Stromal tumours of the ovary: an update

Esther Oliva

Robert H Young

Abstract

Stromal tumours of the ovary are reviewed emphasizing recently described entities and new or uncommon aspects of well known neoplasms. The first, the luteinized thecoma with sclerosing peritonitis, a rare lesion, is controversial with regard to whether it is neoplastic or non-neoplastic an unsettled issue. It often occurs in the young and has distinctive pathologic features. The second, the microcystic stromal tumour has as a main histologic feature the presence of microcysts that may only be focal. Hyaline plaques are common but in contrast to most stromal tumours they are inhibin and calretinin negative but show β-catenin alterations. Sclerosing stromal tumour although having relatively uniform typical morphology, can pose some diagnostic difficulty, especially when seen in pregnant patients. Thecoma and fibroma are the most common stromal tumours but thecoma, in particular, may cause diagnostic difficulty particularly with granulosa cell tumour. Finally, two rare tumours, the signet-ring stromal tumour and myxoma are briefly considered.

Keywords fibroma; luteinized thecoma with sclerosing peritonitis; microcystic stromal tumour; myxoma; sclerosing stromal tumour; signet-ring stromal tumour; thecoma

Introduction

Reviews of sex cord-stromal tumours tend to emphasize some of the disparate epithelial and mixed patterns present in such neoplasms, and as a result pure stromal neoplasms sometimes do not get the consideration merited. It is our intent to correct this imbalance to at least some extent with this essay focusing only on stromal tumours. We emphasize recently described entities about which knowledge is still evolving, particularly the unusual tumour associated with sclerosing peritonitis, and the so-called microcystic stromal tumour. We also consider the well known sclerosing stromal tumour, thecoma and the even more common fibroma. We also cover the ovarian myxoma, a neoplasm not specifically in the stromal group but one whose morphology may overlap with more typical stromal tumours, and the signet-ring cell stromal tumour. Finally, we provide an update on immunohistochemical and molecular findings in these neoplasms.

Esther Oliva *MD The James Homer Wright Pathology Laboratories, Massachusetts General Hospital, Boston, MA and the Department of Pathology, Harvard Medical School, Boston, USA. Conflicts of interest: none declared.*

Robert H Young *MD FRCPath The James Homer Wright Pathology Laboratories, Massachusetts General Hospital, Boston, MA and the Department of Pathology, Harvard Medical School, Boston, USA. Conflicts of interest: none declared.*

Luteinized thecomas with sclerosing peritonitis

Dr. Scully first recognized this uncommon tumour in the stromal category which is characteristically associated with sclerosing peritonitis.[1] Because he felt they were of stromal derivation and had weakly luteinized cells, he descriptively designated them luteinized thecoma with sclerosing peritonitis (LTSP).[2] The nature of this lesion is somewhat controversial but nowadays it is favoured by many to be non-neoplastic and thus the alternative name of "thecomatosis".[2] Irrespective of that dispute, it is a tumour in the sense of a mass lesion. From the etiopathogenic viewpoint some have been discovered to have an association with anticonvulsant or anti β-adrenal blocker therapy or autoimmune diseases.[1–4] None of these lesions has ever metastasized.[2]

Although the tumours can occur at any age (from 10 months to 85 years), they usually affect young women (median age 27 years) who present with abdominal pain frequently, but not always, accompanied by ascites and bowel obstruction due to the associated peritoneal process, and only rarely with an acute abdomen.[5] No endocrine manifestations are noted.[2] Typically both ovaries are involved and range from normal to very large, the smaller ones often showing exaggerated cerebriform outlines. Marked oedema, cyst formation, and haemorrhage are common as is a beefy-tan cut surface. Histologically, the cerebriform appearance seen grossly is due to irregular expansion of the ovarian cortex (Figure 1) with sparing of the medulla. Within the cortex there is a cellular admixture of spindled and weakly luteinized cells. Oedema is common, often separating the spindled cells, imparting a microcystic appearance (Figure 2). Entrapped normal ovarian elements such as follicles and corpora albicantia are frequently encountered. The spindled cells are cytologically bland but show highly variable mitotic activity (up to >40/10 HPFs). They are commonly positive for smooth muscle actin and desmin and may be positive for AE1/3 and react more frequently for progesterone than oestrogen receptors. They rarely may express calretinin or CD56 but they are typically negative for inhibin.[2] These cells are also either focally or diffusely positive for SF-1 and FOXL-2 which supports a stromal origin of this proliferation.[6] The luteinized cells are seen in isolation or in small clusters in between the spindle cells. They

