TODAYS' STAGE IN DIFFERENTIAL DIAGNOSIS BETWEEN CERVICAL CONDYLOMA AND CIN

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Summary: Seven colposcopic signs (acetic acid staining - borders - thickness - surface contour - colour - vascular atypias - iodine staining) are examined in differential diagnosis between condyloma and CIN.

For a better prognostic and therapeutic approach, we think it is useful to follow a diagnostic path whose main steps are: colposcopy, citology, microcervicoscopy, hystology. With the introduction of sofisticated diagnostic techniques (molecular hibridization - morphology cells study - chromosomes map study) it is possible to determine morphologically the observed lesion and predict, as much as possible, the following evolution.

It is well known the important role of colposcopy in the diagnosis of cervical lesions, expecially with regards to the revaluation of this method made by the American researchers in the last decade. In fact the skilled clinicians obtain, through this method, a diagnostic accuray of about 90% of the patologies already observed expecially with regards to virus infections.

Two are the main factors which have made the diagnostic approach extremely interesting and not to be neglected: on one hand the increase in infections and in premalignancy of the cervix covering about 2% of the population (with a specific incidence divided up as follows: 40% of CIN associated with condylomas and about 20% in the premalignant forms alone, not associated with condylomas) and on the other hand the gradual decrease in the age group of patients affected by this type of pathology, with a distribution of the age groups as follows: 28-35 for condylomatous lesions, 29-80 for CIN associated with condylomas and 33-54 for CIN not associated with condylomas.

This once proves the hypothesis of a condyloma as precursor of CIN and therefore cancer of the cervix. With regards to the above and based on the experiences already acquised, it has been thought useful to focalize our critical eye on one of the aspects of major interest and controversy, which is the study of the atypical re-epithelization zone (ARZ). This colposcopic term, considered as the alteration of the re-epithelization, after the applying of acetic acid, is characterized by patterns like those of a mosaic, punctation, leucoplasia which have atypical squamous metaplasia, condylomas and CIN (fig. 1).

It is by starting from this difficult colposcopic distinction and from the confusion behind it that we have tried to analyze into details the fundamental points of one pattern from another (in particular the flat condyloma and the CIN) in order to have a more accurate diagnostic valuation and consequently, in order to have a better approach to the therapy, especially in the light of the excellent possibilities that laser treatment offers today, which the Gynecological Oncology Service has been using for about 6 months. It was in

Fig. 1.

Colposcopy	histology
	atypical squamous metaplasia
ARZ	condyloma
	cin

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Fig. 2. — *Colposcopy differential diagnosis.*

Acetic acid absorption	Condyloma Quick	Cin Slow
Borders	Ill-defined Digitate	Clear cut
Thickness	Thin, sometimes semitransparent	Thick
Surface contour	Micropapillar Flat	Smooth
Colour	Shiny-white	Grey
Vessels	Non-dilated capillary arcades, uniform and with variable but regular caliber	Punctation and/or mosaic
Iodine absorption	Stained J^+ weakly homogenous	J^- homogeneous

1976 Meisels, Fortin and Roy identified cytohystologically a viral lesion and defining it as a «flat condyloma», which is characterized by the presence of cells with a typical perinuclear cytoplasmatic halo which Koss had already described in 1956.

The necessity of obtaining more and more precise and complete information about cervix viral pathology, both for biological reasons-whereby the analytic morphologic description made, possible by colposcopy represent the fundamental sub-stratum-and for a more adequate and personalized therapy programming, brings about a more sophisticated and early diagnosis.

