Osmangazi Tıp Dergisi
Osmangazi Journal of Medicine 2020; 42 (4):412-417

Research Article / Araştırma Makalesi

Clinical Significance of Atypical Squamous Cells in Which High Grade Lesions Cannot Be Excluded; Experience of a Tertiary Hospital in Anatolia

Yüksek Dereceli Lezyonların Dışlanamayacağı Atipik Skuamöz Hücrelerin Klinik Önemi; Anadolu'daki Bir Üçüncül Hastanenin Deneyimi

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Abstract: The primary aim of our study was to evaluate the histological results of patients diagnosed with atypical squamous cells, cannot exclude high-grade lesion (ASC-H) by cervical cytology and to reveal the clinical importance of ASC-H.Twenty thousand one hundred sixty three cervicovaginal smears were evaluated. Seventy six (0.376 %) patients were diagnosed as ASC-H. Files of patients diagnosed with ASC-H were retrospectively reviewed. We referred patients who were diagnosed as ASC-H according to the Bethesda classification system after cervicovaginal smear for colposcopic examination. İf it is necessary, cervical biopsy, endocervical and endometrial curettage were performed by the colposcopy guide. Clinicopathological features of the patients were examined and recorded. Smear results of 20163 patients reviewed. Abnormal cytological results were found in 1188 (5.8%) patients. The abnormal cytological results were ASC-H in 76 (0.37%) patients. Abnormal cervical dysplasia was detected in 36 (47.3%) of 76 patients diagnosed as ASC-H. Twenty (20/76-26.3%) of these abnormal lesions were high-grade cervical intraepithelial neoplasia (CIN2 / 3), 12 (12/76-15.7%) of them were low-grade cervical intraepithelial neoplasia (CIN 1) and 4 (4 /76-5%) of them were cervical carcinoma. ASC-H is a diagnosis with significant association with precancerous and cancerous lesions. Therefore, further evaluation of ASC-H patients should be performed with the necessary care and attention

Keywords: ASC-H, Cervical cytology, Cervical intraepithelial neoplasia

Özet: Çalışmamızın öncelikli amacı servikal sitolojide yüksek dereceli skuamöz lezyonların dışlanamadığı atipik skuamöz hücre (ASC-H) tanısı almış hastaların histolojik sonuçlarının değerlendirilmesi ve bu durumun klinik öneminin ortaya çıkarılmasıdır. Yirmibin yüzaltmışüç hastanın smear sonuçları değerlendirildi. Yetmiş altı (0.376 %) hastada ASC-H tanısı kondu. ASCH tanısı konan hastaların dosyaları retrospektif olarak gözden geçirildi. ASCH tanısı konan tüm hastalara kolposkopik muayene işlemi yapıldı. Kolposkopik muayenede gerekli görülen hastalara eksizyonel işlemler ile servikal ve endoservikal biyopsi işlemleri uygulandı. Hastaların klinik patolojik bilgileri dosyalarından incelenip toplandı. Gözden geçirilen 20163 smear sonucunda 1188 (5.8%) hastada servikal anormal sitoloji tespit edildi. Bu anormal servikal sitolojilerin 76 tanesinde ASCH (0.37%) tespit edildi. ASCH tanısı alan 76 hastanın 36 (47.3%) tanesinde anormal servikal displazi tespit edildi. Bunlarında 20 (20/76-26.3%) tanesinde yüksek dereceli servikal intraepitelyal neoplazi (CIN2-3) ,12 (12/76-15.7%) tanesinde düşük dereceli servikal intraepitelyal neoplazi(CIN1) ve 4 (4 /76-5%) tanesinde servikal invazif kanser tespit edildi. ASCH tanısı önemli oranda prekanseröz ve kanseröz lezyonlarla ilişkilidir. Bu nedenle ASCH hastalarının yönetiminde ileri değerlendirme yapılırken gerekli özen ve dikkat sağlanmalıdır.

