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REVIEW: 50TH ANNIVERSARY ISSUE

Ovarian sex cord-stromal tumours and their mimics

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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

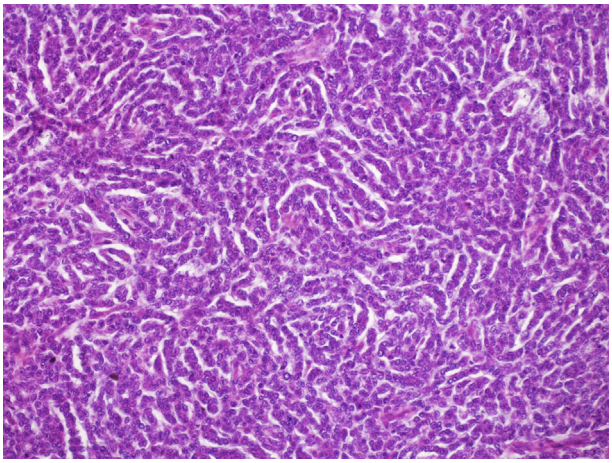

Fig. 1 Adult granulosa cell tumour. Delicate thin cords are conspicuous.

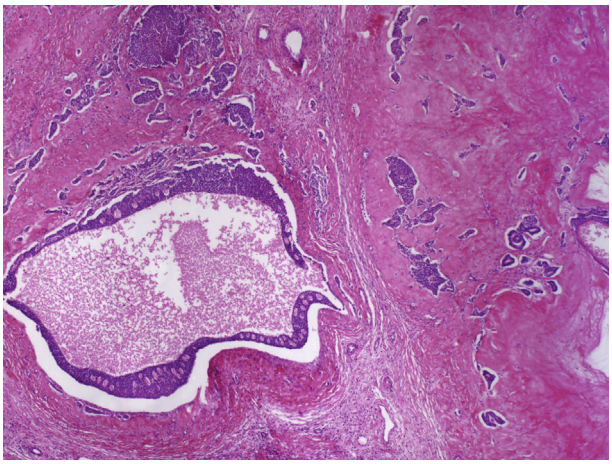

Fig. 2 Adult granulosa cell tumour. This tumour is unusual because of marked sclerosis and the presence of tubules (right). Note Call–Exner bodies surrounding a cyst (left).

pattern, cells with appreciable pale cytoplasm and tinctorial properties reminiscent of the cells in many thecomas are seen. In other cases the tumour cells have abundant moderate to abundant eosinophilic cytoplasm (are luteinised) and in them nuclear grooves tend to be less conspicuous and nucleoli more prominent than in non-luteinised neoplasms.[12,13] The conspicuousness of nuclear grooves is highly variable in AGCTs overall and is perhaps overemphasised to a degree in writings on this tumour. The mitotic rate is also variable, but generally low. The cytological features in most tumours are low grade. However, an occasional tumour which can be placed in the granulosa cell category, particularly if immunostains are confirmatory, has features that are more worrisome than average. In such cases a notation is obviously appropriate. Enigmatically, otherwise typical granulosa cell tumours have, in about 2% of cases, pleomorphic so-called bizarre nuclei (Fig. 4) which when unassociated with any greater than average mitotic activity do not appear to have an adverse effect on prognosis.[14] They are usually a focal finding but may be numerous on occasion with the typical foci of granulosa cell neoplasia being sometimes seen in limited zones between pleomorphic regions only after very careful scrutiny.

The stromal component varies from scanty in tumours with a diffuse pattern to most of the neoplastic tissue in some cases. The stroma, which may be richly vascular, ranges from fibrous, rarely very oedematous (less often so than in Sertoli–Leydig cell tumours), to more cellular and commonly contains theca externa-like cells, or occasionally, luteinised theca interna-like cells (Fig. 3) with moderate to abundant eosinophilic cytoplasm or more often pale lipid-rich cytoplasm. Stromal cells with eosinophilic cytoplasm can rarely be identifiable as Leydig cells if Reinke crystals are present; rarely they are hepatocytic.[15] Non-specific stromal fibrosis, chronic inflammation, old or recent haemorrhage, haemosiderin, and non-specific cysts are often present and may complicate the appearance.

AGCTs are usually reactive for markers of sex-cord differentiation. The best and all that is needed in most cases are inhibin and calretinin but occasional examples are inhibin negative. Shah *et al.* found a mutation in *FOXL2*, a gene encoding a transcription factor required for granulosa-cell development, in 97% of them.[16] This writer has minimal experience with *FOXL2* and refers an interested reader to various papers that have explored this area within the past few years.

Differential diagnosis

This includes other tumours in the sex cord-stromal category, considered first, and those from unrelated categories. Stromal tumours, both thecoma and cellular fibroma, may be quite a challenge. With regard to thecoma it is largely because some AGCTs have cells with pale cytoplasm which resemble, indeed can be indistinguishable from, the cells of a thecoma and in the absence of overt epithelial differentiation thecoma can be a very plausible diagnosis. We have found the reticulum stain of great aid in this differential as it outlines aggregates of neoplastic cells in zones of granulosa cell