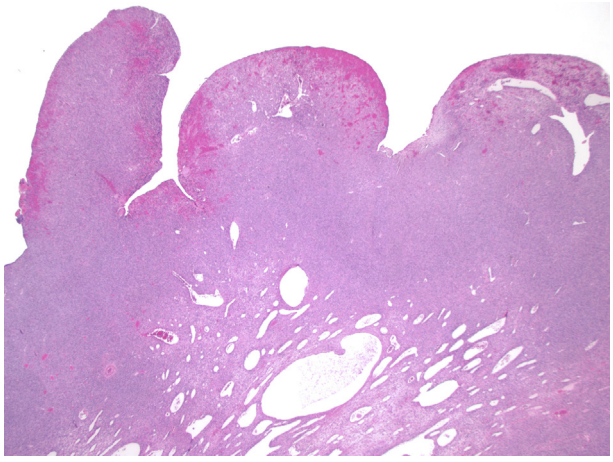

Figure 1 Luteinized thecoma associated with sclerosing peritonitis. This low power shows the exaggerated cerebriform contour that in some cases presents a distinctive low power picture.

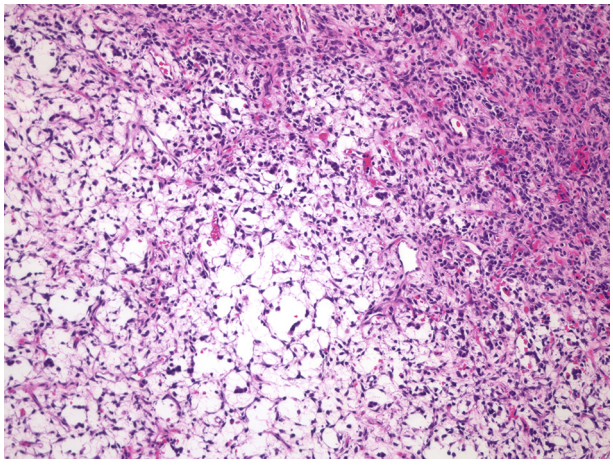

Figure 2 Luteinized thecoma associated with sclerosing peritonitis. Cellular and acellular zones are seen, the latter showing a vague microcystic morphology.

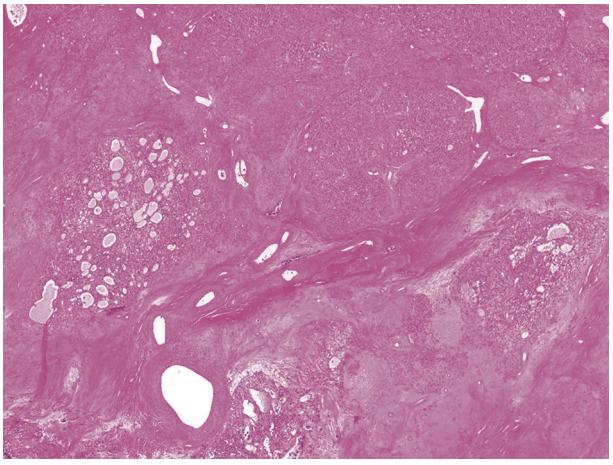

Figure 3 Microcystic stromal tumour. Characteristic low power showing solid cellular nodules while others are punctuated by microcysts. The nodules are separated by conspicuous fibrous stroma.

are small with relatively scant cytoplasm and round nuclei but in contrast to the spindle cells they are not mitotically active. They express inhibin as well as calretinin, and/or CD56.[2]

