

Cytological versus histological results in ASCUS cervical dysplasia – a retrospective study

Cytologické verzus histologické nálezy pri ASCUS cervikálnej dysplázii – retrospektívna štúdia

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Summary: Aim: The cytological category of atypical squamous cells of undetermined significance describes cellular abnormalities that are more severe than inflammatory changes, but are quantitatively or qualitatively insufficient to be included in the squamous intraepithelial lesion category. This study aims to determine the risk level for the presence of high-grade dysplasia in patients with this cytological abnormality.

Methods: We retrospectively searched our database for women with cytologically proven atypical squamous cells of undetermined significance lesions between January 2020 and June 2024. A total of 104 patients who had undergone colposcopy-directed biopsies were included in the study.

Results: Among the 104 women with confirmed atypical squamous cells of undetermined significance cytological lesions who had undergone biopsies, 56 cases (53.8%) were negative, while 48 cases (46.2%) demonstrated cervical intraepithelial neoplasia. Cervical intraepithelial neoplasia 2+ was present in 23.1% (N = 24) of the cases. Furthermore, among 77 human papillomavirus positive women, the precancerous condition was not histologically confirmed in almost half of the cases (N = 36), while in 16 of the 23 human papillomavirus negative biopsies, the precancerous condition was not confirmed. Human papillomavirus status was unknown in 4 cases. **Conclusion:** We identified a 23.1% presence of cervical intraepithelial neoplasia 2+ lesions in patients with atypical squamous cells of undetermined significance cytological findings. Our study also suggests a lower specificity, but a better negative predictive value of the human papillomavirus test in detecting cervical intraepithelial neoplasia in these patients.

Key words: ASCUS – human papillomavirus – cervical dysplasia

Súhrn: Cieľ: Cytologická kategória atypických skvamózných buniek neurčitého významu zahŕňa bunkové abnormality, ktoré sú viac závažné ako zápalové zmeny, avšak sú nedostatočné na zaradenie do kategórie skvamózných intraepitelových lézií. Táto práca je zameraná na určenie miery rizika prítomnosti high-grade dysplázie cervixu u žien s touto cytologickou abnormalitou. **Metodika:** Retrospektívne boli zozbierané dáta od žien s cytologickým nálezom atypických skvamózných buniek neurčitého významu, ktoré podstúpili kolposkopické vyšetrenie medzi januárom 2020 až júnom 2024. Celkovo 104 pacientok, ktoré podstúpili kolposkopicky navigovanú biopsiu, bolo zaradených do štúdie.

Výsledky: Medzi 104 biotickými vzorkami cervixu od pacientok s cytologickým nálezom atypických skvamózných buniek neurčitého významu bol histologický výsledok v 56 prípadoch (53,8 %) negatívny na prítomnosť prednádorových zmien. V 48 prípadoch (46,2 %) bola potvrdená cervikálna intraepitelová neoplázia, pričom v 23,1 % (n = 24) bola potvrdená cervikálna intraepitelová neoplázia 2+. Zároveň medzi 77 pozitívne testovanými ženami na prítomnosť vysokorizikových typov ľudského papilomavírusu neboli prednádorové zmeny krčka maternice histologicky potvrdené takmer v polovici prípadov (n = 36), zatiaľ čo medzi 23 ženami negatívne testovanými na prítomnosť vysokorizikových typov ľudského papilomavírusu neboli prednádorové zmeny potvrdené v 16 prípadoch. V 4 prípadoch nebol výsledok testovania na prítomnosť vysokorizikových typov ľudského papilomavírusu známy. **Záver:** Práca poukazuje na 23,1% mieru prítomnosti cervikálnej intraepitelovej neoplázie 2+ u žien s cytologickým nálezom atypických skvamózných buniek neurčitého významu. Zároveň naznačuje možnú nižšiu špecifitu, ale vyššiu mieru negatívnej prediktívnej hodnoty testu na prítomnosť vysokorizikových typov ľudského papilomavírusu pri detekcii prednádorových zmien u žien s touto cytologickou abnormalitou.

Kľúčové slová: ASCUS – ľudský papilomavírus – cervikálne dysplázie

Introduction

The terminology of human papillomavirus (HPV) – associated diseases of the lower anogenital tract has changed in the last 120 years as a result of changes in the understanding and treatment strategies of these diseases [1]. Mucosal cervix lesions were first described by Sir John Williams in 1888 [2]. Subsequently, terms such as “surface carcinoma,” “intraepithelial carcinoma,” and later “carcinoma *in situ*” (CIS) were included in the terminology [3]. In 1952, Reagan identified atypical hyperplasia in cervical lesions, whose histological features did not fulfill the criteria for CIS [4]. According to the description of cervical carcinogenesis as a continuous process from mild dysplasia to cervical cancer [5], the term cervical intraepithelial neoplasia (CIN) was introduced into the terminology [6]. Later, the Bethesda System replaced three levels of CIN with two levels of squamous intraepithelial lesion (SIL): low-grade SIL (LSIL) and high-grade SIL (HSIL) [7].

