

LYMPHOPLASMACYTE INFILTRATE IN CERVICAL INTRAEPITHELIAL NEOPLASIA GRADE III

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SUMMARY

The behaviour of the lymphoplasmacyte reaction, regarded as an immunitary defence reaction of the organism, has been evaluated in 167 patients affected by cervical intraepithelial neoplasia or by microcarcinoma.

It was observed that in surely *in situ* forms (atypical metaplasia, severe dysplasia and carcinoma *in situ*) there is a clear prevalence of cases with a minimal or absent reaction, while in the potentially invasive carcinoma and in the microcarcinoma there is a predominance of cases with a marked reaction, as if the first biological modifications that lead to invasion were accompanied by a massive activation of the immunitary defence mechanisms.

We finally noticed that no relation exists between the appearance of CIN-lesion recurrences and the intensity of the stromal reaction. This further confirms the hypothesis that in the first steps of the carcinogenetic process exogenous causes are mainly involved.

Many Authors examined the behaviour of lymphoplasmacyte infiltrate, considered an immunitary defence reaction of the host against the cancer, in the invasive carcinoma of several organs such as the stomach⁽¹⁶⁾, the larynx⁽¹⁵⁾, the breast^(10, 11, 12), the endometrium⁽⁸⁾ and the uterine cervix^(1, 4, 5, 6).

These Authors demonstrated that the more marked the infiltration, the more favourable the prognosis.

The same investigation, however, has not yet been carried out in intraepithelial neoplastic forms.

In fact, the lymphoplasmacellular infiltration has been considered a distinctive morphological finding of invasive forms, in which it is rather frequent. It was never reported in intraepithelial forms in which, however, it was never examined.

Only few studies⁽³⁾ on intraepithelial cervical neoplasia (CIN) report processes of stromal disorganization, accompanied by a stimulation of the fibroblast biosynthetic activity and an increased heparinoid synthesis by stromal reproductive cells.

Therefore, it seems very interesting to study the behaviour of the lymphoplasmacyte stromal reaction in high-risk precancerous lesions, such as severe dysplasia and carcinoma *in situ*, classified^(7, 14) as intraepithelial cervical neoplasia grade III, and clinically described as stage 0.

The aim of this work is to verify:

- whether an immunitary defensive reaction can be detected, histologically characterized by lymphoplasmacyte infiltration around the atypical cells;

- the real incidence of this reaction, and its possible relation with the single histological pictures, which are classified together as cervical intraepithelial neoplasia - grade III.

MATERIAL AND METHODS

The research was carried out on 167 patients who attended the Obstetric and Gynecological Clinic of Padua University between 1970 and 1979; their mean age ranged between 20 and

70 years, and cervical intraepithelial neoplasia – grade III (CIN grade III) was diagnosed in each case, following hysterectomy, conization, or simple biopsy.

Each tissue specimen was reexamined, and re-evaluated mainly considering the following parameters:

- cyto-histological type;
- lymphoplasmacyte stromal infiltration, as far as it expresses the immunitary response. We excluded all cases presenting an acute phlogistic reaction (with a granulocyte – infiltration of both the cervical epithelium and the underlying stroma) or a chronic one (with mono – or polymorphonucleate cells not only under the damaged epithelium but widely spread into the whole stroma).

The histologic specimens were collected at the Institute of Pathology and the Colpocytological Service of the Obstetric and Gynecologic Clinic of Padua University.

The W.H.O. classification⁽¹³⁾ of the histological types seems the most suitable for the purpose of our work, as it includes all the degrees of the disease: from the precursors of the CIN to its various morphological expressions (included the one which exhibits a potential invasivity), and, lastly, to the initially invasive forms:

Atypical metaplasia

Lack of differentiation and maturation of the cervical epithelium in which the basal or immature cells are dislocated in an abnormal position towards the surface, and show various degrees of atypia.

Severe dysplasia

Some epithelial layers are replaced by cells with a very high degree of atypia. There is polarity loss and the cells crowded have voluminous and intensely coloured nuclei.

Carcinoma in situ

All, or nearly all, the epithelium shows carcinoma cellular characteristics without invasion of the stroma.

Potentially invasive carcinoma in situ

There are aspects of carcinoma in situ, and sometimes dysplasia, with focal areas that may be suspected to penetrate the stroma.

Microcarcinoma

There is no doubt of stromal invasion, however slight.

During the revision of the histological preparations, originally considered as CIN III, some of these presented the characteristics of potentially invasive carcinoma in situ and microinvasive

carcinoma. However, these were taken into consideration as possibly useful comparison data.

The cases presenting different associated lesions were grouped according to the most serious of them: the one with the highest oncogen risk.

The intensity of the lymphoplasmacyte stromal reaction was evaluated as follows:

- marked – when the lymphocytes and/or plasmacells clearly separate the atypic area from the surrounding healthy tissue;
- moderate – when the lymphocytes stromal the plasmacells are less numerous but can still surround the lesions with sufficient regularity;
- minimal or absent – when these cells are not present, or limit neoplastic buds in a discontinuous way.

