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REVIEW: 50TH ANNIVERSARY ISSUE

# Ovarian sex cord-stromal tumours and their mimics

ROBERT H. YOUNG

*James Homer Wright Pathology Laboratories, Massachusetts General Hospital, Harvard Medical School, Boston, MA, United States*

**Summary**

Sex cord-stromal tumours of the ovary include many of the most morphologically intriguing ovarian neoplasms and albeit many of them are rare, they factor into the differential diagnosis more often than their frequency might suggest. The most common malignant form, the adult granulosa cell tumour, may grossly simulate various surface epithelial neoplasms. Microscopically, confusion with endometrioid carcinoma may occur because the cords and microfollicles of the granulosa cell tumour may be mimicked by endometrioid carcinoma and the latter may have pale nuclei with nuclear grooves. Thorough sampling generally resolves this differential and if not immunohistochemistry aids. Although the adult granulosa cell tumour typically has cells with scant cytoplasm in some cases the tumour cells are luteinised and others have cells with abundant pale cytoplasm. A reticulum stain may be of great aid in indicating whether cells of the type just noted are of granulosa or theca nature. Variations in the morphology of the juvenile variant of granulosa cell tumour that can be diagnostically challenging include those that have a macronodular pattern with scant follicular differentiation, those with marked sclerosis, and those that are unusually pleomorphic. The uncommon but histologically varied Sertoli–Leydig cell tumour is considered, emphasis being placed on the most recently described variant, the retiform pattern, with its potential to mimic surface epithelial neoplasms and even mixed mesodermal tumours. Considering the usual young age of the patient may be paramount in making this tumour come to the mind of the pathologist. The rare pure Sertoli cell tumour is briefly noted as is the sex cord tumour with annular tubules, well known because of its association in some cases with Peutz–Jeghers syndrome. Most do not have that association, however, but have their own interesting features including a greater than average risk, among sex cord stromal tumours, of nodal metastasis and progesterone production, and an occasional development from them of an otherwise typical Sertoli cell tumour. The stromal family includes the common fibroma which is challenging when it is cellular with some mitotic activity and the approach to such neoplasms is reviewed. Emphasis in the consideration of thecoma is placed on its typical cytological features and the overlap with what may be seen in some adult granulosa cell tumours. The review concludes with three fascinating pure stromal tumours all described within the last several decades: the sclerosing stromal tumour, the unusual luteinised thecoma associated with sclerosing peritonitis and the microcystic stromal tumour. The first is sometimes misdiagnosed when pure stromal neoplasms of other types are vascular and may have pseudolobules and it is essential that the pseudolobules of the sclerosing stromal tumour contain a haphazard admixture of fibroblasts and weakly luteinised cells. The remarkable tumours associated with peritonitis exhibit brisk mitotic activity but appear not to have a metastatic potential; they can cause significant problems because of the sclerosing peritonitis. The microcystic stromal tumour may mimic a steroid cell tumour or thecoma but unlike them is inhibin and calretinin negative, and stains for CD10 and β-catenin. It often shows bizarre nuclei atypia but limited mitotic activity and appears to be clinically benign on the basis of still limited experience.

*Key words:* Ovary; tumours; sex cord-stromal.

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## INTRODUCTION

It is a pleasure to contribute to the 50th anniversary issue of *Pathology*. Elsewhere I have reviewed the history of gynaecological pathology, in one essay in this journal surveying Australasian contributions.[1,2] The year 2018 marks another anniversary, the 60th of the publication of *Endocrine Pathology of the Ovary* by Dr John M. Morris and Dr Robert E. Scully.[3] That work focused largely on sex cord-stromal tumours and my long association with Dr Scully[4] (in my opinion one of the two giants of gynaecological pathology) enabled me to see numerous examples within this fascinating category of ovarian neoplasia. It is of further historical interest that the second of the two giants of gynecological pathology, Dr Robert Meyer,[5] had earlier contributed significantly to this area. Near the end of his career Dr Scully co-authored with me an essay basing the differential diagnosis of ovarian tumours on their various patterns and cell types;[6] the great diversity of patterns in the sex cord-stromal tumour group made them neoplasms frequently considered in that work. Finally, although the correct diagnosis of ovarian tumours is obviously important in a patient of any age, it is particularly important in young females in whom, if possible, conservative surgery to preserve optimal reproductive and endocrine function is ideal and many sex cord-stromal tumours occur in the young.[7]

A reader who does not specialise in gynaecological pathology may reflect that this group of neoplasms includes many which are rarely encountered by them. That is true but the differential diagnosis of a great number of ovarian tumours frequently includes sex cord-stromal tumours even if

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the neoplasm being studied does not belong in that category after careful evaluation. Furthermore, their morphological spectrum is remarkable and all lovers of histopathology will I hope enjoy the reflections and accompanying illustrations about these neoplasms.

