GRANULOSA-CELL TUMOURS OF THE OVARY

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Granulosa-cell tumours are rare and form about 2% of any collection of ovarian tumours (Dockerty). Over 600 cases are on record in the literature. Hodgson et al, from Mayo Clinic, reported 62 granulosa-cell tumours in a series of 3,800 ovarian neoplasms—giving an incidence of 1.63%. Menon and Valiath from Visakhapatnam, India, found 3 such cases in a study of 13 uncommon ovarian tumours in a series of 204 ovarian neoplasms (about 1.5%). In a survey of material received in the pathology department of Stanley Medical College, Madras, for the past 10 years, in 85 primary ovarian tumours only two granulosa-cell tumours were seen.

Till very recently these tumours were said to arise from redundant granulosa rests left over in the process of follicle formation—a view championed by Robert Meyer. Novak traces the histogenesis to a still earlier progranulosa or prothecal cell in the ovarian mesenchyma. He likes to group all the granulosa-cell tumours and thecomas under one term, the feminising mesenchymomas. Similarly, Willis is of the opinion that a majority of the tumours are from the formative mesenchyma or the multipotent stroma with a capacity to exhibit divergent differentiation and maturation. He regards "Granulosa-theca-luteal" group of tumours as forming a single histogenetic group arising from the ovarian stroma.

Microscopic appearance varies from a diffuse sarcomatous picture to the characteristically micro- or macro-folliculoid pattern of the granulosa cells. Functionally they are oestrogen producing. Excessive amounts may be found in the circulation and in urine, resulting in precocious puberty in children, menorrhagia during the reproductive period, and post-menopausal bleeding in women. The uterine response may vary from a simple endometrial and myometrial hyperplasia to the formation of myomata and frank endometrial malignancy. The result is a bulky uterus with a swiss-cheese endometrium. The mammary gland also may show carcinomatous changes. Menorrhagia is a main complaint in 74% of Dockerty's cases. Menometrorrhagia may also be seen depending upon the hormonal levels consequent on necrosis and degeneration of the tumour.

The tumour is usually unilateral

and appears at any age. Five to 10% arise in childhood, 45% during maturity and the remainder after menopause. The youngest recorded was in a child of 9 months (Lull). Meinsien reported a granulosa-cell tumour of the ovary in a child aged 1 year 9 months, operated for an abdominal tumour associated with prominent breasts and painless rhythmic bleeding per vaginam. Jacob's case is a child aged 3 years with a tumour of 8 months' duration. Intraperitoneal haemorrhage from the tumour is a rare complication. French collected 25 such cases from the literature and added 2 of his own. The size of the tumour may vary from a minute growth in an apparently normal looking ovary to a growth filling the pelvis and palpable per abdomen. The smallest recorded is 4 mm. in diameter and the largest 40 cm. in diameter and weighed about 34 lbs. in weight (Hodgson et al).

Behaviour of the tumour is difficult to judge microscopically. Statistics regarding malignancy varied from 10 to 55%. Barzilae doubts the efficacy of correlating the histological picture with clinical malignancy, as there is very little difference to be appreciated between benign and malignant granulosa-cell tumours. Clinical malignancy is diagnosed when there is rupture of the capsule, or obvious secondaries over the peritoneum or abdominal viscera are seen. Local recurrence in 10 to 20 years after the operation is recorded in 25 to 30% of the tumours. The microscopic appearance of primary and the recurrent growths is more or less alike. Metastases have been described in the abdominal viscera, lungs and brain.

Removal of tumour with sparing of the uterus and the other ovary is the operation of choice in younger age groups with well encapsulated tumours (majority are unilateral). In older age groups and where the capsule is not entire, radical hysterectomy is preferable.

The following two cases are recorded because of their rarity and as they present some of the interesting features.

