CALIFORNIA TUMOR TISSUE REGISTRY

104th SEMI-ANNUAL CANCER SEMINAR ON

TUMORS OF THE UTERUS AND OVARIRES

CASE HISTORIES

PRELECTOR:

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June 7, 1998
Westin South Coast Plaza
Costa Mesa, California

CHAIRMAN:

Mark Janssen, M.D.
Professor of Pathology
Kaiser Permanente Medical Center
Anaheim, California
CASE HISTORIES 104TH SEMI-ANNUAL SEMINAR

CASE #1 – ACC. 28232
A 48-year-old, gravida 3, para 3, female on oral contraceptives presented with dysmenorrhea and amenorrhea of three months duration. Initial treatment included Provera and oral contraceptives. Pelvic ultrasound revealed a 7 x 5 cm right ovarian cyst and a possible small uterine fibroid. Six months later, she returned with a large malodorous mass protruding through the cervix of an enlarged uterus. The 550 gram uterine specimen was 13 x 13 x 6 cm. The myometrium was 4 cm thick. An 8 x 6 cm polyoid, pedunculated mass protruded through the cervix. The cut surface of the mass was partially hemorrhagic, surrounded by light tan soft tissue. (Contributed by David Seligson, M.D.)

CASE #2 – ACC. 24934
A 70-year-old female presented with vaginal bleeding of recent onset. A total abdominal hysterectomy and bilateral salpingo-oophorectomy were performed. The 8 x 9 x 4 cm uterus was symmetrically enlarged. The endometrial cavity was dilated by a 4.5 x 3.0 x 4.0 cm polypoid mass composed of loculated, somewhat mucoid tissue. Sections through the broad stalk revealed only superficial attachment to the myometrium, without obvious invasion. (Contributed by Paul Ortega, M.D.)

CASE #3 – ACC. 28293
An 80-year-old female presented with complaints of pelvic pain. A hysterectomy was performed. The uterus without adnexa weighed 223 grams and measured 7.6 x 9.2 x 6.2 cm. The serosal surface was fairly smooth tan. However, at the parametrial margins there were fleshy tan protrusions. The endometrial cavity was fairly symmetrical with a slightly shaggy, red-tan surface. The myometrium was up to 2.5 cm thick. There was some accentuation of the trabecular architecture. (Contributed by Kenneth Frankel, M.D.)

CASE #4 – ACC. 17531
A 17-year-old, gravida 1 para 1 female presented with abdominal swelling and pain. Physical examination revealed an enlarged uterus of approximately 8 weeks size, with bilateral ovarian masses. Chest x-ray showed small round lesions scattered throughout both lung fields. A pregnancy test was positive in a high dilution. After two courses of methotrexate, the uterus appeared to decrease in size, although the ovarian cysts were still palpable. The uterine specimen measured 15 x 12 x 7 cm. In the right and left cornu were two irregular, friable, yellow tumor masses invading the myometrium but not penetrating the serosa, each measuring 2 x 2 x 2 cm and blending with overlying endometrium. Throughout the myometrium were small yellow, fairly well-defined nodules. (Contributed by Milton Bassis, M.D.)

CASE #5 – ACC. 23764
A 57-year-old Caucasian female presented with periumbilical and supra-pubic pain. Physical examination revealed a fixed uterus enlarged to four months gestation. The uterus with attached adnexa weighed 280 grams. The uterus measured 9.5 x 5.0 x 4.0 cm, but the cervical portion was much larger than the fundus and had a diameter of 6.0 cm. The mucosa of the portio vaginalis was somewhat granular and studded with millimeter-sized pale yellow papules. The external os was 1.5 cm broad and had prominent red-tan tissue on the anterior lip. The lower portion of the endometrial canal, as well as the cervical canal, was lined by soft, pale gray-tan gelatinous material up to 0.8 cm thick. This same type of material was present throughout the wall of the cervix. (Contributed by Melvin Anderson, M.D.)

CASE #6 – ACC. 28375
A 22-year-old Caucasian female presented with irregular uterine bleeding and an abnormal Pap smear. Pelvic examination showed a fungating cervical mass. Patient’s past medical history was unremarkable. She had used BCP at age 16 for several months and was on Triphasil (combination BCP containing levonorgestrel and ethynylestradiol) for nine months prior to her presentation. A hysterectomy was performed. The anterior and lateral cervical walls were replaced by a fungating papillary mass. (Contributed by Fattaneh Tavassoli, M.D.)

CASE #7 – ACC. 28376
A 14-year-old female presented with weight loss and fever of unknown origin. On physical examination, the uterus was enlarged and fixed to surrounding tissues. At laparotomy, a massive tumor involved the uterus and extended to the upper vagina and parametrium. (Contributed by Fattaneh Tavassoli, M.D.)
CASE #8 – ACC. 28377
A 71-year-old female was found to have a uterine mass on routine physical examination. A hysterectomy and bilateral salpingo-oophorectomy were performed. The anterior fundus contained a hemorrhagic, partly necrotic, 7 x 8 cm mass. The endometrial surface was intact and was not involved by tumor, but did have a small polyp (0.7 cm in maximum diameter). (Contributed by Fattaneh Tavassoli, M.D.)

CASE #9 – ACC. 18101
A 42-year-old gravida 5, para 5. Caucasian female presented with an enlarging pelvic mass of several months' duration. Recent Pap smear was negative. Menses had been irregular for the last six months. Physical examination revealed an abdominal mass, 24-26 weeks in size, in the left adnexal area. TAH-BSO was performed. The 1400 gram left ovary was 30 x 25 cm. The external surface was smooth and gray with no excrescences. The cut surface showed a soft yellow to tan lobulated tumor mass with a few small foci of hemorrhage and a few small cysts. (Contributed by Avrum Jacobson, M.D.)

CASE #10 – ACC. 22614
A 5-year-old female presented with a six month history of breast enlargement and development of axillary hair. She also had an abdominal mass which filled the abdomen. Preoperative plasma FSH was less than 1.0 ml U/ml (normal 0 to 6 ml U/ml), luteinizing hormone 2.6 ml U/ml (normal 0 to 6 ml U/ml). HCG was non-detectable. Total estrogen was 27 mcg. 24-hour urine was composed of Estrone 7 mcg/24-hours, Estradiol 5 mcg/24-hours, and Estriol 15 mcg/24-hours (normally trace amounts only in prepubescent females). Plasma Estriol was 1.1 mg/ml (normal less than 0.2 mg/ml). At laparotomy, a smooth, firm, well-encapsulated, freely mobile tumor replaced the left ovary. The 14 x 12 x 10 cm mass had a soft, variegated red-yellow, and finely cystic cut surface, marked by interlacing narrow fibrous bands. (Contributed by T. J. Cosgrove, M.D.)

CASE #11 – ACC. 28378
A 24-year-old Caucasian female presented with a pelvic mass. The right ovary was enlarged on physical examination. At laparotomy, a 17 x 14 x 8 cm right ovary was removed. It weighed 1100 grams. The cut surface was yellowish, solid with focal cystic areas and a 4.0 cm area of necrosis. There was no gross peritoneal or omental seeding. Three months earlier, the patient had had a C-section; at that time, both ovaries and tubes appeared normal. (Contributed by Fattaneh Tavassoli, M.D.)

CASE #12 – ACC. 22743
A 32-year-old Caucasian female presented with severe lower quadrant pain and accompanying backache. Physical examination revealed a cystic mass of the right ovary. An emergency TAH-BSO was performed. (Contributed by Horace Spear, M.D.)

CASE #13 – ACC. 28166
A 42-year-old, gravida 1 para 1, female presented with a right ovarian mass. Right salpingo-oophorectomy was performed. The specimen consisted of a 38 gram, moderately firm mass which measured 6.5 x 4.0 x 3.8 cm. The external surface was bosselated and pink-white. The cut surface was solid pink-white with areas of light gray softening and focal cystic changes beneath the capsule. (Contributed by Arthur Kcehler, M.D.)

CASE #14 – ACC. 28379
A 63-year-old female presented with a pelvic mass. A 7 x 5 x 2 cm, partially cystic left ovarian mass was removed along with the contralateral ovary, uterus, omental segment, and para-aortic lymph nodes. (Contributed by Fattaneh Tavassoli, M.D.)

