Progression Low Squamous Intraepithelial Lesion and Human Papillomavirus Infections

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ABSTRACT

Introduction: Infection with human papillomavirus is the main cause of cervical carcinoma. In Bosnia and Herzegovina (BIH) 556 cases of cervical carcinoma are diagnosed annually, and 141 women die from it. Aim: To determine the most common HPV type found in ASCUS and LSIL and progression, regression and persistence of lesions. Methods: In a retrospective study, 11,051 PAP tests, performed in several private gynecological practices located in Tuzla Canton from January 2016 to December 2019, were analyzed. In processing of data, X2 – statistical method was used. Results: 11,051 PAP test were inspected. Normal findings were found in 90.48% (N-10,002) and pathological findings in 9.49% (N-949). ASCUS was present in 4.9% (N-544), LSIL in 3.04% (N-337), HSIL in 0.74% (N-84), ASC-H in 0.27% (N-30) and AGC in 0.49% (N-55) of cases. The most common is HPV 16, found in 50.5% (N-44) of ASCUS and LSIL. Monoinfection with HPV 16 was found in 40.9% (N-3) ASCUS (N-3) and LSIL (N-15), and a combination of HPV 16 with other types like HPV 18, 31, 33, 39 in 59% (N-26). Progression of ASCUS lesion in HSIL 1.6% (N-2), and LSIL 9.6% (N-12). Progression of LSIL to HSIL was found in 9.0% (N-10). HSIL progresses significantly more frequent from LSIL (p<0.05) than from ASCUS changes. Lesions that progress into higher grade HSIL are HPV 16 positive. Progression into HSIL is not found in patients with low-risk HPV 6 and 11 infection. Conclusion: Women infected with HPV 16 have more a frequent progression of a lesion into higher grade HSIL. They should be intensively monitored because of the increased risk for development of cervical carcinoma.

Keywords: Cervical cancer, HPV 16, cervical lesions.

1. INTRODUCTION

Cervical carcinoma is the most common carcinoma in women of the age of 15 to 44. In Bosnia and Herzegovina (BIH) 556 cases of cervical carcinoma are diagnosed annually, and according to the report of ICO/IARC from 2019, 141 women die from it (1).

Human Papillomavirus infection is the main cause of cervical carcinoma. There are at least 15 high-risk HPV types that are significantly connected with progression of squamous intraepithelial lesion (SIL) into cervical carcinoma (2).

The most common high-risk HPV type that causes cervical carcinoma in BIH is HPV 16 in 59.3%, followed by HPV 18 in 8.8%, HPV 33 in 2.7% and HPV 31 in 2% of cases. Low risk HPV 6 and 11 are found in 0.0–1.3% of cases.

Cervical carcinoma can successfully be prevented if the changes that lead to it, like squamous intraepithelial lesion of low (LSIL) and high (HSIL) grade, including obligatory typing of HPV that caused such a change, are discovered in time.

According to the report of the ICO/IARC (HPV Information Centre), BIH has no data from 2019 about frequency of HPV infection in women with abnormal PAP test.

HPV 16 and HPV 18 are high-risk types and their prevalence is over 50% in HSIL and in 80–90% in cervical carcinoma (3). According to the existing literature, progression of ASCUS and LSIL in women that are HPV 16 positive is bigger than in women with same changes that are caused by other HPV high-risk types. Also, progression of lesion with HPV 16 infection is the same whether it is just a HPV 16 infection, or if the HPV 16 is combined with other types (4,5). Data about the frequency of the high-risk
HPV in low grade lesions, like ASCUS and LSIL, can help in establishing a strategy for monitoring and treating women with a high risk of developing cervical carcinoma. Simultaneously, it is a preventive measure against development of a large number of cervical carcinoma found in our country.

2. AIM

The aim of the study is to determine the most common HPV type found in ASCUS and LSIL and progression, regression and persistence of cervical lesions, ASCUS and LSIL, in the most commonly isolated HPV type.

3. PATIENTS AND METHODS

In a retrospective study, 11,051 PAP tests, performed in several private gynecological practices located in Tuzla Canton in a four year period from January 2016 to December 2019, were analyzed. The study was performed in Gynecological Centre "Dr. Mahira Jahic" Tuzla, Gynecological Practice "Dr Blitvic" Tuzla, Gynecological Practice "Prim Zukic" Srebrenik. PAP tests and HPV tests were analyzed using gynecological protocols.