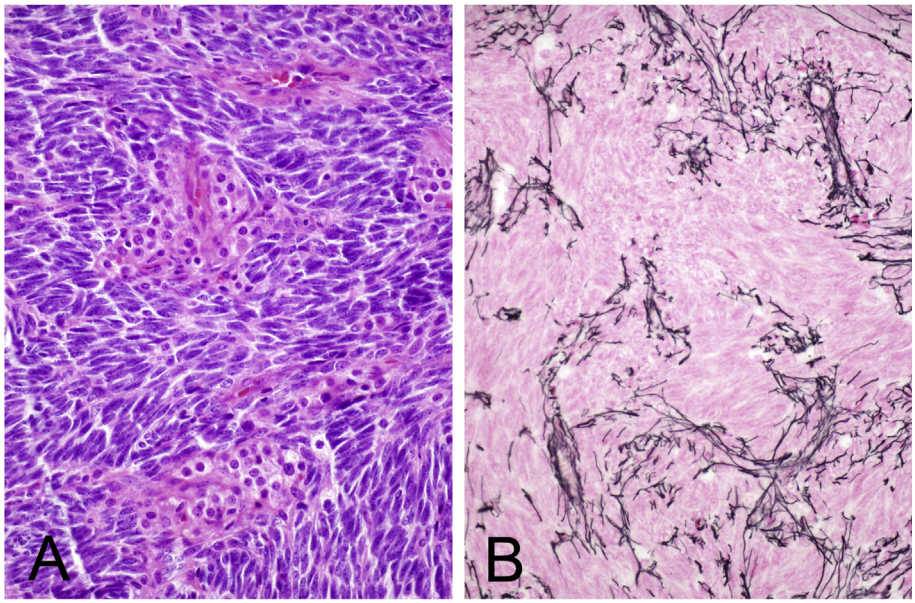

Fig. 3 Adult granulosa cell tumour. Many of the tumour cells are spindled (left). A reticulum stain (right) shows a dearth of fibrils in many areas indicating a prominent granulosa cell component. Note many luteinised stromal cells (left).

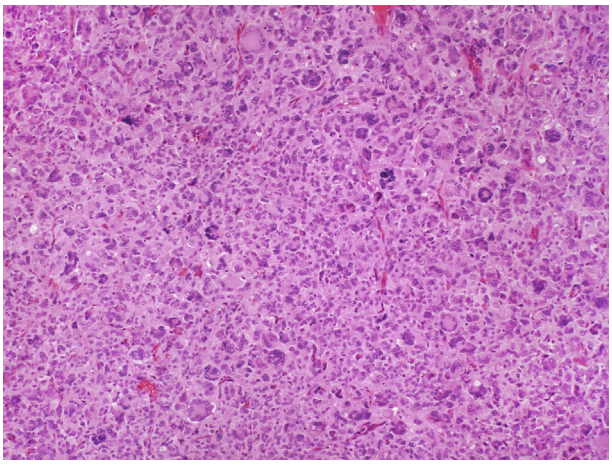

Fig. 4 Adult granulosa cell tumour. This neoplasm has many bizarre nuclei, some of them multinucleate. More typical granulosa cells can be seen in the background.

neoplasia whereas in pure thecomas there is individual cell investment. In some AGCTs growth of neoplastic granulosa cells in a so-called sarcomatoid pattern may make the differential with cellular fibroma in the absence of confirmatory epithelial differentiation or reticulum stains (Fig. 3) challenging so the former should be assiduously sought and the latter stain generously utilised. Fibromas appear to lack the *FOXL2* mutation so this is potentially a new modality to aid[17] as noted earlier but the reticulum stain is quite satisfactory. A rare tumour that falls in the stromal category, a so-called stromal tumour with minor sex cord elements merits brief mention.[18] We reserve this designation for tumours that are in vast part typical fibroma or thecoma but have a few minor sex cord elements here and there and common sense indicates the likelihood of them being of prognostic significance is nil. It should be noted that some granulosa cell tumours are stromal predominant and if granulosa elements are more than minimal the diagnosis of granulosa cell tumour should be made. However, although it is unlikely proof will ever be obtained because of the rarity of such neoplasms and the difficulty in getting long-term follow up, it seems logical that stromal predominant neoplasms might have a better prognosis than those that are epithelial rich and a comment is warranted in such cases.

The other major category of neoplasm of mixed type in the sex cord stromal family, the Sertoli–Leydig cell tumour, has its own distinctive features as noted below which with rare exceptions are considerably different from those of the AGCT, such that distinction between the two should rarely be an issue. Inevitably one can see overlap to a degree in occasional cases, such as the rare tubular differentiation in some AGCTs noted briefly above. Furthermore, occasional tumours have overt components of each category. In the older literature these were referred to as gynandroblastoma but it is now our preference to use the approach used for germ cell tumours, namely to call such neoplasms sex cord-stromal tumours of mixed forms and then indicate the patterns present and their relative proportions. In my experience it is more common to see a Sertoli–Leydig cell tumour admixed with a juvenile rather than adult granulosa cell tumour (see below).

Endometrioid carcinomas can have sex cord-like foci which, when extensive, can lead to confusion with a sex cord-stromal tumour to a remarkable degree, so in the following comments features favouring endometrioid carcinoma are germane to both the AGCT and Sertoli–Leydig cell tumour,[19] each being mimicked on occasion. Solid areas in endometrioid carcinomas may have cells with pale nuclei and even nuclear grooves, in isolation sometimes being indistinguishable from GCT. Occasionally, a diffuse, insular, or trabecular pattern is also present, mimicking those patterns in AGCTs. Solid areas sometimes punctured by tubular, round, or tiny rosette-like glands may simulate the microfollicular pattern of a GCT. Small hollow tubular glands, solid tubules, or anastomosing cords can result in a sertoliform appearance. Tumour cells with pale cytoplasm on the background of a tubular pattern can suggest a lipid-rich Sertoli cell tumour. Luteinised stromal cells can mimic Leydig cells or be considered the luteinised cells of a GCT, potentially increasing the likelihood of misdiagnosis. One or more of bilaterality, associated endometriosis, foci of typical endometrioid carcinoma, luminal mucin, squamous differentiation (sometimes abortive), and an adenofibromatous component help establish a diagnosis of endometrioid carcinoma rather than a sex cord-stromal tumour. The importance of thorough sampling cannot be over-emphasised. An EMA+/CK7+/inhibin–/calretinin–/SF1–/WT1– immunoprofile indicates endometrioid carcinoma.