Anahtar Kelimeler: ASC-H, Servikal sitoloji, Servikal intraepitelyal neoplazi

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Received 08.08.2019 ***Accepted*** 09.09.2019 ***Online published*** 09.09.2019

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Cite this article as:
Cakmak Y, Oge T. Clinical Significance of Atypical Squamous Cells in Which High Grade Lesions Cannot Be Excluded; Experience of a Tertiary Hospital in Anatolia, Osmangazi Journal of Medicine, 2020;42(4):412-417 ***Doi:*** *10.20515/otd. 603831*

1. Introduction

Cervical cancer is the second most common gynecological cancer in developing countries (1,2). Presence of the screening tests are affected the incidence of cervical cancer. Screening programs can be detected and treated precancerous lesions and early stage cancers. Papanicolaou (Pap) smear is widely used all over the world because it is cheap and easily accessible for cervical cancer screening. Terms of cervical cytology was standardized by the Bethesda System in 1988(3). This system has been revised several times and the last review was made in 2014 (4-6). Although atypical squamous cells are different from normal cells, they do not fully meet the diagnosis of squamous intraepithelial neoplasia (5). In the 2014 Bethesda system, ASCs are divided into two groups; the first one is undetermined group (ASC-US) and the other is high-grade lesions cannot be excluded (ASC-H) (5-6). ASC-H smear results are seen between 0.07-0.56 percent in the literature (7-11). Although it constitutes a small part of the abnormal cervical cytology, it is usually associated with high-grade precancerous lesions (8). Careful evaluation of patients diagnosed ASC-H in the Pap test is necessary due to the high coexistence with premalign and malign lesions. The American Society for Colposcopy and Cervical Pathology (ASCCP) 2012 management guidelines and The American College of Obstetricians and Gynecologists recommend colposcopy in patients with ASC-H, which is related to a risk of a high-grade squamous intraepithelial neoplasm (12,13,14). Endocervical curettage or cervical excisional biopsy is recommended in case of colposcopic insufficiency.

The primary aim of our study was to evaluate the histological results of patients diagnosed with ASC-H by cervical cytology and to reveal the clinical importance of ASC-H.

2. Material and Method

The records of 21000 patients who were examined in the gynecology outpatient clinic between June 2010 and July 2018 and underwent cervicovaginal smear were retrospectively reviewed. Eight hundred thirty-seven patients were excluded due to lack of medical data records. Twenty thousand one hundred sixty three cervicovaginal smears were evaluated. Seventy six (0.376 %) patients were diagnosed as ASC-H. Files of patients diagnosed with ASC-H were retrospectively reviewed. Conventional Pap smear test method was used for cervical cytology. The patients were taken to the gynecologic table in the lithotomy position and the vulva, vagina and cervix were evaluated. In the smear procedure, endocervical brush was used and a sample of squamocolumnar junction and endocervical canal was taken. The cells on the brush were spread on the slide and fixed with 95 % ethyl alcohol and examined by a pathologist specialized in gynecology. We referred patients who were diagnosed as ASC-H according to the Bethesda classification system after cervicovaginal smear for colposcopic examination. Colposcopy device with Welch Allyn brand number 13153 was used for colposcopic examination of patients. Three percent acetic acid and lugol solutions were used during the examination. İf it is necessary, cervical biopsy, endocervical and endometrial curettage were performed by the colposcopy guide. During the procedure, Para cervical block was applied with 5 ml 2 % lidocaine. After histological diagnosis, Conization in 2 patients, total abdominal hysterectomy in 2 patients, loop electrosurgical excision procedure (LEEP) in 20 patients and radical hysterectomy in 1 patients were performed. Specimens obtained were evaluated by the same gynecological pathologist.

Age, gravida, parity, systemic diseases and clinicopathological features of the patients were examined and recorded. Distributions of the patients according to age groups in which started at the age of 20 years and were formed in 10 year intervals were evaluated.

Patients whose medical file could not be accessed or lacked and patients who did not consent to diagnostic procedures were excluded from the study. Ethics committee approval was obtained for our study.

Data were analyzed using IBM SPSS 21 package program. Summary values of quantitative data were shown as mean or

median (Q1-Q3). Summary values of qualitative variables are shown as frequency and percentage. The normal distribution of quantitative variables was investigated by Shapiro Wilk test. Quantitative comparisons of two groups were performed by Mann Whitney test. Results with p <0.05 were considered significant.

