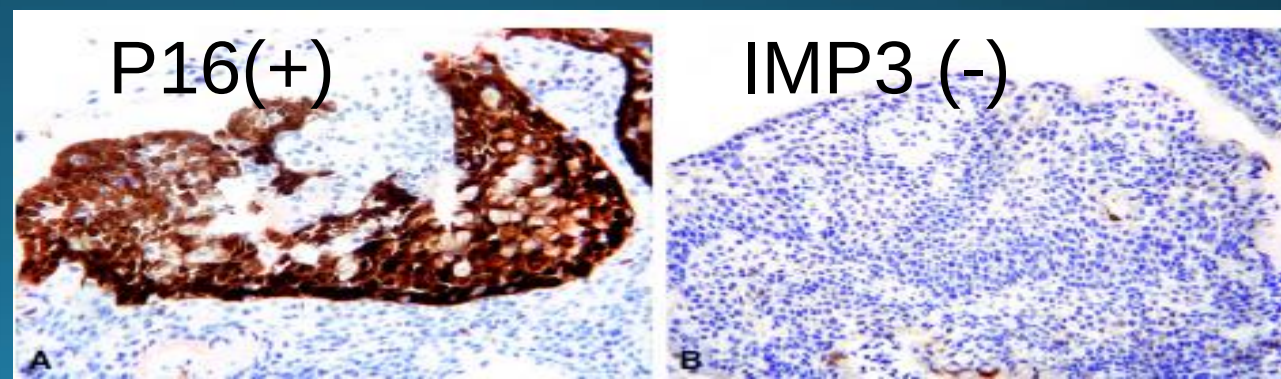
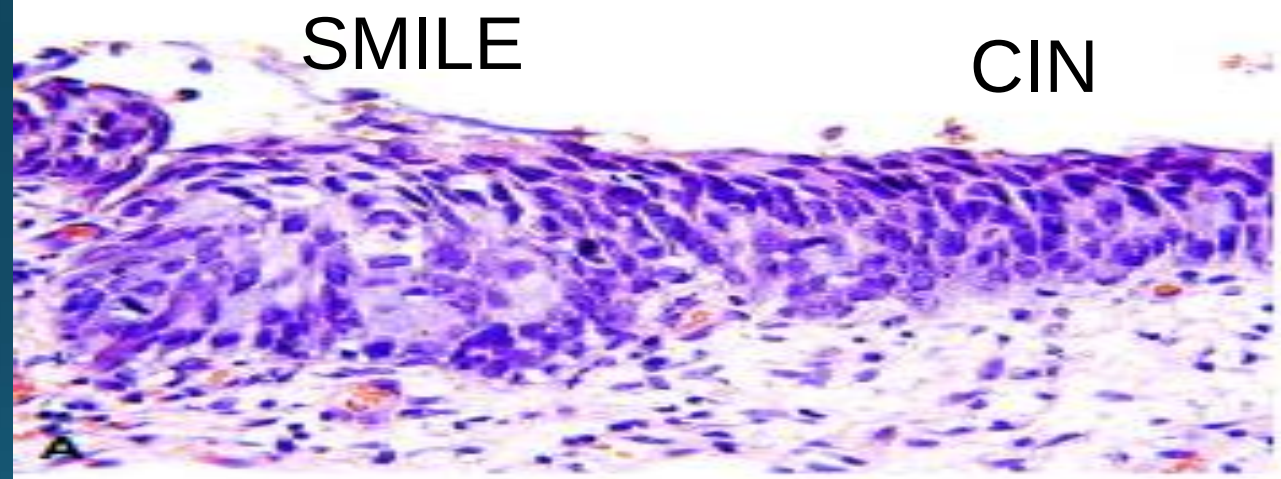
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Table 2. Coexistence of SMILE with other lesions

Diagnosis	<i>n</i>	%
SMILE alone	3	4
CIN I*	1	1
High-grade CIN	64	93
AIS	29	42
Carcinoma	7	10

*In the absence of high-grade CIN.



Cytologic Features of Stratified Mucin Producing Intraepithelial Lesion of the Cervix—A Case Report

2013

Abha Goyal, M.D.,* and Bin Yang, M.D., Ph.D.