The two most common monodermal teratomas, struma ovarii and carcinoid, may occasionally be in the differential diagnosis. Issues largely pertain to potential confusion of microfollicles—Call–Exner bodies of the AGCT—with similar sized rounded structures that may be seen in these and indeed various other neoplasms, one already mentioned, endometrioid carcinoma. Tiny acini of struma usually will contain at least focally colloid-like material and the background will generally be helpful in the differential with AGCT. However, the diversity of patterns in struma ovarii is remarkable[20] and some of them pose additional challenges. For example, trabecular patterns in some cases of struma may be very reminiscent of GCT and there is one case in the literature in which a struma with this morphology was diagnosed as an AGCT.[20] Although the association with a dermoid cyst was retrospectively a major clue to the correct diagnosis, it was confirmed by immunostaining for thyroglobulin many years after the misdiagnosis had been made. An association with a dermoid either grossly or microscopic may also aid in the differential diagnosis with carcinoid if the nuclear and cytoplasmic features do not themselves speak to the right diagnosis in cases with prominent acini. This is another area where immunostains will be helpful.

The highly malignant small cell carcinoma of hypercalcaemic type (SCCHT)[21] may be realistic in the differential diagnosis of both AGCT and JGCT so they are discussed together here. The main reason is the presence of follicles in SCCHT and the small cells with scant cytoplasm that typifies most examples are of similar size to those of the AGCT and also have scant cytoplasm. The variant of SCCHT in which the cells have abundant eosinophilic cytoplasm (so-called large cell variant) may make JGCT realistic because of the shared abundant cytoplasm, and again follicles. The cells in AGCTs have a more regular arrangement and pale grooved nuclei and almost always lack the highly malignant nuclear features and striking mitotic rate of SCCHTs. Paradoxically, bizarre nuclei are more common in both GCTs. JGCTs also usually have a more orderly architecture and cells with uniformly eosinophilic, pale, or clear cytoplasm, this finding

being only focal in the SCCHT with rare exceptions. Both GCTs often have a theca cell component and are typically positive for inhibin unlike SCCHT.

Three metastatic tumours may be in the differential of AGCT. The first is metastatic malignant melanoma because a small cell phenotype and cells with pale nuclei may be reminiscent of AGCT. Features favouring or establishing melanoma include the history of an extraovarian melanoma, bilateral ovarian involvement, malignant nuclear features, melanin pigment, and positivity for melanoma markers. The second is metastatic breast carcinoma (especially lobular type). This tumour (which rarely presents as an ovarian metastasis) is distinguished from AGCT by the absence of the typical cytological features of granulosa cells, the presence in some tumours of mucin-containing intracytoplasmic vacuoles, and positivity for one or more of EMA, GCDFP, and GATA3. JGCT may also be mimicked by metastatic melanoma because the latter often has cells with abundant eosinophilic cytoplasm, a shared feature with JGCT. Furthermore, metastatic melanoma, like many metastatic tumours, may form follicle-like spaces reasonably confused with the true follicles of JGCT. Standard features that enable the distinction between primary and metastatic tumours to the ovary including those relevant to the differential with AGCT will generally resolve this differential. Finally, although less often a problem, brief mention is merited on an AGCT being mimicked by metastatic low-grade endometrial stromal sarcoma. Both tumours have cells of similar size with scant cytoplasm most of the time. The history (sometimes needing to be investigated), bilaterality, nature of tumour vessels and immunohistochemistry if needed will usually resolve the problem by pointing to stromal sarcoma.

Juvenile granulosa cell tumour

Microscopic features

The most common microscopic pattern is sheets of cells interrupted by follicles that range from few to numerous (Fig. 5). They are often of variable size and shape with luminal eosinophilic to basophilic fluid. Tiny ones sometimes can be seen seemingly emerging out of a background solid growth (Fig. 6). A uniformly solid ('afollicular') pattern, that may be nodular (Fig. 7), may occur. Call–Exner bodies are almost never seen. The follicles are lined by granulosa cells, occasionally with an outer mantle of theca cells. The granulosa cells typically have abundant eosinophilic or vacuolated cytoplasm and generally round, non-grooved, euchromatic or hyperchromatic nuclei with minimal to severe nuclear atypicality, the latter being present in about 15% of cases. A minority of tumours have cells with scant cytoplasm imparting a different appearance from that usually seen, the low power being more basophilic. However the immature cytological features are still those of the JGCT. Occasionally, hobnail-type cells are present lining follicles. The mitotic rate is often brisk.

An uncommon finding is the presence of pseudopapillae, which can also occur in AGCTs but are more common in JGCTs.[22] The tumours may be grossly cystic with papillary, friable tumour projecting from the cyst lining. The pseudopapillae represent projections of neoplastic cells with surrounding necrotic debris and/or undulating folds of neoplastic cells without appreciable necrosis. The correct diagnosis rests on the presence of the typical architectural features of JGCT (or AGCT) elsewhere in the tumour and typical cytological features of granulosa cells throughout the tumour. Other uncommon findings in JGCT include small foci of AGCT, a prominent fibrothecomatous stromal component, areas of sclerosis (Fig. 7) that are sometimes extensive even

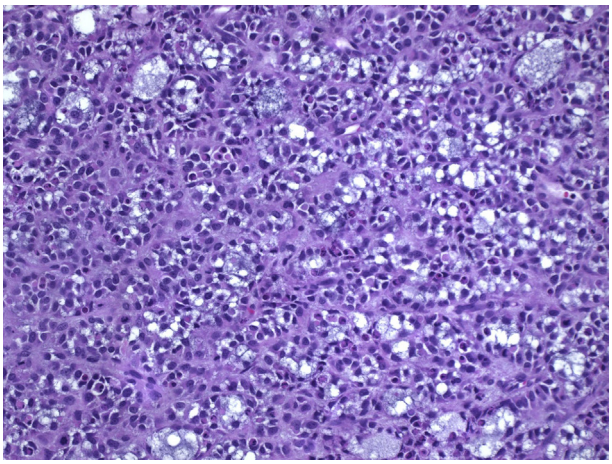

Fig. 6 Juvenile granulosa cell tumour. Many small follicles seem to almost emerge from the background more solid proliferation of tumour cells.