CASE #15 – ACC 10286
A 59-year-old Caucasian female presented with lower abdominal pain and a 15 pound weight loss over a three-month period. Pelvic exam revealed a large mass. Bilateral oophorectomy, pelvic exploration and multiple biopsies of the peritoneum were done. The right ovary was replaced by a 219 gram globoid mass. Its cut surface consisted of a latticework of slimy glistening gray-tan tissue exuding mucoid material. The left ovary measured 4 x 2 x 2.5 cm, and had similar lacy-looking tumor present in its central portion. (Contributed by John Gilrane, M.D.)
CASE #16 - ACC. 25047
A 72-year-old Caucasian female presented with complaints of indigestion, urinary frequency, and swelling of the right lower extremity of a few days duration. A large mass was palpable, filling both lower abdominal quadrants. At laparotomy, a cystic and solid mass was removed. The 9 cm cystic mass had soft, red-brown, polypoid masses filling it. The outer surface was smooth to slightly wrinkled. The wall averaged 0.2 to 0.4 cm in thickness, with solid tan areas in the wall up to 3.0 cm in diameter. The patient had undergone hysterectomy and removal of right and left fallopian tubes and right ovary twenty-six years previously for endometriosis. (Contributed by Edward Klatt, M.D.)

CASE #17 - ACC. 24904
A 42-year-old Caucasian female presented with vague abdominal pain, hirsutism and irregular menstrual periods, and was found to have a 5 x 8 cm cystic periumbilical mass. Hysterectomy with bilateral salpingo-ooophorectomy was performed. The specimen consisted of a 9 x 7 x 5 cm multinodular, cystic mass with a firm white capsule. The center of the cyst contained hair and yellow-white, greasy material. A 5 x 4 x 3 cm bright yellow, solid area was noted during sectioning. (Contributed by Douglas Andorka, M.D.)

CASE #18 - ACC. 17746
A 19-year-old, gravida 0, para 0, Black female presented with vaginal bleeding, a five month history of amenorrhea and three months of rapid abdominal enlargement. IVP showed a pelvic mass with hydronephrosis. A pregnancy test was negative. At surgery, a large left ovarian mass and para-aortic nodes were noted, as well as a nodular liver. The 2600 gram left ovarian tumor was 29 x 17 x 12 cm. The tumor had multilocular cystic spaces with intervening firm, rubbery, yellow areas. There were also areas filled with greasy, gritty, keratin debris and dark black hair, as well as one area with a cartilaginous consistency. (Contributed by C. P. Schwinn, M.D.)

CASE #19 - ACC. 21050
A 33-year-old Caucasian female presented with left-sided pelvic discomfort and pain. Physical examination revealed a large left adnexal mass which extended up to the umbilicus. A pregnancy test was negative. At laparotomy, the 1520 gram, 18 x 14 cm left ovary was firm, nodular and reddish-purple. The cut surface was yellow-tan, spongy and mucoid with areas of degeneration and hemorrhage. (Contributed by John Swift, M.D.)

CASE #20 - ACC. 28380
A 32-year-old female presented with a pelvic mass. An 8.0 x 5.3 x 4.4 cm lobulated, circumscribed right ovarian tumor was removed at laparotomy. Cut surface of the tumor was granular and tan-yellow. (Contributed by Fattaneh Tavassoli, M.D.)
CALIFORNIA TUMOR TISSUE REGISTRY

104TH SEMI-ANNUAL SLIDE SEMINAR

GYNECOLOGIC PATHOLOGY

“Ovarian and Uterine Tumors”

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Sunday, June 7, 1998
8:30 a.m. – 4:30 p.m.
Westin South Coast Plaza
Costa Mesa, California

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**CME Objectives:** Participants will be able to:

a) Define current issues and diagnostic problems in gynecologic pathology.

b) Identify recently recognized tumor entities.

c) Explore some useful applications of currently available markers and techniques in diagnostic pathology.
CASES 1 & 8

History (Case #1 - Acc. 28232)
A 48-year-old, gravida 3, para 3, female on oral contraceptives presented with dysmenorrhea and amenorrhea of three months duration. Initial treatment included Provera and oral contraceptives. Pelvic ultrasound revealed a 7 x 5 cm right ovarian cyst and a possible small uterine fibroid. Six months later, she returned with a large malodorous mass protruding through the cervix of an enlarged uterus. The 550-gram uterine specimen was 13 x 13 x 6 cm. The myometrium was 4 cm thick. An 8 x 6 cm, polyloid, pedunculated mass protruded through the cervix. The cut surface of the mass was partially hemorrhagic, surrounded by light tan soft tissue. (Contributed by David Seligson, M.D.)

Diagnosis: Leiomyosarcoma

Note: Despite the history of progestin therapy, the significant diffuse atypia and the abundance of mitotic figures (exceeding 10 per 10 HPF) including many abnormal forms is the basis for designation of this tumor as a leiomyosarcoma.

History (Case #8 - Acc. 28377)
A 71-year-old female was found to have a uterine mass on routine physical examination. A hysterectomy and bilateral salpingo-oophorectomy were performed. The anterior fundus contained a hemorrhagic, partly necrotic, 7 x 8 cm mass. The endometrial surface was intact and was not involved by tumor, but did have a small polyp (0.7 cm in maximum diameter). (Contributed by Fattaneh Tavassoli, M.D.)

Diagnosis: Malignant giant cell tumor (leiomyosarcoma with osteoclastic giant cells)

DISCUSSION

Leiomyosarcomas account for 45% of uterine sarcomas. They occur mostly in women over 40 years of age. Leiomyosarcomas are generally solitary, large lesions rarely smaller than 5 cm. They may be intramural, subserosal, or pedunculated into the endometrial cavity. The appearance of the cut surface is highly variable ranging from uniformly solid to highly variegated.

Classification of smooth muscle tumors into benign and malignant relies heavily, but not exclusively, on the assessment of mitotic activity in the tumor. To obtain a reliable mitotic count, it is important to adequately sample the tumor (1 tissue section per every 1-2 cm of the maximum tumor diameter). The number of mitotic figures is expressed per 10 high power fields and is often obtained after scanning each slide and counting 50 HPF in the most active areas of the tumor and getting an average per 10 HPF. Variations in mitotic count due to delay in fixation, differences in size of the high power fields in different microscopes, variable ratio of the number of mitotic figures relative to the number of cells in a given field are sources of problems in reproducibility. These issues have raised questions concerning the influence of mitotic activity as a prognostic factor in smooth muscle tumors. A recent study highlights the importance of using features other than mitotic index to predict outcome in uterine smooth muscle tumors; coagulative tumor cell necrosis emerged as a crucial feature (Bell et al, Table 1).

As a rule, a uterine smooth muscle tumor would qualify as a leiomyosarcoma if it displays 10 or more mitotic figures per 10 HPF along with significant nuclear atypia. Aside from the abundant mitotic activity, leiomyosarcoma may manifest atypical mitotic figures, infiltrative margins, extrauterine extension, and areas of necrosis due to large size. The presence of coagulative tumor cell necrosis is helpful, but sometimes it is difficult to determine what is coagulative tumor cell necrosis. We have noted an increasing number of smooth muscle tumors with areas of...
“necrosis” or “infarction” in young women who have been treated with leuprolide a gonadotropin-releasing hormone agonist (GnRHa).

Furthermore, while mitotic activity is generally considered a cardinal feature of leiomyosarcomas and an indication of aggressive behavior, **mitotically active smooth muscle tumors** occur in women less than 40 years of age as a response to hormonal stimulation either during pregnancy or as a result of oral contraceptive steroid use, and even possibly due to elaboration of nongestational endogenous hormones. The mitotic activity in these tumors exceeds 4/10HPF and is often less than 10/10HPF, but may exceed 10 per 10 HPF. Rarely, such tumors have over 20 mitotic figures per 10 HPF. These are so rare that there is not enough information available concerning their behavior and prognosis. Atypia is absent or minimal, however. Tumors in this setting often, but not always, have areas of edema, hemorrhage and necrosis with the mitotic activity most conspicuous around the degenerating foci. Therefore, the mitotic activity in these tumors is considered a reactive response to the hormonal stimulus or a reparative process around the foci of degeneration. Intra tumoral vascular extension is present in 15% of these tumors (Prayson and Hart, 1992). The designation of mitotically active smooth muscle tumor is appropriate for these lesions and follow-up of the patient is recommended. It is important to obtain clinical information regarding use of oral contraceptives and pregnancy (current or recent) when evaluating mitotically active tumors from young women as it is well known that progestins increase mitotic activity in uterine smooth muscle tumors. The term “apoplectic leiomyoma” or “hemorrhagic cellular leiomyoma” has been used for a group of leiomyomas occurring in women taking oral contraceptives or those who are pregnant. These women often present with acute abdominal signs secondary to rupture of the tumor into the peritoneal cavity. The leiomyoma shows areas of hemorrhage often associated with cystic change. Microscopically, there are stellate areas of hemorrhage and up to 8-9 mitotic figures per 10 HPF, but there is no atypia and not even significantly increased cellularity. In addition, the vessels show intimal myxoid change. A transition to typical smooth muscle is evident in most instances. Immunostains for desmin show intense positivity in cellular leiomyomas, whereas endometrial stromal tumors are basically negative.

