

Correlation between atypical colposcopy findings and detection of human papillomavirus (HPV) infection of the uterine cervix

M. Perovic¹, M.D. M.A.; M. Berisavac¹, M.D. Assoc. Professor; N. Kuljic-Kapulica², M.D.; T. Jovanovic³, M.D. Professor

¹Institute of Obstetrics and Gynaecology, University Clinical Centre of Serbia; ²Medical Military Academy, Institute of Microbiology;

³Institute of Microbiology and Immunology, Dept. of Virology, Medical University, Belgrade, (Yugoslavia)

Summary

Reports on the detection of genome human papillomaviruses (HPV) in genital neoplasia differ to a great extent either in the overall prevalence or in the frequency of certain types. The aim of the study was to determine the correlation between the HPV infection and the occurrence of premalignant and malignant diseases of the uterine cervix and to investigate the ratio between clinical features and infection findings starting from the assumption that infection by human papillomaviruses is a key factor in the occurrence of premalignant and malignant disease of the uterine cervix. The investigation was carried out on 48 patients who formed the study group (Group I). Based on suspicious colposcopy findings, a Papanicolaou (Pap) smear and biopsy were performed and a histopathological analysis of the sample was carried out. A cervical smear was done on all the patients for HPV detection and typing. The patients in whom HPV infection was not found formed a control group (C Group). In spite of certain divergences it has not been proved that the ratio between colposcopy findings and HPV type has any statistical importance ($\chi^2 = 3.305$; $p > 0.05$). The distribution of Pap smear results did not show a significant difference with respect to HPV type ($\chi^2 = 0.105$; $p > 0.05$). When the data are analyzed the diagnosis of low-grade squamous intraepithelial lesions (LGSIL) is evident in 20% of the HPV cases whereas it is significantly lower with respect to the group where HPV was not detected (42.5%). Histopathological (HP) findings of a high-grade squamous intraepithelial lesions (HGSIL) in both groups are diagnosed in approximately the same percentage while 6.7% of cancer in situ was registered in the group of HPV positive patients. Based on this it can be concluded that if a diagnosis of LGSIL or HGSIL in particular has been made on the basis of HP findings there is a great probability that the infection was due to one or more joined types of human papillomaviruses.

Key words: Atypical colposcopy findings, HPV

Introduction

Over 70 types of human papillomaviruses (HPV) are known today [1] of which 22 types have the affinity for the anogenital tract [2, 3]. Types 16 and 18 have the greatest oncogenic potential. Reports on their detection in genital neoplasia differ greatly - not only in the overall prevalence but also in the frequency of particular types. The results vary depending on the identification method, geographical area, features of studied populations and presence of other risk factors that contribute to the occurrence of HPV infection.

Human papillomaviruses cannot be propagated in vitro, thus acceptable serologic tests do not exist. Application of immune-cytochemical methods and electronic microscopy detect a viral capsid antigen and viral particles in an unspecific manner only in productive viral infections (as in aculeated condylomas) while the difference between certain types of viruses cannot be ascertained based on characteristic morphological changes. The only method to diagnose HPV and differentiate its types is the detection of viral DNA by applying the techniques of recombinant DNA technology, i.e. DNA -

DNA hybridisation in cervical cells obtained by smears or biopsy [4, 5].

The aim of the study was to determine the correlation between HPV infection and the formation of premalignant and malignant diseases of the uterine cervix and to establish the frequency of the presence or absence of HPV infection in patients with atypical colposcopy findings starting from the initial assumption that infection by human papillomaviruses is a key factor in the occurrence of premalignant and malignant diseases of the uterine cervix.

Material and Methods

The study was carried out at the Institute of Gynaecology and Obstetrics at the Clinical Centre of Serbia (IGA KCS) from January 1998 to September 2000. Forty-eight patients were included and formed the study group (Group I). Based on a suspicious colposcopy finding, a Pap smear and biopsy were performed and a histopathological analysis of the sample was carried out. A cervical smear test was done on all the patients for HPV detection and typing by using the REATECH-"Rembrandt" test (in situ hybridisation - ISH) for HPV screening/typing Kreatech Diagnostics - DIANOVA, the Netherlands.

Revised manuscript accepted for publication August 8, 2001

After individual analysis of the studied parameters and their statistical processing, all parameters were examined with respect to the presence of HPV infection. The patients in whom HPV infection was not detected formed a control group (C group).

For statistical analysis the χ^2 test, Fisher test and Student's t-test were used.

Results

Colposcopy findings

Table 1 shows that in spite of certain divergences the ratio between colposcopy findings and HPV typing was not statistically significant ($\chi^2 = 3.305, p > 0.005$).

In most cases colposcopy findings showed inflammatory changes (27.3% in the C Group and 33.3% in Group I) and the combination of two or more pathological findings (21.2% in the C Group and 33.3% in Group I). (Note: there was a mosaic in all patients in combinations of two or more pathological findings). Table 1 shows that mosaic and papillary condyloma findings were the most frequent.

