

OVARIAN CORTICAL STROMAL HYPERPLASIA WITH ASSOCIATED LESIONS OF THE UTERUS AND BREAST

(And a Brief Review of Literature)

by

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The gynaecologist is often puzzled to locate the cause of uterine bleeding, particularly in the post-menopausal women or accord aetiological significance to certain lesions of the ovaries reported on the hysterectomised specimens in these cases. He seeks the advice of the pathologist. The pathologist is equally surprised at the endometrial lesions observed in some of the postmenopausal women and is anxious to establish causal relationship with the unusual morphological changes, both gross and microscopic, observed in the cortex of the ovaries of these women. In recent years the pathologist is also familiar with identical changes in the ovaries removed in cases of advanced carcinoma of breast. The constancy with which the pathologist observes these ovarian lesions in endometrial hyperplasias and malignancy as also cancer breast has lead, first to the

hypothesis and later to the demonstration of cortical cells as the extra-follicular source for oestrogens.

The ovarian cortex in these cases is increased in thickness and cellularity. Spindle-shaped cells with bulky nucleus, some of them laden with lipid, and cholesterol clefts in the neighbourhood contribute to the density of the cortex. These cells are in whorls and in places form the so called "Cortical Granuloma". The inactive stromal cells assume linear pattern. These changes over the cut surface of the ovary appear as small papillary excrescences projecting over the surface reminiscent of intramural miliary leiomyomata of the uterus. The same in haematoxylin and eosin stained sections look as dense bluish spherical masses in the cortex. The stromal cell hyperplasia may be circumscribed and spherical and limited to the greatly broadened and thickened width of the cortex or may be diffuse and extend into the medulla. Some have attempted to grade ovarian cortical stromal hyperplasia and we feel that this serves an useful purpose. Grades I, II and III of stromal hyperplasia are based on

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the density and width and circumference of the hyperplastic cells.

Ovarian cortical stromal hyperplasia, an anatomic change, was first described by Smith in 1941 who observed it associated with endometrial carcinoma. Woll *et al.* found that ovarian cortical stromal hyperplasia is extremely rare in women before the 4th decade and appears between the 4th and 5th decades of life, attaining its peak incidence in the 6th decade after which regression sets in. This is a reaction to hypophyseal stimulation in the absence of functioning follicles of the ovary in the postmenopausal women. The biological potential of the cortical stromal cell and the high urinary oestrogen values in some cases are strong evidence in favour of the idea of the cortical stromal hyperplasia being associated with increased oestrogen secretion. Menopause does not necessarily mean cessation of ovarian activity. Compensatory cortical stromal hyperplasia in the postmenopausal women, as an extra-follicular source of oestrogens, rescues her from the disturbing symptoms that set in at the time of the menopause. The cortical stromal cell is capable of morphological alterations from a theca cell to a fibroblast and during this process has the known capabilities of secreting oestrogens. The possibility that it may at times secrete progesterone and even androgen cannot be ruled out.

MacKay *et al.* have subscribed to the hypothesis that the majority of theca cell tumours originate in cortical stromal hyperplasia. This is evidenced by the histological pattern of both tissues being virtually identi-

cal; transitional stages between cortical stromal hyperplasia and thecomas are seen, and patients with theca cell tumours usually show cortical stromal hyperplasia of the opposite ovary. Both conditions occur in the postmenopausal women. The ovarian mesenchyme from which stroma arises in the reproductive period contributes to the cells of granulosa layer, theca interna, corpus luteum and albicans. The spindle cell of the ovarian stroma becomes larger and stouter and accumulates anisotropic fat. It then regresses and is replaced by scar tissue. This spindle cell is multi-potential. Woll *et al.* concluded that in the senile ovary stromal cell is capable of recapitulation of the normal sequence of the granulosa layer, theca interna, corpus luteum and their neoplastic derivatives without the presence of primordial ovum. They had seen numerous instances of this process in its various transitional stages without relation to atretic follicles or their scars.

