COLPOSCOPIC AND CYTOLOGICAL STUDIES IN LEUKOPLAKIA OF THE CERVIX

by

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Today in our gynaecological armamentarium against cancer, we include two procedures, namely, exfoliative cytology and colposcopy, which have been found to be very useful in the detection of the early stages of exocervical cancer.

Exfoliative cytology, which was first demonstrated by Papanicolaou and Traut (1943) as a useful tool in early cancer diagnosis, consists in the microscopic study of cells shed from the mucosa and stained by Papanicolaou's technique. Smears taken from the cervix may be of five types according to Papanicolaou's classification (1954):

Class I. The normal smear in which there is an absence of atypical or abnormal cells.

Class II. Atypical cytology but with no evidence of malignancy.

Class III. Cytology suggestive of but not conclusive for malignancy.

Class IV. Cytology strongly suggestive of malignancy.

Class V. Cytology conclusive for malignancy.

Colposcopy, described over 30 years ago by Hinselmann (1925), is a method by which a stereoscopic inspection of the cervix and vagina can be carried out under a magnification of from 10 to 40 times with direct illumination from a built-in light source. The findings depend on the architecture and thickness of the epithelium and on the arrangement of the blood vessels. In a previous paper (Kamat and Israel, 1959), we have found it convenient to classify the findings as follows:

Group I Normal	1. Original mucosa: exocervix covered with intact roseate squamous epithelium. 2. Ectopy: columnar epithelium appearing as glistening 'grape-like' clusters beyond the external os. 3. Transformation zone: intermingling of squamous and columnar epithelium.
Group II Uncharacteristic	1. Endocervicitis & polyps. 2. Atrophic mucosa: a fine network of vessels seen through thin squamous epithelium. 3. Clusters of capillaries, petechial haemorrhages and bleeding points. Often associated with trichomonas infestation.

Group III
Abnormal

1. Leukoplakia: True
   Mosaic
   Ground
   Encircling gland mouths
2. True erosion: abrasion of squamous epithelium.
3. Abnormal transformation zone: glassy yellow appearance.
4. Adaptive vascular hypertrophy: corkscrew and comma shaped blood vessels.

Group IV
Cancer

I shall limit my discussion here to one of these abnormal findings.

'Leukoplakia' is a word of Greek origin and means a 'white plate'. It is not a clinical diagnosis but is a descriptive term which is used by the colposcopist to denote a white or yellow-white area of increased epithelial opacity which does not take the iodine stain. Hinselmann (1953) has described four degrees of abnormality found associated with cervical leukoplakia ranging from a slight increase in basal cell activity to pronounced activity with hyperchromatosis, mitosis and budding into the underlying stroma. He originally regarded all these grades as precancerous. This statement was not, however, corroborated by his own later findings or by those of others. Limburg (1958) states that about 10% of the cases of the various forms of leukoplakia are associated with preinvasive and invasive cancer.

Leukoplakia of the cervix was practically unheard of before the introduction of colposcopy. With the use of this method it has been shown to be relatively frequent. Wespi in 1949 wrote that among 3736 women examined by colposcopy, 7.1% showed the presence of cervical leukoplakia.

Leukoplakic areas generally appear in the transformation zone or the area where the borderline fight between squamous and columnar epithelium is continually going on. Three types of leukoplakia have been described:

1. True leukoplakia in which there is a raised white area which may or may not be visible on naked eye examination.

2. Mosaic or 'field' leukoplakia or 'zoning' which appears as a raised area consisting of polygonal or round yellow-white zones separated by fine red lines.

3. Ground leukoplakia or 'base' which is characterised by a depressed yellow-white area with fine red stippling.

Each of these three varieties of leukoplakia becomes well demarcated after the application of 3% aqueous acetic acid while after painting the cervix with Lugol's iodine solution* the leukoplakic area becomes very distinctly stencilled out against the mahogany stained normal epi-

* Iodine, 4 gms; potassium iodide, 6 gms; distilled water, 100 ml.

thelium. This is a positive Schiller test.

To the three types of leukoplakia already described, a fourth variety may be added in which the mouths of glands present in the transformation zone are surrounded by a thick rim of leukoplakia.

The material comprising this paper was obtained from two family planning clinics of the Indian Cancer Research Centre. The women attending these clinics were of three types:

1. 440 women had come for birth control advice. These were apparently 'normal' women with no symptoms. 92% of them were between the ages of 16 and 35, and 71% of them had had from 2 to 6 pregnancies. 62% of them had had their last delivery from 1 to 12 months previously.