Diagnostic Cytopathology, Vol. 42, No 9

Table I. Comparison of Cytologic Features of SMILE with Differential Diagnoses

<i>Cytologic feature</i>	<i>SMILE</i>	<i>AIS</i>	<i>HSIL</i>	<i>Tubal metaplasia</i>	<i>Reactive endocervical glandular cells</i>	<i>Normal endocervical glandular cells</i>
Nuclear crowding	Mild	Marked	Marked	Mild	Mild	Absent
Nuclear hyperchromasia	Slight	Moderate to marked	Marked	Mild	Usually hypochromatic	Absent
Nucleoli	Indistinct	Usually indistinct	Indistinct	Indistinct	Prominent	Indistinct
Cell cluster edge	Relatively smooth	Feathering at edges	Smooth	May show feathering	Usually smooth	Smooth
Other		Apoptotic bodies		Cilia and terminal bars		

Cytologic Features of Stratified Mucin Producing Intraepithelial Lesion of the Cervix—A Case Report

2013

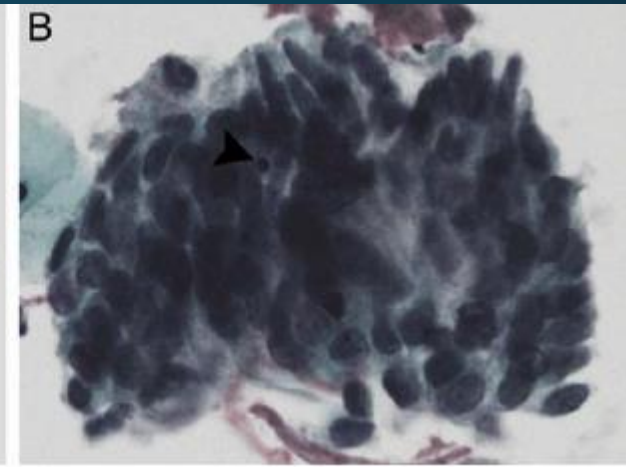
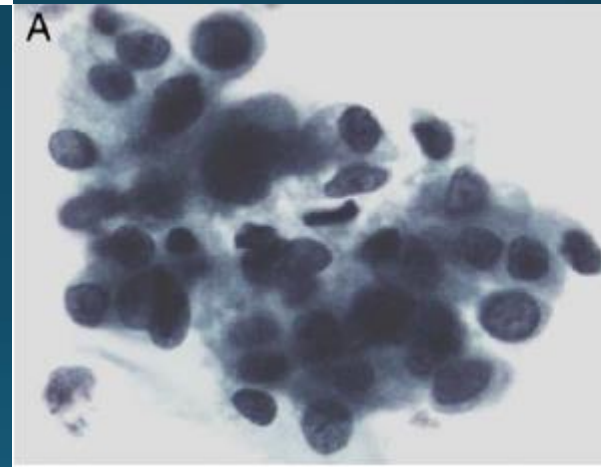
Abha Goyal, M.D.,* and Bin Yang, M.D., Ph.D.

Diagnostic Cytopathology, Vol. 42, No 9

- HPV DNA Pozitifliği
HSIL % 92
ACIS % 100
- SMILE sitolojik bulguları hafif
- Reaktif endoservikal glandüler hücreler ile karışabilir.
- HPV DNA test kullanılmalı

SMILE

ACIS



Stratified mucin-producing intraepithelial lesion with invasive carcinoma: 12 cases with immunohistochemical and ultrastructural findings☆

Junji Onishi MD, PhD^a, Yuichiro Sato MD, PhD^{b,*}, Akira Sawaguchi MD, PhD^c, Atsushi Yamashita MD, PhD^d, Kazunari Maekawa MD^d, Hiroshi Sameshima MD, PhD^a, Yuiiro Asada MD, PhD^c