Papanicolaou (Pap) smear

Table 2 shows that there was not a significant difference in the distribution of Pap smear results with respect to the findings of HPV ($\chi^2 = 0.105; p > 0.05$).

Comparing the studied group of patients as a whole it is significant that the number of patients with a regular

Table 1. — *The ratio between colposcopy and HPV findings.*

Colposcopy findings	HPV findings			
	Negative		Positive	
	N	%	N	%
Inflammatory changes	9	27.3	5	33.3
Papillary condylomas of the uterine cervix	4	12.1	3	20.0
Pointed	2	6.1	2	13.3
Mosaic	9	27.3	0	0.0
Leukoplakia	1	9.1	0	0.0
Atypical vascularisation	1	9.1	0	0.0
Combination of two or more findings	7	21.2	5	0.0
Total	33	100.0	15	100.0

$\chi^2 = 3.305; DF = 2; p > 0.05$

Table 2. — *The ratio between Pap smear results and HPV in studied patients.*

Pap smear results	HPV findings			
	Negative		Positive	
	N	%	N	%
Class II	25	75.7	12	80.0
Class III	8	24.3	3	20.0
Class IV	—	—	—	—
Class V	—	—	—	—
Total	33	100.0	15	100.0

$\chi^2 = 0.105; DF = 1; p > 0.05$

Pap smear was the highest (80%). However, every fifth woman (i.e. 20%) had an unfavourable Pap smear result.

Histopathological (HP) findings

Histopathological findings with respect to HPV types showed certain variations but statistical analysis proved that they were insignificant (Table 3).

The most frequent HP finding was normal chronic cervicitis (40% in Group I and 24.2% in the C Group), then flat condylomata (20% in Group I and 27.3% in the C Group), whereas cervical intraepithelial neoplasia (CIN) II and III was found in 13.3% of Group I and 21% of the C Group. CIN I was present only in the C group in 15.2% whereas carcinoma in situ was evident in 6.7% of Group I.

HPV typing between studied patients was done (Table 4).

Table 3. — *The ratio between HP and HPV findings in studied patients.*

HP results	HPV findings				
	N	Negative		Positive	
		%	N	%	
Chronic cervicitis	8	24.2	6	40.0	
Papillary condylomas of uterine cervix	0	0.0	3	20.0	
LGSIL	9	27.3	3	20.0	
Condyloma (flat)	5	15.2	0	0.0	
CIN I	7	21.0	2	13.3	
HGSIL	0	0.0	1	6.7	
CIN II and III	4	12.1	0	0.0	
Ca in situ	4	12.1	0	0.0	
No findings	4	12.1	0	0.0	
Total	33	100.0	15	100.0	

$\chi^2 = 2.037; DF = 2; p > 0.05$

Table 4. — *HPV typing in studied patients.*

Findings	Number	%
Negative	33	68.8
Positive	15	31.2
6/11	4	8.3
16/18	3	6.3
6/1, 16/18	2	4.2
16/18, 31/33	4	8.3
6/11, 16/18, 31/33	2	4.2
Total	48	100.0

Discussion

Statistical analysis showed that there was no significant difference in distribution between groups of patients with and without HPV infection with respect to colposcopy findings. This means that the presence or absence of HPV infection occurs according to a similar law of probability ($\chi^2 = 3.305; DF = 2; p > 0.05$) (Table 1). When the

importance of criteria are reduced and $p < 0.10$ applied, it can be proven that the probability of the occurrence of HPV infection is significantly greater if colposcopy findings are chronic cervicitis or papillary condyloma. This shows a greater probability for the detection of HPV even in benign findings on the uterine cervix. The table shows that the most frequent colposcopy finding was mosaic. However, this finding did not significantly determine the occurrence of HPV as with a similar probability a positive HPV finding may not necessarily occur. Based on this analysis it can be concluded that a colposcopy finding on its own does not give significant information for the presence of HPV infection. With a margin error of 10% some importance should be given to colposcopy findings of chronic cervicitis and papillary condylomas to an increased probability of HPV occurrence. The results of the study are in agreement with those of other authors that show that a huge percentage of HPV infections can be detected by colposcopy [6]. It also shows the advantages over cytodiagnosis [7], however the presence of HPV infection cannot be diagnosed only on the basis of colposcopic examination [6, 8].

The data on Pap smears were taken in to account in the analysis of predictors, which may indicate the presence of HPV infection. This comparative analysis is given in Table 2. A significantly large number of patients had a normal Pap smear result (Pap II class). When the probability of HPV occurrence is considered from this point of view the statistical analysis shows that the distribution of Pap smear results did not manifest a significant difference in the probability that HPV would occur or not when the Pap smear was normal ($\chi^2 = 0.105$; DF = 1; $p > 0.05$). A similar result is obtained even if the Pap smear is unfavourable. Based on this it can be concluded that Pap smears do not correlate with HPV. This means that a Pap smear is not a significant indicator of the presence or absence of HPV. It is clear that a Pap smear on its own plays an important role in making a diagnosis on the state of the uterine cervix, but the Pap smear results of class III coupled with the occurrence of coilocytolysis, dyskeratosis and multinuclear formations could even indicate HPV infection [9].