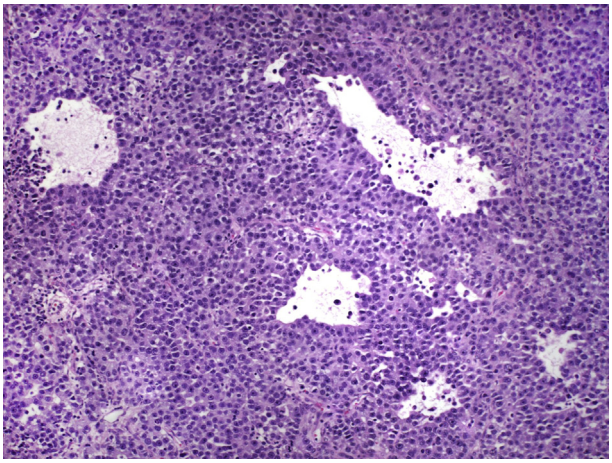

Fig. 5 Juvenile granulosa cell tumour. A solid proliferation of cells with moderate to abundant cytoplasm is punctuated by follicles of variable sizes and shapes.

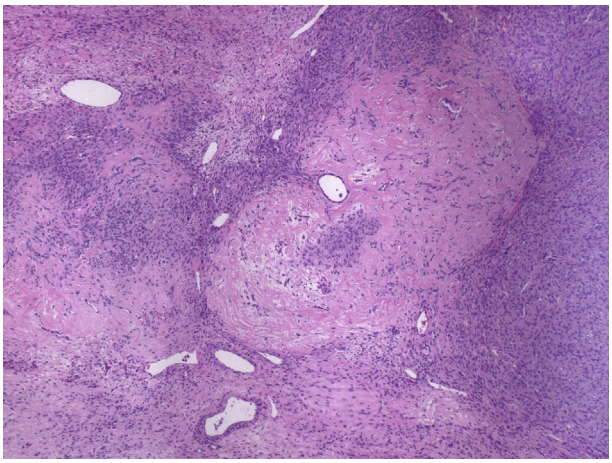

Fig. 7 Juvenile granulosa cell tumour. This neoplasm had a nodular pattern and some of the nodules show extensive sclerosis.

resembling the 'burnt out' foci of some testicular germ cell tumours, and sheet-like aggregates or variably sized clusters of anaplastic cells exhibit striking nuclear atypia. The correct diagnosis may require thorough sampling to reveal typical foci of JGCT with follicles in cases with these unusual features.

Differential diagnosis

Features favouring JGCT over AGCT include follicles that are irregular in size and shape, numerous luteinised cells, round non-grooved hyperchromatic nuclei and brisk mitotic rate.

The yolk sac tumour (YST), including the polyvesicular vitelline variant, may rarely be an issue because there may be some similarity between follicles and the cysts in both typical and polyvesicular YST. Features favouring or diagnostic of these tumours include an association with other germ cell elements (e.g., dermoid cyst), a typical reticular pattern, Schiller–Duval bodies, syncytiotrophoblastic elements, positivity for AFP or glypican 3 and negativity for inhibin and calretinin.

Clear cell, undifferentiated and transitional cell carcinoma-like patterns in surface epithelial carcinomas may be suggested by cystic follicles lined by hobnail-like cells, nuclear pleomorphism and pseudopapillae. These carcinomas are rare in the young, and while they may focally exhibit some overlapping features, they lack true follicles, have their own distinctive features when well sampled, and lack positivity for inhibin and calretinin. The differential with SCCHT and metastatic melanoma have been considered with AGCT above.

As JGCT occurs mostly in the young an occasional patient will be pregnant and pregnancy luteoma may rarely be an issue because the latter may have follicle-like spaces, and of course their cells have abundant eosinophilic cytoplasm like many JGCTs.[23] These lesions, unlike JGCTs, tend to have more homogenous patterns and cytological features. In addition, the pregnancy luteoma is frequently multiple, bilateral, or both.

SERTOLI CELL TUMOUR

These are less common than Sertoli–Leydig cell tumours and in most cases are characterised by a pure tubular pattern, although occasional variant morphologies may be seen in tumours that are less well differentiated than most.[24] It should be emphasised that so many tumours can mimic a Sertoli cell tumour by having acinar and tubular patterns confusable with Sertoli cell neoplasia that the Sertoli cell tumour is a diagnosis of exclusion and except perhaps in classic cases should be buttressed by appropriate immunohistochemical confirmation. Only a few noteworthy aspects are noted here. The rare lipid-rich type when it occurs in children may result in isosexual pseudoprecocity and two of the small number of patients in this category have had Peutz–Jeghers syndrome.[25] Sertoli cell tumours are almost invariably unilateral and stage one and typically have lobulated solid yellow to brown sectioned surfaces. On microscopic examination the tubular pattern may be hollow or tubular. Rare neoplasms have a more or less diffuse pattern of growth which on low power can be vaguely reminiscent on occasion of dysgerminoma because of an alveolar pattern (analogous to an issue described recently in testicular tumour pathology), and other less common patterns of Sertoli cell neoplasia include cords, trabecular, pseudopapillary, retiform and spindled.[24] Even the latter tumours usually have elsewhere a recognisable tubular pattern suggesting the correct interpretation. The tumour cells usually have relatively limited pale cytoplasm except for the lipid-rich type noted above and rare neoplasms that have abundant eosinophilic cytoplasm. A few of the latter have also, enigmatically, occurred in patients with Peutz–Jeghers syndrome. Most Sertoli cell tumours have limited cytological atypia but a rare neoplasm has conventional criteria of malignancy and can have a behaviour that matches that morphology. The differential diagnosis overlaps to a large extent with that of Sertoli–Leydig cell tumours and suffice it to say that as noted at the outset, the diagnosis should be made with caution, recognising the propensity of various other neoplasms to have a somewhat 'Sertoli-like' microscopic appearance.