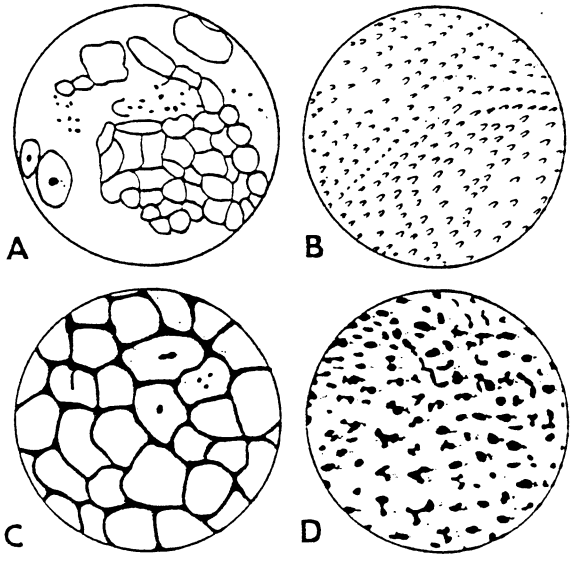
It is for this reason that in reality the flat even condylomas are rarely «flat». More often or not their surface is covered by contours or microcontours or even when they are flat they are characterized by a vascular network which forms or a mosaic and a punctation more or less regular. Such horizontal or vertical capillaries relate to connective contours which come to the epithelial surface. The condyloma is therefore an epithelian connective proliferating lesion in which the equilibrium of the 2 components is different and the papillomatosis is constant. The term flat condyloma is a clinical one. At an anatomy pathological point of view this term is an error and has no meaning (condylos in Greek means point); consequently, in early diagnosis, it is better to speak about a Papovaviral subclinical infection (SPI) rather than the flat condyloma.

We managed to make an ever early diagnosis in the natural history of the virus infection.

The cervical intraepithelial neoplasia (CIN) is different from the subclinical infections given by Papilloma virus (SPI) because of the presence of atipical cells, both in the deeps layers and middle layers (CIN 1-2), and on the whole thickness of the epithelial (CIN 3) surface.

Ried should be given credit for having demonstrated that SPI on one hand, and CIN on the other had different colposcopic characteristics (fig. 2); characteristics which were already known in part. The absorption of acetic acid by the condyloma is very rapid, but slower in CIN; the borders of the lesion are diffused, almost digitate in the condyloma, clean cut in the CIN; the flat condylomas after acetic acid has been applied, appear to be shiny and then, almost semitransparent while the lesion in the CIN appears to be grey and dull; the condyloma surface is often micropapillate or flat, but always smooth in the CIN. The vascular network of the condyloma is characterized by capillary humps condyloma and when visible they are uniform, not swollen and are various sizes but regular, with a horizontal or vertical tracing typical of the CIN (mosaic or punctation), but certainly less course (fig. 3). Finally with the Schiller test, the condylomas appear only to be weakly iodo positive and sometimes iodopositive and iodonegative (stained) at the same time (in as much as the cervix at the level of the pa-

Fig. 3. — Genital warts and cervical cancer.



pillas does not absorpt the lugol while it gets it at the level of intracapillary creases in which the glycogen is normally present).

It should be noted however that none of these aspects is perfectly patognomic and for its reason we have also complied with the Ried score (fig. 4), in order to define as correctly as possible the nature of the lesion.

The evaluation is based on several scores (0-1-2) given to 5 different parameters (thickness - surface - colour - vascular network - iodine absorption), which brings to such results:

0-2 Points - SPI or CIN 1

3-5 Points - CIN or CIN 2

6-8 Points - CIN 2 or CIN 3.

Fig. 4. — *Method for scoring the colposcopic index.*

Criterion	POINTS		
	Zero	One	Two
Thickness	Borderline	Definite	——
Contour	Condylomatous or micropapillary	Flat	——
Color	Shiny, show-white	Shiny, gray-white	Dull, greysh
Vessels	Warty vessels	No vessels	Punctation or mosaic
Iodine	Positive or minor negative	Partial uptake	Significantly negative

Interpretation: 0-2 points = subclinical pallomaviral infection (SPI) or grade 1 cervical intraepithelial neoplasia; 3-5 points = grade 1 or grade 2 cervical intraepithelial neoplasia; 6-8 points = grade 2 or 3 cervical intraepithelial neoplasia (By Reid R., 1984).

Fig. 5. — *Diagnostic parameters with prognostic perspectives.*

HPV		CIN
Koilocytes Hibridization	CYTOLOGY	Cells atypias Grade
	COLPOSCOPY	
Minor lesions	Diagnosis	Major lesions
0-2 SPI-CIN 1	Score	3-8 CIN 2-CIN 3
Geography of the lesion Koilocytosis	MICROCERVICOSCOPY	Geography of the lesion Nucleo-cytoplasmatic abnormalities

At this point in other to camp out an efficient pre-therapy staging it is possible to identify a diagnostic path between different types of lesions (SPI and CIN) a path which lies on different methods sufficient to determine the diagnosis, but at the same time very much disposed one with the other (figg. 5-6).