I begin by considering those which have an epithelial component because the granulosa cell tumour is one of the more common malignant ovarian tumours if one excludes the surface epithelial carcinomas. Consideration of it is followed by other epithelial or epithelial dominant tumours before concluding with the pure stromal tumours about which there have been some recent descriptions of interest. Due to space constraints I will largely focus on their microscopic features, focusing to some degree on unusual aspects I have seen in a very large experience with these tumours. Their standard clinical and routine microscopic features are well known having been covered in numerous sources. Due to the ease of finding references through the computer now I will be selective in referencing and only include some of particular, including historical, interest and selected examples from certain categories to enable the reader quick access to some bibliography. Additionally, Dr Scully's second fascicle contains an extensive bibliography on the literature as of the time of publication of that work.[8]

## GRANULOSA CELL TUMOURS

Granulosa cell tumours are divided into adult (AGCTs) and juvenile (JGCTs) categories; the latter accounts for about 5% of all GCTs. These are terms of convenience to connote a spectrum of appearances typically seen in adults or juveniles, but AGCTs occasionally occur in young individuals[9] and JGCTs may occur, albeit even less often, in older patients.[10] Tumours of each type are usually pure but occasional tumours have significant components of each or may be associated with a component of Sertoli–Leydig cell tumour. AGCTs peak between 50 and 55 years of age but occur at all ages; they are rare in the first decade. Over 90% of JGCTs occur in the first three decades. The usual presentation of each is due to the typical symptoms of an adnexal mass but endocrine manifestations (sexual precocity in cases of prepubertal JGCT) may be striking. Acute abdominal symptoms from tumour rupture and haemoperitoneum occur in 10% of cases, more often than is the case with other ovarian tumours.

GCTs are usually between 5 and 15 cm and >95% are unilateral. The cut surfaces are typically solid and cystic with fluid or blood-filled cysts separated by solid, yellow to white, soft to firm tissue. However, some are entirely solid or conversely entirely cystic so many tumours, including those in the surface-epithelial category, can be mimicked on gross inspection. Friable tissue lining cysts can enhance the resemblance just noted. It is at the microscopic level that significant differences exist in the morphology of the two subtypes and accordingly they are each considered separately now.

### Adult granulosa cell tumour

*Microscopic features*

AGCTs have a wide variety of patterns, usually admixed, including diffuse, insular, trabecular, corded, nodular, follicular, and sarcomatoid. A diffuse pattern is most common in my experience. It is characterised by densely cellular sheets of cells with scant cytoplasm imparting a 'small blue cell tumour' appearance. Careful scrutiny, however, usually shows at least some, often subtle, foci of epithelial-type patterns, sometimes most evident at the periphery. A variably prominent insular pattern, discrete nests usually surrounded by a conspicuous stroma, is quite common. Thick trabeculae or thin cords, more often the latter, with a regular to irregular arrangement are often seen, at least in minor amount, and are often diagnostically helpful. In some tumours they dominate. Photogenetic delicate patterns in this family are those in which gyriform or moire-silk arrangements are seen (Fig. 1). A nodular pattern, generally smoothly contoured rounded aggregates, with a largely diffuse of arrangement of cells within the nodules is seen in a minority of cases.

Much emphasised in many texts is a microfollicular pattern in which small cavities (Call–Exner bodies) that may contain eosinophilic fluid, degenerating nuclei, hyalinised basement membrane material, or rarely basophilic fluid are seen. These may be diagnostically helpful but also confusing as we shall see below. In my experience they are present in no more than 10% of the tumours, and neoplasms in which they dominate are rare. A macrofollicular pattern is even less common and almost never dominates. Small hollow or solid tubules occasionally are seen to a limited degree and rarely are more conspicuous (Fig. 2). In general, they are of course more typical of Sertoli and Sertoli–Leydig cell tumours but when their cytological features are classic of GCT and other features of the tumour are of that nature they can be considered a variant pattern of AGCT. A final, but not rare pattern of growth, is in the form of cells that range from fusiform to unequivocally spindled (Fig. 3) and can make cellular fibroma very realistic in the differential diagnosis (see below).

A morphological aspect of the AGCT, shared with the Sertoli–Leydig cell tumour, is alterations in its appearance when excised in the last trimester of pregnancy. These tumours often exhibit prominent oedema or luteinisation which may alter the appearance in sufficient regions as to make the diagnosis challenging.[11] Thorough sampling and mere awareness of this phenomenon can be crucial in not leading to a misdiagnosis.

The granulosa cells usually have scant cytoplasm and pale, uniform, angular to oval, often grooved nuclei that are often arranged haphazardly in relation to one another. In some tumours, particularly in my experience those with a nodular

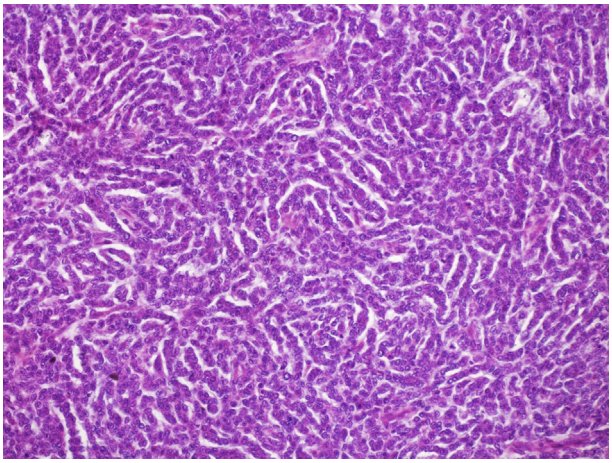

**Fig. 1** Adult granulosa cell tumour. Delicate thin cords are conspicuous.

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