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Diagnostic Approach to Patients with Atypical Squamous Cells of Undetermined Significance Cytologic Findings on Cervix

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ABSTRACT

Background: Atypical squamous cells of undetermined significance (ASCUS) is a term that refers to inflammatory, reactive and reparative processes which are atypical and of higher level and insufficient to be classified as cervical intraepithelial lesions (CIN). **Aims:** Examine of frequency of HPV infection in ASCUS lesions and regression, stagnation and progression during six-month period. **Subjects and Methods:** Prospective study was conducted over a period of 3 years. In private gynecological ambulance „Dr Mahira Jahic“. Analysis of PAP smears and HPV typization have been done in 50 patients and PAP test has been repeated after six months. X² test was used for statistical analysis. **Results:** Analysis of 1784 PAP smears showed normal results in 86,6% (N-1530), and abnormal in 13% (N-254). ASCUS in 7,4% (N-133) and ASC-H in 0,5% (N-9), LSIL in 4,4% (N-80), HSIL in 1,3% (N-24), CIN II in 1,2% (N-20), CIN III in 0,2% (N-4). Progression occurred in 18% (9), persistence in 74% (37) and regression in 8%. Patients with ASC-H lesion 0,5% (N-9), PH results showed 22% (N-2) Carcinoma in situ, 33% (N-3) CIN II, 22% (N-2) CIN I and 22% (N-2) chronic cervicitis. Patients with CIN I in 88% (N-7) were positive on HPV of high risk. Patients with persistent ASCUS result were positive in 51% (N-19). The number of CIN I lesions found in women with ASCUS is bigger and statistically significant ($p < 0,05$) in relation to number of CIN I findings found in regular examinations. **Conclusion:** Monitoring women with ASCUS lesion, especially HPV positive to high risk group is the best way of selection of women who should be treated and monitored in order to prevent cervical cancer.

Key words: Cervical cancer prevention, ASCUS, Pap test, HPV.

1. INTRODUCTION

Worldwide, cervical cancer is the third most common cancer among women and the second most common cause of death, with 300,000 deaths per year (1). PAP test is cheap, simple and most commonly used technique for cervical cancer and preinvasive cervical lesions screening. Atypical squamous cells (ASC) is a term that refers to inflammatory, reactive and reparative processes which are atypical and of higher level and whose quality and quantity is insufficient to be classified as cervical intraepithelial lesions (CIN). ASC was first described in Bethesda classification in 1988,

and revised in 2001 and 2014 when it was divided into ASCUS (atypical squamous cells of undetermined significance) and ASC-H (atypical squamous cells-high level of lesion cannot be excluded). ASC continues to be defined as general category with subcategorisation as ASCUS and ASC-H (2, 3).

Every year, over 2 million women in the USA are found with atypical squamous cells in PAP test (4). Frequency of ASCUS lesions is between 1,6% and 9% (5), and their frequency shouldn't exceed two to three times frequency of low grade lesions (LSIL) (6). Metaanalysis showed that progression of ASCUS can progress

into invasive cervical cancer may occur in 0,25% within 2 years, HSIL in 7,13%, while regression occurs in 68,19% (7). Out of 1000 women with atypical squamous lesions one already has invasive cervical cancer (8).

Aims of this study were to examine: a) Frequency and age of the examinees with ASCUS lesions; b) Frequency of HPV infection in ASCUS lesions; c) Regression, stagnation and progression of ASCUS lesion during six-month period.

2. MATERIALS AND METHODS

Prospective study was conducted over a period of 3 years, from January 2012 to December 2014. In private gynecological ambulance „Dr Mahira Jahić“ 1784 PAP tests were examined as routine screening in first year. Patients with ASCUS were reevaluated after local treatment with PAP test and have been monitored in period of one year. ASCUS treatment includes repeated cytology, HPV typization and colposcopy. Protocol of monitoring depended on the result of repeated PAP test. PAP test was normal in 1530 patients and they were advised to make control test once a year. ASCUS was found in 133 patients and 50 of them agreed to be monitored. Analysis of vaginal secretion and HPV typization have been done in these 50 patients and PAP test has been repeated after six months. All cytology samples were screened in the same laboratory. PAP tests were taken by conventional method, colored by method of Papanicolaou and examined with Kruss microscope. Analysis of vaginal discharge was performed from a PAP test and HPV typization-In situ by hybridization of HPV. X² test was used for statistical analysis of data.

3. RESULTS

Analysis of 1784 PAP smears showed normal results and benign cellular changes in 86,6% (N-1530), and abnormal in 13% (N-254) of women. ASCUS was found in 7,4% (N-133) and ASC-H in 0,5% (N-9), LSIL in 4,4% (N-80), HSIL in 1,3% (N-24), CIN II in 1,2% (N-20), CIN III in 0,2% (N-4) (Table 1).

Patients with ASC-H lesion 0,5% (N-9) were trans-

Diagnosis	Number	Percent %
Normal	201	11.2
Benign cellular changes	1329	74.4
ASCUS	133	7.4
ASC-H	9	0.5
L-SIL	80	4.4
H-SIL	24	1.3

Table 1. Results of 1784 PAP tests

ferred to biopsy of cervix and PH results showed 22% (N-2) Carcinoma in situ (CIS), 33% (N-3) CIN II, 22% (N-2) CIN I and 22% (N-2) chronic cervicitis.