Woll *et al.* recorded 44% of women over 30 years of age showing ovarian cortical stromal hyperplasia, and 84% in women with uterine carcinoma. Sommers and Teloh demonstrated a high incidence of cortical stromal hyperplasia in patients with carcinoma breast. Eighty-three per cent of cases of carcinoma breast presented cortical stromal hyperplasia while the same was seen in 37% of non-cancerous series (Table 1). Hertig, in 1957, reported cortical stromal hyperplasia in 90% of cases of endometrial carcinoma. He reiterated that cortical cells are similar to theca cells and are the prime source of oestrogens in the

TABLE I

Ovarian Cortical Stromal Hyperplasia Recorded in Cases of Endometrial Carcinoma and Carcinoma Breast and Control Series

Author	Ovarian Cortical Hyperplasia Recorded			
	Malignant Lesions		Control Series	
	No.	%	No.	%
	Endometrial carcinoma			
Schneider & Bechtel	331	52.3	—	35
Novak & Mohler	—	63.0	—	21
Shah & Dastur	48	50.0	200	0.5
Woll et al	—	84.0	Over 30 years of age.	44
Hertig	—	90.0	—	—
Smith	—	87.0	—	—
Sommers & Meissner	—	73.0	—	—
	Carcinoma Breast			
Sommers & Teloh	—	83.0	—	37.5

postmenopausal women. Novak in a series of 36 cases of endometrial hyperplasia, in whom hysterectomy and removal of all ovarian tissue was carried out, noted that 67% of these showed ovarian cortical stromal hyperplasia. Ovarian cortical stromal hyperplasia is seen in 56.92% of uterine and mammary malignancies and the same was only encountered in 36 to 43% in the control group for the same age group. Unopposed oestrogen stimulation has been suggested as an aetiological factor in the production of carcinoma of the endometrium. The source of this oestrogen in the postmenopausal women has been the object of investigation.

We were so much impressed by the frequent finding of ovarian cortical stromal hyperplasia of all grades in the ovaries of hysterectomised specimens for fibroids, adenomyosis, endometrial hyperplasia and carcinoma, that we undertook a review of the gynaecological specimens registered at the department of Pathology, Guntur Medical College, primarily to

evaluate the true nature and significance of ovarian cortical stromal hyperplasia. We could with confidence predict ovarian cortical stromal hyperplasia when we observed the above uterine lesions and vice versa.

Material and Methods

Clinical history and histological sections stained with haematoxylin and eosin of 720 hysterectomised specimens registered at the Department of Pathology, Guntur Medical College, for the period 1957 to July 1962 were reviewed. Special attention was paid to gross and microscopic appearances of 420 ovaries available in this series. Cut surfaces of these ovaries were carefully inspected for thickening and widening of the cortex and for the presence or absence of spherical nodules of cortical hyperplasia. Sections of ovaries were reviewed and all ovaries which showed stromal hyperplasia of the cortex, medulla or both, of grade III were sorted out. Similarly sections of the uterus, endometrium and cervix and

lesions if any were screened. An attempt was made to correlate the ovarian stromal hyperplasia with the uterine lesions observed in association with the available clinical history. In some cases the age recorded in the requisition forms was disproportionate to the age assessed from the structural changes of the ovaries observed. Ovaries from 4 cases of carcinoma breast were included in this study. One case of adenomyosis and endometrial hyperplasia from the biopsy material of the Upgraded Department of Pathology, Andhra Medical College, is included in this

review. Sections of ovaries of uteri free from lesions for the corresponding age groups from the necropsy material of Guntur Medical College were screened.

Findings

We have given significance to ovarian nodular stromal hyperplasia of grade III and our findings are based on this. We found that in a significant percentage of cases ovarian cortical nodular stromal hyperplasia was associated with pathological changes in the uterus (Table 2). Most frequent single or in combina-

TABLE II
Uterine Lesions Observed in 420 Ovarian Sections Reviewed

Name of lesion	Absence of uterine lesion	Functional uterine bleeding	Cervicitis with epidermadisation	Tubal gestation	Chorion epithelioma	Tuberculous endometrium	Total
Number in each	10	5	3	1	1	1	21

TABLE III
Ovarian Cortical Nodular Hyperplasia Observed in Miscellaneous Lesions of Uterus and Adnexia