2. 97 women sought treatment for primary, secondary or relative sterility. 85% of them belonged to the age group 16 to 30 years.

3. 68 women sought advice on some gynaecological problem such as leucorrhoea, menorrhagia, backache and so on. The women in this group were from different age groups ranging from 16 to 63 years and had varying obstetric histories.

Classification of Initial Colposcopic and Cytological Findings

The findings of the initial colposcopic and cytological examinations in these women, i.e. prior to any treatment or the use of contraceptives, were grouped according to the classification already described.

Of 605 cases examined, 31.4% showed normal cervices, 52.4% had an uncharacteristic appearance of the cervix and in 15.2% leukoplakia was present.

TABLE I

Findings at Initial Colposcopic Examination

	Total cases	Percent
1. Normal	190	31.4
2. Uncharacteristic	317	52.4
3 Abnormal:		
Leukoplakia	92	15.2
True erosion & adaptive vascular hypertrophy	4	0.7
4. Cancer	2	0.3
	605	100.0

TABLE I

Findings at Initial Cytological Examination

	Total cases	Percent
Class I. Normal	407	67.3
Class II. Slight atypia	188	31.1
Class III. Marked atypia	6	1.0
Class IV. Suspicious for malignancy	4	0.7
	605	100.1

On cytological examination, 67.3% of the cases had class I smears, 31.1% class II smears, 1% had class III smears and 0.7% of the smears showed the presence of malignant cells.

A comparison of the initial colposcopic and smear pictures is made in Table III.

It will be seen that there is a definite shift from the normal to the atypical smears as the colposcopic findings shift from class I to class III.

TABLE - III

Correlation between Colposcopic and Cytological Findings in 605 Women at Initial Examination

Colposcopy	Exfoliative Cytology			Total
I Normal	I	144	(75.8%)	190
	II	45	(23.7%)	
	III	1	(0.5%)	
	IV	—	—	
II Uncharacteristic	I	214	(67.5%)	317
	II	100	(31.5%)	
	III	2	(0.6%)	
	IV	1	(0.3%)	
III Abnormal				
(a) Leukoplakia	I	47	(51.1%)	92
	II	41	(44.6%)	
	III	3	(3.3%)	
	IV	1	(1.1%)	
(b) True erosion & adaptive vascular hypertrophy	I	2		4
	II	2		
	III	—		
	IV	—		
IV Cancer	I	—		2
	II	—		
	III	—		
	IV	2		

An analysis of the 92 cases of leukoplakia showed that leukoplakia around the gland mouths and a combination of two or more varieties of leukoplakia were the most frequently seen (Table IV).

TABLE IV

Analysis of 92 Cases of Leukoplakia

	Total cases	Percent
True leukoplakia	13	14.1
Mosaic leukoplakia	14	15.2
Ground leukoplakia	18	19.6
Leukoplakia around gland mouths	24	26.1
Two or more varieties present	23	25.0
	92	100.0

Type of Smear and Leukoplakia

The smears in the 92 cases of leukoplakia were graded as atrophic, intermediate or mature according to the modified Schmitt classification described by Peters and others (1958). 32% of the smears from the cases with leukoplakia were of the intermediate type while 60% were of the mature type. In comparison, the cases with class I colposcopic findings showed 21% of intermediate smears and 74% of mature smears.

Trichomonas vaginalis Infestation and Leukoplakia

A diagnosis of trichomonas infestation by wet vaginal smear or by

Papanicolaou smear or by both methods was made in 124 out of 605 cases (12%). Of the 92 cases of leukoplakia, 20 (22%) were associated with trichomonas.

Gonorrhoeal Infection and Leukoplakia

In 189 cases, endocervical smears were taken as a routine, stained by Gram's method and examined for the presence of gonococci. The smears showed gonococci in 20 cases (11%). Smears were taken as a routine in 52 cases showing leukoplakia and, among these, 4 (8%) showed the presence of gonococci.

Wespi (1949) comments on the high incidence of gonorrhoea in his cases of early and surface carcinoma and mentions the possibility of inflammation being a predisposing factor in the development of cervical cancer. Carter and others (1956) state that of 275 cases of carcinoma in situ, about 65% were associated with cervicitis.