A diagnosis of leiomyosarcoma should be made with extreme caution in young women with a clinical history of endogenous or exogenous progestin stimulation. The addition of progestins to the postmenopausal hormone replacement regimens is also having an impact on the morphology of tumors in older women substantially complicating the diagnostic process in some cases.

With increasing use of Tamoxifen in treatment of breast cancer as well as for preventive purposes in women at increased risk for breast cancer, the effect of this hormone on uterine smooth muscle tumors will need evaluation. A rare case report has suggested that Tamoxifen may stimulate growth of leiomyomas (Kang et al, 1996), but data on this issue is limited.

Smooth muscle tumors may assume a variety of morphologic features and appear cellular, vascular, atypical, epithelioid or xanthomatous.

**Cellular Leiomyma**

Cellular leiomyomas are densely cellular lesions that are significantly more cellular than the adjacent myometrium. These tumors are devoid of nuclear atypia, and coagulative tumor cell necrosis. Mitotic activity is limited and there are fewer than 5 mitotic figures per 10 HPF. Grossly, they may appear yellow-tan and have a fleshy consistency simulating an endometrial stromal tumor. Microscopically, they may also mimic endometrial stromal tumors because of their compact cellularity. They lack the typical vascularity of endometrial stromal tumors, however. Hemorrhage and necrosis are evident in a minority of cases. Immunostains for desmin show intense positivity in cellular leiomyomas, whereas endometrial stromal tumors are basically negative.

**Epithelioid Smooth Muscle Tumors** (leiomyoblastoma, clear cell leiomyoma)

Mixtures of epithelioid, clear cell, and plexiform pattern are not uncommon in smooth muscle tumors either as a focal or a diffuse change. A transition to typical smooth muscle is evident in most instances, confirming smooth muscle origin of the pure lesions. Features related to a favorable prognosis include the presence of clear cells, an expansile tumor margin, extensive hyalinization, and absence of extensive necrosis. At AFIP, the presence of an epithelioid differentiation in smooth muscle tumors is considered comparable to the presence of atypia. Therefore, the presence
of 5 mitotic figures per 10 HPF in an epithelioid smooth muscle tumor is sufficient for a diagnosis of leiomyosarcoma. When 3 to 4 mitotic figures per 10 high power fields are encountered in an epithelioid smooth muscle tumor, careful evaluation and additional sampling of the tumor is warranted to exclude the presence of areas with more abundant mitotic activity that would qualify the tumor as a sarcoma.

Epithelioid smooth muscle tumors show immunoreactivity with actin and desmin, but sometimes only focally, some also immunoreact with epithelial markers.

**Intravenous leiomyomatosis**

Intravenous leiomyomatosis (IVL) is a rare uterine neoplasm characterized by nodular masses of histologically benign smooth muscle (may be myxoid, cellular, edematous, etc.) growing within veins. The intravascular growth takes the form of visible worm-like projections that may extend variable distances into the uterine and hypogastric veins. Direct extension from the pelvic veins into the inferior vena cava and into the right atrium has occurred, and in some of these instances the outcome was fatal. There are two theories of origin of IVL; it may originate either from the wall of veins within the myometrium or reflect extensive vascular invasion of a leiomyoma. When the vascular extension is limited to a microscopic field in an otherwise benign leiomyoma, the term leiomyoma with vascular extension is preferred. The presence of any vascular extension should be noted in the diagnosis since it implies a capability to metastasize to the lungs.

**Myxoid Leiomyosarcoma**

Rarely, uterine smooth muscle tumors appear grossly gelatinous and microscopically display abundant acellular mucoid matrix. The myxoid change may be diffuse or patchy in distribution. The abundant myxoid matrix is rich in acid mucins as confirmed by Alcian blue or colloidal iron stains. Pretreatment with hyaluronidase does not remove the material that stains with colloidal iron. Hydropic changes may mimic myxoid alterations, but lack stainable mucoid material. When these tumors display infiltrating margins or vascular invasion, they display aggressive behavior generally in the form of local recurrences, despite a very limited number of mitotic figures. Using the conventional approach to counting, the mitotic activity rarely exceeds 0-2/10HPF. Therefore, this type of tumor is an exception to the general rule requiring increased mitotic activity for a diagnosis of leiomyosarcoma. Considering the hypocellular appearance of these tumors and the abundance of myxoid material in a given field, assessment of the number of mitotic figures per a given number of cells (Mitotic index = # m.f. / # cells) may provide a better assessment of their aggressive potential.

Recurrent disease or distant metastases have developed within 6 months to 10 years after the diagnosis in almost all reported cases. The recurrent lesions are generally morphologically similar to the primary tumor.

Our experience with myxoid leiomyosarcomas has not confirmed this invariable aggressive behavior. Only tumors with vascular infiltration have behaved aggressively.

**Unusual Smooth Muscle Tumors**

**Smooth muscle tumor with osteoclastic giant cells and malignant giant cell tumor.**

Rarely, smooth muscle tumors show admixture of smooth muscle bundles with osteoclastic type giant cells. The giant cells may be distributed focally or diffusely in the tumor. Depending on the mitotic activity of the smooth muscle cells, the lesion is designated either as a leiomyoma or a leiomyosarcoma with osteoclastic giant cells. The osteoclastic giant cells are negative for actin or desmin, but intensely positive for KP1 and acid phosphatase confirming their histiocytoid nature.

**Malignant giant cell tumors** devoid of any smooth muscle component rarely occur in the uterus (Lars-Kindblom and Seidal, 1981). These are characterized by an admixture of osteoclastic giant cells, pleomorphic mono and multinucleated cells, and occasional fibroblast-like spindle cells. The nuclei of the mononucleated cells in the background are irregularly shaped and chromatin rich. Mitotic activity is very high and atypical mitotic figures are
easily identifiable. Phagocytic activity by both cell populations may occur. At the ultrastructural level, the giant cells show abundant intracytoplasmic lipid droplets and mitochondria. The surrounding mononucleated tumor cells also may contain phagosomes, lipid droplets and lysosomal structures. These tumors are identical to malignant giant cell tumor of soft parts (MGCT) which is considered to be a variant of malignant fibrous histiocytoma. This lesion is highly aggressive and the patient reported by Lars-Kindblom and Seidal died within 15 days after presentation; she had pulmonary metastases at the time of presentation.

In the uterus, osteoclastic giant cells often immediately surrounded by mononucleated cells similar to those of GCT are most often seen in smooth muscle tumors. The proportion of these areas relative to the smooth muscle component is highly variable. Association of osteoclast-like giant cells with leiomyosarcomas has been noted in 8.7% of deep-seated nonvisceral leiomyosarcomas (Mentzel et al, 1994). Whether the MGCTs of the uterus are pure lesions or reflect overgrowth of this component in a smooth muscle tumor is difficult to establish but favored at sites where smooth muscle tumors are common also due to the fact that careful assessment of these tumors often shows at least focal aggregates of smooth muscle cells that stain positively for actin and desmin.

**Xanthomatous smooth muscle tumors**

Even more infrequently, a prominent population of large cells with abundant intracytoplasmic lipid vacuoles are found admixed with typical smooth muscle bundles; these tumors are designated as xanthomatous leiomyosarcomas or leiomyomas depending on the mitotic activity of the typical smooth muscle component and nuclear features of the xanthomatous component.

**Plexiform Tumorlet**

Generally, an incidental microscopic finding, it often presents as a solitary nodule composed of a plexiform nest of cells. Several multifocal examples have also been reported. So far, both the solitary and the multifocal lesions have behaved in a benign fashion. Nonetheless, follow-up of the multifocal lesions is prudent because of the limited experience with them. Immunohistochemical and ultrastructural analysis support smooth muscle differentiation in these tumors.

**Immunohistochemistry And Special Studies**

Of little assistance in very primitive or poorly differentiated mesenchymal tumors, immunohistochemistry is very helpful in differentiating a variety of unusual and usual smooth muscle tumors from endometrial stromal tumors. It is particularly helpful in distinguishing a cellular leiomyoma from a stromal nodule. Smooth muscle tumors are diffusely positive with actin and desmin, while endometrial stromal tumors fail to react with desmin, but may display often focal and minimal positivity with actin. Immunohistochemistry has been particularly helpful in establishing the myoid nature of a variety of unusual uterine mesenchymal tumors (Devaney & Tavassoli).

