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CLINICAL & BASIC RESEARCH

Interpreting a Diagnosis of Atypical Squamous Cells of Undetermined Significance in Cervical Cytology and its Association with Human Papillomavirus

A retrospective analysis of 180 cases in Kuwait

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تفسير تشخيص الخلايا الحرشفية اللانمطية غير محددة الدلالة في شريحة خلايا عنق الرحم وارتباطها بفيروس الورم الحليمي البشري

تحليل استعادي لـ 180 حالة في الكويت

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ABSTRACT: ***Objectives:*** Atypical squamous cells of undetermined significance (ASC-US) represent a diagnostic challenge during cervical cytology. This study aimed to review and identify high-risk human papillomavirus (HR-HPV) genotypes among previously diagnosed ASC-US cases in Kuwait. ***Methods:*** This retrospective study analysed 180 cases diagnosed as ASC-US between June 2017 and May 2018 at the Mubarak Al-Kabeer Hospital, Kuwait. Cervical specimens were assayed to determine the presence of HR-HPV DNA; subsequently, positive cases underwent genotyping and were categorised into three groups (HPV 16, HPV 18/45 and other HR-HPV types). ***Results:*** In total, ASC-US was confirmed in only 105 cases (58.3%), with the remaining cases reclassified as negative for intraepithelial lesions or malignancy (NILM; 32.2%) and epithelial cell abnormalities (ECA; 9.4%). Of these, HR-HPV DNA was present in 20 ASC-US (19%), one NILM (1.7%) and six ECA (35.3%) cases. There were 62 Kuwaiti and 43 non-Kuwaiti women with confirmed ASC-US; of these, three (4.8%), six (9.7%) and four (6.5%) Kuwaitis and one (2.3%), one (2.3%) and five (11.6%) non-Kuwaitis had HPV 16, both HPV 16 and 18/45 and other HR-HPV genotypes, respectively. Of those with HR-HPV DNA, the NILM case had the HPV 18/45 genotype, while the six ECA cases had the HPV 16 (n = 1), both HPV 16 and 18/45 (n = 1) and other HR-HPV (n = 4) genotypes. ***Conclusion:*** Overall, HR-HPV DNA was present in 19% of ASC-US cases compared to 1.7% of NILM cases initially misdiagnosed as ASC-US. Re-review of cervical cytology diagnoses may reduce unnecessary costs associated with HR-HPV genotyping.

Keywords: Cervical Smears; Atypical Squamous Cells of Undetermined Significance; Human Papilloma Virus; Cytological Techniques; Papanicolaou Test; Kuwait.

الملخص: الهدف: تمثل الخلايا الحرشفية اللانمطية ذات الدلالة غير المحددة (ASC-US) تحديًا تشخيصيًا أثناء دراسة مسحات عنق الرحم. هدفت هذه الدراسة إلى مراجعة وتحديد الأنماط الجينية عالية الخطورة لفيروس الورم الحليمي البشري (HR-HPV) بين حالات ASC-US التي تم تشخيصها سابقًا في الكويت. **الطريقة:** حللت هذه الدراسة بأثر رجعي 180 حالة تم تشخيصها على أنها ASC-US بين يونيو 2017 ومايو 2018 في مستشفى مبارك الكبير، الكويت. تم فحص عينات عنق الرحم لتحديد وجود الشيفرة الوراثية (DNA) لفيروس الورم الحليمي البشري. بعد ذلك، تم تصنيف الحالات الإيجابية جينيا إلى ثلاث مجموعات (HPV 16 و HPV 18/45 وأنواع أخرى من HR-HPV). **النتائج:** في المجموع، تم تأكيد ASC-US في 105 حالة فقط (58.3%)، مع إعادة تصنيف الحالات المتبقية على أنها سلبية للآفات داخل الظهارة أو الأورام الخبيثة (NILM؛ 32.2%) وتشوهات الخلايا الظهارية (ECA؛ 9.4%). من بين تلك، كان DNA HR-HPV موجودًا في 20 US-ASC (19%) ، وحالة NILM واحدة (1.7%) وست حالات ECA (35.3%). كانت هناك 62 امرأة كويتية و 43 امرأة غير كويتية لديهن حالات مؤكدة من ASC-US؛ من هؤلاء، ثلاثة (4.8%) وستة (9.7%) وأربعة (6.5%) كويتيون وواحد (2.3%) وواحد (2.3%) وخمسة (11.6%) من غير الكويتيين لديهم فيروس الورم الحليمي البشري 16، وكل من HPV 16 و 18/45 والأنماط الجينية الأخرى HR-HPV، على التوالي. من بين الذين لديهم DNA HR-HPV، كانت حالة NILM تحتوي على النمط الوراثي HPV 18/45، في حين أن حالات ECA الست كانت تحتوي على واحد من HPV 16 وواحد من HPV 16 و 18/45 وأربعة من HR- فيروس الورم الحليمي البشري من الأنماط الجينية. **الخلاصة:** بشكل عام، كان HR-HPV DNA موجودًا في 19%من حالات ASC-US مقارنة بـ 1.7% من حالات NILM التي تم تشخيصها بشكل خاطئ في البداية على أنها ASC-US. قد تؤدي إعادة مراجعة تشخيص الخلايا العنقية إلى تقليل التكاليف غير الضرورية المرتبطة بالتنميط الجيني HR-HPV.