The atypical squamous cells (ASC) category, as part of the 2014 Bethesda System for Reporting Cervical Cytology [8,9], is divided into atypical squamous cells of undetermined significance (ASCUS) and atypical squamous cells that cannot exclude a high-grade squamous lesion (ASC-H). The ASC-H category is associated with a higher risk of high-grade lesions than ASCUS, while ASCUS accounts for more than 90% of ASC cases [10]. The ASCUS category describes cellular abnormalities that are more severe than inflammatory changes but are quantitatively or qualitatively insufficient to be included in the SIL category. ASCUS cells show enlargement of the nucleus with possible variations in its shape and mild hyperchromasia, with predominantly smooth and regular outlines of the nucleus. The differential diagnosis of this cytology finding is between benign change and LSIL [11]. On the other hand, ASCUS cytological diagnosis may conceal high-grade lesions,

with the risk of immediate CIN2+ presence being less than 0.1% in HPV-negative women and 13.5% in high-risk HPV-positive patients. This data refers to a group of 25- to 65-year-old women with an unknown previous history of HPV testing and cytology [12].

Methods

The aim of this paper is to describe the risk of immediate CIN2+ lesion presence in ASCUS patients examined at the colposcopy, as we noticed a significant number of high-grade biopsy results in this cytological category. We also evaluated HPV status, transformation zone (TZ), and menopausal status as factors that can affect biopsy results.

The pathology database was searched retrospectively for women who were referred by an outpatient gynecologist to the Department of Gynecology and Obstetrics, Jessenius Faculty of Medicine in Martin, Comenius University in Bratislava, and University Hospital Martin with cytologically proven ASCUS lesions. The patients underwent colposcopic examination from January 1, 2020, to June 30, 2024. Women who were pregnant, immunosuppressed, or had a history of treatment for cervical cancer or its precursors were excluded. Only patients who had undergone a biopsy were included in the study. Cervical cytology was performed using either a liquid-based cytology technique or conventional Papanicolaou staining. The Cobas® HPV Test was used to identify HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68). Colposcopy was performed routinely with 5% acetic acid and Schiller's test. A colposcopy-directed, lesion-targeted punch biopsy was performed from the area of the identified lesion. In ten cases, the histological diagnosis was determined from cervical conization or endocervical curettage, as colposcopy-guided biopsy was not performed because of a TZ type III. CIN classification was determined after hematoxylin and eosin staining of the cervical tissue.

Results

The age range of the study group was 20 to 72 years. There were 104 women with a demonstrated ASCUS cytological lesion: 77 were HPV positive, 23 were HPV negative, and the HPV status was unknown in 4 cases. We divided the patients with HPV-positive tests into five categories according to the identified HPV types. HPV16 infection was confirmed in 17 cases, HPV18 infection in 3 cases, and infection with other high-risk HPV types in 35 cases. Four women were simultaneously infected with HPV16 and one or more other high-risk HPV types, excluding HPV18. In 18 cases, high-risk HPV infection was confirmed, but the specific HPV type was unknown. Twenty-three women were HPV negative, and in 4 cases, the HPV status was unknown (Tab. 1).

Biopsies were performed on all 104 patients. Of these, 56 cases (53.8%) were negative, while 48 cases (46.2%) demonstrated CIN. Among those with histologically proven precancerous changes, CIN1 was identified in 24 patients. CIN2+ was defined as CIN2 lesions or worse, with dysplastic cells not extending beyond the basal membrane. This degree of intraepithelial changes was observed in 24 cases, representing 23.1% of the examined women. CIN2 was demonstrated in 7 patients, and in one patient, it was not possible to categorize the CIN2+ lesion from the examined sample. In the remaining 16 patients, the biopsy showed CIN3/CIS, with all mentioned HPV categories present in this group (Tab. 1).

We also evaluated the relationship between the biopsy results and the cervical TZ, since the type of TZ can also affect the biopsy results. Colposcopic examination showed TZ type 1 in 54 patients, TZ type 2 in 18 women, and TZ type 3 in 27 cases. In the remaining 5 patients, the TZ was not evaluated. In the TZ 1 group, biopsy confirmed precancerous changes in 26 cases, while 28 biopsies were negative for SIL. In the TZ 2 group, 9 samples

Tab. 1. Biopsy results in relation to HPV testing results.

Tab. 1. Výsledky biopsie vo vzťahu k výsledkom testovania HPV.