Nature of lesion	Number in each	Ovarian cortical nodular stromal hyperplasia	
		Number	Percentage
Fibromyoma	130	66	50.0
Adenomyosis	67	27	40.0
Fibromyoma with adenomyosis	20	2	10.0
Endometrial hyperplasia	52	18	30.4
Endometrial hyperplasia with adenomyosis	12	7	60.0
Fibromyoma with endometrial hyperplasia	8	3	37.4
Carcinoma cervix	17	8	47.0
Carcinoma uterus	13	6	46.0
Inflammatory lesions of cervix or fallopian tube	40	25*	62.0
No lesion	55	18**	32.7
Chorion epithelioma	8	—	—
Total	420	180	

* 3 cases of cervicitis was associated with epidermadisation.

** 5 cases of functional uterine bleeding.

tion with other lesions, seen by us in association with ovarian cortical nodular stromal hyperplasia, was fibromyoma and endometrial hyperplasia or both. These also form a large section of gynaecological biopsy material of any laboratory. In 6 of 13 cases of endometrial carcinoma, and in two cases of carcinoma breast ovarian cortical nodular stromal hyperplasia was observed. This association is also noticed in some cases of carcinoma cervix and cervicitis with epidermadisation and some feel oestrogens do promote the appearance of these lesions. In 22% of ovarian cortical nodular stromal hyperplasia (43 or 183 cases) no uterine lesion was observed and this is in conformity with the published reports. The review of autopsy material did not disclose a single instance of ovarian cortical nodular stromal hyperplasia. Although stromal hyperplasia of the ovary observed belonged to patients in the 4th and 5th decades in our series, in not a few cases this change was seen in patients between 20 and 40 years of age (Table 4). In these

cases evidence of functioning follicles was demonstrated side by side with stromal hyperplasia. Corpus luteum was invariably present in these cases. It is presumed that nodular stromal hyperplasia observed in the age group 20 and 40 years in association with uterine pathology may be due to the excess of oestrogen.

Fibromyoma associated with ovarian nodular stromal hyperplasia

Case Report 1

R, Hindu female, aged over 40 years, was admitted for profuse painful periods since 6 years. Fibromyoma was diagnosed. Hysterectomy and salpingo-oophorectomy were done.

Biopsy Report (4081-84/59): Multiple subserous and submucous fibromyomata were noticed. Sections of the same confirmed fibromyomata with extensive hyaline change (Fig. 1). The ovaries were enlarged and sections of the same showed cortical nodular stromal hyperplasia (Fig. 2).

Endometrial hyperplasia associated with ovarian stromal hyperplasia

Case Report 2

G.A., Hindu Female, aged 40 years, was admitted into the hospital for prolonged and profuse periods lasting for 10 days

TABLE IV
Age Incidence of Ovarian Cortical Nodular Stromal Hyperplasia
in some Cases of Uterine and Mammary Lesions

Lesion	Age in years	20-30	35-40	45-50	55-60	Total
Fibromyoma	—	13	23	29	3	68
Adenomyosis	—	3	20	15	1	39
Endometrial Hyperplasia	—	4	2	15	1	22
Functional Uterine bleeding	—	—	—	4	—	4
Carcinoma breast	—	—	2	—	—	2
Carcinoma Cervix	—	4	1	1	—	6
Carcinoma Uterus	—	—	2	2	—	4
Total	—	24	50	66	5	145

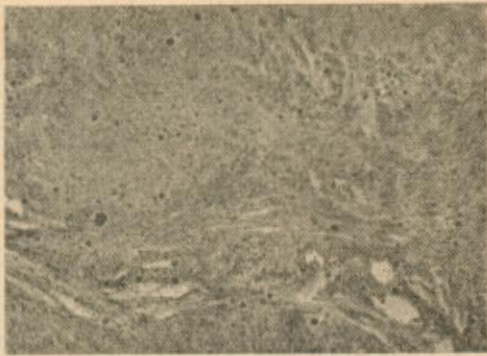


Fig. 1
Case 1—Photomicrograph illustrates fibromyoma with hyaline change. (H & EX 72).