At the same time all patients were invited to the Obstetric and Gynecologic Clinic and re-evaluated through control examinations (clinical objectivity, colpocytology, colposcopy and eventually a direct-biopsy) in order to assess their present state and the eventual presence of recurrences. By recurrence we meant the appearance, after a period of at least 6 months, of a lesion classified as cervical intraepithelial neoplasia grade I, II or III.

RESULTS

Table 1 reports the case distribution based on the intensity of the stromal reaction and the histological type of the lesion.

The stromal reaction was minimal or absent in 63.47% (the majority of cases), moderate in 21.55% and marked in 14.98% of the cases.

As for the relationship between the stromal reaction and the histological type we observed that:

- most of the cases (90.90%) of atypical metaplasia presented a minimal or absent reaction, only 9.10% a moderate one, and none a marked one;

- most of the cases (82.85%) of severe dysplasia presented a minimal or absent reaction, while 11.43% had a moderate one and the remaining 5.72% a marked one;

- a similar behaviour was shared by the carcinoma *in situ*: 61.70% of the cases had a minimal or absent reaction, 28.40% a moderate one and the remaining 9.90% a marked one;

Table 1. — Case distribution based on the intensity of the stromal reaction and related to the type of histological lesion.

Histological type	Lymphoplasmacyte infiltrate						Total
	Minimal or absent		Moderate		Marked		
	Case No.	%	Case No.	%	Case No.	%	
Atypical metaplasia	10	90.90	1	9.10	—	—	11
Severe dysplasia	29	82.85	4	11.43	2	5.72	35
Carcinoma in situ	63	61.70	29	28.40	10	9.90	102
Potentially invasive carcinoma	2	40	—	—	3	60	5
Microinvasive carcinoma	2	14.29	2	14.29	10	71.42	14
Total	106	63.47	36	21.55	25	14.98	167

— the potentially invasive carcinoma, on the contrary, presented a marked reaction in 60% of the cases, and a minimal or absent one in the remaining 40%;

— the microinvasive carcinoma had a marked reaction in 71.42% of the cases, while it had a minimal or absent one in 14.29% and a moderate one in 14.29% of the patients.

Briefly, the presence of stromal infiltration clearly separates two distinct groups: that of certainly *in situ* forms where the

stromal reaction is present in the minority of cases whatever the histological type, and that of potentially initially invasive forms in which it is mostly present.

The statistical analysis of the case distribution (table 2) shows that:

— the difference between the *in situ* forms and those which are potentially invasive and microinvasive is highly significant;

Table 2. — Statistical analysis (χ^2) of the difference between the groups based on the histological type and the stromal reaction.

Histological type		Lymphoplasmacyte stromal reaction	
		Minimal and moderate	Minimal and moderate + marked
Atypical metaplasia	- Severe dysplasia	P=NS	P=NS
Atypical metaplasia	- Carcinoma in situ	P=NS	P=NS
Severe dysplasia	- Carcinoma in situ	P=NS	P=NS
Potentially invasive carcinoma	- Microcarcinoma	P=NS	P=NS
Atypical metaplasia	- Potentially invasive carcinoma	P<0.001	P<0.01
Severe dysplasia	- Potentially invasive carcinoma	P<0.001	P<0.01
Carcinoma in situ	- Potentially invasive carcinoma	P<0.001	P<0.01
Atypical metaplasia	- Microcarcinoma	P<0.001	P<0.01
Severe dysplasia	- Microcarcinoma	P<0.001	P<0.01
Carcinoma in situ	- Microcarcinoma	P<0.001	P<0.01
Atypical metaplasia	- Potentially invasive carcinoma + microcarcinoma	P<0.001	P<0.01
Severe dysplasia	- Potentially invasive carcinoma + microcarcinoma	P<0.001	P<0.01
Carcinoma in situ	- Potentially invasive carcinoma + microcarcinoma	P<0.001	P<0.01

Table 3. — Recurrences according to the type of lesion histological and the stromal intensity reaction.

Histological type	Stromal intensity reaction							
	Minimal		Moderate		Marked		Total	
	Recur- rences	No-recur- rences	Recur- rences	No-recur- rences	Recur- rences	No-recur- rences	Recur- rences	No-recur- rences
A.M.	—	1	—	—	—	—	—	1
S.D.	2	10	—	2	—	1	2	13
K.S.	11	21	2	11	2	2	15	34
P.I.	—	—	—	—	1	1	1	1
M.C.	—	—	—	1	1	2	1	3
Total	13	32	2	14	4	6	19	52

A.M. = atypical metaplasia; S.D. = severe dysplasia; K.S. = carcinoma in situ; P.I. = potentially invasive carcinoma; M.C. = microcarcinoma; I.C. = invasive carcinoma.

— no significant difference between the various histological types is found within the CIN III;

— no significant difference between the potentially invasive forms and microcarcinoma is present.

Finally, we compared the data concerning the lymphoplasmacyte infiltration and the histological type with the appearance of recurrences.

71 patients could be followed — up and re — evaluated: 26.76% of them had a recurrence within a time span of 1-5 years from the surgical treatment (conization or hysterectomy) of the primitive lesion.

