

Colposcopy staging and treatment of Papillomavirus infection of the cervix

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Summary: The specificity of colposcopy findings in HPV infections allows the colposcopic differentiation of these lesions. In all of these colposcopically selected cases, additional tests included cytology with immunoperoxidase reaction (IPR), and, recently, virus typing with the use of ViraPap HPV DNA Detection test and ViraType HPV DNA Typing test became also available. When needed, histological examination of the specimen was carried out. In 202 detected and treated cases of HPV infections in females, and in 5 in males, four groups of lesions have been colposcopically distinguished. Group I contains early and fully developed, unsuspected typical papillomas; Group II - atypical papillomas which are usually colposcopically suspected of CIN and/or cancer; Group III - the so-called subclinical forms, i.e. cases with secondary diminution of epithelial transparency, i.e. acetic acid white epithelium, secondary simple punctation and/or mosaic (flat condylomas) that are visible only in colposcopic magnification and usually suspected of CIN; and Group IV - the so-called latent lesions without any colposcopic findings and only with positive IPR. CIN 3 (including CIS) was determined histologically in five cases of Group II. and CIN 1-2 in ten cases of Group III. HPV virus type 16/18 was found only in cases of CIN 3. The cases of atypical papilloma (Group II) and recently those containing HPV virus type 16/18 were treated by means of surgical conisation or cryosurgery. The remaining cases (Groups I, II, IV) were treated with orally administered Tetracyclin and Vitamin A. The effectiveness of this antibiotic/vitamin therapy in the group of typical papilloma and subclinical HPV lesions amounted to 75%. The regression of a part of CIN, especially grade 1 and 2, accompanying the HPV infection, was obtained after such treatment. In our opinion colposcopy as the first diagnostic step, supplemented by cytology and virus typing tests, and in necessary cases by histologic examinations, is the best method for the detection and differentiation of cervical lesions that develop on the basis of HPV infection. The best mode of treatment in atypical papillomas and lesions containing HPV virus 16/18 type is conisation. In other cases we recommend Tetracyclin and Vitamin A administered orally. This treatment modality of HPV infections of the lower genital tract can thus be recognized as prophylactic management of CIN and cancer.

Key words: Colposcopy; Cervix; Papillomavirus.

As follows from the results of contemporary studies^(3, 15, 16, 18, 19), HPV infections, and especially certain types of these infections occurring within the lower ge-

nital tract (LGT), are most likely related to the development of carcinoma in this region, especially CIN and cervical carcinoma.

Thus contemporary studies aiming at the development of effective and possibly uncomplicated methods of HPV detection and determination of the virus type become more and more important. Similar significance is attached to determination of the morphological properties and clinical symptoms of the infections that will faci-

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litate detection, selection and proper therapeutic management in such cases, thus extending our abilities to prevent neoplasm located within LGT.

Colposcopy is a highly specific and sensitive clinical method used in the morphological evaluation of the vulva, vagina and especially of the cervix^(3, 17). Often colposcopy is called a «prebiopsy». A majority of cases of CIN, early stages of carcinoma and all the overt and subclinical forms of HPV infections located within colposcopically accessible regions of the vaginal portion can practically be detected using this method^(2, 8, 9, 17). Therefore, we are of the opinion that HPV DNA typing using hybridization techniques cannot yet fully replace morphological methods and colposcopy in establishing the diagnosis and, first of all, therapeutic qualifications in CIN and/or HPV infections. Here colposcopy is irreplaceable.

MATERIALS AND METHODS

On the basis of our observations of 202 cases of HPV infections we have developed a management strategy for screening, detection and treatment of cervical HPV infections. This strategy is closely related to our screening and management strategy for CIN and early cervical cancer^(12, 13, 14). In both procedures, colposcopy is the first screening step in the evaluation of the cervix. Initially in our HPV infection screening program routine colposcopic examinations were supplemented by the immunoperoxidase test⁽¹¹⁾, and recently by the ViraPap HPV DNA detection test and/or Vira Type HPV DNA typing test, employed for the time being only in cases colposcopically less suspected of CIN and in cases of unsatisfactory colposcopy, especially in women under 30 years of age. These cases are just colposcopically more suspected for HPV infection and, therefore, the determination of this infection is very important here. Finally, the determination of the HPV type has, as we know, a prognostic value in these cases⁽¹⁶⁾. In the near future we would like to include in our colposcopy CIN screening program these virological examinations for all the women examined. A cytologic examination of this group of the examined women is the second step in determination of HPV infections

and/or CIN of the cervix. Histological examinations of the specimens are carried out only in women with HPV infections simultaneously suspected of CIN and cancer.