Recent studies have shown a lack of gamma-smooth muscle isoactin gene expression in 100% of 10 leiomyosarcomas, two of which were uterine; twelve leiomyomas, however, did express the gene (Trzyna et al, 1997). Cytogenetic studies have noted del(11)(q22) in some leiomyosarcomas suggesting that genomic alterations in this region may be specific for malignant smooth muscle tumors (Laxman et al, 1993). Cytogenetic instability has been noted in a metastatic uterine leiomyosarcoma, whereas a leiomyoma studied by the same investigators demonstrated cytogenetic stability. Furthermore, the leiomyosarcoma was hyperdiploid, whereas the leiomyoma was hypodiploid (Fletcher et al).

**Clinical Behavior and Treatment**

Leiomyosarcomas are aggressive tumors with a tendency to recur both locally and at distant sites. Median interval to recurrence is about 2 years. Most metastases are in the lungs and abdomen. Overall, less than 5% show metastases to pelvis or para-aortic lymph nodes; the frequency is higher for advanced stages. Five-year survival is about 50% for stage I disease and less than 10% for stages II to IV. The tumor stage is the best prognostic indicator. Only those with early stage disease have a chance for survival. Total abdominal hysterectomy and bilateral salpingo-
Oophorectomy is the main treatment; adjunctive therapy in the form of either radiotherapy or chemotherapy seems to be mainly palliative effect with limited impact on the outcome (Gadducci et al, 1996).

The use of leuprolide acetate (GnRH-a), a gonadotropin-releasing hormone analog can reduce the uterine tumor volume; this is used mainly for leiomyomas. The impact of leuprolide treatment of morphology of smooth muscle tumors is controversial. Some investigators have reported reduced cellularity, but no significant change in mitotic activity (Upadhyaya, et al), fibrosis or edema as a result of leuprolide treatment. The reduction in cellularity has been attributed to the degree of hyperestrogenism induced and it reverts soon after cessation of GnRH-a therapy. The endometrium becomes thinned with inactive glands, reduced vascularity and atrophic stroma. In contrast, Colgan et al observed increased cellularity in uterine myomas following treatment with GnRH-a. The reduction in tumor size was attributed to cellular atrophy and ischemic injury. Necrosis also occurs following leuprolide treatment. Sreenan et al (1996) compared 107 uterine leiomyomas treated with Leuprolide acetate with 126 controls and concluded that LA-treated tumors do not significantly differ from the untreated lesions in their cellularity, atypia, mitotic activity, coagulative necrosis, myxoid changes, hydropic changes, calcification or hemorrhage.

### TABLE 1

<table>
<thead>
<tr>
<th>Low to medium magnification assessment of tumor:</th>
<th>Diffuse, significant cellular atypia?</th>
<th>Coagulative tumor cell necrosis?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Both features absent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leiomyoma</td>
<td>Make mitotic count</td>
<td></td>
</tr>
<tr>
<td>&quot;Leiomyoma with increased mitoses&quot; if MI &gt; or = 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI &lt; 10</td>
<td></td>
<td></td>
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<tr>
<td>Diffuse significant cellular atypia only</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atypical leiomyoma with low risk of recurrence</td>
<td>Coagulative tumor necrosis only</td>
<td></td>
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<tr>
<td>Failure: 1/46</td>
<td>Leiomysarcoma</td>
<td></td>
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<tr>
<td>Smooth muscle tumor of low malignant potential,</td>
<td>Leiomysarcoma</td>
<td></td>
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<tr>
<td>Limited experience</td>
<td>Failure: 7/14</td>
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<tr>
<td>Failure: 1/4</td>
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<td>MI &gt; or = 10</td>
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<tr>
<td>Atypical leiomyoma with low risk of recurrence</td>
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<td>Failure: 1/46</td>
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<tr>
<td>Smooth muscle tumor of low malignant potential,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Limited experience</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Failure: 1/4</td>
<td></td>
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</tr>
</tbody>
</table>

104th Semi-Annual CTTR Seminar: Gynecologic Pathology
### TABLE 2
Simplified histologic criteria exclusive of tumor cell necrosis

<table>
<thead>
<tr>
<th>Mit. Figs./HPF</th>
<th>Cytologic Atypia</th>
<th>Cellularity</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4</td>
<td>-</td>
<td>Hyper-</td>
<td>Cellular LM</td>
</tr>
<tr>
<td>0-4</td>
<td>++ (diffuse)</td>
<td>Variable</td>
<td>Atypical LM</td>
</tr>
<tr>
<td>5-15</td>
<td>-</td>
<td>Normo-</td>
<td>Mitotically Active LM</td>
</tr>
<tr>
<td>≥ 10</td>
<td>++</td>
<td>Hyper</td>
<td>Leiomyosarcoma</td>
</tr>
<tr>
<td>≥ 5</td>
<td>Minimal</td>
<td>Hyper-</td>
<td>UMP</td>
</tr>
</tbody>
</table>

### TABLE 3
Types of uterine smooth muscle tumor

<table>
<thead>
<tr>
<th>Benign</th>
<th>Uncertain Malignant Potential (UMP)</th>
<th>Malignant</th>
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<tbody>
<tr>
<td>Leiomyoma (LM)</td>
<td>Intravenous Leiomyomatosis</td>
<td>Leiomysarcoma</td>
</tr>
<tr>
<td>Vascular LM</td>
<td>Smooth Muscle tumor of UMP</td>
<td></td>
</tr>
<tr>
<td>Myxoid LM</td>
<td>(rarely used now)</td>
<td></td>
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<tr>
<td>Cellular LM</td>
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<td></td>
</tr>
<tr>
<td>Atypical LM</td>
<td></td>
<td></td>
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<tr>
<td>Epithelioid LM</td>
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<tr>
<td>Mitotically Active LM</td>
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</table>

104th Semi-Annual CTTR Seminar: Gynecologic Pathology
REFERENCES


CASE 2

History (Case #2 – Acc. 24934)
A 70-year-old female presented with vaginal bleeding of recent onset. A total abdominal hysterectomy and bilateral salpingo-oophorectomy were performed. The 8 x 9 x 4 cm uterus was symmetrically enlarged. The endometrial cavity was dilated by a 4.5 x 3.0 x 4.0 cm polypoid mass composed of loculated, somewhat mucoid tissue. Sections through the broad stalk revealed only superficial attachment to the myometrium, without obvious invasion. (Contributed by Paul Ortega, M.D.)

Diagnosis: Adenosarcoma of the uterus

DISCUSSION

Approximately 250 cases of uterine adenosarcoma have been reported. Some of these tumors have been referred to as adenofibroma (cystic or papillary) in the literature particularly prior to the description of the adenosarcomas in 1974 (Clement and Scully). Patients generally range in age between 50-70 years, the median in the largest series (Clement and Scully, 1990) was 58 years. Almost a third of the tumors occur in women less than 50 years of age, however, and at least 10 adenosarcomas have been reported in young women in the second decade of life. Occasional cases have been reported in women with Stein-Leventhal syndrome, ovarian thecoma or exogenous estrogen therapy. Two recent reports have noted the development of adenosarcomas in women on tamoxifen therapy (Clement et al 1996; Bocklage et al 1992).

Clinical Features

The most common presentation is abnormal vaginal bleeding, usually accompanied by a pelvic mass and associated by lower abdominal or pelvic pain. The uterus is enlarged in most of the women. Endometrial adenosarcoma typically forms a sessile, polypoid mass that fills the endometrial cavity. In half of the cases, the lesion protrudes through the external os presenting as a large polyp. A massive polyp at any age and recurrent polyps should be assessed carefully to exclude the possibility of adenosarcoma. Approximately 10% of adenosarcomas are endocervical in origin. Typically stage 1 at presentation, the presence of extratine tumor is a reflection of either multicentricity or metastatic tumor. Metastases occur most often in association with tumors that have sarcomatous overgrowth and/or myometrial invasion.

Pathologic Features

Typically polypoid, surface erosion or ulceration, hemorrhage and necrosis occur in approximately one quarter of cases. The cut surface of the tumor has a spongy appearance with small cysts filled with watery or mucoid secretion. In most cases there is no evidence of myometrial invasion on gross examination, but in about one sixth of the cases areas suggestive of myometrial invasion are apparent at the base of the lesion.