Case 1: Mrs. L, aged 44 years, was admitted into the Government Lying-in Hospital, Madras, on 19-9-1951 with a complaint of profuse periods for the past three years and swelling of the lower abdomen of 1 month's duration. Menstrual history: She attained puberty at the 14th year. Periods were regular at intervals of a month and lasting for a week, moderate in amount and not painful. For the last three years, periods have become prolonged and profuse, lasting 10 to 15 days at intervals of a month, not accompanied by pain. She is having continuous bleeding per vaginam for the last 15 days following an amenorrhoea of 1½ months' duration. Obstetric history: Married in the 15th year. She had two full term spontaneous deliveries—both children alive—last child age 23 years.

On Examination: She was anaemic. Per abdomen: there was a well defined nodular, partly cystic, lump in the left iliac fossa. Restricted in mobility, it was not tender but dull on percussion. Vaginal examination showed a broadened cervix with a retroverted normal but fixed uterus.

A nodular cystic swelling, extending 1½ to 2 inches above the left inguinal ligament, was felt in the left fornix. The right fornix was free. Blood pressure: 110/74 mm. of mercury. Haemoglobin: 65%. Urine showed no abnormality.

With a provisional diagnosis of malignant ovarian tumour, left side, the abdomen was opened under a heavy spinal anaesthesia. Numerous firm nodular deposits were found over the omentum, caecum, appendix and the sigmoid. The left ovary was enlarged to about 4 inches by 3 inches by 2 inches with multiple cysts and haemorrhagic areas. The uterus was normal in size but presented a few nodules on its posterior aspect. Right tube and ovary were apparently healthy. A firm nodular mass about one inch in diameter was palpable over the bladder wall. Stomach and liver were free from deposits. In view of the widespread metastases a radical operation was substituted by a left salpingo-oophorectomy. Deposits over the sigmoid were taken for biopsy. Abdomen was closed in layers.

Pathological report by Professor G. D. Valiath: *Macroscopic Appearance:* Left ovary is enlarged to about 4″ X 3″ X 2″, partly solid and partly cystic with a nodular surface. Capsule seems to be entire. Section showed greyish solid areas and cystic spaces with evidence of haemorrhage and degeneration. *Microscopic examination* shows sheets of more or less uniform oval and spindle shaped cells with no definite arrangement or specific pattern. Here and there some of them show hyperchromatic nuclei and mitoses. There is very little evidence of connective tissue invasion, dividing the cells into groups or columns. This may be considered as a diffuse or parenchymatous type of granulosa-cell tumour of the ovary. Metastatic deposits showed a similar picture (Figs. 1, 2 and 3).

Convalescence was uneventful. A skiagram of the chest on 12-10-1951 showed no evidence of secondaries in the lungs. She was started on a course of deep X-ray from 22-10-1951 and was discharged on 22-11-1951 after 20 exposures. There were no palpable masses in the pelvis at the time of discharge. Follow up: On 29-1-1954 the patient is reported to be doing well.

Case 2: Mrs. G, aged 50 years, was admitted into the Government Lying-in Hospital, Madras, on 15-5-1953 with a complaint of continuous bleeding per vaginam for the past six months. Menstrual history: Menarche at 14th year; periods regular, once in thirty days, lasting for three to four days; moderate in amount and not painful. For the past two years the periods were profuse and prolonged, once in three months, lasting for about 2 months each time. In the last six months the bleeding has become continuous. Obstetric history: Married after puberty. She had 11 full-term normal deliveries. Only three are alive. Last child aged 15 years. She had 6 abortions at 12 to 16 weeks, last being 14 years ago.