DISCUSSION

We have distinguished four colposcopy stages of cervical lesions related to HPV infections of the cervix (Table 1 and Figs. 1-6). Within the material studied we de-

Table 1. – *Colposcopy staging of the cervical lesions, which are or may be connected with the HPV - infection.*

Group	Type of lesions	Number of cases	Altogether	%
1)	Lesions non-suspected of CIN and cancer:			
	A) Early and advanced typical papillomatous growth	51	72	35.65
	B) Colpitis with early diffuse papillomatous growth	21		
2)	Lesions suspected of CIN and cancer:			
	A) Early and advanced atypical papillomas	26	32	15.84
	B) Focally papilloma-like lesions	6		
3)	Subclinical lesions-usually suspected of CIN			
	A) Secondary white epithelium inside transformation zone	31		
	B) Secondary simple punctation and/or mosaic	21		
	C) Secondary focal diminution or epithelial transparency inside colposcopically typical squamousus epithelium	16	68	33.66
4)	Latent infections			
	A) No colposcopic patterns are seen. PAP test or hybridisation tests are positive.			
	Koilocytosis	30	30	14.85
	Altogether	202	202	100.0

tected only one case of CIN I in the first, and five cases in the third group, three cases of CIN 2 in the second, and five cases in the third group, three cases of CIN 3 α (severe dysplasia) and two cases of CIN 3 β (CIS) in the second group of our staging. No patient with latent infection revealed CIN (Table 2).

HPV virus type 16/18 was observed in only five cases if CIN 3, i.e. in two cases of CIS and three cases of severe dysplasia in Group 2, and in five cases of CIN 2 in Group 3. No full correlation between CIN and HPV virus type 16/18 has been determined so far (Table 2).

Table 2. - HPV infection and Cin.

Group of the lesion	Number of cases	CIN				Altogether	%
		1	2	3 α	3 β		
I	72	1	-	-	-	1	0.72
II	32	-	3	3*	2*	8	25.0
III	68	5	5*	-	-	10	14.7
IV	30	-	-	-	-	0	0
Altogether	202	6	8	5	-	19	0.94

α) severe dysplasia - β) CIS - (*) HPV 16/18

For a long time we treated first of all the progressive HPV lesions coexisting with CIN (group 2 in our staging system - Table 1) and recently lesions containing HPV type 16/18 by means of cold-knife conisation and - in selected cases from this group - by cryotherapy (Table 3).

Table 3. - Type of treatment.

Cryotherapy	- Selected cases of groups I - III our staging
Cold - Knife conisation	- All progressive cases especially CIN and virus type 16/18
Tetracycline+ Vitamin A	- all other cases

After conisation and cryotherapy recurrent papillomas were observed in 1% of the patients. Nevertheless, following cryotherapy, the healing process in the cervix continued up to several weeks. These patients often revealed persistent signs of subclical or even overt forms of HPV infection and required repeated cryotherapy. Since 1960 all other HPV lesions (groups 1 and 3 in our staging) have been managed with oral Tetracycline and Vitamin A^(5-8, 10).

We felt inclined to use Tetracycline in treatment of papilloma-induced lesions in relation to the opinion that this antibiotic was effective against the so-called "large" viruses. Moreover, Vitamin A was introduced in view of its beneficial effect upon the processes of differentiation and maturation of squamous epithelium.

Up to 1988 such an antibiotic/vitamin treatment was used in 72 women and 5 men, partners of the women treated⁽¹⁰⁾ (Table 4), unfortunately without determi-

Fig. 1. — Typical squamous papilloma after acetic acid test. The high whitening of the papilloma tissue (group 1a).

Fig. 2. — Atypical squamous papilloma with leukoplakia-like pattern coexisting with CIS (group 2a).

Fig. 3. — Atypical squamous papillomatosis coexisting with CIN 1. Prominent mosaic-like patterns (group 2b).

Fig. 4. — Secondary white epithelium and mosaic within ectopy and transformation zone (groups 3a, b).

Fig. 5. — Native squamous epithelium before acetic acid test.

Fig. 6. — The same surface after acetic test. Few foci of flat diminution of transparency (group 3c).