Microscopically, the surface of the tumor is characterized by broad papillae covered by benign appearing epithelium that resembles glands of proliferative or hyperplastic endometrium. Within the substance of the polyp, small and sometimes dilated glands are dispersed randomly within a variably appearing stroma composed of either fibroblasts or endometrial stromal cells. The glands are generally lined by proliferative type endometrial epithelium. Epithelial atypia as manifest by nuclear enlargement, hyperchromasia and nuclear enlargement may be seen in one third of cases). The atypical cells are often stratified with intraluminal tufting. However these changes are always focal. Metaplastic mucinous or squamous epithelium often lines a portion of the epithelium. The mesenchymal component of the neoplasm is a sarcoma despite its often-benign appearance. Alternating between hypo and hypercellular areas, it is at least focally hypercellular around the glandular epithelium, forming a characteristic cuff of stromal condensation. All grades of cytologic atypia may be seen. Even though up to 40 mitotic figures per 10 HPF has been
reported, the mitotic activity tends to be low and often confined to the subepithelial or periglandular stromal condensation. At AFIP, we require a minimum of 4 mitotic figures per 10 HPF in the stromal component particularly if the periglandular stromal condensation is not well developed. Heterologous elements including cartilage, striated muscle and adipose tissue have been reported in approximately one quarter of cases. The cartilage may be of the fetal type similar to what occurs in embryonal rhabdomyosarcoma of the vagina and cervix. In young women, distinction of adenosarcoma from an embryonal rhabdomyosarcoma can be very difficult. Smooth muscle is rarely present in the stroma. Occasionally, adenosarcomas contain sex cord-like elements similar to those described in endometrial stromal tumors and uterine tumors resembling ovarian sex cord tumors. Adenosarcomas may also demonstrate sarcomatous overgrowth. The sarcomatous overgrowth may be of the homologous or heterologous type. The homologous sarcomas display more atypia and mitotic activity and may occupy at least 25% of the tumor volume. In a series of adenosarcomas with sarcomatous overgrowth reported from the Gynecologic Oncology Group (GOG), 60% of the cases had rhabdomyosarcoma as the pure heterologous element (Kaku et al, 1991). Depending on the consultation practice, 10% to 55% of adenosarcomas may have sarcomatous overgrowth. Myometrial and lymphatic vessel invasion is more common in adenosarcomas with sarcomatous overgrowth. A case of adenosarcoma with a stroma composed exclusively of angiosarcoma has been described (Lack et al, 1991).

**Differential Diagnosis**

Adenosarcomas should be distinguished from adenofibroma, benign endometrial polyps, adenomyomas and other tumors that are either typically biphasic (carcinosarcomas) or occasionally manifest a biphasic appearance (endometrial stromal sarcoma with endometrial glands). Adenofibromas and polyps lack the periglandular stromal condensation typical of adenosarcomas. The stroma is less cellular, fibrotic or edematous in adenofibromas and polyps. The low mitotic activity, reduced cellularity and absence of cytologic atypia differentiate adenofibroma from adenosarcoma. Adenomyomas display predominantly a smooth muscle stromal component, lack periglandular stromal cuffing, as well as the atypia and mitotic activity of adenosarcomas. Glandular atypical hyperplasia and squamous metaplasia are also noted in the atypical adenomyomas. Endometrial stromal sarcomas have a uniformly hypercellular stroma along with an infiltrative and often intravascular tumor in the myometrium. Carcinosarcomas and mixed mesodermal tumors are composed of malignant epithelial as well as stromal components. Adenosarcoma, in contrast, contains benign epithelium while the stroma is malignant.

**Behavior and Treatment**

Twenty-five percent of adenosarcomas recur and/or metastasize. Metastases and recurrences are most commonly abdominopelvic or vaginal, although they can develop outside the pelvis in a small proportion of patients. Hematogenous spread has been noted in less than 5% of cases. Recurrences often develop within 5 years of the diagnosis in one third of the patients; rarely tumors recur 10 or more years after hysterectomy. Long term follow-up of the patients is, therefore, prudent. The composition of the recurrent tumor has been pure sarcoma in 70% of the cases, adenosarcoma in 30% and a carcinosarcoma in one case (Clement and Scully, 1990). The recurrent tumor rarely contains heterologous elements not apparent in the initial lesion. Features associated with an increased risk of recurrence include the presence of myometrial invasion with or without lymphatic space involvement and sarcomatous overgrowth. In the absence of myometrial invasion, 12.7% of tumors recur in comparison with 46% of those with myometrial invasion (Clement & Scully, 1990). The tumors demonstrating sarcomatous overgrowth are more aggressive, with a greater rate of progression. When sarcomatous overgrowth is present, 70% develop recurrent disease, 40% manifest hematogenous spread, and 60% die from the tumor (Clement and Scully, 1989). Recurrences may take the form of a pure sarcoma, an adenosarcoma or even a heterologous malignant mixed mesodermal tumor. Overall approximately 10% of patients die of tumor. The mean interval from diagnosis to death is 7 years. Similar tumors may occur in the cervix, ovary and adnexal region.

Treatment is total hysterectomy and bilateral salpingo-oophorectomy. Staging of the tumor has been recommended by GOG to include peritoneal washings. Tumors invading greater than halfway through the myometrium and those with sarcomatous overgrowth have a high likelihood of recurrence, and consequently, postoperative pelvic radiation or chemotherapy may be tried, but the value of such adjuvant therapy has not been established. Recurrences have been successfully treated with local excision in 50% of cases.
REFERENCES


CASE 3

History (Case #3 – Acc. 28293)
An 80-year-old female presented with complaints of pelvic pain. A hysterectomy was performed. The uterus without adnexa weighed 223 grams and measured 7.6 x 9.2 x 6.2 cm. The serosal surface was fairly smooth tan. However, at the parametrial margins there were fleshy tan protrusions. The endometrial cavity was fairly symmetrical with a slightly shaggy, red-tan surface. The myometrium was up to 2.5 cm thick. There was some accentuation of the trabecular architecture. (Contributed by Kenneth Frankel, M.D.)

Diagnosis: Endometrial stromal sarcoma, low grade

DISCUSSION

Accounting for 10 to 15% of uterine sarcomas, endometrial stromal tumors are composed of neoplastic cells that resemble the proliferative phase endometrial stromal cells. Endometrial stromal tumors are subdivided into two major categories based on the presence or absence of an infiltrative margin of growth. The clinically benign endometrial stromal tumor, designated as a stromal nodule, is a circumscribed lesion that displays a pushing growth pattern. The sarcomas, in contrast, have infiltrative margins and have been further subdivided into low grade (LGESS) and high grade (HGESS) based mainly on the number of mitotic figures per 10 HPF. In our current practice, however, we rarely use the designation of high-grade endometrial stromal sarcoma. This is due to the fact that non-smooth muscle sarcomas with significant mitotic activity often also display atypia and no longer resemble endometrial stromal cells. In most cases, a designation of “high-grade undifferentiated uterine sarcoma” is more appropriate; many of these tumors may not be of endometrial stromal origin.

Clinical Features

Endometrial stromal tumors most often occur in peri- and post-menopausal women whose median age ranges from 42 to 58 years. A majority of the women (75%) are younger than 50 years of age at presentation; occasional cases have been reported in children (Chuaqui et al. 1994). Women with high-grade tumors in one report (Norris and Taylor) were significantly older those with LGESSs, with median ages of 61 and 39 years respectively. Specific risk factors are not known, but rare association with prolonged estrogenic stimulation, tamoxifen therapy and history of pelvic irradiation has been noted (Kempson and Hendrickson, 1988).

Abnormal vaginal bleeding is the most frequent symptom; it is usually more severe than in patients with leiomyomas. Some patients present with pelvic or abdominal pain, while occasional patients are asymptomatic. An enlarged uterus with an irregular contour is noted on physical examination. Occasionally, tumor protrudes through the external os. Most tumors involve the endometrium, but rarely LGESS presents as recurrent cervical “polyps.” Rarely metastases present prior to detection of the primary lesion. Presentation may be with hematuria when there is involvement of the urinary bladder (Dgani et al, 1989), as a primary ovarian tumor due to metastases to one or both ovaries (Young and Scully, 1990), or with pulmonary nodules appearing before detection of the uterine primary (Abrams, et al 1989).

Extrauterine extension is present in up to a third of the women with LGESS at the time of hysterectomy. The extension may appear as worm-like plugs of tumor within the vessels of the broad ligament and adnexa. Rarely removed for assessment, the retroperitoneal lymph nodes have been negative on histological examination.
Gross Appearance

Presenting either as an endometrial (40%) or an intramural lesions (60%), the endometrial stromal nodule presents as a well-circumscribed, non-encapsulated, solitary, rounded mass located. Some are confined to the endometrium (7%) and may appear as a polypoid mass. Approximately 20% protrude into the endometrial cavity.