Fig. 3
Case 2—Photomicrograph shows endometrial hyperplasia with cystic dilatation of the glands. (H & EX 60).



Fig. 2
Case 1—Photomicrograph illustrates ovarian cortical nodular stromal hyperplasia—Grade III. (H & EX 60).



Fig. 4
Case 2—Photomicrograph illustrates ovarian cortical stromal hyperplasia—Grade III. (H & EX 60).

each time since one year. Per vaginam uterus appeared normal; cervix showed evidence of cervicitis. Panhysterectomy was done.

Biopsy Report (160-166/58): Endometrium appeared to be more than the normal thickness. Sections of the uterus showed endometrial hyperplasia with tendency to cystic dilatation (Fig. 3). Both the ovaries showed multiple cysts. Sections of them showed cortical nodular stromal hyperplasia of grade III (Fig. 4).

Case Report 3

K.S., Hindu female, aged over 45 years, was admitted to the hospital for profuse

and prolonged vaginal bleeding for 6 months. Per vaginam uterus was enlarged to 16 weeks' size. Panhysterectomy was done. There was a submucous fibromyoma.

Biopsy Report (1795/61): Sections of the tumour showed fibromyoma with hyaline change. Sections of the uterus showed endometrial hyperplasia (Fig. 5). Sections of the ovary showed cortical nodular stromal hyperplasia of grade III (Fig. 6).

Adenomyosis associated with cortical stromal hyperplasia

Case Report 4

K.S., Hindu widow, aged about 35 years, was admitted to the hospital for severe dys-

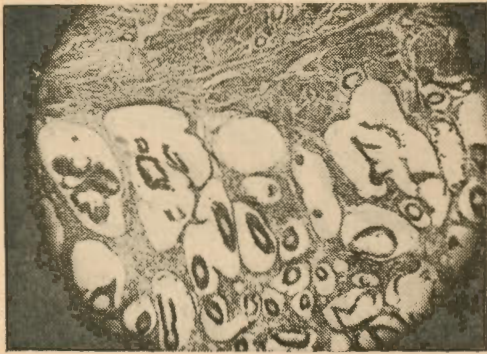


Fig. 5

Case 3—Photomicrograph shows endometrial hyperplasia. (H & EX 40).

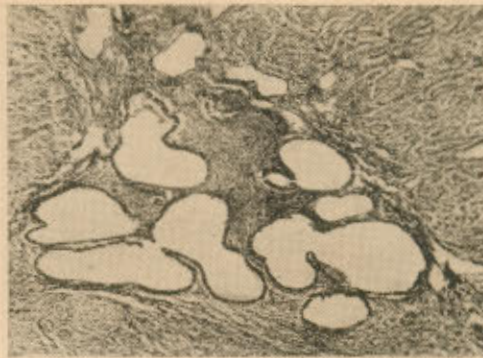


Fig. 7

Case 4—Photomicrograph illustrates adenomyosis. (H & EX 72).

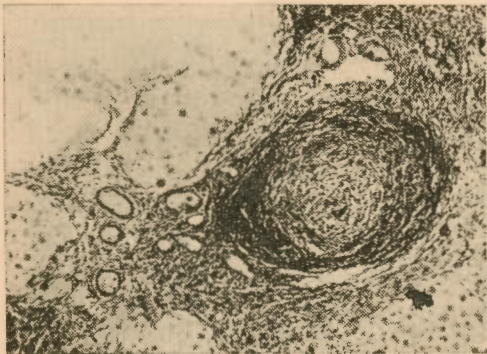


Fig. 6

Case 3—Photomicrograph illustrates ovarian nodular stromal hyperplasia—Grade III. (H & EX 100).