الكلمات المفتاحية: مسحات عنق الرحم؛ الخلايا الحرشفية اللانمطية ذات الدلالة غير المحددة؛ فيروس الورم الحليمي البشري؛ تقنيات الخلايا؛ اختبار بابانيكولاو الكويت.

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Advances in Knowledge

- *This study identified the prevalence of high-risk human papillomavirus (HR-HPV) genotypes in cervical smears previously diagnosed as atypical squamous cells of undetermined significance (ASC-US) in Kuwait. Despite the relatively high incidence of epithelial cell abnormalities, few studies on this topic have been conducted in the Gulf Cooperative Council region.*
- *The current study found that only 58.3% of previously diagnosed cases of ASC-US were confirmed retrospectively. Moreover, HR-HPV genotypes were found in 19% of confirmed ASC-US cases compared to only 1.7% of normal cases initially misdiagnosed as ASC-US.*

Application to Patient Care

- *The findings of this study indicate that the re-review of ASC-US cases is important, not only to avoid potential misdiagnosis and causing unnecessary emotional distress for the patient, but also to determine which cases warrant further HR-HPV typing, a needless expense in low-risk cases.*

The presence of atypical squamous cells on cervical smears represents a diagnostic challenge for both pathologists and clinicians.[1] According to the revised Bethesda classification system, cervical epithelial abnormalities are categorised as either atypical squamous cells of undetermined significance (ASC-US), atypical squamous cells without ruling out a high-grade lesion (ASC-H), low-grade squamous intraepithelial lesions (LSIL), high-grade squamous intraepithelial lesions (HSIL) or squamous cell carcinomas.[2] Under this system, a diagnosis of ASC-US is issued when the cervical epithelial cells demonstrate cytological changes suggestive of a squamous intraepithelial lesion, but without definitive qualitative or quantitative confirmation.[3] Despite the existence of these diagnostic criteria, accurate identification of ASC-US cases remains difficult, thus resulting in high rates of misdiagnosis and overinterpretation during cervical cytology screening.[1,3]

In humans, the vast majority of cases of cervical cancer are linked to human papillomavirus (HPV) infections.[4] As such, HPV testing is highly recommended for patients diagnosed with ASC-US in order to determine whether further follow-up, in the form of an urgent colposcopy, is necessary.[5] There are over 100 different HPV genotypes, of which approximately 40 are known to infect the genital tract; of these, 18 are believed to play a significant role in the pathogenesis of cervical cancers, most commonly types 16, 18 and 45.[6] These variants are therefore considered to represent high-risk HPV (HR-HPV) genotypes.[4,6]

Few studies have sought to assess the spectrum of HR-HPV genotypes among women in Gulf Cooperation Council (GCC) countries, which differ significantly from those reported elsewhere in the world likely as a result of racial diversity.[7–11] For instance, previous research indicates that HR-HPV genotypes in Kuwait mostly consist of types other than 16, 18 and 45.[8] Similarly, Ali *et al*. showed that HR-HPV types other than 16 and 18 were most prevalent in GCC countries.[7] This study aimed to review previously diagnosed ASC-US cases at a hospital in Kuwait to determine the rate of overinterpretation as well as to identify the prevalence of specific HR-HPV genotypes among Kuwaiti and non-Kuwaiti women.