The median tumor diameter was 4.0 cm (range 0.8 to 15 cm) in the only series of such cases reported (Tavassoli and Norris).

Frequently protruding into the endometrial cavity, LGESSs often present as a solitary and predominantly intramural mass. Extensive permeation of the myometrium is common, with extension to the serosa in approximately half of the cases. The cut surface appears yellow to tan and the tumor has a softer consistency compared to leiomyomas. Cystic and myxoid degeneration as well as necrosis and hemorrhage are seen occasionally.

The high-grade endometrial sarcomas more commonly resemble MMMTs, characterized by one or more fungating, polypoid, fleshy, gray to yellow endometrial masses, often with prominent hemorrhage and necrosis. Myometrial invasion is common but lacks the diffuse permeative pattern typical of LGESS.

Both low and high-grade endometrial stromal sarcomas may develop in the endocervix. In this location, they are either polypoid or diffusely infiltrative, but rarely may appear as an indurated ulcer (Abell and Ramirez, 1977).

Microscopic Features

The distinction between ESN and ESS requires assessment of the tumor margin. ESN has a pushing, circumscribed growth margin, while LGESS infiltrates the myometrium in often well-rounded aggregates that may show an angulated edge or extend into lymphatic channels. Mitotic activity cannot be used to separate the nodules from sarcomas, because some ESNs may have mitotic activity that exceeds 10 per 10 HPF, while many LGESS hardly contain any mitotic figures and rarely would they have more than 3-4 mitotic figures per 10 HPF. Therefore, distinction of a LGESS from ESN is not possible on curettage specimen.

Both ESN and LGESS are densely cellular tumors composed of uniform, oval to spindle-shaped cells of endometrial stromal-type; significant atypia and pleomorphism are absent. A network of delicate small arteries resembling the spiral arterioles of the late secretory endometrium is typically present. Stainable intracytoplasmic lipid is present focally in almost half of the cases, and cells with foamy cytoplasm (tumor cells, foamy histiocytes, or both) are prominent in some cases. Focal deciduial change is evident in some tumors; this may reflect an endogenous or exogenous gestational effect. Both lesions are characterized by a very low mitotic rate. Over 90% of the ESNs in the series reported by Tavassoli and Norris had 3 or fewer MFs/10HPFs and almost half the tumors had no discernible mitotic activity. Three cases, however, had over 10 mitotic figures per HPF. Likewise, LGESSs usually have 3 or fewer MF/10HPFs; higher mitotic rates can be encountered occasionally.

Perivascular hyalination is a common finding and may be prominent enough to obscure the basic pattern of the tumor; the term angiosclerotic stromal tumor has been used for these. A stellate pattern of hyalization occurs in some cases. Reticulin stains usually reveal a dense network of fibrils surrounding individual cells or small groups of cells. Necrosis is typically absent or inconspicuous.

It is not unusual to find focal smooth muscle differentiation or cells with differentiation that is ambiguous between stromal and smooth muscle cells in endometrial stromal tumors. When the smooth muscle component is prominently evident, we use the term combined smooth muscle stromal tumor. Some have used the designation of stromomyoma. Rarely, foci of osteoid or trabecular bone may occur. Benign endometrioid glands have been described in both ESN and LGESS; this feature is of no clinical consequence. Rare cases of LGESS with prominent benign endometrioid glands have been described and designated as interpreted extraterine LGESSs with prominent glandular differentiation.

High-grade ESSs are composed of spindle to polygonal cells with marked degrees of nuclear pleomorphism and...
admixed multinucleated giant cells. Mitotic rates exceed 10/10HPFs, and are often beyond 20 or 30 MF/10HPFs. Atypical mitotic figures are also commonly identified. The distinctive vascular pattern of the low-grade tumors is typically absent. In contrast to LGESSs, there is usually destructive invasion of the myometrium with frequent areas of necrosis. The vascular invasion lacks the permeative pattern seen in LGESSs.

The cells of the high-grade tumors do not resemble endometrial stromal cells. It has been suggested that some of these may be monophasic variants of MMMTs with exclusive overgrowth of the sarcomatous component (Evans, 1982). Indeed, additional histologic sampling of an apparently pure high-grade endometrial sarcoma may reveal rare foci of carcinoma that were missed on initial sampling, warranting a final diagnosis of MMMT. A recurrent LGESS following pelvic irradiation displayed a high-grade morphology, possibly reflecting dedifferentiation (Smith et al, 1980; Chumas et al, 1990).

**Immunohistochemical Features and Other Special Techniques**

The neoplastic cells of both stromal nodules and LGESSs are immunoreactive for vimentin and actin. Desmin-positivity has been noted in some studies, but in my experience endometrial stromal tumors have been consistently negative for desmin with the exception of one case that had focal positivity. Both of these tumors also display positivity for both estrogen and progesterone receptors (ER and PR). High-grade stromal sarcoma, however, are negative for ER and PR.

ESNs and LGESSs are typically diploid and with a low S-phase fraction; the high-grade endometrial sarcomas are typically aneuploid.

**Differential Diagnosis**

Cellular smooth muscle tumors are the major lesions that should be distinguished from endometrial stromal tumors. The endometrial location and lack of immunostaining for desmin help make this distinction.

LGESSs containing endometrioid glands should be distinguished from adenosarcomas. This distinction is important because as stage I tumors, LGESSs have a higher recurrence rate (36%) compared to adenosarcomas (24%). Also, LGESSs are probably more responsive to radiation and progestin therapy. The efficacy of such therapy in the management of adenosarcomas remains unknown. In contrast to the localized distribution of glands within LGESSs, those of adenosarcomas are scattered more diffusely throughout the tumor, and are typically surrounded by cellular condensations of the sarcomatous stroma. Furthermore, adenosarcomas lack the vascular and myometrial permeation typical of LGESSs.

**Behavior and Treatment**

As noted earlier, categorization of endometrial stromal tumors into ESNs, LGESSs, and high-grade endometrial sarcomas is important because of prognostic and therapeutic implications. The benign ESNs are adequately treated by hysterectomy. Even stromal nodules with up to 15 mitotic figures per 10 high power fields have had a benign course with close to two decades of follow-up. In a young women whose curettage specimen is interpreted as endometrial stromal tumor, laparoscopic assessment of the lesion and imaging to confirm a circumscribed margin may help avoid or delay hysterectomy, but careful follow-up of all such women is absolutely essential.

LGESSs are characterized by an indolent growth and late recurrences. Up to half of these women develop pelvic or abdominal recurrences. The interval to recurrence has ranged from 3 months to 23 years; the median interval to recurrence is between 3 to 5 years. For higher stage tumors, the interval is only a few months rarely exceeding a year. Multiple recurrences following hysterectomy have been reported. Pulmonary metastases occur in 10% of stage I tumors and manifest in about 10 years after the initial diagnosis; when cystic, these have been misinterpreted as cystic hamartomas. Blood borne metastases and metastases to other sites are rare.
In most cases, both recurrent and metastatic ESS may remain localized for long periods and are amenable to successful treatment by resection, radiation therapy, progestin therapy, or combinations thereof. Approximately 90% to 100% of patients survive 10 years. Tumor-related deaths may occur as late as 30 years after the initial diagnosis.

The surgical stage is the best predictor of recurrence (and survival) for LGESSs. Of patients with stage I disease, 36% developed recurrent disease compared to 76% of patients with stage III-IV disease. Stage I patients had a 92% survival rate compared to 66% for higher stage cases (stages III-IV). In other studies that have utilized progestagen therapy, 100% survival rates have been achieved even for stage III patients (Piver et al, 1984). Tumor size, mitotic rate and nuclear atypia are not useful predictors of recurrence in patients with stage I tumors.

Optimal initial management of patients with LGESSs requires total abdominal hysterectomy including bilateral salpingo-oophorectomy along with wide parametrical excision. Conservation of the adnexa is not advised, because of the presence of microscopic adnexal extensions of tumor and the possible stimulatory effects of estrogen from the retained ovary (Berchuk et al, 1990). The tumor should be analyzed for hormone receptors and patients with Stage I receptor positive tumors could benefit from progestagen therapy. In case of a receptor negative stage I tumor, postoperative radiation may be justifiable. Overall, however, pelvic irradiation does not appear to significantly decrease the relapse rate for stage I tumors (Chang et al, 1990). Postoperative hormonal therapy, radiation therapy, or both may be used for patients with higher stage tumors after excision of the tumor to the extent technically feasible.

The high-grade endometrial sarcomas are aggressive tumors, with death from tumor dissemination within three years after hysterectomy in most cases. A more favorable prognosis may ensue when the tumor is limited to the endometrium. The frequency of pelvic recurrence may be diminished by preoperative or postoperative radiation.