Patients diagnosed with ASCUS and LSIL were reevaluated after local treatment with repeated PAP tests and were monitored in a 1 year period. ASCUS and LSIL management includes repeated cytology, HPV typing and colposcopy. Monitoring protocol depended on findings in repeated PAP test. PAP test was normal in 10,002 patients, so they were advised to do an annual control. ASCUS was found in 544 patients with 127 agreeing to monitoring, and LSIL was found in 337 patients with 111 agreeing to monitoring. In 145 monitored patients with ASCUS and LSIL, HPV typing was done, and after 12 months PAP test was evaluated. All cytological samples were screened in the same laboratory. PAP tests were done by a conventional method, dyed with Papanicolau method and examined by a Kruss microscope. Analysis of vaginal secretion was done by PAP test and HPV typing with HPV in situ hybridization and HPV Genotypes 14 Real-TM Quant (16,18,31,33,39,45,51,56,58,59,66,68).

Gathered data were analyzed using X² test for statistical analysis of data.

4. RESULTS

In total 11051 PAP tests were examined. Normal findings were found in 90.48% (N-10002) and pathological findings in 9.49% (N–1049) of cases. ASCUS occurred in 4.9% (N-544), LSIL in 3.04% (N-337), HSIL in 0.74% (N-84), ASC-H in 0.27% (N-30) and AGC in 0.49% (N-55) of cases (Table 1).

The most common high-risk HPV type in ASCUS and LSIL is HPV 16 in 20.6% (N-18) of women. Monoinfection with HPV 16 was found in 16% (N-15) of women with ASCUS (N-3) and LSIL (N-15), and a combination of HPV 16 with other types (HPV 18, 31, 33, 39) was found in 39% (N-26). The next high-risk type is HPV 18 found in 29.8% (N-26) of cases, that occurs combined with other types, and in a single form was not found in examined women. The next one is HPV 35 found in 24.1% (N-21), and HPV 51 in 16% (N-14). Other types like HPV 39, 45, 51, 56, 66 occur in a significantly smaller number (Table 2).

HPV 6 and 11 that belong to low-risk types are found in 22.9% (N-35) of cases and combined with high-risk types in 14.9% (N-13) of cases.

In 544 patients with ASCUS lesions, 22.7% (N-124) were monitored. HPV typing was done in 27.4% (N-34). In 50% (N-17) of patients, HPV was positive, and in 50% (N-17 HPV) negative.

Progression of ASCUS lesion in HSIL was found 1.6% (N-2) women with 1-HPV 16 and 1-HPV 16, 18, while progression of LSIL was found in 9% (N-10): 5-HPV 16, 4-HPV 16,18, 1-HPV Negative (Table 5).

Progression of ASCUS in HSIL was found significantly more frequent from LSIL (p<0.05) than from ASCUS changes. Lesions that progress into higher grade HSIL are HPV 16 positive. Regression of a lesion into normal findings is more frequent in ASCUS changes in 30.6% with 10.5% HPV 16 positive.

### Table 1. Results of PAP tests

| HPV type      | ASCUS | LSIL | Total | %  | P<0.05 |
|---------------|-------|------|-------|----|--------|
| 6,11,16,18    | 2     | 6    | 8     | 9.1| no     |
| 6,11,16,18,31,33 | 0   | 3    | 3     | 3.4| no     |
| 16,18         | 4     | 10   | 14    | 16.0| no    |
| 31,33         | 0     | 8    | 8     | 9.1| no     |
| 6,11          | 5     | 15   | 20    | 22.9| no    |
| 6,11,31,33    | 0     | 2    | 2     | 2.2| no     |
| 16,39         | 0     | 1    | 1     | 1.1| no     |
| 18,39         | 0     | 1    | 1     | 1.1| no     |
| 31,56,66      | 0     | 1    | 1     | 1.1| no     |
| 39,45         | 0     | 1    | 1     | 1.1| no     |
| 39,66         | 1     | 0    | 1     | 1.1| no     |
| 51,56,66      | 0     | 1    | 1     | 1.1| no     |
| 16            | 3     | 15   | 18    | 20.6| no    |
| 33            | 3     | 5    | 8     | 9.1| no     |