3. Results

Smear results of 20163 patients reviewed. Abnormal cytological results were found in 1188 (5.8%) patients. The abnormal cytological results were ASC-US in 710 (3.5%) patients, low grade squamous intraepithelial lesion (LSIL) in 227 (1.1%) patients, High grade squamous intraepithelial lesion (HSIL) in 89 (0.44%) patients, Atypical glandular cells undetermined signification (AGUS) in 86 (0.42%) patients and ASC-H in 76 (0.37% patients). The mean age of the patients diagnosed as ASC-H was 47.8 (27-77) and the mean gravida was 3.28 (0-6). Forty-seven (61.8%) of the patients were in the premenopausal period, while 29 (38.1%) of the patients were in postmenopausal patients. The clinical features of the patients are shown in Table 1.

Tablo 1. Characteristic features of patients with ASC-H (n:76)

Gravidy (n) mean (min-max)	**3.28 (0.8)**	**Not using contraception n (%)**	**61 (80.2%)**
Parity (n) mean (min-max)	2.21 (0-8)	Insufficient colposcopy n (%)	3 (3.9%)
Abortus (n) mean (min-max)	0.96 (1-3)	Diabetes mellitus n(%)	6 (7.8%)
Age (years) mean (min-max)	47.8 (27-77)	Hypertansion n(%)	3 (3.9%)
Marriage duration (years) mean	25	Hypothyroidism n(%)	3 (3.9%)
Postcoital bleeding n(%)	7 (9%)	Premenopausal n(%)	47 (61.8%)
Abnormal cervical discharge n (%)	17 (2.3%)	Postmenopausal n(%)	29 (38.1%)

ASC-H ,Atypical squamous cell; cannot exclude high-grade intraepithelial lesion

Abnormal cervical dysplasia was detected in 36 (47.3%) of 76 patients diagnosed as ASC-H. Twenty (20/76-26.3%) of these abnormal lesions were high-grade cervical intraepithelial neoplasia (CIN2 / 3), 12 (12/76-15.7%) of them were low-grade cervical intraepithelial neoplasia (CIN 1) and 4 (4 /76-5%) of them were cervical carcinoma.

When patients are stratified according to 10-year age increments ASC-H was mostly diagnosed between 40-49 years age group (n=22, 28.9%). The second most common age group with 19 (25%) patients was the 50-59 age group. The distribution of ASC-H patients according to age groups is shown in Table 2.

Table 2. Distribution of patients with ASC-H according to age groups

Age groups (years)	**20-29**	**30-39**	**40-49**	**50-59**	**60-69**	**70-79**	**Total**
ASC-H n(%)	3 (3.9%)	18 (23.6%)	22 (28.9%)	19 (25%)	13 (17.1%)	1 (1.3%)	76 100%

ASC-H ,Atypical squamous cell; cannot exclude high-grade intraepithelial lesion

When the distribution of high grade cervical intraepithelial (CIN2/3) lesions according to age groups was examined, it was seen that 11 (14.4%) patients were most frequently observed in the 30-39 age group. Low grade CIN1 was observed with 5 patients in the 40-49 and 50-59 age group. Invasive cervical cancers are seen in the age group of 40 years and older. The distribution of the lesions according to age groups is shown in Table 3.

Table 3. Colposcopic biopsy results of patients with ASC-H diagnosed as ≥ CIN 1 according to age groups

Age groups (years)	20-29	30-39	40-49	50-59	60-69	Total
CIN I	-	2	5	5	-	12 (15.7%)
CIN II	1	2	1	-	2	6 (7.8%)
CIN III	-	9	3	2		14 (18.4%)
Invazive carcinoma	-	-	1	1	2	4 (5.2%)
Total	1 (1.36%)	13(17.1%)	10(13.1%)	8(10.5%)	4 (5.2%)	36 (47.3%)

CIN, Cervical intraepitelial neoplasia

When the menopausal status of 36 patients with abnormal cervical lesion is examined, it is seen that approximately 2/3 of them are in the premenopausal period and 1/3 of them are in the postmenopausal period. Of the 36 abnormal cervical pathologic outcome identified as a result of further evaluation, 12 (12/36-33.3%) of the CIN1, 6 (6/36-16.6%) of them were CIN2, 14 (14 /36-38.8%) of them were CIN3 and 4 (4/36-11.1%) of them were invasive cervical cancer. The distribution of lesions according to menopausal status is shown in Table 4.

Two of the patients with cervical invasive cancer were Figo stage1 and two were stage 2. One of the patients with cervical cancer underwent primary radiotherapy for advanced stage and the other patients underwent surgical treatment.