REFERENCES

CASE 4

History (Case #4 - Acc. 17531)

A 17-year-old, gravida 1, para 1, female presented with abdominal swelling and pain. Physical examination revealed an enlarged uterus of approximately 8 weeks size, with bilateral ovarian masses. Chest x-ray showed small round lesions scattered throughout both lung fields. A pregnancy test was positive in a high dilution. After two courses of methotrexate, the uterus appeared to decrease in size, although the ovarian cysts were still palpable. The uterine specimen measured 15 x 12 x 7 cm. In the right and left cornu were two irregular, friable, yellow tumor masses invading the myometrium but not penetrating the serosa, each measuring 2 x 2 x 2 cm and blending with overlying endometrium. Throughout the myometrium were small yellow, fairly well-defined nodules. (Contributed by Milton Bassis, M.D.)

Diagnosis: Choriocarcinoma

Note: The extensive fibrinoid change replacing tumor cells is a result of chemotherapy.

Follow-up: On the third postoperative day, patient developed a hard and distended abdomen and a fast pulse. Her hematocrit was 11. She was transfused and taken to the operating room where laparotomy disclosed bleeding from vaginal cuff. Patient did well for 4 days but was found dead. Suspected cause of death was pulmonary embolus.

DISCUSSION

About 50% of all choriocarcinomas occur subsequent to molar pregnancies (complete hydatidiform moles), but only about 3% of complete moles are followed by choriocarcinoma (Ringertz 1970). Approximately, a quarter of choriocarcinomas follow normal pregnancies. Rarely, a gestational choriocarcinoma develops during a seemingly normal pregnancy within a non-molar placenta (Brewer and Mazur 1981). Gestational choriocarcinomas become clinically apparent within several months after the pregnancy.

Abnormal uterine bleeding is often the presenting sign. Because of the capability of trophoblasts to invade vascular structures, hemorrhage is an important feature of choriocarcinoma whether it occurs in the uterus or when it metastasizes to the lungs or the brain. The lungs are the most frequent site of metastatic disease being involved in 90% of cases when dissemination occurs. Brain and liver metastases also occur.

Pathologic Features

Grossly, the tumor is often well circumscribed and hemorrhagic in appearance. Histologically, solid or plexiform cords and clusters display a biphasic proliferation of cyto- and syncytiotrophoblasts admixed with extensive hemorrhage and necrosis. Intermediate trophoblasts are also admixed with the other trophoblasts. Atypia and mitotic activity may be marked. Vascular invasion is often prominent. Placental villi are absent. Early or incipient choriocarcinoma is rarely diagnosed in a background of chorionic villi, however. Since there is usually deep invasion of the myometrium and its vessels associated with necrosis, the curettings often contain fragments of myometrium destroyed by the invading trophoblast. It has been suggested that choriocarcinomas with predominance of syncytiotrophoblasts may have a better prognosis (Deligdisch). High-grade malignancy has been suggested by the formation of tumor islands that display massive proliferation of intermediate-type trophoblast, perpendicular invasion of the myometrium, and cytological atypia (Nishikawa et al 1985).

Differential Diagnosis

Choriocarcinoma should be distinguished from placental site trophoblastic tumor (PSTT), poorly differentiated carcinoma with trophoblastic differentiation, and residual trophoblast or invasive mole following evacuation of a
molar pregnancy. Distinction from PSTT is facilitated by the fact that it is a monophasic proliferation of predominantly intermediate trophoblasts in contrast to the biphasic pattern of choriocarcinoma. Few syncytiotrophoblasts may be present, but they are not abundant. Therefore, serum beta-HCG titers are low in PSTT, but elevated in choriocarcinoma. Immunostains for HCG and HPL are helpful and would favor PSTT when there is predominance of HPL positive cells. Furthermore, PSTT lacks the hemorrhagic aspect of choriocarcinoma. Also, placental site trophoblastic tumor invades the myometrium by splitting muscle fibers in contrast to diffuse destruction. With limited sampling, distinction from carcinomas with trophoblastic differentiation can be difficult on the basis of morphology alone. The trophoblastic cells in the carcinoma are also immunoreactive for HCG. Extensive sampling often shows areas of recognizable adenocarcinoma that is the ultimate feature of greatest diagnostic value. All trophoblasts are cytokeratin positive rendering immunostains for cytokeratin worthless in discriminating between the two lesions. The absence of chorionic villi and the extensive tumor necrosis with hemorrhage enable one to distinguish choriocarcinoma from an invasive mole. Malignant chorial invasion must also be distinguished from a benign invasion (exaggerated placental site reaction) which can be best recognized by the advance of individual trophoblastic cells along preformed clefts without injury to adjacent muscle cells. In uterine curettings, choriocarcinoma can be definitely diagnosed only when large sheets of cytologically atypical trophoblasts invading the endomyometrium are present, and placental villi are absent.

Placental site nodule

This well circumscribed accumulation of intermediate trophoblast may be found in endometrial curettings or in the superficial myometrium, usually as a remnant and sometimes many years after intrauterine gestation. It is characterized by hyaline, and appears degenerated. There is no or very little mitotic activity (Young et al 1990). The immunohistochemical reactions for PLAP (positive in 100% of the cases), cytokeratin (96%), EMA (84%), HPL (78%) and B-HCG (42%) (Huettner and Gersell 1994; Shitabata and Rudgers 1994) may be used to differentiate the nodules from carcinoma or sarcoma. The distinction from placental site trophoblast tumor is possible by the nodular shape, absence of myometrial invasion, rare if any mitotic figures, and hyalinization of the placental site nodule.

Metastatic choriocarcinoma

The frequency of spread of choriocarcinoma of the uterus to the ovary has varied from one series to another. In an autopsy study of 44 patients, Ober et al found no examples of ovarian metastasis; however, in other series the frequency has ranged from 6 to 22%. Although a choriocarcinoma that develops in a prepubertal girl is obviously of germ cell origin, the occurrence of a similar tumor in a woman of child-bearing age that is not clearly metastatic from a uterine or tubal choriocarcinoma requires thorough sampling in an attempt to demonstrate the presence of teratomatous or other germ cell elements, thereby establishing the germ cell origin of the tumor. The way to distinguish gestational from non-gestational choriocarcinoma is to perform DNA analysis. Gestational choriocarcinoma has contribution from both maternal and paternal DNA; nongestational choriocarcinoma has the same DNA as the patient (Fisher et al, 1992). Post hydatidiform mole choriocarcinomas have an androgenetic origin. If such elements are not found, it may be difficult to differentiate between a primary choriocarcinoma of the ovary, either gestational or germ cell origin and a metastatic tumor from a choriocarcinoma of the uterus that has regressed without special studies. Invasive hydatidiform mole has also been documented to spread to the ovary and at least two placental site trophoblastic tumors have spread through the uterine wall to involve an ovary.

Management

Detailed protocols are now available for management of patients with a variety of trophoblastic disease. Of significant value is the possibility of monitoring disease and response to therapy with assessment of the serum levels of beta-HCG in those lesions where it is elevated (complete mole and choriocarcinoma).

Choriocarcinoma responds very well to chemotherapy (methotrexate) and patients with choriocarcinoma can often be cured with proper management.
TABLE 4
WHO Classification of Gestational Trophoblastic Disease

<table>
<thead>
<tr>
<th>Hydatidiform Mole</th>
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</tr>
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<tbody>
<tr>
<td>a. complete</td>
<td></td>
</tr>
<tr>
<td>b. partial</td>
<td></td>
</tr>
</tbody>
</table>

| Invasive hydatidiform mole             |                          |

| Choriocarcinoma                        |                          |
| Placental site trophoblastic tumor     |                          |
| Miscellaneous trophoblastic lesions    |                          |
| a. exaggerated placental site          |                          |
| b. placental site nodule or plaque     |                          |

Unclassified trophoblastic lesions

TABLE 5
Types of Trophoblast

1. **Cytotrophoblast**: The precursor cell to the other trophoblastic cells, it is a polyhedral cell with distinct borders, clear cytoplasm, and central vesicular nucleus; it is found at the periphery of villi, beneath syncytiotrophoblast. Mitotic activity is seen. In early gestation, it proliferates at one pole of the developing villous.

2. **Intermediate trophoblast**: A polyhedral to spindle shaped cell, it is larger than cytotrophoblast, has an eosinophilic cytoplasm, a single central nucleus and prominent nucleolus. Binucleated and multinucleated forms occur particularly at the implantation site. The intermediate trophoblast is found within fibrin, endomyometrium, or in the wall and lumens of spiral arterioles. Mitotic activity is seen.