On examination there were no palpable masses in the abdomen. Vaginal examination revealed a bulky anteverted uterus about 8 to 10 weeks' size and an eroded cervix;

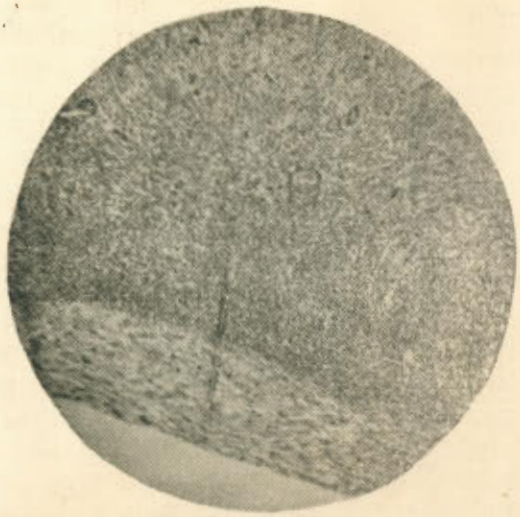


Fig. 1: Shows the diffuse spindle shaped or oval cells with no tendency to arrange in a specific pattern. There is very little connective tissue dividing the tumor into lobules (Low Power).

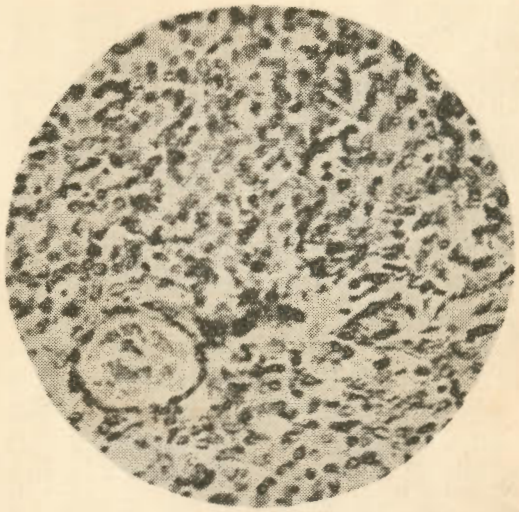


Fig. 2: Same as figure one—high power. Shows prominent hyperchromatic nuclei; a few in mitoses.

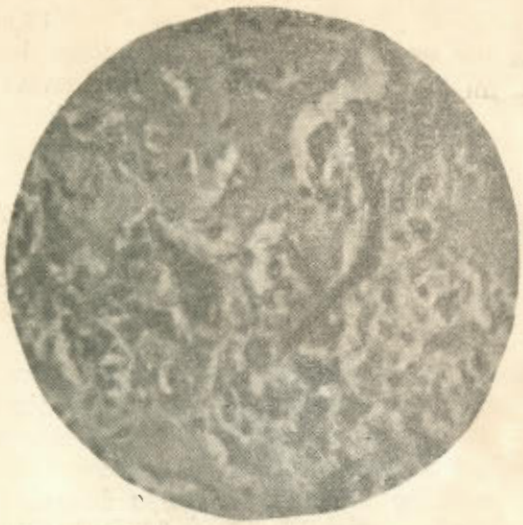


Fig. 3: Section of a secondary deposit. Picture is more or less similar but there is comparatively more marked stromal reaction.

fornices were free. Speculum examination showed follicular erosion of the cervix. Blood pressure: 110/60 mm. of mercury. Haemoglobin 60%. Urine showed no abnormality.

On 20-5-1953 under general anaesthesia, cervical dilatation and endometrial curettage was done. The scrapings were thick and microscopic examination showed bits of endometrium in oestrin phase. No evi-

dence of malignancy could be detected. Five days later she was discharged and was free from vaginal bleeding for a month. On 27-7-1953 she was readmitted for a recurrence of the complaint. Vaginal examination revealed similar findings as before.

On 8-8-1953 under heavy spinal anaesthesia abdomen was opened by a right para-median incision. The uterus appeared soft and bulky. Both tubes and ovaries were apparently healthy. Total hysterectomy with bilateral salpingo-oophorectomy was done and abdomen was closed in layers.