The first step of such a methodology can already see an important moment to find a way and to differentiate the two tipes of lesion, even though a high percentage of false negatives (40-50%) above all in condyloma lesions, and over or under diagnosis, induce a certain caution before making such a diagnosis.

The pathognomic element of the lesion caused by the Papova virus is the already mentioned Koilocyte. This is a malpighian cell, very often of an intermedium tvpe, sometimes superficial or parabasal, which presents a large cytoplasmatic vacuole, which appears empty with clear cut borders but sometimes irregular.

The cytoplasm margin is basophilic and sometimes amphophilic and in the center of the vacuole the nuclei are normal or more or less dyskeratotic, and sometimes multiple. On the smears the koylocites can be numerous, but very often or not they are rare and must be looked for with great care. When such features are missing the diagnosis relies on other cytohystological signs: the paraceratosis and the changes in the nuclei in direct connection with the viral offence (binucleation and multinucleation — large nuclei — normal mitosis and above all atypical).

With the differential cytology it is possible to distinguish by analysing the various grade and the extension of the nucleocytoplasmatic atypias the various tvpes of the CIN (1-2-3), according to the classification of Richard.

The possibility offered by some sophisticated diagnostic methods based on the study of the viral DNA and therefore on the characteristics of the HPV families

Fig. 6. — *Diagnostic parameters with prognostic perspectives.*

HPV	HISTOLOGY	CIN
	Morphologic study	
6-11 Absent Diploidy Polyploidy	HPV Types Abnormal mitosis Study cromosomes map	16-18... ? Present Aneuploidy
SPONTANEOUS REGRESSION	PROGNOSIS	ABSENCE OF SPONTANEOUS REGRESSION
TREATMENT?		TREATMENT

(rapid molecular in situ hybridization of cervical cells) in order to pick out and predict the clinical path of the presumed precursor of cervical cancer in each patient and on the basis of a cytologic depistage ([13]). This technique is employed for the study and the identification of the different types of HPV present in the cells, therefore not just with a Utopian prospect of a routine screaning for those members of the risk population. The results obtained give support, in accordance with similar studies on bioptic samples, to a hypothesis of a double biological path and therefore necessarily therapeutical-prognostic ones of the viral lesions of the condylomas.

In particular the 16-18 families would be in relation with the small group of cases with a high progression risk and therefore with a high developing cervical cancer risk, while the families 6-11 would make up the group with more lesions at a low lesions risk. In the first group treatment is necessary and immediate; in the second group, even through there is some uncertainly, the possibility to observe the biological evolution of the lesion and therefore the possibility of refraining from an immediate treatment.

By following the different diagnostic path between CIN and condylomas we go back to colposcopy, which has, already been examined into details.

The differences between minor and major lesions (SPI and CIN 1) are to be underlined (CIN 2 and CIN 3), and are possible by using a valid valuation and interpretation of the Reid's score.

Further clinical diagnostic investigation which includes the colposcopy and which can bring about new and useful results in the microcervicoscopy with observations in vivo (with a magnification of 150:1) of the epithelial lining of the cervix after having been coloured in Waterman blue or toluidine blue.

After the first colposcopic valuation on the seriousness and topography of the lesion one can procede with the microcervicoscopy.

Such an examination is necessary when the squamo-columnar junction is not entirely visible by colposcopy (1 on 10), but it is useful to use this even when the lesion is entirely ectocervical. This infact permits a more precise valuation of the seriousness and the nature of the pathological process.

The microcolposcopic valuation depends essentially on the study of cells nuclei: size, aspect of the borders and hyperchromasia.

The cytoplasms are more difficult to be analysed. The blue colours them very discreetly and the intracytoplasmatic vacuoles are sometimes evident and sometimes are not evident and for this reason it is not always easy to pick out the koylocites. But the picking out of the koylocite does not make up the only diagnostic criteria, or the most important. Other signs, at a cell level, have a probationary importance, especially the one depending on the nuclei (binucleation, chromatin anomalies).

The architectural shapes and signs on the other hand are of fundamental importance; papillomatosis in all its morphological aspects is almost always a pathognomonic phenomenon. By considering all the symptoms and not only the presence or the absence of koylocites a connection does exist between hystology and microcolposcopy in viral lesions up to 70-80%, certainly higher than the hystlogical-cytological connection which is about 50%.