Table 4. Menopausal status of patients dianosed as ≥ CIN 1 after ASC-H cytology

	CIN I	CIN II	CIN III	Invazive Carsinoma	Total n:36
Premenopausal n(%)	6	4	12	1	23(63.8%)
Postmenopausal n(%)	6	2	2	3	13(36.1%)
Total	12 (33.3%)	6 (16.6%)	14 (38.8%)	4 (11.1%)	36 (100%)

CIN, Cervical intraephytelial neoplasia

4. Discussion

In our study, we aimed to investigate the clinical importance of ASC-H cases in which seen together high grade dysplastic lesions. We detected cervical dysplastic lesion in 36 (47.3%) patients as a result of histopathologic evaluation of 76 patients diagnosed as ASC-H by cervicovaginal smear. Two thirds of these dysplastic lesions consisted of clinical high-grade intraepithelial lesions (CIN2/3) and cervical cancer.

In the present study, smear result of 20163 patients was diagnosed as abnormal cervical cytology in 5.8% of cases. The majority of cervical abnormal cytology results are atypical squamous cell (ASC) (3.8%). Although abnormal cervical cytology rates detected in smears are reported in a wide range, this rate is seen in 2-5% in large number of patients (7-9). Total abnormal cytology results are consistent with the literature.

In our study, 76 (10.7%) of 786 patients diagnosed as ASC were ASC-H. The ratio of this ASC-H diagnosis in all cervicovaginal smears is 0.376%. This rate is 0.17-0.56% in the literature (10-12,21,23). ASC-H ratio varies reported between 0.10-0.49 in multi-center studies conducted in our country (22,23,26). Our ASC-H detection rate in our study is consistent with the literature and studies conducted in our region.

The rate of abnormal cervical dysplasia detected after histopathologic examination of patients with ASC-H varies between 10-85% in the literature (10-12,15,28). High grade cervical lesion rates were found in a wide range between 12-68% (10,24-25). In our study, the rate of abnormal dysplastic lesions detected in ASC-H patients was 47.3%. The rate of high grade dysplastic lesion and cervical cancer was 31.5%.

There are many reasons why the rate of abnormal cervical dysplastic lesion detected by histopathological evaluation after ASC-H diagnosis is widely distributed. In some of the studies for cervical cytology, cells were collected by using endobrush by conventional method and in some by liquid-based Thin Prep technology method were used. Number of cells sampled, fixation defect and inappropriate sampling rates vary in conventional smear techniques (6,12,16). More diagnostic cells are collected in liquid-based Thin Prep sampling (26). Although there are abnormal cytological changes for the diagnosis of ASC-H, there is no definite criteria (5-6). Therefore the reproducibility rates of ASC-H diagnosis among pathologists vary. Another important factor in the studies was the differentiation of HPV infection rates and vaccination status in the sample group (7,8,10). There are differences between risk factors for premalignant and malignant lesions between countries (1,8,16). In addition, Colposcopic examination of the ASC-H by experienced people will affect the pathological diagnosis rates. Most studies have not provided information on the hormonal status that causes cellular change in smears (27). All these reasons may explain the differences between studies.

Also age factor has an effect on abnormal cervical cytology rates. Patton et al. emphasized the significance of age in the predicting the risk of dysplasia in ASC-H cases (27).

In our study, unlike other studies, the diagnosis of ASC-H in patients under 30 years of age was observed only in 3 patients. Although the most common ASC-H diagnosis was seen in the 40-49 age group, CIN 2/3 lesions were most commonly observed in the 30-39 age group. The number of patients under 30 years of age is very low in the literature (10). This is due to the small number of patients under the age of 30 who applied to our clinic for smears. In the literature on the investigation of anomalous cervical dysplasias in ASC-H patients, different age limits have been used in many studies (10,18-19).

There are some restrictive aspects of our study. Conventional Pap test was used in all patients for economic reasons. Retrospective study limited access to some clinical information about patients.

As a result, effective use of Pap test and proper management of Pap test results are crucial in reducing cervical cancer rates in countries with limited economic resources. ASC-H is a diagnosis with significant association with precancerous and cancerous lesions. Therefore, further evaluation of ASC-H patients should be performed with the necessary care and attention

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