Pathological report by Professor G. D. Valiath: *Macroscopic Appearances:* The uterus is soft and bulky; about 8 to 10 weeks in size of pregnancy. On *section* the uterine wall is much thickened, measuring about an inch. The endometrium is velvety, showing polypoidal projections of varying sizes from that of a pin head to one measuring about $\frac{1}{2}''$ in its longest diameter, near the left cornua. The endocervix is thickened. The portio vaginalis shows a few Nabothian follicles. Both tubes look normal except for a number of subserous cystic lesions and pedunculated fimbrial cysts at the right fimbrial end. Both ovaries look fibrotic with occasional yellowish areas. The left is bigger than the right but shows no gross abnormality (Fig. 4). *Microscopic appearance:* The endometrial glands show well marked cystic dilatation of the lumen—suggestive of swiss-cheese hyperplasia. There is no evidence of secretion (Figs. 5 & 6).

Left ovary shows an early granulosa-cell tumour with typical folli-

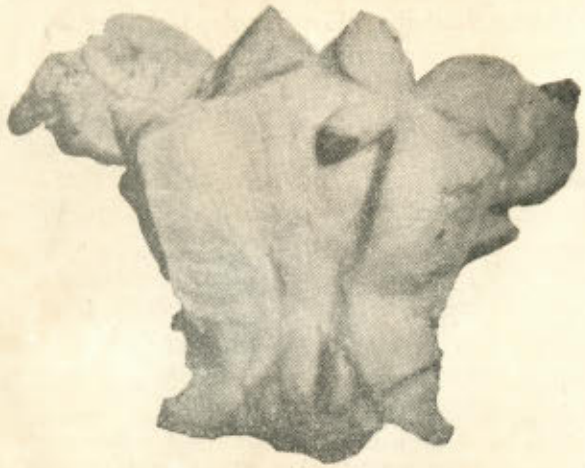
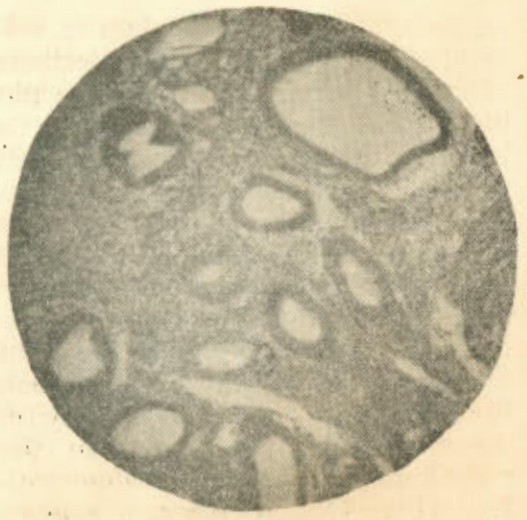


Fig. 4: Specimen of uterus and ovaries. Note the big polypus at the left cornu, and marked thickening of the uterine wall.

culoid arrangement of granulosa cells (Figs. 7 & 8).

The post-operative period was smooth. The skiagram of the chest taken a fortnight after the operation showed no secondaries. In view of possible malignancy, a course of deep X-ray exposures was given. The



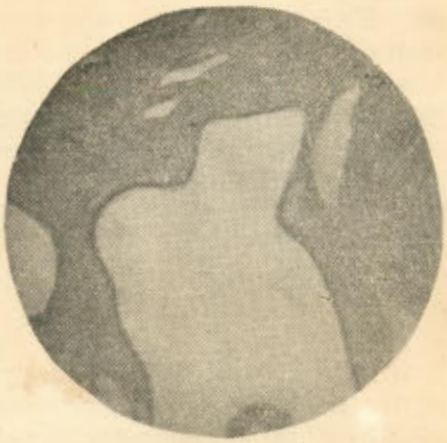


Fig. 5 & 6: Show the cystic glandular hyperplasia of the endometrium. Note the absence of secretion and marked dilatation of the lumina.

patient was discharged a month later.