Follow-up of Cases

In 32 women, who had leukoplakia of the cervix at the initial examination, colposcopic examinations were repeated after from 1 month to 15 months. In 9 of them the leukoplakia had regressed while in 23 it persisted. In 27 women with leukoplakia at the first examination, smears were repeated after from 1 month to 7 months. In 14 cases the smears remained the same, in 7 the atypia had regressed while in 6 cases the smears showed increased atypia.

In 26 cases showing colposcopic findings class I or II at the initial examination, a re-examination from 1 month to 16 months later showed the presence of leukoplakia. Of these, 12 could be followed up further and in 8 of them the leukoplakia persisted while in 4 of them it disappeared.

Leukoplakia and Cancer

In this series of 605 cases there were 4 cases which were proved to have cervical carcinoma either by biopsy or by post-operative examination of sections of the cervix. Two of these had cervical leukoplakia, one had cervicitis with bleeding areas and the fourth had a friable bleeding tumour. The first showed a class III smear with trichomonads, the second showed class III smears at first and later class IV smears (case 1), the third had a class IV smear and gonococci in the Gram's smear and the last case showed class IV smears.

In 2 other cases the smears were of the class IV type; in one of these there was leukoplakia while the second showed atypical vessels and a bleeding polyp and was considered, on colposcopic examination, to be a case of cancer. In a third case the initial colposcopic and cytological findings were normal but at a later examination leukoplakia was present and the smears on one occasion were class IV (case 2). In all three cases the biopsy was negative. These cases are being followed up by colposcopy, cytology and biopsy.

The following two cases will illustrate the usefulness of these methods in indicating the 'dangerous' cases which need careful investigation.

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The following two cases will illustrate the usefulness of these methods in indicating the 'dangerous' cases which need careful investigation.

Case 1. A woman, aged 27, came to the clinic for birth control advice. She was breast-feeding her child of 2½ years and was menstruating regularly. On routine colposcopic examination, an area of true leukoplakia with posteriorly a zone of ground leukoplakia was observed (Fig. 1). The Schiller test was positive. The smear showed large cells with bizarre nuclei and, on repeating the smears, malignant cells with large nuclei showing chromatin stippling were seen (Fig. 2). The biopsy showed basal cell hyperplasia. The smears were, however, persistently class IV type and two months after the initial examination, Wertheim's hysterectomy was done at the Tata Memorial Hospital. Most of the sections of the post-operative specimen appeared like sections of chronic cervicitis. One of the serial sections, however, showed evidence of epidermoid carcinoma in situ at the squamo-columnar junction (Figs. 3 & 4).

This is the type of case which has often resulted in the conversion of a 'Papanicolaou Saul' into a 'Papanicolaou Paul'!

Case 2. A 16-year-old woman who had had her last baby 5 months previously and who was menstruating regularly came to the clinic for birth control advice. On examination it was found that she had a small ectopy (Fig. 5) and the Schiller test showed irregular staining. The smears were class I. Seven months later, on re-examination, two areas of ground leukoplakia were seen which did not stain with iodine. The smears were still class I. Two months later a small growth was seen on

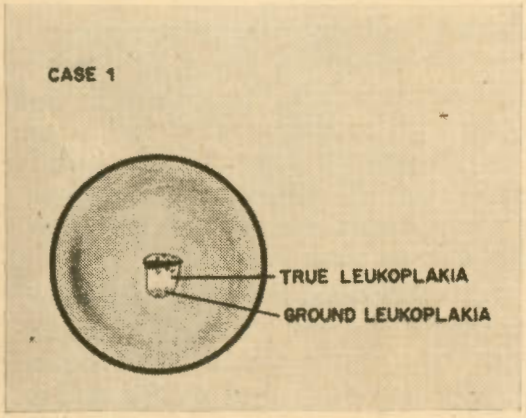

Fig. 1
Case 1. Findings on colposcopy at initial examination.

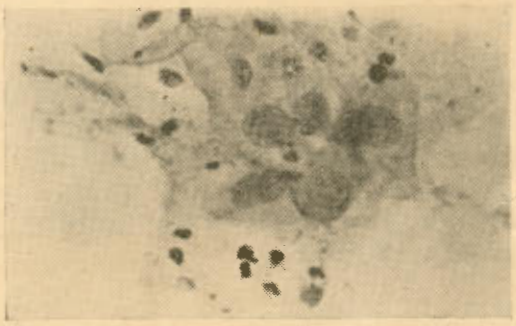

Fig. 2
Case 1. Cervical scraping showing cancer cells. x400.