Human Pathology (2016) 55, 174–181

Table 1 Clinicopathological findings in SMILE and invasive carcinoma

Case no.	Age	Symptom	Stage (size)	Other tumor	Treatment	Prognosis (mo)
1	48	Gen	0	HSIL + AIS (u)	Cone + Hyst	Alive (48)
2	30	Ab cyt	0	HSIL + AIS (u)	Cone + Hyst	Alive (30)
3	32	Ab cyt	0	HSIL + AIS (u + i)	Cone	Alive (25)
4	40	Gen	Ib (2.5 cm)	AIS (u) + ISMC + SCC	Hyst + Chemo	Alive (126)
5	62	Ab cyt	Ib (1.8 cm)	AIS (u) + Ade (u)	Hyst + Chemo	Alive (52)
6	48	Gen	IIb (5 cm)	AIS (u) + Adesq	Hyst + Chemo	Alive w/ LN meta (86)
7	41	Ab cyt	Ia (0.5 mm)	HSIL + AIS (u) + Ade (u)	Hyst	Alive (47)
8	44	Gen	IIb (5 cm)	HSIL + ISMC (LN meta)	Hyst + Rad	Alive (39)
9	49	Ab cyt	Ib (0.8 cm)	HSIL + AIS (u) + Adesq	Hyst	Alive (24)
10	37	Gen	Ib (1.9 cm)	HSIL + AIS (u) + LCNEC	Hyst + Chemo	Alive (17)
11	37	Gen	IIa (3 cm)	HSIL + AIS (u + i) + Ade (vg)	Hyst	Alive (13)
12	66	Gen	Ib (3 cm)	AIS (u) + ISMC	Hyst	Alive (13)

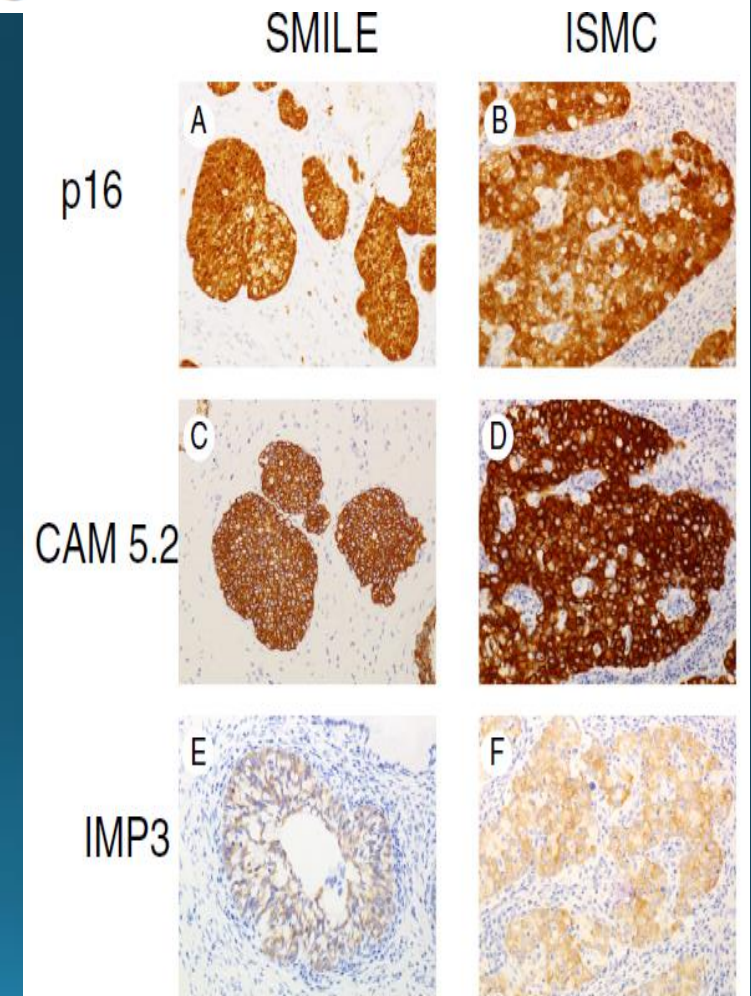
Abbreviations: Ab cyt, abnormal cytology; Ade, adenocarcinoma; Adesq, adenosquamous carcinoma; Chemo, chemotherapy; Cone, conization; Gen, genital bleeding; Hyst, hysterectomy; LN, lymph node; meta, metastasis; Rad, radiation; SCC, squamous cell carcinoma; u, usual; i, intestinal; vg, villoglandular.