25% (N-10) of patients with ASCUS lesion didn't give birth and 70% (N-35) didn't have abortion. 94% (N-47) were married and 6% (N-3) weren't. 14% (N-7) of women used contraception (Table 2). Progression occurred in 18% (9), persistence in 74% (37) and regression in 8% out of 50 women with ASCUS lesion after treatment and repeated PAP test (Table 3). There wasn't progression into

Vital characteristics	N-50
Age	37,6±12,6
Marital status (married/single)	47/3
Number of births	1,26
Number of abortions	0,38

Table 2. Vital characteristics of patients with ASCUS lesion

high grade lesions (HSIL) in this period of time. Bacterial vaginosis has been found in 10% (N-4) of patients with ASCUS and CIN I in 33% (N-3) while patients with normal PAP results didn't have it. Patients with CIN I in 88% (N-7) were positive on HPV of high risk. Patients with persistent ASCUS result were positive in 51% (N-

Total	Normal	ASCUS	CIN I
50	4	37	9
%	8	74	18

Table 3. Results of PAP tests of 50 women with ASCUS lesions after 6 months

19). Grade of lesion was higher with the higher incidence of HPV infection (Table 4). The number of CIN I lesions found in women with ASCUS is bigger and statistically significant (p<0,05) in relation to number of CIN I find-

Cause	Normal/inflammatory result (N-4)	ASCUS (N-37)	CIN I (N-9)
Candida sp.	1 (25%)	8 (21%)	3 (33%)
Mixed bacterial flora	1 (25%)	18 (48%)	3 (33%)
Trichomonas vag.	1 (25%)	7 (18%)	0 (0%)
Bacterial vaginosis	1 (25%)	4 (10%)	3 (33%)
No infection	0 (0%)	0 (0%)	0 (0%)
HPV			
High risk	0 (0%)	19 (51%)	7 (88%)
Absent	4 (100%)	18 (48%)	2 (22%)

Table 4. Distribution of patients (N-50) after repeated PAP test in relation to infection

ings found in regular examinations of 1784 women (Table 5).

4. DISCUSSION

The average age of patients with ASCUS lesion was

Findings	Regular screening (N-1784)	ASCUS (N-50)	Statistical signif.
CIN I	80	9	p<0,05
%	4,4	18	

Table 5. Difference in frequency of CIN I findings in regular screening (N-1784) in relation to repeated ASCUS findings (N-50)

37,6 ± 12,6 years, and frequency of 7.4% is in accordance with data cited in literature (9), but Jahic in her research found ASCUS in 12.9% and CIN I in 5.4% (10). Cytologic diagnosis of ASCUS is 1.7 times more often than frequency of LSIL which was 4.4% of total number of analyzed PAP tests. The category of ASCUS is by far the most commonly reported abnormal cervical cytology interpretation. Lack of specific criteria for the diagnosis of ASCUS results in differences in the incidence of these lesions in works (11). One of the obstacles in the interpretation of cytologic finding is presence of inflammation. Miguel and ass. analyzed 50 cervical and vaginal smears

in which 15 of them, at first, were interpreted as ASCUS and 34 as normal (12). After report using Bethesda criteria for ASCUS, he found changes that associate with the presence of *Candida* sp., and reclassified 10 out of 16 cases as normal findings (13). *Candida* was present in 24% (N-12) of patients provided that in ASCUS lesion was more often 21% (N-8) and 3 women were reevaluated as normal findings. HPV of high risk was positive in 52% (N-26) and negative in 48% (N-24) of patients. Boardman found presence of high risk HPV in 68% of 527 women with ASCUS (14). Other authors state frequency of HPV in ASCUS lesion from 49 to 51% (15) and 46% in CIN I (16). Our study showed similar representation of HPV infection in 51% (N-19) of women with ASCUS. During monitoring, regression was found in 8% (4), persistence in 74% (37) and progression to CIN I in 18% (N-9). Progressions to high grade lesions such as HSIL weren't found in this study, although some authors state it is possible in 7.13%. Frequency of HPV of high risk was bigger with higher grade of lesion. Similar incidence of 20% of CIN I was found in Barcelos' study of analysis of ASCUS and cytologic criteria. Barcelos states that it is necessary to seriously monitor patients with ASCUS lesions. In her monitoring of patients with normal/inflammatory cytology, 85.7% had normal findings after six-months monitoring and one was CIN I, so she recommended that repeated PAP test should be performed in six months time if cytologic diagnosis after ASCUS lesion is normal. Basically, changes that are ASCUS lesion are of low grade but they enable selection of women who should be examined more often because of the possible progression of lesion or possible higher grade of lesion hidden behind this diagnose. Reports say that 10-30% of LSIL and HSIL are diagnosed in women with ASCUS lesion who were monitored (17). Rinku finds cervicitis as a result of biopsy after ASCUS in 11 out of 17 cases, but repeated PAP test after 4-8 months shows ASCUS in all patients. After monitoring in next six months 6 was ASCUS, 2 LSIL and 1 HSIL (18). Persson warns that there will be approximately 30% of women with ASCUS and HPV positive finding for high risk group who will progress to CIN II in period of 3.8 years (19). Castle and ass. advise that patients can get back to regular monitoring procedure if 5-year risk of CIN III is lower than 2%, if the risk is 2-10% they recommend annual monitoring and if it's >10% than colposcopy is obligatory (20, 21, 22). Risk assessment based on genotypization probably won't change clinical management always since the risk of precancerous lesions can be so high that colposcopy should be done immediately (23).

5. CONCLUSION

This study shows the importance of monitoring women with ASCUS lesion, especially HPV positive to high risk group for early detection of lesion that can progress to higher level of change such as cervical cancer. It is statistically significant frequency of CIN I changes in women with ASCUS than in regular screening. This is also the best way of selection of women who should be treated and monitored in order to prevent cervical cancer.

• Conflict of interest: none declared.

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