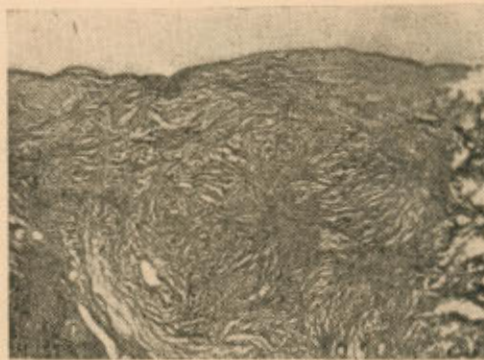


Fig. 8

Case 4—Photomicrograph illustrates ovarian cortical nodular stromal hyperplasia—Grade III. (H & EX 72).

menorrhoea of 3 years' duration. Her last menstrual period was 10 days back. Clinically adenomyosis was suspected. Hysterectomy with salpingo-oophorectomy was done.

Biopsy Report (535-40/58): The uterus was enlarged and sectioned surface presented multiple spots of haemorrhage. Sections of the uterus showed adenomyosis. (Fig. 7). Sections of the ovary showed cortical nodular stromal hyperplasia of grade III (Fig. 8).

Case Report 5

K.S., Hindu female, aged 45 years, was admitted for painful periods and white dis-

charge. Hysterectomy with salpingo-oophorectomy was done.

Biopsy Report (556-58/59): Sections of the uterus showed adenomyosis (Fig. 9). Sections of the ovaries showed characteristic cortical nodular stromal hyperplasia of grade III (Fig. 10).

Case Report 6

A, Hindu female, aged over 40 years, was admitted into King George Hospital for prolapse uterus. She was a widow since 24 years. Last menstrual period was 6 years ago. Per vaginam uterus was retroverted, normal in size. Curettings were done on 23-3-63.

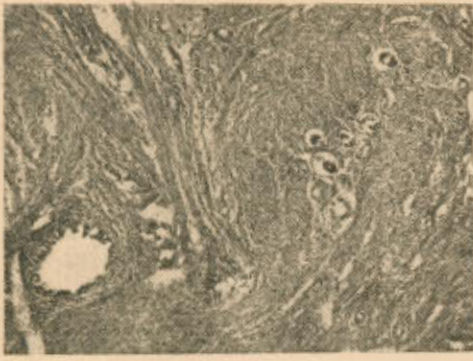


Fig. 9
Case 5—Photomicrograph illustrates adenomyosis. (H & EX 84).

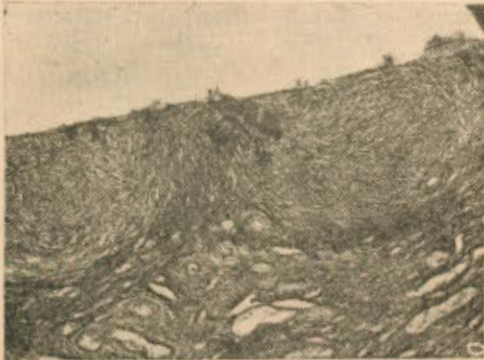


Fig. 10
Case 5—Photomicrograph illustrates ovarian cortical nodular stromal hyperplasia—Grade III. (H & EX 60).

Biopsy Report 4 (1256/63): Endometrium was in the proliferative phase with foci of necrobiosis. Hysterectomy was done on 27-3-63 and clinically diagnosed as carcinoma of body of the uterus.

Biopsy Report (1389 A-I/63): The uterus was enlarged. There was polypoidal hyperplasia of the endometrium (Fig. 11). Sections of the uterus showed cystoglandular hyperplasia of the endometrium and adenomyosis (Figs. 12 and 13). Sections of the ovaries showed cortical nodular stromal hyperplasia with cell nests of lutenisation of the stromal cells (Fig. 14).

Case Report 7

B.D., Hindu female, age not intimated,

was admitted for dysmenorrhoea of 4 years' duration. Per vaginam uterus irregularly

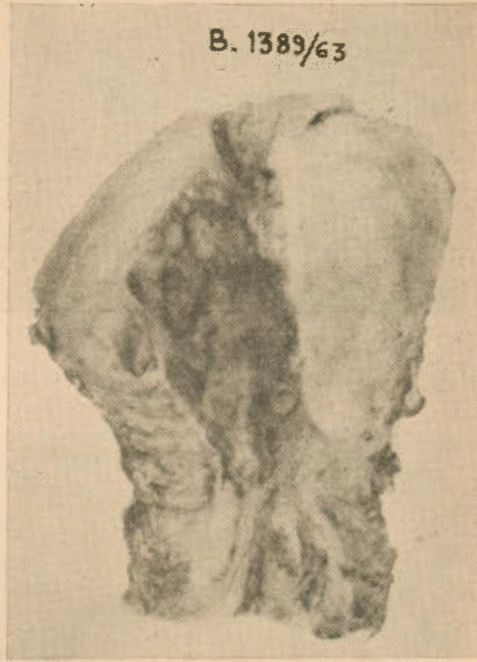


Fig. 11
Case 6—Photograph shows polypoidal hyperplasia of the endometrium.