SERTOLI–LEYDIG CELL TUMOUR

Sertoli–Leydig cell tumours (SLCTs) are rare[26] but may be in the differential of a number of more common entities. They typically occur in young women: 75% of patients are <30 years of age; and only 10% are >50. Notably, retiform SLCTs occur at a particularly young age, mean age 15 years.[27] The patients present with abdominal swelling or pain, and in 50%, androgenic manifestations; the latter are less common in retiform tumours and those with heterologous elements. Schultz *et al.*[28] found that ~98% of SLCTs had a *DICER1* mutation and a significant literature is evolving on this matter that an interested reader can explore. Familial SLCTs have been associated with thyroid disease and pleuropulmonary blastoma; a combination of these lesions should suggest a DICER1 syndrome.[29] Unusual findings have included elevated plasma levels of AFP and an occasional but possibly more than coincidental association with embryonal rhabdomyosarcoma of the cervix.

SLCTs typically have solid, lobulated, yellow sectioned surfaces and are variable in size, being on average perhaps slightly smaller than GCTs. Some tumours, especially those with heterologous[30] or retiform components, are cystic. Tumours with a large heterologous mucinous component may mimic a mucinous cystic tumour. The cysts in the retiform tumours may contain papillary or polypoid excrescences, potentially resembling a serous tumour. Some retiform tumours have a spongy sectioned surface. Poorly differentiated tumours, including those with mesenchymal heterologous elements,[31] tend to be larger and may be extensively haemorrhagic and necrotic.

Microscopic features

Well differentiated tumours are characterised by Sertoli cells in a predominantly tubular pattern, with lobules composed of hollow or less often solid tubules, and Leydig cells in the intervening stroma. The hollow tubules are typically round to oval and small, but may be cystic. Pseudoendometrioid tubules can be present and occasionally predominate.[32]

The typical low-power appearance of tumours of intermediate differentiation (the most common subtype) is that of cellular masses, often in a striking lobular pattern. The most obvious differentiation into Sertoli cell aggregates and Leydig cell clusters is often at the periphery of the lobules. The cellular masses are composed of immature Sertoli cells (often in an alveolar arrangement) (Fig. 8) with small, round,

oval, or angular nuclei admixed with Leydig cells. Larger nests, solid and hollow tubules, thin usually short cords, or occasionally broad columns are also frequent. Conspicuous small or large cysts are present in some tumours, occasionally containing eosinophilic secretion, resulting in a struma-like appearance. Occasional follicles may be seen.

The stromal component ranges from fibromatous to densely cellular to, most often, oedematous, and typically contains Leydig cells. The stromal component may focally consist of immature cellular mesenchymal tissue resembling a non-specific sarcoma, such an appearance being more common in poorly differentiated tumours. Other features of the Sertoli and/or Leydig cells include variable amounts of lipid and, in rare cases, cells with bizarre nuclei.[14]

Poorly differentiated SLCTs exhibit only focally distinctive patterns of SLCT. The tumours are usually composed extensively of solid sheets of poorly differentiated cells that range from epithelial-like to primitive mesenchymal in nature, and areas may resemble an embryonal sarcoma, fibrosarcoma, an undifferentiated carcinoma, or a primitive germ cell tumour; the mitotic rate is almost invariably high.

Retiform SLCTS, which account for 15% of SLCTs, exhibit focal to extensive patterns resembling those of the rete testis, usually occurring within otherwise typical intermediate and poorly differentiated SLCTs; heterologous elements may also be present. Low-power examination reveals irregularly branching, elongated, narrow, often slit-like tubules (Fig. 9) and cysts with intraluminal papillae or polypoid projections. The tubules and cysts are lined by epithelial cells with varying degrees of stratification and nuclear atypicality. Columns or ribbons of immature Sertoli cells are frequently present. The papillae and polyps are of three types: small and rounded or blunt and often hyalinised; large and bulbous, often with oedematous cores; and delicate and branching and lined by stratified cells and cellular buds, simulating the papillae of a serous tumour. The stroma varies from hyalinised (this being more common than in non-retiform tumours) or oedematous (most common) to moderately cellular, to densely cellular and immature.

Heterologous elements are seen in 20% of SLCTs. It is most often mucinous epithelium but may be, usually in poorly differentiated tumours, islands of fetal-type cartilage, rhabdomyosarcoma, or both. The sex cord elements in these

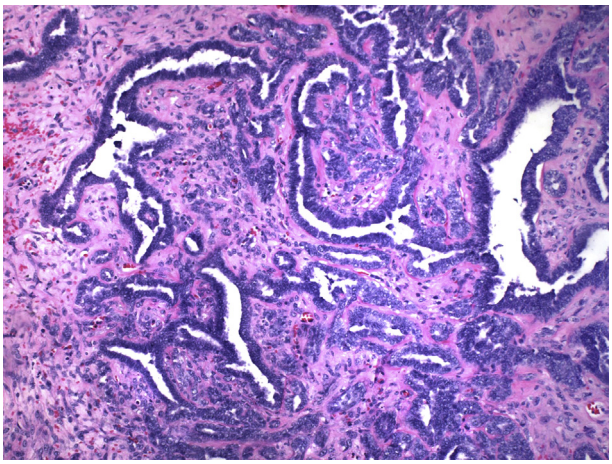

Fig. 9 Sertoli–Leydig cell tumour with retiform pattern. Characteristic elongated tubules. Additionally the stroma is focally somewhat hyalinised, another feature of the retiform variant.

tumours are usually conspicuous but are occasionally limited. The mucinous epithelium varies from benign, to borderline, to low-grade adenocarcinoma. Insular or mucinous-goblet cell carcinoids, usually of microscopic size, occasionally arise from the mucinous epithelium.