Methods

This retrospective study reviewed 180 cases diagnosed as ASC-US between June 2017 and May 2018 at the Mubarak Al-Kabeer Hospital, Kuwait. Cytological data from ThinPrep® cervical smears (Hologic Corp., Bedford, Massachusetts, USA) were retrieved from the files of the cytology laboratory. Each case underwent blinded peer-review by two pathologists and one senior cytotechnician to confirm or correct the initial ASC-US diagnosis. Cases were classified using the 2014 revised Bethesda system as either negative for intraepithelial lesions or malignancy (NILM), ASC-US, atypical glandular cells (AGC), LSILs or HSILs.[2]

Subsequently, the cervical samples were assayed to determine the presence of HR-HPV DNA. The assay technique was conducted using the Panther system of the Aptima™ HPV Assay (Hologic Corp.). Samples from the ThinPrep® vials were transferred to the Aptima™ transfer tube in order to capture, amplify, detect and report specific HR-HPV E6/E7 messenger ribonucleic acid transcripts. Cases were then categorised as either HR-HPV-positive (relative light unit/cut-off [RLU/CO] of ≥0.5) or HR-HPV-negative (RLU/CO of <0.5). Subsequently, the Aptima™ HPV 16 18/45 Genotype Assay (Hologic Corp.) was used to detect HR-HPV 16 and 18/45 genotypes in HR-HPV-positive cases.

Based on the results of the assay, HR-HPV-positive cases were subdivided into the following categories: (1) positive for HPV 16; (2) positive for HPV 18/45; (3) positive for both HPV 16 and 18/45; or (4) negative for both HPV 16 and 18/45. For the latter category, the absence of both HPV 16 and 18/45 genotypes was considered to imply the presence of other HR-HPV genotypes, given the HR-HPV-positive findings observed during the initial assay. For

Table 1: Reclassification of and prevalence of human papillomavirus genotypes among cervical cytology cases previously diagnosed as atypical squamous cells of undetermined significance (N = 180)

Reclassification	HPV status, n (%)						
	Total	Negative	Type 16	Type 18/45	Types 16 and 18/45	Other	Unknown*
NILM	58 (32.2)	56 (96.6)	0 (0)	1 (1.7)	0 (0)	0 (0)	1 (1.7)
ASC-US	105 (58.3)	84 (80)	4 (3.8)	0 (0)	7 (6.7)	9 (8.6)	1 (1)
AGC	7 (3.9)	7 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
ASC-US and AGC	2 (1.1)	2 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
LSIL	6 (3.3)	2 (33.3)	1 (16.7)	0 (0)	1 (16.7)	2 (33.3)	0 (0)
HSIL	2 (1.1)	0 (0)	0 (0)	0 (0)	0 (0)	2 (100)	0 (0)
Total	180 (100)	151 (83.9)	5 (2.8)	1 (0.6)	8 (4.4)	13 (7.2)	2 (1.1)

HPV = human papillomavirus; NILM = negative for intraepithelial lesions or malignancy; ASC-US = atypical squamous cells of undetermined significance; AGC = atypical glandular cells; LSIL = low-grade squamous intraepithelial lesions; HSIL = high-grade squamous intraepithelial lesions.
**Testing not performed.*

Table 2: Reclassification of and prevalence of human papillomavirus genotypes among cervical cytology cases previously diagnosed as atypical squamous cells of undetermined significance in the Kuwaiti group (N = 104)

Reclassification	HPV status, n (%)						
	Total	Negative	Type 16	Type 18/45	Types 16 and 18/45	Other	Unknown*
NILM	36 (34.6)	34 (94.4)	0 (0)	1 (2.8)	0 (0)	0 (0)	1 (2.8)
ASC-US	62 (59.6)	49 (79)	3 (4.8)	0 (0)	6 (9.7)	4 (6.5)	0 (0)
AGC	2 (1.9)	2 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
ASC-US and AGC	2 (1.9)	2 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
LSIL	2 (1.9)	0 (0)	1 (50)	0 (0)	0 (0)	1 (50)	0 (0)
HSIL	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Total	104 (100)	87 (83.7)	4 (3.8)	1 (1)	6 (5.8)	5 (4.8)	1 (1)

HPV = human papillomavirus; NILM = negative for intraepithelial lesions or malignancy; ASC-US = atypical squamous cells of undetermined significance; AGC = atypical glandular cells; LSIL = low-grade squamous intraepithelial lesions; HSIL = high-grade squamous intraepithelial lesions.
**Testing not performed.*

the purposes of statistical analysis, the results of HR-HPV testing were correlated with both the corrected cytological diagnosis (i.e. NILM, ASC-US, AGC, LSIL or HSIL) and nationality (i.e. Kuwaiti or non-Kuwaiti).

This study was conducted in accordance with the Combined Ethics Committee of the Kuwaiti Ministry of Health and the Faculty of Medicine of the Health Science Centre, University of Kuwait. The procedures of the study conformed to the ethical guidelines outlined in the revised Declaration of Helsinki. Informed verbal consent was obtained from all patients.