Fig. 12
Case 6—Photomicrograph shows cystoglandular hyperplasia of the endometrium. (H & EX 50).

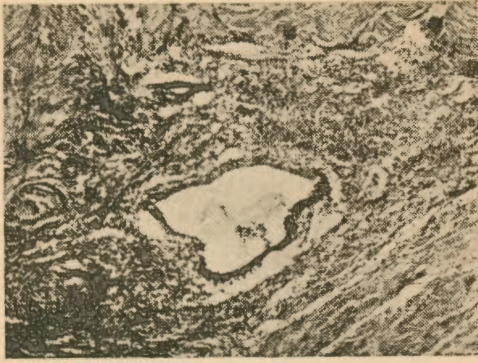


Fig. 13

Case 6—Photomicrograph illustrates adenomyosis. (H & EX 50).

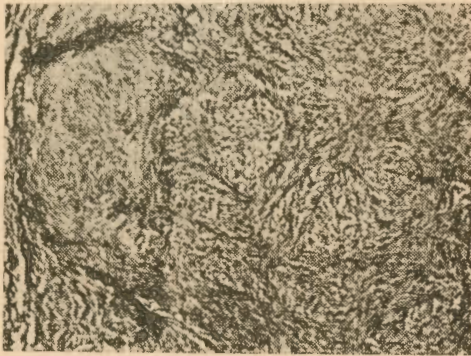


Fig. 14

Case 6—Photomicrograph illustrates ovarian nodular stromal hyperplasia with cell nests of lutenised stromal cells. (H & EX 80).

enlarged; fibromyoma was suspected. Hysterectomy was done.

Biopsy Report (394-A/61): Sections of the uterus showed endometrial hyperplasia and adenomyosis. The sections of the tumour confirmed the clinical suspicion of fibromyoma with hyaline change. The ovaries showed multiple cysts and sections of the same showed cortical nodular stromal hyperplasia of grade III.

Endometrial Carcinoma and Uterine Sarcoma Associated with Ovarian Stromal Hyperplasia

Case Report 8

R., Hindu female, aged 50 years, was admitted into People's Clinic, Guntur, for

irregular bleeding and pain over the lower abdomen. Her last menstrual period was 6 years ago. A bit from the growth protruding from the cervix was sent for examination on 3-1-62.

Biopsy Report (3425/62): Adenocarcinoma showing squamous metaplasia was reported. Panhysterectomy was done.

Biopsy Report (3698 A-J/62): The uterus weighed 1086 grammes. The cervix was detached from the uterus. The fundus of the uterus was filled with a friable growth. This tumour appeared to protrude into the cervix. The ovaries were greatly enlarged (Fig. 15).



Fig. 15

Case 8—Photograph illustrates endometrial carcinoma with greatly enlarged ovaries.

Sections of the uterus and cervix showed adenocarcinoma of the uterus extending into the cervix. The surface epithelium of the cervix was normal. Extensive squamous metaplasia of the adenocarcinoma was observed (Figs. 16 and 17). The tumour was seen infiltrating to varying depths of the endometrium. Sectioned surface of the ovaries showed minute nodules, poorly demarcated one from the other in the cortex and medulla (Fig. 18). Sections of the ovaries showed nodular stromal hyperplasia (Fig. 19).

Case Report 9

N.R.L., Hindu female, aged 45 years, was admitted into Government General Hospital, Guntur, for tumour abdomen associated with postmenopausal bleeding. Hysterectomy was done.