Fig. 7. — Atypical papilloma. White grains, variform and divertiform within transformation zone, before acetic acid test.

Fig. 8. — The same surface after acetic acid test. Diffuse, secondary whitening of the epithelium with different thickness. Histology: papilloma coexisting with CIN 3.

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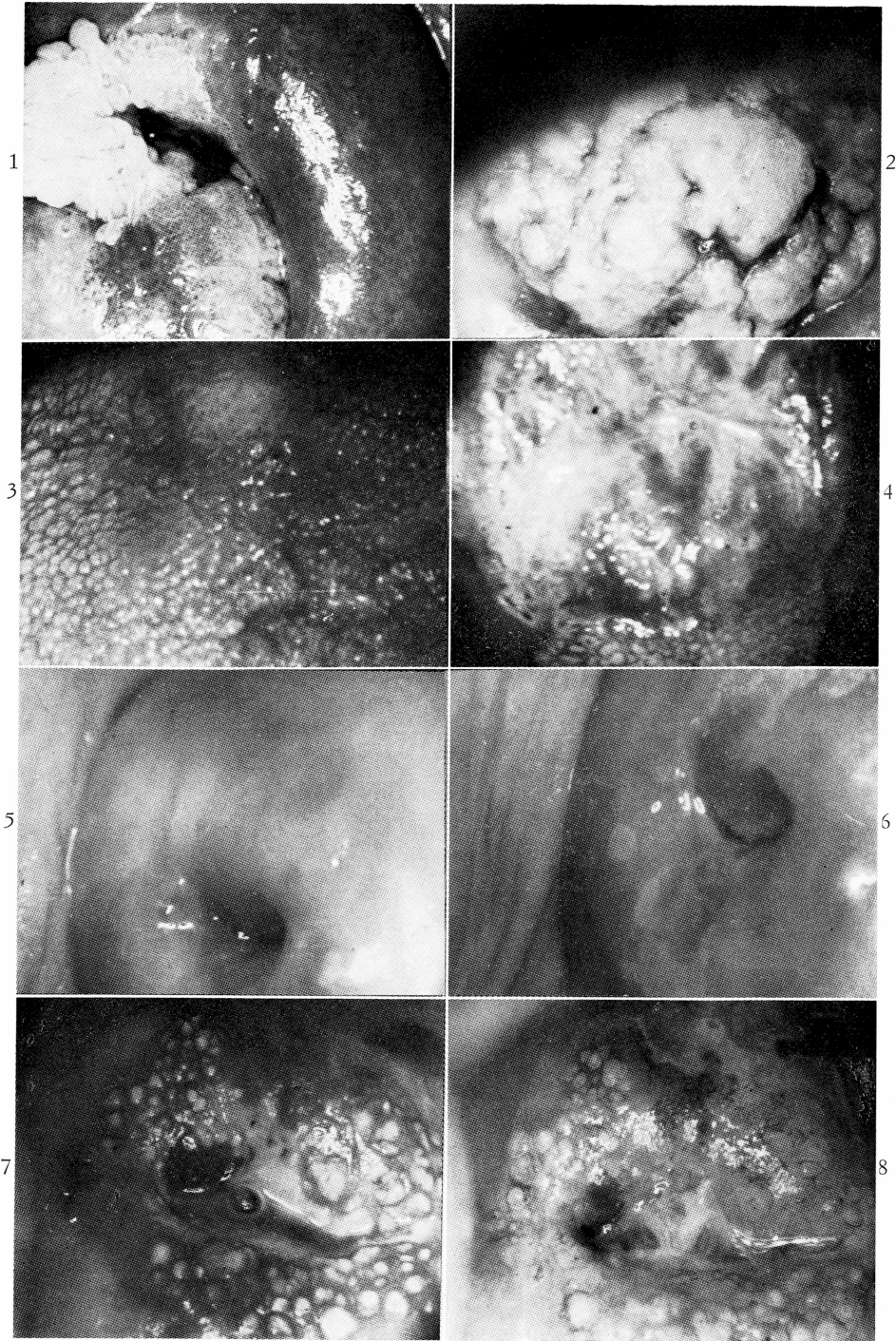


Table 4. - Results of antibiotic/vitamin treatment.