One of the most common forms of mixed sex cord-stromal tumours is a composite of SLCT and JGCT. Foci of the latter occasionally develop within lobules of SLCT and can provide a striking divergent picture with follicles of JGCT surrounded by typical SLCT (Fig. 10).

Differential diagnosis

One important differential with endometrioid carcinoma has been considered in the section on AGCT. The one metastatic tumour in the differentiation with a SLCT is a tubular Krukenberg tumour. As the first word of the descriptive designation just given implies, issues arise when a Krukenberg tumour has a prominent tubular pattern which can be Sertoliform with signet ring cells sometimes either absent in significant areas or certainly not prominent. Further confusion may be caused, particularly when the patients are young as they often are, if there is a lobular low power pattern, or if

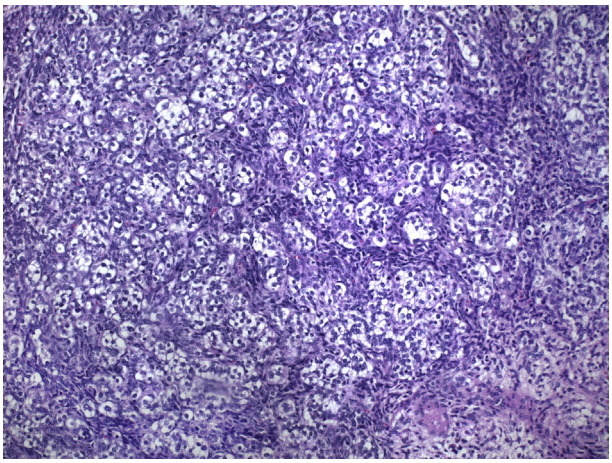

Fig. 8 Sertoli–Leydig cell tumour of intermediate differentiation. There is a striking so-called alveolar pattern of Sertoli cells with pale cytoplasm.

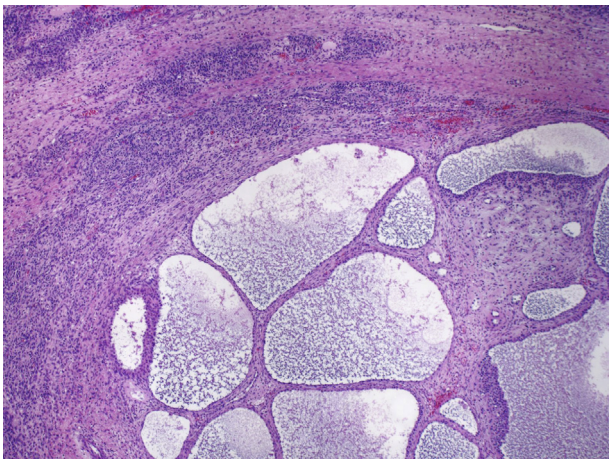

Fig. 10 Mixed Sertoli–Leydig cell tumour and juvenile granulosa cell tumour. A macrofollicular pattern of juvenile granulosa cell tumour is present within a large nodule and is mantled by typical Sertoli–Leydig cell tumour of intermediate differentiation.

stromal lutein cells confused with Leydig cells (and they may result in virilisation) are present; all these features can make the misdiagnosis of a SLCT understandable, albeit well sampled tumours should show features that are unacceptable for it. An admixture of the following findings will indicate that the tumour is indeed a Krukenberg tumour:[33] bilaterality, marked atypicality of tubular lining cells, signet-ring cells unassociated with mucinous carcinoid and staining for EMA but not sex cord markers. Luteinised stromal cells in Krukenberg tumours, however, usually stain for sex cord markers.

The many patterns of SLCT result in overlap with a number of other tumours and only a few of the more interesting or common are mentioned here. When a heterologous SLTCT has a particularly conspicuous component of mucinous elements it may simulate grossly a mucinous cystic tumour in greater part. Minor solid yellow typical SLCT regions can be potentially overlooked, particularly at the time of frozen section. On microscopic examination most heterologous tumours have relatively obvious foci of Sertoli cells between mucinous glands and cysts but regions of some neoplasms may have a dearth of such diagnostic foci, indicating the crucial importance of sampling as in so many areas of ovarian tumour interpretation. A somewhat similar comment pertains to the differential diagnosis between a pure sarcoma and a sarcoma dominating the morphology in a poorly differentiated SLCT. Another basic of ovarian tumour interpretation, awareness of the patient age, is relevant to the differential diagnosis between SLCT and a serous neoplasm or even a malignant mixed mesodermal tumour, the latter in particular occurring at a different age range with very rare exceptions. A biphasic pattern of spindle cell sarcoma admixed with epithelial elements, such as retiform, has been misconstrued as representing malignant mixed mesodermal tumour in our experience. In one such example from a 12-year-old girl, there was even heterologous cartilage further suggesting malignant mixed mesodermal tumour with heterologous components. The differential diagnosis between an SLCT and germ cell tumours is limited. Rare very poorly differentiated SLCTs have primitive cells suggestive of embryonal carcinoma but other patterns will generally aid and the rarity of embryonal carcinoma should always be reflected upon. Occasionally small cysts in a SLCT may have a vague suggestion of a reticular-microcystic pattern so common in yolk sac tumours but again other regions will be diagnostic in one direction or the other. The oedema that typifies many sex cord stromal tumours when they occur in pregnancy[11] is another aspect of the differential of the SLCT and yolk sac tumour, the oedema sometimes producing a picture mimicking to a degree the loose reticular pattern of yolk sac tumour. More typical foci of SLCT are still usually present and if necessary immunohistochemical stains will aid, particularly staining of the SLCT strongly for inhibin and calretinin in almost all cases. It should be noted that some SLCTs may exhibit some focal staining for alpha fetoprotein.