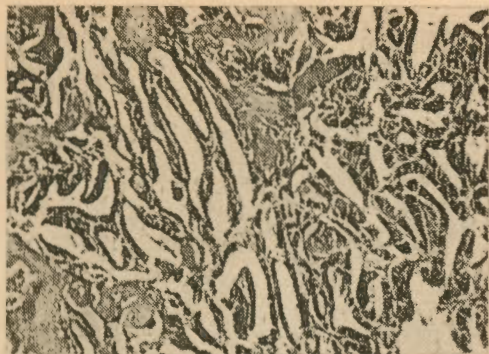


Fig. 16
Case 8—Photomicrograph illustrates adenocarcinoma with squamous metaplasia. (H & EX 63).

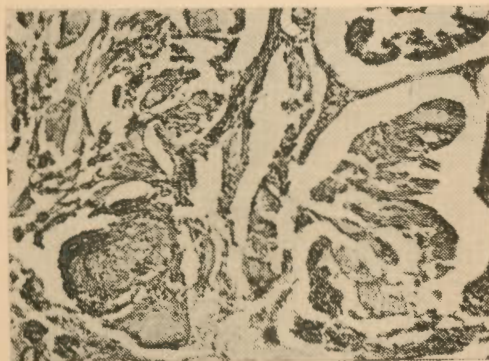


Fig. 17
Case 8—Photomicrograph illustrates adenocarcinoma with squamous metaplasia. (H & EX 100).



Fig. 18
Case 8—Contact photograph shows poorly demarcated nodules of stromal hyperplasia over the cut surface of the ovary. (X 2).

Biopsy Report (56-A-U/62): Multiple pedunculated tumour masses arising from the posterior wall of the uterus were seen. The endometrium was raised into papillary projections (Fig. 20). Interstitial fibromyo-

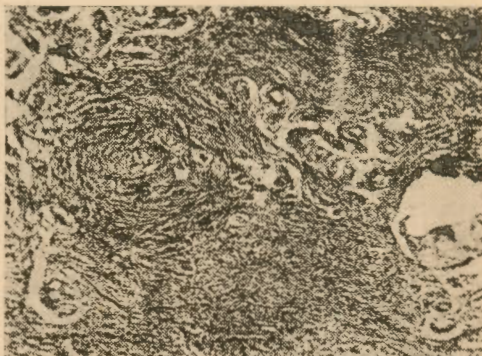


Fig. 19
Case 8—Photomicrograph illustrates ovarian nodular stromal hyperplasia. (H & EX 60).



Fig. 20
Case 9—Photomicrograph shows cut surface of the tumour with papillary projections.

mata were seen. Sectioned surface of the tumour nodules showed foci of necrosis and haemorrhage. Sections studied from multiple blocks showed red degeneration, hyaline and sarcomatous change of the fibromyomata (Fig. 21). Sections from tissue adjacent to the sarcoma and taken from the papillary projections showed adenocarci-

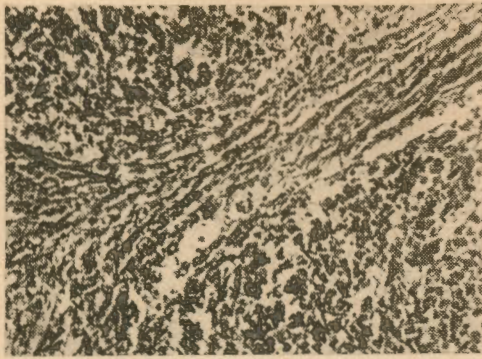


Fig. 21

Case 9—Photomicrograph illustrates sarcomatous change in a fibromyoma. (H & EX 110).

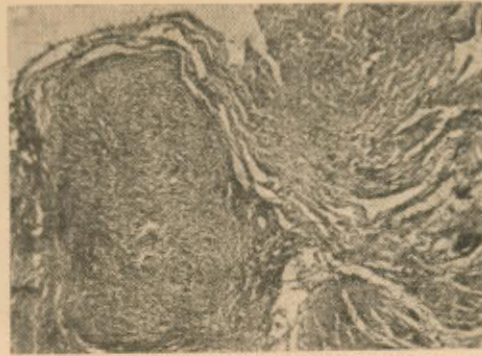


Fig. 23

Case 9—Photomicrograph illustrates ovarian cortical nodular stromal hyperplasia. (H & EX 50).