### Table 2. HPV types found in ASCUS (N-17) and LSIL (N-70)

| HPV type      | ASCUS | LSIL | Total | %  | P<0.05 |
|---------------|-------|------|-------|----|--------|
| 6,11,16,18    | 2     | 6    | 8     | 9.1| no     |
| 6,11,16,18,31,33 | 0   | 3    | 3     | 3.4| no     |
| 16,18         | 4     | 10   | 14    | 16.0| no    |
| 31,33         | 0     | 8    | 8     | 9.1| no     |
| 6,11          | 5     | 15   | 20    | 22.9| no    |
| 6,11,31,33    | 0     | 2    | 2     | 2.2| no     |
| 16,39         | 0     | 1    | 1     | 1.1| no     |
| 18,39         | 0     | 1    | 1     | 1.1| no     |
| 31,56,66      | 0     | 1    | 1     | 1.1| no     |
| 39,45         | 0     | 1    | 1     | 1.1| no     |
| 39,66         | 1     | 0    | 1     | 1.1| no     |
| 51,56,66      | 0     | 1    | 1     | 1.1| no     |
| 16            | 3     | 15   | 18    | 20.6| no    |
| 33            | 3     | 5    | 8     | 9.1| no     |
HPV is found in ASCUS lesions in 50% and LSIL in 63% of cases. High-risk HPV is significantly more frequent to be found as the lesion grows. The percentage of representation of HPV is significantly more frequent in HSIL (90% to 100%). Untreated LSIL can progress in 13% of cases to HSIL during 2 years of monitoring (9,10). Women infected with HPV 16 have a transition of LSIL into HSIL in 9% of cases. We found a progression from ASCUS to HSIL in 1.6% (N-2) and LSIL in 9.6% (N-12). With similar researches during a 12-month period, a progression of ASCUS in LSIL and HSIL was monitored and found that a progression in LSIL occurs in 15.6% (N-11) and in HSIL in 2.5% (N-2) of cases (11). Results with a somewhat bigger percentage of progression were found by Barken, who states that 13% to 16% of untreated LSIL progresses into cervical carcinoma (12). Regression of HPV infection can occur spontaneously, but in 10-20% of women that infection persists and these women have a risk of developing LSIL, HSIL or cervical carcinoma (13). Monitoring data of untreated ASCUS and LSIL lesions state that LSIL regresses in 28.9%, and ASCUS in 29.8%. LSIL persists in 52.6%, and ASCUS in 58% of cases (14).

During analysis we found the persistence of ASCUS in 58%, a regression in 50.6% of cases. Persistence of LSIL was found in 64%, regression in 26%, ASCUS in 12.6% and normal findings in 13.6% of cases. In his study, Cortes found a bigger spontaneous regression of LSIL in 50% and a smaller progression of HSIL in 6% of cases during two years of monitoring. Other authors also found a bigger regression of LSIL in 57%, and a smaller persistence than ours in 32%, while progression to HSIL in 11% was similar to ours (15,16). A few authors wrote about a big regression of medically untreated LSIL (17,18,19).

From the above mentioned data, progression is higher in women with HPV 16 and LSIL than in women with ASCUS and HPV 16, but regression is faster in HPV negative women with ASCUS and LSIL than in HPV 16 positive.

Progression of lesions, ASCUS and LSIL, into HSIL did not occur in patients with low-risk HPV 6 and 11 infection.

5. DISCUSSION

The nature of history of cervical cancer contains reversible changes in the cervix tissue, in which there are no neoplastic changes in squamous epithelial, to different grades of abnormal changes in cells that conditionally lead to cervical carcinoma. Risk factors for progression of ASCUS and LSIL changes, that lead to a higher grade HSIL, are connected with high-risk HPV 16. Namely, many researches confirm a high percentage of HPV 16 in cervical carcinoma, so accordingly, ASCUS and LSIL can progress into a HSIL and invasive cervical carcinoma, or can regress to normal findings, depending on numerous factors, most important being a HPV 16 infection (6). Our research showed that HPV 16 is the most common type of virus found in ASCUS and LSIL in 50.5% of cases. HPV 16 is found in a single form in 40.9% (N-18) women with ASCUS (N-3) and LSIL (N-15), and combined with other high-risk types HPV 18, 31, 33, 39 in 59% (N-26). In researches HPV 16 and 18 were confirmed in over 70% of cervical cancers, 41% to 67% HSIL, 16% to 32% LSIL. HPV 16 and 18 are the most common types, followed by: HPV 31, 33, 45, 52 and 58 that are found in 20% of cervical carcinoma in the world (7,8).

Nicolas states that 52% ASCUS, LSIL 61%, and HSIL 71% are HPV positive (6). Manos finds 40 to 50% HPV in ASCUS, which is in accordance to our results, which are the positive

6. CONCLUSION

Women infected with HPV 16 have more a frequent progression of a lesion into higher grade HSIL. They should be intensively monitored because of the increased risk for development of cervical carcinoma.

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