Results

Of the 180 previously diagnosed ASC-US cases, the original diagnosis was confirmed retrospectively by peer-review in only 105 cases (58.3%). The remaining cases were reclassified as either NILM (n = 58; 32.2%) or epithelial cell abnormalities (ECA; n = 17; 9.4%), with the latter comprising seven AGC (3.9%), six LSIL (3.3%), two HSIL (1.1%) and two ASC-US with AGC (1.1%). Among the 58 NILM cases, only one (1.7%) was HR-HPV-positive; in contrast, HR-HPV DNA was present in 20 ASC-US (19%) and six ECA (35.3%) cases. Overall, the HPV 16, HPV 18/45 and both HPV 16 and 18/45 genotypes were present in five (2.8%), one (0.6%) and eight (4.4%) cases, respectively. The remaining 13 cases (7.2%) were negative for both HPV 16 and 18/45, indicating the presence of HR-HPV variants other than types 16 and 18/45 in these specimens. Only one of the NILM cases (1.7%) and two of the ECA cases (11.8%) demonstrated the common HR-HPV genotypes 16 or 18/45 [Table 1].

Table 3: Reclassification of and prevalence of human papillomavirus genotypes among cervical cytology cases previously diagnosed as atypical squamous cells of undetermined significance in the non-Kuwaiti group (N = 76)

Reclassification	HPV status, n (%)						
	Total	Negative	Type 16	Type 18/45	Types 16 and 18/45	Other	Unknown*
NILM	22 (28.9)	22 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
ASC-US	43 (56.6)	35 (81.4)	1 (2.3)	0 (0)	1 (2.3)	5 (11.6)	1 (2.3)
AGC	5 (6.6)	5 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
ASC-US and AGC	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
LSIL	4 (5.3)	2 (50)	0 (0)	0 (0)	1 (25)	1 (25)	0 (0)
HSIL	2 (2.6)	0 (0)	0 (0)	0 (0)	0 (0)	2 (100)	0 (0)
Total	76 (100)	64 (84.2)	1 (1.3)	0 (0)	2 (2.6)	8 (10.5)	1 (1.3)

*HPV = human papillomavirus; NILM = negative for intraepithelial lesions or malignancy; ASC-US = atypical squamous cells of undetermined significance; AGC = atypical glandular cells; LSIL = low-grade squamous intraepithelial lesions; HSIL = high-grade squamous intraepithelial lesions. *Testing not performed.*

Table 4: Distribution of human papillomavirus genotypes according to nationality among cases with confirmed diagnoses of atypical squamous cells of undetermined significance (N = 105)

Nationality	HPV status, n (%)						
	Total	Negative	Type 16	Type 18/45	Types 16 and 18/45	Other	Unknown*
Kuwaiti	62 (59)	49 (79)	3 (4.8)	0 (0)	6 (9.7)	4 (6.5)	0 (0)
Non-Kuwaiti	43 (41)	35 (81.4)	1 (2.3)	0 (0)	1 (2.3)	5 (11.6)	1 (2.3)
Total	105 (100)	84 (80)	4 (3.8)	0 (0)	7 (6.7)	9 (8.6)	1 (1)

*HPV = human papillomavirus. *Testing not performed.*

In terms of nationality, the specimens originated from 104 Kuwaiti women and 76 women of other nationalities. In the Kuwaiti group, 16 cases (15.4%) were HR-HPV-positive; of these, the HPV 16 genotype was present in four (25%) cases, HPV 18/45 in one (6.3%) and both HPV 16 and 18/45 in six (37.5%). However, five cases (31.3%) were negative for both HPV 16 and 18/45, indicating the presence of other HR-HPV variants [Table 2]. In the non-Kuwaiti group, 11 cases (14.5%) were HR-HPV positive. These included one case (9.1%) with the HPV 16 genotype and two (18.2%) with both HPV 16 and 18/45. Other HR-HPV genotypes were assumed in the remaining eight cases (72.7%) [Table 3].

The diagnosis of ASC-US was confirmed in 62 Kuwaiti and 43 non-Kuwaiti cases. Of these, HR-HPV DNA was present in 13 (21%) and seven (16.3%) cases, respectively. In the Kuwaiti ASC-US group, genotyping for the HPV 16, both HPV 16 and 18/45 and other HR-HPV variants was positive in three (4.8%), six (9.7%) and four (6.5%) cases, respectively. In contrast, genotyping for these types was positive in one (2.3%), one (2.3%) and five (11.6%) cases, respectively, in the non-Kuwaiti ASC-US group [Table 4].