Stratified mucin-producing intraepithelial lesion with invasive carcinoma: 12 cases with immunohistochemical and ultrastructural findings☆

Junji Onishi MD, PhD^a, Yuichiro Sato MD, PhD^{b,*}, Akira Sawaguchi MD, PhD^c, Atsushi Yamashita MD, PhD^d, Kazunari Maekawa MD^d, Hiroshi Sameshima MD, PhD^a, Yuiiro Asada MD, PhD^c

Human Pathology (2016) 55, 174–181

- İntraepitelyal lezyonlar arasında SMILE % 1.2
- Adenokanserler arasında ISMC ise % 10
- Birliktelik: ACIS % 92, HSIL % 58
- HPV tip 18 > 16 pozitifliği
- Tedavi ACIS gibi Cone, re-cone, histerektomi



Stratified Mucin-Producing Intraepithelial Lesion of the Cervix: Subtle Features Not to Be Missed

Joerg Schwock Hyang Mi Ko Valérie Dubé Marjan Rouzbahman
Matthew Cesari Zeina Ghorab William R. Geddie

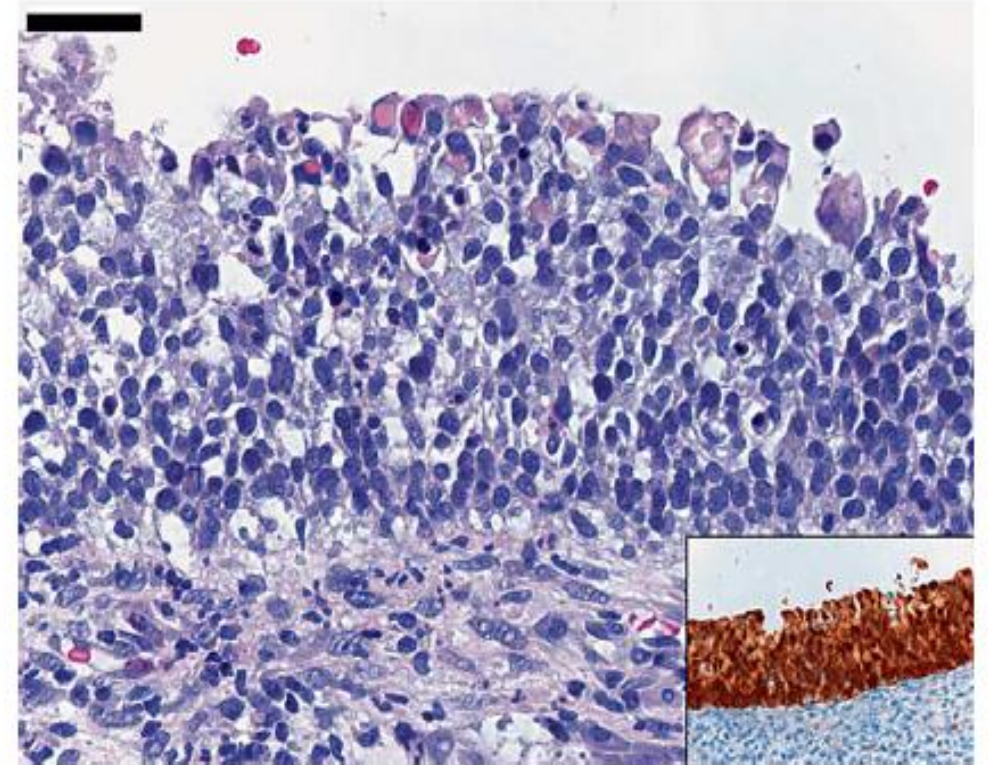
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Acta Cytologica 2016;60:225–231

DOI: 10.1159/000447940

- 13 SMILE vakası
- Birliktelik: ACIS % 62, HSIL % 77
- HPV tip 18 > 16 pozitifliği
- ACIS'nin bir varyantı
- Epitelyal stratifikasyon
- Diffüz müsin üretimi
- Tipik bez yapısının yokluğu