	Biopsy – negative (N = 56)	Biopsy – CIN1 (N = 24)	Biopsy – CIN2+ (N = 24)
HPV other HR positive (N = 35)	20 (19.2%)	9 (8.7%)	6 (5.8%)
HPV16 positive + HPV other HR positive (N = 4)	2 (1.9%)	0 (0%)	2 (1.9%)
HPV16 (N = 17)	8 (7.7%)	3 (2.9%)	6 (5.8%)
HPV18 (N = 3)	1 (1.0%)	1 (1.0%)	1 (1.0%)
HPV HR positive (unknown type) (N = 18)	5 (4.8%)	6 (5.8%)	7 (6.7%)
HPV negative (N = 23)	16 (15.4%)	5 (4.8%)	2 (1.9%)
HPV unexamined (N = 4)	4 (3.8%)	0 (0%)	0 (0%)

CIN – cervical intraepithelial neoplasia, CIN2+ – CIN2 lesion and worse, dysplastic cells not extending beyond the basal membrane, HPV – human papillomavirus, HPV other HR positive – other high-risk HPV types than HPV 16 and 18

were positive and 9 negative for pre-cancerous changes. Finally, in women with TZ type 3, 8 cases had a positive histology results for CIN presence, and 19 cases it was negative. The biopsy results were distributed similarly in the TZ 1 and TZ 2 groups, while negative histological results dominated in the TZ 3 group (Tab. 2). According to menopausal status, biopsy confirmed a precancerous condition in 43 premenopausal, 2 perimenopausal, and 2 postmenopausal patients, while 46 premenopausal, 6 perimenopausal, and 5 postmenopausal women were SIL negative. Menopausal status did not affect the biopsy results in our study.

Discussion

According to Schlecht et al. [13], the majority of ASCUS lesions regressed to normal findings (147/173), while half of them regress within 6 months. The time of regression depends on the HPV type. In the group with oncogenic HPV types, the mean time for regression from ASCUS to normal findings was 16.8 months, while in the group with non-oncogenic HPV types, it was 7.7 months. Additionally, progression from ASCUS to LSIL or worse was shorter in the group with oncogenic HPV types than in HPV-negative women. As Schlecht et al. [13] described, the majority of ASCUS lesions do not progress to HSIL, but some findings may conceal high-grade changes [13].

The available studies demonstrate different rates of CIN in samples from patients with ASCUS. According to Lytwyn et al. [14], more than 10% of colposcopy-guided biopsies of ASCUS patients histologically show CIN of grades 2 and 3 [14]. Hughes et al. [15] showed the presence of high-grade changes in just 3.8% of biopsies in ASCUS patients [15]. In the ALTS clinical trial, the prevalence of histologically confirmed CIN3+ in the ASCUS group was 5%. This study proved HPV triage as a useful tool in the management of these lesions, as cancer-associated HPV DNA testing identified 96% of patients with CIN3+ [16]. Ding et al. [17] also confirmed the high value of HPV testing in ASCUS patients. In their study, HSIL or worse lesions of the cervix were significantly higher in the group with HPV16 infection (52.3% of cases) compared to women with other types of HPV infection (17.9% of cases). Furthermore, this study pointed out colposcopy guided punch-biopsy and hrHPV status as efficient tools in the immediate identification of high-grade lesions among women with ASCUS [17].

We also suggest biopsy as a method that can improve the immediate detection rate of precancerous conditions among women with ASCUS, given a 46.2% risk of CIN (48/104). The HPV test was positive for hrHPV in 85.4% of cases of biopsy-proven CIN (41/48). On the other hand, in the biopsy-negative

Tab. 2. Biopsy results and type of transformation zone.

Tab. 2. Výsledky biopsie a typ transformačnej zóny.

	TZ 1	TZ 2	TZ 3
Positive biopsy	26	9	8
Negative biopsy	28	9	19

TZ – transformation zone, negative biopsy – tissue negative for dysplasia, positive biopsy – tissue positive for dysplasia

group, there were 4 patients without an HPV infection examination, and in the rest of the biopsy-negative group, 64.3% of the patients were HPV positive (36/56), while only 16 patients were HPV negative. This suggests that the HPV test alone is not sufficiently specific to suspect the presence of CIN in women with ASCUS cytology, also considering the fact that only 16 patients in the group with a negative biopsy and HPV positivity were younger than 30 years, among whom HPV infection is common. The study by Fleider et al. [18] showed a 98.7% sensitivity of the Cobas® test, while specificity was 87.2% [18].

Ortashi et al. [19] reported a prevalence of only 0.8% for high-grade CIN in patients with ASCUS, and a 26% chance of having high-grade CIN in ASC-H patients [19]. In our study, CIN2+ lesions were present in almost one-quarter of women with ASCUS (24/104). Ortashi et al. [19] also observed no high-grade

CIN in patients with a negative HPV test, whereas in our study, two patients with a negative HPV test showed CIN2+.