Today it is known that HP results do not correlate with HPV types in cases of LGSIL [10, 11]. On the other hand, this study has confirmed that there is a greater correlation between HP results and associated HPV types in HGSIL [11, 12, 13, 14].

Table 3 shows HP findings in which HPV occurred in the control group (without HPV). The analysis of the interrelation of the ratio of this parameter with HPV should demonstrate to what extent the presence or absence of HPV can be detected on the basis of HP findings. It is even more important to establish what the probability is of joint occurrence of certain HPV types and HP findings of low grade squamous intraepithelial lesions (LGSIL) and high grade squamous intraepithelial lesions (HGSIL), i.e. micro invasive or invasive carcinoma. With respect to HPV typing HP findings showed that certain variations exist, but statistical analysis did not

prove their importance ($\chi^2 = 2.037$; DF = 2; $p > 0.05$). When the data are analyzed in the HPV group the diagnosis of LGSIL is evident in 20% of cases whereas it is significantly lower with respect to the group where HPV was not detected (42.5%). HP findings of HGSIL in both groups was diagnosed in approximately the same percentage while 6.7% of carcinoma in situ has been registered in the group of HPV positive patients. Based on this it can be concluded that if a diagnosis of LGSIL or HGSIL in particular has been made on the basis of HP findings there is a great probability that it is due to infection by one or more joined types of human papillomaviruses.

References

- [1] West A. B., Soloway G. N., Lizarraga G. *et al.*: "Type 73 human papillomavirus in esophageal squamous cell carcinoma: a novel association". *Cancer*, 1996, 77, 2440.
- [2] de Villiers E. M.: "Heterogeneity of the human papillomavirus group". *J. Virol.*, 1989, 63, 4898.
- [3] Meisels A., Ivorin C.: "Morphology of lesions of the uterine cervix related to human papillomavirus (TIPY)". *J. Exp. & Clin. Canc. Res.*, 1990, 9, 94.
- [4] Gissman L., de Villiers E. M., zur Hausen H.: "Analysis of human genital warts (condylomata acuminata) and other genital tumors for human papillomavirus type 6 DNA". *Int. J. Cancer*, 1982, 29, 143.
- [5] Lorincz A. T.: "Human papillomavirus detection methods". In: "Sexually Transmitted Diseases", 2nd Ed. (eds.) Holmes K. K., Mardth P. A., Sparling P. F., Wiesner P. J., New York: McGraw Hill, 1990.
- [6] Singh V., Parashari A., Sochani P. *et al.*: "Colposcopy as a tool for detection of human papillomavirus infection of uterine cervix in the setting of high prevalence of gynecologic infections". *Singapore Med J.*, 1996, 37, 588.
- [7] Schneider A., Sterzik K., Buck G. *et al.*: "Colposcopy is superior to cytology for the detection of genital HPV infection". *Obstet. Gynecol.*, 1988, 71, 236.
- [8] Switiker M., Cutlip A. C., Ogle D.: "A comparison of uterine cervical cytology and biopsy results: indications and outcomes for colposcopy". *J. Fam. Pract.*, 1994, 38, 40.
- [9] Mayelo V., Garaud P., Renjard L. *et al.*: "Cell abnormalities associated with human papillomavirus-induced squamous intraepithelial cervical lesions. Multivariate data analysis". *Am. J. Clin. Pathol.*, 1994, 101, 13.
- [10] Bergeron C., Barrasso K., Beaudenon S. *et al.*: "Human papillomavirus associated with cervical intraepithelial neoplasia. Great diversity and distinct distribution in low- and high-grade lesions". *Am. J. Surg. Pathol.*, 1992, 16, 641.
- [11] Lungu O., Sun X. W., Felix A. *et al.*: "Relationship of human papillomavirus type to grade of cervical intraepithelial neoplasia". *JAMA*, 1992, 267, 2493.
- [12] Willet G. D., Kurman R. I., Reid R.: "Correlation of the histological appearance of intraepithelial neoplasia of the cervix with human papillomavirus types". *Int. J. Gynecol. Pathol.*, 1989, 8, 18.
- [13] Herrington C. S., Evans M. F., Gray W. *et al.*: "Morphological correlation of human papillomavirus infection of matched cervical smears and biopsies from patients with persistent mild cervical cytological abnormalities". *Hum. Pathol.*, 1995, 26, 951.
- [14] Alani R. M., Munger K.: "Human papillomavirus and associated malignancies". *J. Clin. Oncol.*, 1998, 16, 330.

Address reprint requests to:
MILICA PEROVIC, M.D.M.A.
Nemanjia 13
11080 Zemun
Yugoslavia