	Number of treated	Result		Series of treatment	
		satisfactory	unsatisfactory	1 - 2	3 - 4
I) Women					
72	62%	10%	51%	11%	
II) Men					
5	5*	-	5	-	

(*) Including 2 men with recurrence of papiloma after electrocoagulation.

nation of the virus type, as at that time we did not have the facilities. The lesions in the men treated were located within the penis and anal region. In two of them the lesions were recurrent and developed after electrocoagulation of primary papiloma foci of the penis.

In 62, i.e. 86% of the women treated and in all the men the results of such an antibiotic/vitamin therapy were very good. The best results were obtained in women with recently redeveloped widespread foci of papilloma within the cervix, vagina, vulva and anal region, when laser vaporization or Podophylline administration were difficult to use. Regression was also observed in several cases of mild and moderate dysplasia concomitant with HPV lesions. The cure was usually obtained after 1-2, and in exceptional cases, 3-4 series administered once a month. One series consisted of 6.0 Tetracycline given four times daily at the dose of 250 mg, and 50 capsules of Vitamin A administered a capsule twice a day (Table 5).

In the subsequent 51 patients (Table 6) we also followed the course of subclinical HPV infections in one group with tetracycline and Vitamin A treatment and in women without any therapy. The comparison of the results makes it possible to conclude that the remission rate of HPV-induced lesions in the group treated with oral Tetracycline and Vitamin A was twice as high as in the untreated and locally treated group, including two cases with 16/18

virus type. In the untreated patients the infection progressed or remained unchanged twice as often as in the orally treated group. Recurrent infections were noted solely in the untreated individuals.

We also directed our attention to the role of Vitamin A in carcinogenesis and thus we commenced more detailed studies of the problem. To this end we (¹¹) determined the Vitamin A level in 60 cases of women with histologically confirmed CIN. We found that blood serum Vitamin A and procarotene levels were much lower in these women than in the controls, the difference being statistically significant ($x_1 = 35.8 \mu\text{g}\%$ $x = 57\mu\text{g}\%$. $x - x = 17.9\mu\text{g}\%$). In another group of 300 women with histologically confirmed CIN 1-3 (66 with CIN 1, 92 with CIN 2 and 143 with CIN 3) and with HPV infections, as well as in the control group of 380 women without CIN and HPV infections, all of them studied at our center by Basta (¹), determinations were made of blood serum retinol (Vitamin A) level. Retinol concentration values were found

Table 5. - Tetracycline and Vitamin A administration. One series treatment consists of.

Tetracycline	- 6.0 - 4 times daily a' 250 mg
Duration	- 6 days
Vitamin A	- 50 capsules - twice daily 1 capsula (12.000 I.U. each capsule)
Duration	- 25 days

Table 6. - Subclinical stage HPV infection treatment.

	Without	Local	Oral
N. of cases-51	16	15	20
Series	-	3	1-3
Regression	6(37.5%)	6(40.0%)	15(75.0%)
Progression	2(12.5%)	1 (6.7%)	1(5.0%)
Stationary	8(50.0%)	8(53.3%)	4(20.0%)
Recurrence	1(6.25%)	2(13.3%)	-

to be statistically significantly lower in CIN and HPV patients than in the controls. HPV infection was diagnosed using colposcopic and cytologic estimation with supplementary immunoperoxidase test and HPV DNA hybridization techniques for types 6, 11, 16, 18, 31, 33 and 35. These observations can also confirm the point of view of Grubb⁽⁴⁾ who regarded Vitamin A and procarotene deficiency as factors playing a role in carcinogenesis. In our opinion it might constitute an additional carcinogenic factor, necessary, along with an HPV infection for the generation of a malignant phenotype of the cells.

CONCLUSIONS

In concluding, we can say that colposcopy as the first diagnostic step, supplemented by hybridization tests for virus typing, or else cytologic and histological examinations when necessary, constitutes a simple screening method in detecting HPV infections of the uterine cervix. Such a management strategy allows for a determination of the stage of the lesion and, first of all, for the selection of the best therapeutic modality.

In our opinion the best form of treatment is conisation in colposcopically atypical papillomas with virus type 16/18, especially when concomitant with CIN (group 2 in our staging system, Table 1).

In other groups of our classification we recommend Tetracycline and Vitamin A therapy, with rigorous follow-up, especially of patients with HPV virus type 16/18. When no remission after two series of this treatment is obtained surgical or laser conisation should be used in these cases. As an exception, and only in the centers with perfectly mastered colposco-

py-virology-cytology and with histological diagnostic possibilities, should the use of laser vaporization be allowable.

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