SEX CORD TUMOUR WITH ANNULAR TUBULES

The distinctive pattern of neoplasia captured by the name of this entity[34] still is somewhat controversial from the perspective as to whether it does, or does not, merit separate categorisation. We believe its distinctive morphology and the interesting clinical associations of many cases warrant separate categorisation. The pattern first came to light when it was noted as typifying usually small, often microscopic lesions found in the ovaries of patients with Peutz–Jeghers syndrome and that, although not an invariable finding in such patients, is certainly sufficiently common as to represent a unique entity. In that scenario small, usually no greater than 3 cm, lesions are typically bilateral and multifocal. They have the characteristic annular tubules of this lesion, often associated with calcification.

Lesions bearing the same name found sporadically in patients who do not have Peutz–Jeghers syndrome contrast with those that are syndrome associated by almost always being larger, unilateral, and not calcified. They are occasionally associated with evidence of progesterone production and although usually clinically benign seem to spread to lymph nodes somewhat more frequently than do other sex cord tumours that behave in malignant fashion. Grossly, they are usually solid and yellow but occasionally examples are markedly cystic.

Reflective of the spectrum of morphology seen in the sex cord stromal tumour family in general is the fact that occasional granulosa cell tumours have areas that in isolation have the pattern of sex cord tumour with annular tubules and from the perspective of a male pattern of differentiation occasional Sertoli cell tumours have arisen out of the background of sex cord tumour with annular tubules including some with Peutz–Jeghers syndrome.[25]

FIBROMA, INCLUDING CELLULAR FIBROMA

I will restrict my comments on fibromas, most of which have bland features and rarely cause problems, to our approach to cellular fibromatous neoplasms. Such tumours are not rare. The issue in differential with granulosa cell tumours is considered above. Most we encounter are shared with us because of the issue of distinction from the very rare fibrosarcoma and the clinical implications of a cellular fibroma diagnosis particularly when mitotic figures are found with some ease. Factors such as size, presence or absence of rupture and even adhesions can be as important prognostically to record as the morphological features of the tumour. When we diagnose a cellular fibroma that is large with some other feature just noted that might increase the risk of recurrence we draw attention to that and indicate that such a tumour should be considered from the clinical viewpoint to have some low malignant potential. The diagnosis of fibrosarcoma should be made very sparingly because of its ominous implications and such are simply rare neoplasms. The vast majority of cellular fibromatous tumours are best placed in the category of a cellular fibroma. Although by definition intensely cellular they are not uniformly hypercellular as are almost all fibrosarcomas, and patchy hypercellular and more normocellular regions can be reassuring that the tumour should be considered a cellular fibroma. Mitotic counts over 4 per 10 high power fields are consistent with a tumour being placed in the cellular fibroma category, so-called mitotically active cellular fibroma.[35]

Fibromas may contain lutein cells. These were formally referred to as luteinised thecomas but that term has fallen out of favour and the ubiquitous presence of lutein cells in so many ovarian tumours requires only a brief comment, particularly if it correlates with some clinical finding of note

as it may in the case of the rare tumour that is in essence a fibroma but may be associated with androgenic manifestations due to stromal lutein cells. An occasional neoplasm that initially appears to be a cellular fibroma contains signet ring cells which fail to stain for both lipid and fat and fall in the category of the rare so-called signet ring stromal tumour.

THECOMA

A recent paper in the literature updated our experience with this neoplasm[36] so we will not belabour it here. Suffice to say that the thecoma is the other typically oestrogenic tumour of the ovary, sharing that attribute with the granulosa cell tumour. Thecomas tend to occur at a slightly older age on average than do GCTs and do not have quite as wide a gross spectrum, being a typically smaller tumour with a more exquisitely yellow solid sectioned surface with rare exceptions. In the recent paper referred to we highlighted the typical tinctorial qualities of the thecoma but it should be noted that it is a shared feature with a small subset of AGCTs as considered above, and I re-emphasise here how useful the reticulum stain can be in determining whether such zones are thecomatous or rather granulosa cell in nature.

SCLEROSING STROMAL TUMOUR

This entity has been well known since first described in 1973 because of its tendency to occur in the young, average age 27 years, and usual lack of function which contrasts with thecoma. Sclerosing stromal tumour has a more variegated section surface than either fibroma or thecoma with oedema and cystic change being appreciable in many cases. Microscopic examination shows three definitional features: a pseudolobular pattern, admixed spindled and rounded weakly luteinised cells, and finally, prominent typically ectatic sometimes branching staghorn-like blood vessels. It should be noted that these three must be present together before the diagnosis of sclerosing stromal tumour is made. Many typical fibromas may have some alternating cellular and paucicellular areas and may be somewhat vascular. A tumour only falls in the sclerosing stromal tumour group when the classic jumbled admixture of fibroblasts and lutein cells definitive for the sclerosing stromal tumour is present. In occasional cases the oedematous regions of the sclerosing stromal tumour undergo a myxoid alteration which some have surmised may explain some cases of myxoma but we are not convinced by arguments made in this regard. One aspect of sclerosing stromal tumour recently highlighted is that, inasmuch as they usually occur in the young, the patient may be pregnant.[37] In that circumstance the tumour cells may be extensively and more robustly luteinised than is the usual case and this may serve to obscure the typical bipartite cellular population and indeed the overall features of the tumour. Other neoplasms such as steroid cell tumour are then more likely to factor in the differential diagnosis but minor foci of typical morphology can usually still be appreciated.