The hystological-microcervicoscopy connection in determining the diagnostic of CIN is also very interesting, and reaches up to 85% in CIN 3 with a undervaluation of 15% ([3, 7]) and about 60% in CIN 1-2, with an overevaluation of about 40% of the cases. Essentially this type of method in the diagnostics points out a number of original and useful data:

— the possibility of having immediate and complete access to the transformation zone, a zone in which any type of displasia originates and where it is possible to

identify the initial lesion. The polimorphism of such lesions can be studied and the CIN connections — defined condylomas.

— the possibility to direct the biopsy on the epicenter of the lesion, where the anomalies of the nuclei are more severe.

— the possibility to be able to pick out the squamo-columnar junction and above all in the endocervix.

— the possibility to repeat this atraumatic examination permits a dynamic approach and when it concerns condylomas alone, even powerful and oncogenic monitoring becomes possible.

Microcervicoscopy makes up a complete examination for the colpo-cyto-hystology and certainly allows the geography and the seriousness of the lesion to be better defined, leading the therapy towards even more conservative and selective interventions.

The last step of the diagnostic path is finally reached, of which only hystology gives the definite or almost certain pretherapy staging. It is possible with it to determine morphologically the lesion by using both the classic techniques and the most sophisticated diagnostic techniques (microspectrophotometria-molecular hybridization) in such a way as to be able to define 2 groups of lesions characterized as follows: on the one hand the families 6 and 11 of HPV, with the lack of atypical mitosis and a chromosomes map diploidy and polyploidy, and on the other, lesions characterized by the families 16 and 18 of HPV (and maybe even others?), from atypical mitosis and from a aneuplody chromosomes map.

At this point a hypothesis is suggestive and non utopistic: one can now speak about a diagnosis which is no longer differential between condylomas and CIN but of differential diagnosis between lesions characterized by different morphologic patterns, with a different prognostic and therapeutic attitudes according to the appartenance to the first or to the second group.

A spontaneous regression occurs in the first group and a lack of regression in the second one, and from this the necessity and immediacy is derived for treatment in the second group and the opportunity of a surveillance in the first, without having the certainty that a progression does not exist towards the second one and hypothesizing the necessity of treatment also in the first group.

CONCLUSIONS

We are convinced that at the actual stage, a possibility exists, by using various diagnostic techniques integrated with each other (colposcopy - differential cytology - microcervicoscopy - hystology) to differentiate subclinical viral lesions from the Papova virus (SPI) from the intraepithelial ones (CIN). The possibility to phase the illness does exist, by monitoring its course and directing and choosing a therapy.

To this typical clinical approach, and therefore of a more rigorous gynecologic competence, several useful technical possibilities can be flanked to it to characterize in a biological way the viral lesions between then and differentiate in a better way the actual intraepithelial neoplasia.

We can therefore already obtain from one clinical screening useful information regarding the cervical lesion and be able to underline the more significant morphologic aspects for the evolution of the pattern and at the same time be able to identify the biological parameters (chromosomes map — morphology of the cell — studies of cells hybridization) which are certainly more objective and probably of more prognostic value.

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THE EFFECT OF DEHYDROEPIANDROSTERONE SULFATE PROLACTIN AND TESTOSTERONE HORMONES TO FEMALE FERTILITY AND HIRSUTISM

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Summary: The effect of DHEAS, Prolactin and Testosterone hormones to female infertility and hirsutism have been investigated.

In primary infertility group average DHEAS value is 491 ± 95 ng/ml so it is meaningful low ($p < 0.01$).

In fertil hirsutic group (++++) category average DHEAS value is 4166 ng/ml, meaningful high ($p < 0.01$).

The relation between DHEAS and Prolactin also remarkable.

The effect of Dehydroepiandrosterone sulfate (DHEAS), Prolactin and Testosterone hormones ot female infertility and hirsutism have been investigated. After realizing the value of DHEAS more important than 17-Ketosteroids in adrenal androgen function, it can be thought that DHEAS is in relation with female infertility. Also relation between Prolactin and DHEAS have been confirmed in this research ([2, 3]).

MATERIAL AND METHODS

In primary infertility, fertil hirsutism and control groups, DHEAS, Prolactin and Testosterone hormones are assayed and values compared among these groups.

In primary infertility group there are 20 patients, age is between 20-35, have no acute and chronic disease. Infertility is confirmed with probe curettage. But three of twenty after 3 months epimestrol administration, ovulation was obtained.

In fertil hirsutic group there are 21 patients, age is between 19-38, have no acute and chro-

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