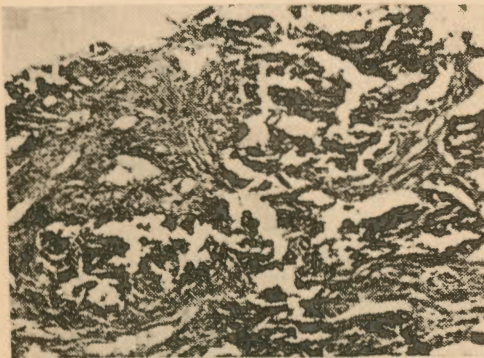


Fig. 22

Case 9—Photomicrograph illustrates adenocarcinoma. (H & EX 50).

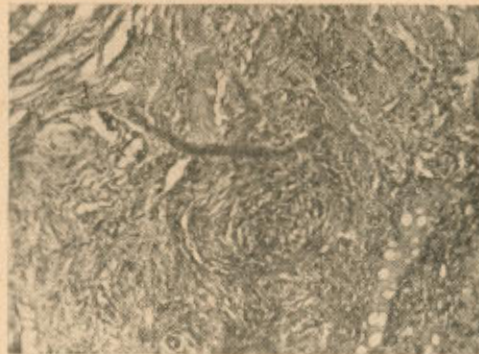


Fig. 24

Case 10—Photomicrograph illustrates ovarian cortical nodular stromal hyperplasia. (H & EX 110).

noma (Fig. 22). Sections of the ovaries showed characteristic cortical nodular stromal hyperplasia (Fig. 23).

Morbid Anatomical Diagnosis: "Uterine sarcoma and coexistent adenocarcinoma associated with ovarian cortical nodular stromal hyperplasia".

Carcinoma breast associated with ovarian stromal hyperplasia

Case Report 10

S.M., Hindu female, aged about 40 years, sought medical aid for carcinoma breast. Bilateral oophorectomy was done.

Biopsy Report (677/62): Sectioned surface of ovaries showed multiple cysts, and nodular stromal hyperplasia (Fig. 24).

Comment

Ovarian cortical nodular stromal hyperplasia was predominantly observed in cases of fibromyomata, endometrial hyperplasia and adenomyosis in our series. The same was observed in a significant number of cases of endometrial carcinoma and carcinoma of breast. We also observed the change in cases of squamous metaplasia and carcinoma of the cervix. In all these lesions earlier reports have confirmed (Gardner et al) the presence of excess oestrogen and that the stromal cell is the source

for the oestrogen was demonstrated. As such ovarian stromal hyperplasia is now recognised as a definite morbid anatomical entity, commonly encountered in postmenopausal women. Ovarian stromal hyperplasia does occur in women without any hormonal disturbances or adverse effects on the uterus, specially as is usually reported in women in the reproductive period. This has also been our experience. Since very often the lesion in the ovaries is disclosed after hysterectomy one is helpless to study hormonal changes before operation for accurate evaluation of the stromal cell potentialities as a source of oestrogen. All that is left to the pathologist is to demonstrate through histochemical methods the presence of lipil in the stromal cells.

The demonstration of ovarian stromal hyperplasia in the younger age groups poses a problem as to what provokes the stromal cell to multiply in the presence of functioning graafian follicles, since it is believed and demonstrated through animal experiments that in the postmenopausal women ovarian stromal hyperplasia takes place under hypophysial stimulation. All these should offer incentive to the biochemist, physiologist, pathologist and the clinician for team work in finding the cause and effect of ovarian stromal hyperplasia.

Summary

1. Literature on ovarian stromal hyperplasia is briefly reviewed.

2. An analysis of uterine lesions and carcinoma of breast associated with ovarian cortical nodular stromal hyperplasia observed in the department of Pathology, Guntur Medical

College, is recorded.

3. The nature and significance of ovarian stromal hyperplasia is discussed.

4. Suggestions are made for further study of this fascinating biological process.

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