Discussion

The diagnosis of ASC-US depends not only on the identification of well-defined cytological patterns, but also on other more subjective criteria; consequently, reproducibility of the diagnosis upon re-review can vary from <50–67.9%.[1,12] Various studies have shown that a number of factors are related to the overinterpretation of atypical squamous cells including reactive changes due to reproductive tract infections associated with *Trichomonas vaginalis*, *Candida* species and bacterial vaginosis, as well as the presence of intermediate squamous cells with bland nuclear enlargement without chromatin and nuclear abnormalities.[5,13] Moreover, ASC-US diagnoses are reported more frequently in women who are pregnant, lactating and postmenopausal due to the excessive glycogenation of intermediate squamous cells caused by hormones.[5,13] In addition, the presence of immature metaplastic cells, suboptimal fixation, drying artifacts and other age-related changes such as degeneration due to atrophic vaginitis may be mistaken for ASC-US.[5,13,14]

In the current study, all cases previously diagnosed as ASC-US at a Kuwaiti hospital over a one-year period were reviewed retrospectively by three cytologists. Overall, only 58.3% of cases received confirmation of the ASC-US diagnosis, while the remaining cases were reclassified as either NILM (32.2%) or ECA (9.4%). This rate of reproducibility was comparable to that reported in previous research.[1,12] The absence of well-defined cytological criteria, subjectivity of the diagnosis and various other factors may account for the overrepresentation of ASC-US diagnoses in routine reporting.[5,13,14] In general, accurate identification of ASC-US remains a diagnostic dilemna for cytopathologists. Consequently, HPV genotyping is often incorporated to enhance cervical screening. However, this can represent a needless expense due to the high rate of false-positive diagnoses. The authors therefore recommend that ASC-US diagnoses be peer-reviewed prior to reporting in order to decrease costs associated with unnecessary HPV genotyping.

In general, the detection of HR-HPV genotypes is a useful tool to supplement abnormal cytological results. Among patients with ASC-US, the presence of an HR-HPV-positive genotype increases the likelihood of cervical intraepithelial neoplasia (CIN) grades II or III, a precursor to cervical cancer; in contrast, a negative HR-HPV test excludes high-grade CIN.[1] As a result, HR-HPV genotyping is usually recommended for patients with ASC-US.[15] However, the American Society for Colposcopy and Cervical Pathology does not recommend HPV testing be performed for women aged 21–29 years, instead encouraging such individuals to undergo cytological screening only every three years.[16] For women aged 30–65 years, both cytological screening and HPV testing is recommended every five years; alternatively, screening with cytology alone can be performed every three years. In addition, HPV testing is recommended for women with LSIL and as a post-colposcopy follow-up measure for those with abnormal cytology.[16–18] Cases found to be positive for HR-HPV should undergo a colposcopic examination, while those classified as NILM should return for repeated cervical cytology screening within six months.

In the current study, the most common HR-HPV types among HR-HPV-positive patients with confirmed ASC-US were HPV types other than 16 and 18/45 (45%). Few studies have been performed to determine the most prevalent HR-HPV genotypes in the GCC region.[7–11] Ali *et al.* found that types other than HPV 16/18 were the most common genotypes among women residing in Saudi Arabia, Qatar, the United Arab Emirates and Bahrain, followed by type HPV 16.[7] Similarly, Mallik *et al.* reported that the most prevalent HR-HPV genotypes in Kuwait were those other than types 16, 18 and 45.[8] However, Al-Awadhi *et al.* reported contradictory findings indicating that HPV type 16 was most frequent in a cohort of women in Kuwait.[11] In the present study, the most common HR-HPV genotypes among HR-HPV-positive Kuwaiti women regardless of cytological diagnosis were both HPV 16 and 18/45 (37.5%), followed by HR-HPV types other than 16 and 18/45 (31.3%), HPV 16 (25%) and HPV 18/45 (6.3%). Among HR-HPV-positive non-Kuwaiti women, the most prevalent genotypes were HR-HPV types other than 16 and 18/45 (72.7%), both HPV 16 and 18/45 (18.2%) and HPV 16 (9.1%).

Conclusion

The rate of overrepresentation of ASC-US cases at a Kuwaiti hospital over a one-year period was moderately high. In addition, HR-HPV DNA was present in 19% of confirmed ASC-US cases compared to only 1.7% of NILM cases initially misdiagnosed as ASC-US. Therefore, the authors strongly recommend that cytological diagnoses of ASC-US be peer-reviewed for diagnostic confirmation before undergoing HR-HPV genotyping. Careful review of cellular changes by multiple cytologists will increase the diagnostic accuracy of cytology screening, thereby reducing the patient's anxiety as well as the cost of unnecessary HPV genotyping for false-positive cases.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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