The associated sclerosing peritonitis may sometimes be grossly visualized with the omentum having an accentuated lobular appearance and a white to brown surface. There is a variable proliferation of spindled cells, most likely submesothelial myofibroblasts set within a myxoid, oedematous or collagenous background in the surface and between the fat lobules. This process can be subtle and only detected histologically or quite extensive, and grossly mistaken for peritoneal carcinomatosis. The peritoneal proliferation is only strongly positive with AE1/3 showing variable positivity for oestrogen and/or progesterone receptors.[1,7] While it usually resolves following bilateral salpingo-oophorectomy, it can progress leading to significant morbidity or rarely death.

The differential diagnosis includes conventional stromal neoplasms (fibromas and thecomas) which may have occasionally luteinized stromal cells, but they are usually unilateral, sometimes hormone-producing, mitotic activity is minimal, luteinized cells are robust, and do not entrap normal elements. Massive ovarian oedema/fibromatosis although also typically bilateral with entrapment of preexistent follicles, are typically much less cellular and more uniform. Sometimes dilated and/or thrombosed lymphovascular spaces can be seen near the ovarian hilus in cases of massive oedema, suggesting that process occurs secondary to long-standing but intermittent torsion.[8] Occasionally other spindle-cell lesions such as fibrosarcoma may at high power enter in the differential diagnosis due to its brisk mitotic activity, especially if luteinized cells are difficult to identify, however, greater cytologic atypia as well as no entrapment of preexistent structures and obliteration of the ovary are helpful in its diagnosis. Furthermore, fibrosarcoma would also rarely be bilateral.[9]

Microcystic stromal tumour

This is a recently defined enigmatic entity likely to be in the category of stromal tumours of the ovary from the limited evidence collected to date.[10] A series of sixteen cases was initially reported in adult women from 26 to 63 years, with only rare (in two out of 16) hormonal manifestations and with benign follow-up. The tumours average 9 cm and are typically solid and cystic with a tan-white cut surface. Microscopically they consistently show three components in various proportions: solid cellular areas often with a lobular growth and an appearance somewhat similar to thecomas (Figure 3); regions of small round to oval microcysts (Figure 4) which sometimes may coalesce to form macrocysts, and collagenous stroma often exhibiting irregularly shaped hyaline plaques. The cells, which frequently contain small vacuoles, have pale to eosinophilic cytoplasm, small round nuclei, and overall bland cytologic features with rare mitoses, but foci of cells with bizarre nuclei are seen in almost half of the tumours. The tumour cells are positive for vimentin, CD10, WT-1, and cyclin-1 (Figure 5), and negative for inhibin and calretinin as well as hormone receptors, neuroendocrine markers including CD56, synaptophysin, and chromogranin A, vascular markers (CD31, CD34, and D2-40), desmin and smooth muscle actin. They may be focally positive for keratin but are negative for EMA. They typically show nuclear β-catenin positivity (Figure 6)[11,12] associated with identical point mutation in exon 3

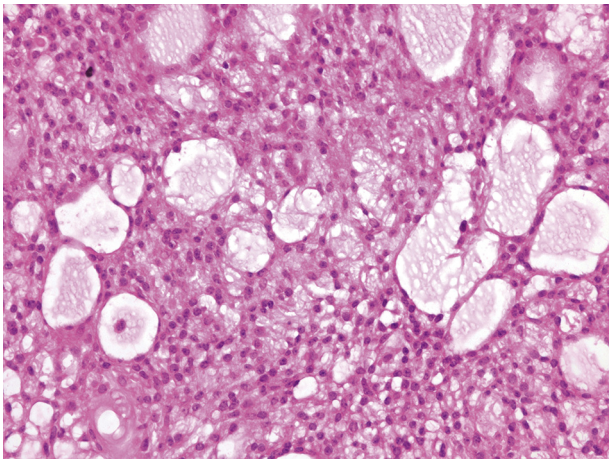

Figure 4 Microcystic stromal tumour. Typical microcysts.