Comment. Our two cases represent the two extremes of the tumour with certain interesting features. In both menorrhagia was the presenting symptom. Case I represents a big sized tumour, palpable per abdomen and with multiple secondaries, over abdominal and pelvic structures, though to the naked eye the capsule looked entire. As such the case was not suitable for radical operation.

Fig. 7: Section of ovary showing the granulosa cell tumor with finely folliculoid pattern and a tendency to cyst formation. (Low Power).

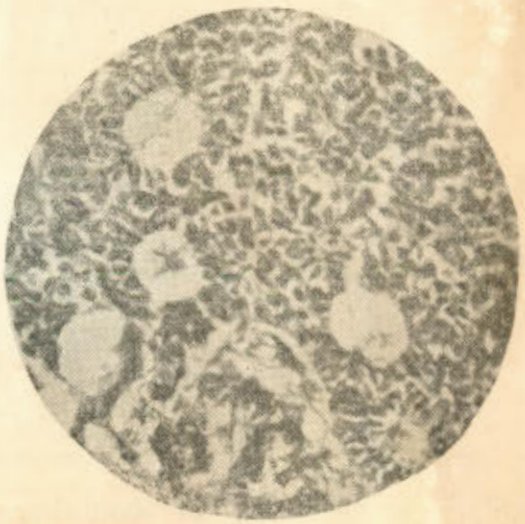


Fig. 8: Enlargement of Figure 5. Showing the detail of clusters and rosettes (High Power).

Local removal of the tumour with post-operative irradiation was chosen as the line of treatment. This is in keeping with the principles accepted by Taylor in the treatment of advanced ovarian carcinomas. Microscopic picture consistent with the clinical picture is of sarcomatoid or parenchymatous pattern. The patient is well upto 29-1-1954 (Over two years after the first diagnosis). Case 2 represents the other extreme. There was continuous bleeding in a woman of menopausal age with endometrium in the oestrin phase. There was polypoidal hyperplasia of endometrium. The finding of a granulosa-cell tumour was only incidental in the routine biopsy examination of an apparently normal ovary. The myohyperplasia, endometrial proliferation, with polypoidal formation is definitely the result of "oestrogen bombardment". Probably there is no relation between the size of the tumour and the amount of oestrogen produced. Panhysterectomy was done because of recurrent uterine bleeding, after currettage in a woman of 50 years of age. The preoperative diagnosis was metropathia, but the discovery of a small granulosa-cell tumour was made on routine microscopic examination. The tumour was for all practical purposes looking benign. The histological picture of a granulosa-cell tumour does not often reflect the true nature of the neoplasm. As already mentioned delayed recurrences are not uncommon. Hence after a radical operation a deep X-ray therapy was given. Brazilai strongly advocates this line of treatment even in all advanced cases.

Opinions differ regarding the radiosensitivity of these tumours. Moreton and Leddy consider them to be moderately sensitive compared to the other ovarian malignant tumours. Traut and Marchetti are of the opinion that they are fairly resistant. However, Dockerty and Barzilai believe that these tumours even when there is delayed recurrence or metastases respond favourably to combined surgical and radiotherapeutic measures. Te Linde and Jones reported a case of recurrent granulosa-cell tumour which responded well to irradiation. Ascites and abdominal masses disappeared at the end of a course of deep X-ray therapy. The patient was symptom-free for nearly $3\frac{1}{2}$ years. It is difficult to assess the radiosensitivity in our two cases. However our case is still symptom-free, nearly 2 years and three months after the first diagnosis and combined treatment.

Summary

1. Out of 85 ovarian tumours studied in the department of pathology, Stanley Medical College, Madras, in a period of 10 years (1944 to 1953) only two cases were granulosa-cell tumours.

2. Two cases of granulosa-cell tumours are described and the treatment discussed.

3. The important clinical and pathological features of the tumour are briefly reviewed.

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