LUTEINISED THECOMAS WITH SCLEROSING PERITONITIS

This is the second of the tumours in the stromal category that Dr Robert Scully astutely first recognised, observing a peculiar pattern of neoplasia characteristically associated with sclerosing peritonitis. He gave them the descriptive designation that heads this section, albeit the nature of the lesion is still somewhat controversial and indeed it is favoured by some, including Australian workers, to be non-neoplastic. Accordingly, in a recent contribution on the topic[38] we gave the designation 'thecomatosis' as an alternative out of respect to that opinion. Classic aspects of this remarkable entity are briefly summarised. The tumours may be seen at any age but peak in the young with an average age of about 27 years. They frequently present with abdominal pain sometimes associated with ascites and bowel obstruction due to the associated sclerosing peritoneal process. No endocrine manifestations have been observed to date. In contrast with other stromal lesions these are typically bilateral and the involved ovaries range from normal in size, but abnormal in appearance due to a hypercerebriform contour, to large masses often having a beefy appearance with oedema and cyst formation. The microscopic appearance varies somewhat according to the degree of the peripheral cerebriform morphology and microcytic change within the cellular neoplasm which is fundamentally composed of admixed, spindled, and weakly luteinised cells. Although oedema is present, accounting for the microcystic appearance of some cases, the appearance is markedly different from that of the other stromal tumour with oedema, the sclerosing stromal tumour, and likewise the other stromal tumour with a microcystic appearance with which this essay ends. In these strange peritonitis associated lesions normal ovarian elements are often present between the proliferating spindle cells which is one reason a non-neoplastic nature is favoured by some. Importantly these lesions are very mitotically active and if the pathologist is not aware of the specific entity it is very easy to think one is looking at a highly malignant process. However, there is no evidence that the ovarian tumour itself has spread, although the sclerosing peritonitis may be associated with considerable morbidity and even mortality. The peritonitis may sometimes be seen grossly if there is an accentuated lobular appearance to the omentum in particular, but is often only seen when biopsies of slightly abnormal peritoneal surfaces are obtained. The appearance of the ovaries in these cases and the associated peritonitis present a very distinctive profile which an observer should be able to recognise provided they are simply aware of the phenomenon.

MICROCYSTIC STROMAL TUMOUR

This rare but fascinating tumour[39] occurs in adults who present with a non-functioning pelvic mass. The reported tumours have been stage I with an uneventful follow-up. They have a mean size of 10 cm and are typically solid and cystic but may be predominantly solid or cystic with solid tissue that is tan to white to rarely yellow. The microscopic appearance varies with the relative prominence of three components: microcysts (dominant in 60% of cases), solid cellular areas, and hyalinised fibrous stroma (Fig. 11). There are usually at least minor microcystic foci but rare tumours are entirely solid and can be recognised by their distinctive features and confirmatory staining for CD10 and β-catenin.[39]

The usually dominant microcystic pattern is characterised by small round to oval cystic spaces, focally coalescing into larger irregular channels; intracytoplasmic vacuoles are also common. The solid cellular areas are usually intersected by fibrous bands and hyaline plaques. The cells contain finely granular, faintly eosinophilic cytoplasm and have bland, round to oval nuclei with fine chromatin, small indistinct

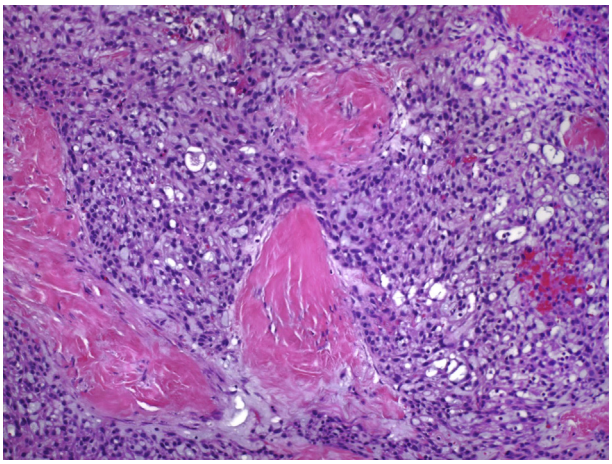

Fig. 11 Microcystic stromal tumour. Typical microcysts and hyaline plaques are shown.

nucleoli, and infrequent mitoses. Foci of bizarre cells are present in 60% of tumours. The tumours show consistent immunoreactivity for CD10 which is diagnostically helpful as other tumours in the differential are CD10–. Nuclear staining for FOXL2, WT-1, cyclin D1, SF-1 is typical.[40] The differential diagnosis of this tumour remains as considered in the original report describing it.

CONCLUSION

It has only been possible in the foregoing remarks to touch upon some of the numerous facets of sex cord stromal tumour that are both academically interesting and practically important in differential diagnosis. Because of the inherent great variations seen in some of them they will always intrigue the diagnostic pathologist and as further exploration of their molecular features takes place in the ensuing years that will undoubtedly just add to the interest and challenges they provide.

Acknowledgement: This essay was finished close to the fifth anniversary of the death of Dr Robert E. Scully and is dedicated to his memory. His knowledge of gynecological pathology is unlikely ever to be surpassed. He loved to travel and always spoke fondly of his trips to Australia where he had many friends, some of whom I hope read these words and reflect on their good fortune to have met such a gentle, kind person.

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