Desteli et al. [20] studied histological samples from 115 women with ASCUS cytology. They found cervicitis in 49 cases (42.6%), CIN1 in 40 cases (34.8%), CIN2 in 15 cases (13.0%), and CIN3 in 11 cases (9.6%) [20]. Our results also indicate a higher number of histologically proven CIN, confirmed in 46.2% (N = 48) of the ASCUS patients.

A multicenter retrospective study reported the results of cervical biopsies in 1,390 patients with ASCUS cytology. The most frequently identified histological finding was a negative biopsy for precursor changes, followed by CIN1 in 38.2% of the cases, CIN2 in 31.4% of the cases, CIN3 in 17.7% of the cases, and cervical carcinoma in 8.6% of the cases. Interestingly, the same representation of patients with histologically proven cervical cancer was also observed in the group with a cytological finding of ASC-H [21]. In our cohort of ASCUS patients, CIN1 was confirmed in 23.1% (N = 24), CIN2 in 6.7% (N = 7), and CIN3/CIS in 15.4% (N = 16) of the cases. In one case, the histologically verified high-grade lesion was not precisely classified within the CIN categories.

Our study highlights the important role of colposcopic examination and biopsy in patients with ASCUS lesions. CIN2+ lesions were detected in 23.1% of the cases, necessitating surgical treatment. A well performed colposcopy is valuable not only for colposcopy-guided biopsies but also for the colposcopic examination itself. This work points to the importance of colposcopic examination and biopsy in patients with ASCUS lesions. Another essential component in the management of ASCUS is HPV testing, including HPV typing and p16/Ki67 dual-staining. While our results do not demonstrate the significance of HPV typing, this may be due to unclear HPV typing in a large number of examined patients. This necessitated

dividing the patient group into 7 categories based on the HPV test results. With such a broad division in a cohort of 104 patients, the significance of the HPV test might not be fully apparent. Overall, 77 women were HPV-positive, but 47.8% (N = 36) of the HPV-positive patients did not have a histologically confirmed precancerous condition. Conversely, in the group of 23 HPV-negative patients, 16 biopsied cases did not show a precancerous condition. This suggests a better negative predictive value for HPV testing, although our cohort is too small to draw definitive conclusions. This is in line with the findings of Petry et al. [22], who demonstrated a 100% negative predictive value of HPV-DNA testing for CIN2+ lesions [22], and with those of Fleider et al. [18], who reported a 98.5% negative predictive value of HPV testing for the detection of cervical cancer and preneoplastic lesions of the cervix [18].

As mentioned above, our results indicate a lower specificity of the HPV test in detecting CIN in patients with ASCUS but a better negative predictive value. This is consistent with the study by Wang et al. [23], which describes how the negative predictive value and specificity of the test move in opposite directions [23].

Our study also highlighted a higher rate of negative cervical biopsies for precancerous changes in patients with TZ 3, while in women with TZ 1 and TZ 2, the distribution of negative and positive biopsies was nearly the same. Menopausal status did not have a significant impact on the biopsy results. In addition to the small sample size, another limitation of our study is its retrospective nature. The results of a biopsy obtained during colposcopy can also be influenced by the experience and skill level of the examining colposcopist. These are making additional examinations such as HPV testing, p16/Ki67 dual-staining, colposcopy, and colposcopy-guided biopsy essential for the management of patients with ASCUS cytology finding [24].

Conclusion

The cytological finding of ASCUS presents a management challenge compared to HSIL lesions, for which the operative procedure is clearly defined. The uncertainty arises from the indeterminate significance of the atypical cells. Our study highlights the potential presence of high-grade cervical dysplasia hidden behind the ASCUS cytological finding, demonstrating a prevalence of up to 23.1% for CIN2+ lesions in these patients. This underscores the complexity of diagnosing ASCUS, while our results also indicate a lower specificity but a better negative predictive value of the HPV test in detecting CIN in patients with ASCUS.

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List of all abbreviations

ASC – atypical squamous cells
 ASC-H – atypical squamous cells that cannot exclude a high-grade squamous lesion
 ASCUS – atypical squamous cells of undetermined significance
 CIN – cervical intraepithelial neoplasia
 CIN2+ – CIN2 lesions or worse, with dysplastic cells not extending beyond the basal membrane
 CIS – carcinoma *in situ*
 DNA – deoxyribonucleic acid
 HPV – human papillomavirus
 HSIL – high-grade squamous intraepithelial lesion
 LSIL – low-grade squamous intraepithelial lesion
 SIL – squamous intraepithelial lesion
 TZ – transformation zone

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