SMILE



p16

Table 1. Clinicopathologic characteristics of the SMILE cases

Case No.	Patient age, years	Original cytology diagnosis 1	Cytology review 2	Cytology review 2 3	Discrepancy ^b	Preparation	Procedure	Interval, months	Surgical pathology review	Margin status	HPV type
1	30	HSIL, AGC	HSIL, AGC	HSIL (w/EGI), AGC	no	TP	LEEP	2	HSIL > SMILE > AIS	negative	18
2	34	HSIL	HSIL, AGC	HSIL (w/EGI), AIS	no	SP	LEEP	2	HSIL > SMILE	negative	16 + other
3	45	HSIL	HSIL	HSIL	no	SP	LEEP	3	HSIL > SMILE > AIS	positive	18 + other
4	23	HSIL	HSIL	HSIL	no	TP	LEEP	2	HSIL > SMILE	positive	16
5	24	HSIL	HSIL, AGC	HSIL	no	DS	LEEP	4	HSIL > SMILE	negative	18
6	33	HSIL (w/EGI)	HSIL	HSIL (w/EGI), AIS	no	SP	LEEP	2	HSIL > SMILE	negative	16
7 ^a	49	NILM, reactive changes	AdCa	AIS	yes	SP	LEEP, ECC	2	AIS > SMILE > HSIL	positive	18
8	25	HSIL	HSIL, AGC	LSIL	yes	SP	Cone Bx, ECC	2	SMILE > HSIL > AIS	negative	18
9	33	LSIL, reactive changes	AGC, HSIL	AIS, LSIL	yes	SP	LEEP	2	SMILE > HSIL > AIS	positive	other
10	51	AGC, ASC-H	AdCa	AdCa	yes	DS	LEEP	3	SMILE > AIS	positive	n.d.
11	40	AIS, LSIL	AdCa	AIS	no	SP	Cone Bx	2	SMILE > AIS > HSIL	positive	18 + other
12	38	AGC	AIS	AIS	yes	TP	LEEP	2	SMILE > AIS	positive	18
13	28	HSIL	HSIL, AGC	AIS	yes	SP	LEEP	1	SMILE	suspicious	16

The thick horizontal line divides the cases according to the estimated proportion of SMILE (≥ 50 vs. $< 50\%$) as detailed in the column 'Surgical pathology review'. Bold type indicates major discrepancies. AdCa = Adenocarcinoma – not otherwise specified; w/ EGI = with endocervical gland involvement; ECC = endocervical curettage; Bx = biopsy; n.d. = not determined.

^a AIS-dominant case.

^b Any difference in interpretation between original and review diagnoses (other than AdCa vs. AIS).

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Acta Cytologica 2016;60:225–231

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- SMILE sitolojik bulguları ACIS ile örtüşüyor ve belirsiz kalabiliyor.
- Sitolog şüpheli olmalı
- HPV DNA testi yardımcı

Table 2. Comparison of the cytologic features of AIS and SMILE

	AIS (%)	SMILE (%)
<i>Architectural features</i>		
Group border	<i>feathered</i> (35) jagged (50) smooth (15)	jagged (90) smooth (10)
Organization	random (55) glandular (35) <i>streaming</i> (10)	random (85) glandular (15)
Cell crowding	<i>mild</i> (10) moderate (35) marked (55)	moderate (80) marked (20)
<i>Cellular features</i>		
Cytoplasm border	distinct (20) indistinct (80)	distinct (45) indistinct (55)
Nuclear shape	spherical (70) elongated (30)	spherical (95) elongated (5)
Nuclear membrane irregularity	mild (70) moderate (30)	mild (45) moderate (50) <i>marked</i> (5)
Chromatin structure	fine (60) coarse (40)	fine (85) coarse (15)
Hyperchromasia	marked (10) moderate (65) mild (25)	marked (40) moderate (55) mild (5)

Follow-up of patients with SMILE (stratified mucin producing intraepithelial lesion) on the cervix—A dilemma

European Journal of Obstetrics & Gynecology and Reproductive Biology 148 (2010) 202–209