Fig. 3
Case 1. Epidermoid carcinoma in situ of the cervix. Post-operative specimen, x8.

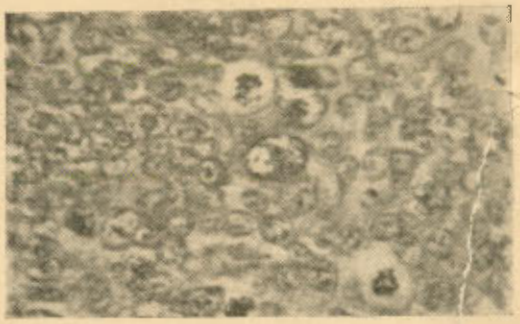

Fig. 4
Case 1. Higher magnification of Fig. 3. x400.

the posterior lip with ground leukoplakia on its surface (Fig. 5). Repeated smears were class III (Fig. 6) and on one occasion class IV. Trichomonads were seen in the smear. Repeated biopsies from the area of the growth showed, however, basal cell hyperplasia (Figs. 7 & 8).

Such a case requires careful follow-up by colposcopy, cytology and, when necessary, biopsy.

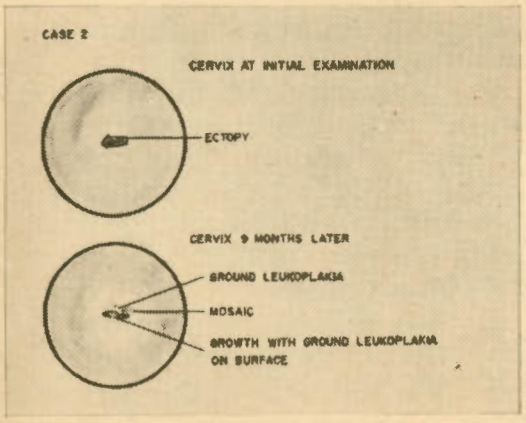

Fig. 5
Case 2. Findings on colposcopy at initial examination and 9 months later.

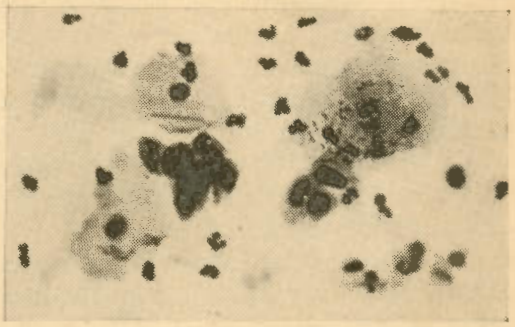

Fig. 6
Case 2. Cervical smear showing groups of cells with large hyperchromatic nuclei. x350.

Fig. 7
Case 2. Basal cell hyperplasia. Cervical biopsy specimen. x54.

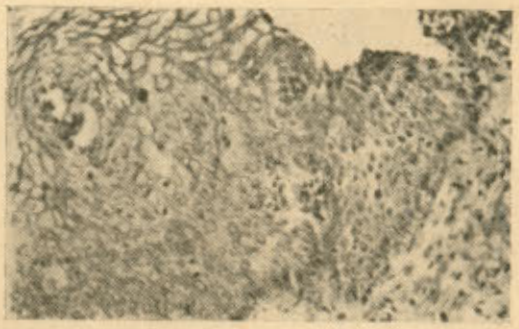

Fig. 8
Case 2. Higher magnification of figure 7. x180.

Note: The smears were stained by Papanicolaou's method and the sections by haematoxylin and eosin.

Leukoplakia of the cervix is thus a colposcopic finding which, in a certain number of cases, may be associated with malignancy as shown by positive cytology and proved by biopsy; in a certain number of cases it may be associated with atypical changes in the smear without accompanying malignancy and in still others the cytology may be perfectly normal. It is interesting to speculate on the reason for the presence of leukoplakia without malignancy. In 1943 Moritz stated that hornification changes can be produced in the mucosa of animals through lack of vitamin A. Hornification has also been shown by others to follow the prolonged administration of folli-

ment of Pathology of the Tata Memorial Hospital for making available to us for study the sections of the tissues. I would also like to thank Mr. A. V. Khopkar and Mr. R. V. Nerurkar for their help in preparing the microphotographs.

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