The relapsing cases were 19, 10 of which with CIN I and 9 with CIN II.

Table 4. — Distribution of recurrences based on the intensity of the stromal reaction in all the histological types.

Lymphoplasmacyte stromal reaction	Recur- rences	No-recur- rence	Total
Minimal	13	32	45
Moderate	2	14	16
Marked	4	6	10
Total	19	52	71

The difference between recurrences in presence of minimal stromal reaction and recurrences in presence of moderate and marked reaction are not significant.

The comparison of the recurrence-rate with incidence of stromal-reaction type showed no statistically significant relation (tab. 3-4).

DISCUSSION

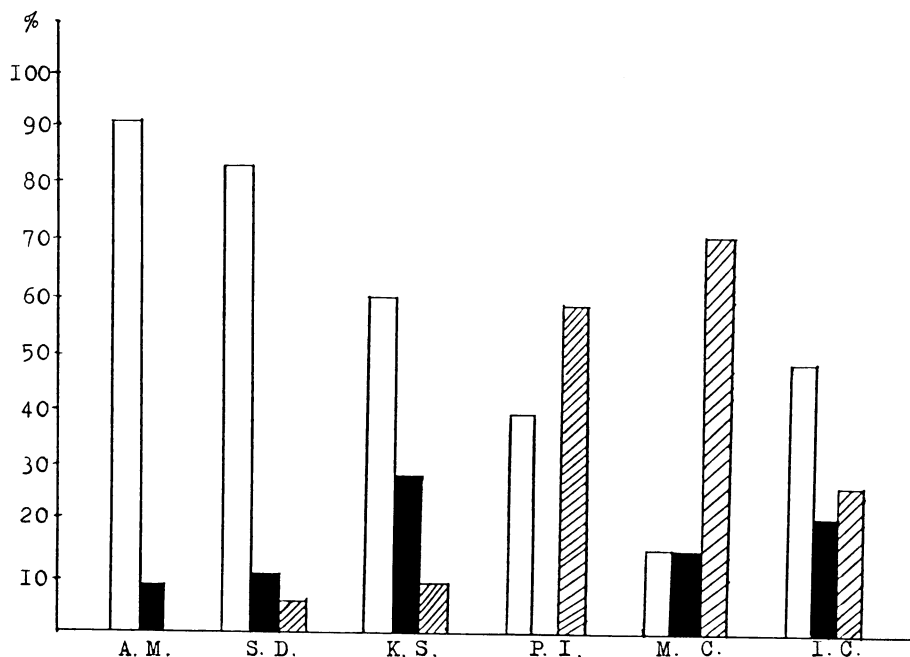
Our research on the lymphoplasmacyte stromal reaction, regarded as an attempt of immunitary defence while the cervical carcinoma is still intraepithelial or initially invasive, provides useful data which might highlight the true significance and the possible prognostic value of this reaction.

In fact, while in atypical metaplasia, the stromal reaction is present only in 9.10% of cases and is always moderate, high and moderate reactions are respectively present in 5.72% and 11.43% of severe dysplasia cases, and in 9.90% and 28.40% for carcinoma *in situ* cases.

This behaviour might suggest that in the pre-invasive stage of cervical carcinoma immunitary defence mechanisms are already present and active in the host's organism.

The stromal reaction rate increases then in a significant way, to reach 60% of the cases, when, the CIN has the morphological characteristics typical of potential invasivity. The immunitary defence mechanisms, then, seem to be massively acti-

Table 5. — *Distribution of the lymphoplasmacyte stromal reaction in epithelial cervical pathology.*



A.M. = atypical metaplasia; S.D. = severe dysplasia; K.S. = carcinoma in situ; P.I. = potentially invasive carcinoma; M.C. = microcarcinoma; I.C. = invasive carcinoma.

□ = Minimum or absent lymphoplasmacyte stromal reaction.

■ = Moderate lymphoplasmacyte stromal reaction.

▨ = Marked lymphoplasmacyte stromal reaction.

vated exactly when the first biological modifications occur, which are responsible for future invasions.

When the stroma invasion begins, immunitary defences appear to increase further (85.71%).

In one of our previous research studies (17) we observed that in the invasive carcinoma a marked stromal reaction was present only in 27.5% of cases, a moderate one in 22%, and a minimal or absent in the remaining 50.5% (table 5).

In conclusion, the behaviour of the lymphoplasmacyte stromal reaction in all

the degrees of cervical epithelial pathology, from the precursors (CIN) to invasive carcinoma, indicates the presence of an "acute" immunitary response at the stage of potential or initial invasivity, which subsequently seems to decline progressively.

Moreover, as the limit between potentially invasive and microcarcinoma can't be exactly set, the stromal invasion must be excluded by all the available diagnostic investigations whenever a marked stromal reaction is present.

Finally, our study showed no significant relationship between the presence of the stromal reaction and recurrences following therapy, and this seems to support the hypothesis that in the first step of the carcinogenetic process exogenous causes are mainly involved.

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