Sweta Gupta*

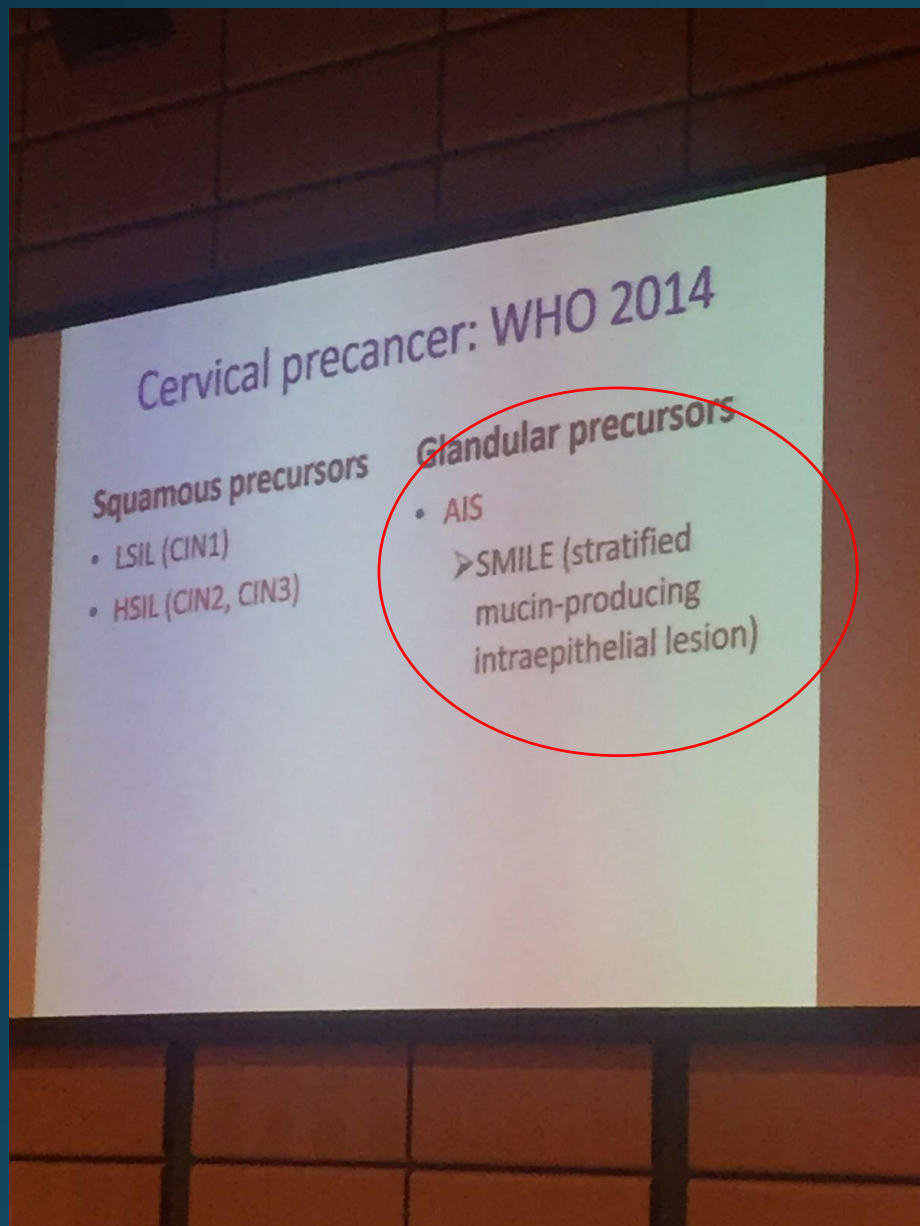
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- Vaka 1: SMILE + CIN III – Loop konizasyon, sınır (-), sitolojik takip
- Vaka 2: SMILE + CIN II – Loop biyopsi → (+) marjin → VH
- Vaka 3: SMILE + CIN II – Loop biyopsi- sınır (-) sitolojik takip
- Belirlenmiş bir algoritma YOK(LEEP - Konizasyon-Histerektomi)
- Yakın takip (Hem ekto-hem endoservikal smear), kolposkopi
- HPV DNA test

WHO/IARC Classification of Tumours of Female Reproductive Organs 2014

Prognosis and predictive factors

In most instances, AIS/HG-CGIN, including SMILE, can be successfully treated with loop excision and close cytological follow up. Hysterectomy may be preferred if childbearing is not an issue. If conservatively managed, close follow-up by colposcopic, cytological and HPV testing are essential.



2000



ESGO-2017



TEŞEKKÜRLER...



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