3. **Syncytiotrophoblast**: This terminally differentiated cell is mitotically inactive but functional. It is multinucleated and a syncytium with amphiphilic to purple cytoplasm and multiple, small hyperchromatic nuclei. Multiple lacunae may be present in the cytoplasm imparting a lacy appearance to the cells. This cell covers all chorionic structures where it is located superficial to the cytotrophoblasts in the villi and peripheral to them interfacing with the maternal blood where they line maternal vascular spaces. During early gestation, these cells are strongly immunoreactive for HCG, but weakly so for HPL. Later in pregnancy, this pattern of immunoreactivity reverses.
TABLE 6

Immunohistochemical Features of Trophoblastic Cells

<table>
<thead>
<tr>
<th></th>
<th>Cytokeratin</th>
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<th>HPL</th>
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<tr>
<td>Cytotrophoblast</td>
<td>+++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Intermediate Trophoblast</td>
<td>+++</td>
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<td>+++</td>
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REFERENCES

CASE 5

History (Case #5 – Acc. 23764)
A 57-year-old Caucasian female presented with periumbilical and supra-pubic pain. Physical examination revealed a fixed uterus enlarged to four months gestation. The uterus with attached adnexa weighed 280 grams. The uterus measured 9.5 x 5.0 x 4.0 cm, but the cervical portion was much larger than the fundus and had a diameter of 6.0 cm. The mucosa of the portio vaginalis was somewhat granular and studded with millimeter-sized pale yellow papules. The external os was 1.5 cm wide and had prominent red-tan tissue on the anterior lip. The lower portion of the endometrial canal, as well as the cervical canal, was lined by soft, pale gray-tan gelatinous material up to 0.8 cm thick. This same type of material was present throughout the wall of the cervix. (Contributed by Melvin Anderson, M.D.)

Diagnosis: Mucinous (colloid) Adenocarcinoma with signet ring cell differentiation

DISCUSSION

A useful classification of endocervical adenocarcinomas which is based mainly on the cell type of the tumor is shown in Table 7.

TABLE 7

CLASSIFICATION OF ENDOCERVICAL CARCINOMAS

I. Mucinous
   a. endocervical type
      i. typical
      ii. minimal deviation (adenoma malignum)
   b. GI type
II. Endometrioid
   a. typical
   b. villoglandular
III. Serous
IV. Clear Cell
V. Adenosquamous cell carcinoma
   a. typical
   b. glassy cell
VI. Adenoid cystic
VII. Adenocarcinoma with neuroendocrine differentiation
VIII. Mixed carcinoma
IX. Mesonephric

There has been a growing interest in endocervical adenocarcinomas because of its apparent increased frequency over the past couple of decades in part due to the decrease in the frequency of squamous carcinomas. Also, an increased frequency in young women and the possible role of oral contraceptives in this increase has attracted attention. One study of women under 50 years of age with adenocarcinoma found a history of BCP use in 82% of cases rising to 92% in those women with adenocarcinoma in situ. A controversial viewpoint presented by Dallenbach-Hellweg (1984) is that microglandular hyperplasia is a precursor lesion of endocervical adenocarcinoma. Considering the well-known relationship between hyperplasia and carcinoma in other sites, this suggestion may not be totally without...
merit. Atypical endocervical glandular hyperplasia and adenocarcinoma in situ are believed to be morphologic precursors of this lesion. Currently, the interest is in relating these tumors to human papilloma virus. A majority of tumors contain HPV-DNA, usually type 18. A disproportionately small percentage of in situ adenocarcinomas contain detectable HPV 18 compared to the invasive lesions; it has been suggested that HPV 18 may induce a more rapid malignant transformation than do some of the other HPV types. Squamous intraepithelial neoplasia has been reported in close of half (43%) of the patients. An increased incidence of primary ovarian carcinomas has also been reported.

Endocervical adenocarcinomas account for 3% to 25% of malignant cervical lesions according to various reports. The clinical profile of women with adenocarcinoma is somewhat different from those with squamous carcinoma. The patients are usually older with a mean age between 48 to 56, better off socio-economically, and lack association with some of the venereal diseases previously noted among women with squamous carcinoma. Vaginal bleeding and profuse discharge are the two main symptoms.

**Pathologic Features**

Grossly, a high proportion (40-50%) are exophytic. Approximately 15% are not grossly apparent, and the remaining are endophytic or barrel shaped.

Microscopic classification has been highly variable in different reports. The WHO basically divides these tumors into the endocervical and endometrioid types. At AFIP, the endometrioid variant is seen with highest frequency, but in general practice, the endocervical type accounts for up to 60% of the cases.

The typical endocervical variant is characterized by the proliferation of cells with abundant intracytoplasmic mucin lining well to poorly formed glands. Abundant intraluminal mucin is present in many. Some of the tumors contain goblet cells and morphologically resemble GI adenocarcinomas; these should be distinguished from metastatic GI cancers. Signet ring cells are sometimes present in those associated with abundant colloid production as seen in the seminar case. We have seen increased nuclear atypia in some recurrent cases following radiation therapy. About 5% to 15% of endocervical mucinous carcinomas are composed of very well differentiated glands and are classified as "minimal deviation adenocarcinoma." Many patients are less than 40 years of age. Some of these lesions have been associated with the Peutz-Jeghers syndrome and simultaneous mucinous ovarian tumors. This is a highly differentiated carcinoma with a poor prognosis and early nodal metastases. Because of its deceptively bland cytology, it is difficult to distinguish from normal endocervical glands. It is the deep location of the glands, often irregular architecture, and a desmoplastic stromal response that indicate the correct diagnosis. Positive immunoreaction for CEA is helpful.

The endometrioid variant constitutes 20% to 30% of endocervical adenocarcinomas in the general pathology practice. These show glands or papillae lined by columnar pseudostratified endometrial-type cells. Squamous metaplasia may be present in this type. The papillary villoglandular adenocarcinoma is generally of endometrioid type (see discussion for case 9). Rarely, a "minimal deviation endometrioid" carcinoma also occurs with less than 20 such cases reported. Women in the reported studies have been 34 to 48 years of age. In contrast to the minimal deviation mucinous carcinomas, the endometrioid variant has a relatively good prognosis.

Both adenoid cystic and adenoid basal carcinomas occur in the cervix. The former is often large and aggressive, while the latter is frequently an incidental finding and has a very indolent course. Adenoid cystic carcinomas occur in older and almost always postmenopausal women with a median age of about 65 years. It may be either exophytic or endophytic in its growth. Composed of basaloid cells with scant cytoplasm and hyperchromatic nuclei, it may form cribriform arrangement, solid nests, cords, or tubules. The spaces formed by the tumor may be empty or contain mucinous and basement membrane-like material. The tumor cells show immunoreactivity for both cytokeratins and actin suggesting myoepithelial differentiation although myoepithelial cells are not a known component of the normal cervix. Lymphatic invasion is common. Cervical intraepithelial neoplasia is evident in 60% of the cases. An associated adenocarcinoma is present in 16%. These are believed to arise from reserve cells. The adenoid basal cell carcinoma has an infiltrative proliferation of clusters and cords of basaloid cells with focal squamous differentiation in some clusters. Small acini lined by a single layer of cuboid to columnar cells are also admixed. The proliferating cells
maybe surrounded by a desmoplastic stromal reaction. Occasionally, the lesion appears to emanate from the basal portion of the overlying epithelium.

The glassy cell carcinoma is a rare variant of adenosquamous carcinoma with a poor prognosis. It is composed of large cells with abundant eosinophilic to amphophilic cytoplasm, distinct cell borders, large nuclei and one or more prominent nucleoli. The cytoplasm has a ground glass appearance and a distinct membrane. Actual gland formation is evident in some cases.

Mesonephric adenocarcinomas are extremely rare tumors. The handful of reported cases have occurred in women ranging in age from mid thirties to late sixties. These arise from and are almost invariably seen in association with residual mesonephric remnants. They are generally deeply located in the lateral wall of the cervix. These may show gland formation or papillary processes. Some show a distinct transition from normal to atypical mesonephric remnants around the areas of overt carcinoma. The cells are often cuboidal in shape and do not contain intracytoplasmic mucin or glycogen. Many of the reported cases have described patients who died from the tumor.

Adenocarcinoma metastatic to the endocervix

The cervix most frequently shows involvement by endometrial carcinomas either by contiguous spread along the surface epithelium or by stroma invasion. The differentiation of primary adenocarcinoma of the endometrium from an endocervical can be very difficult when an endometrioid pattern is encountered. Primary mucinous carcinomas account for less than 5% of endometrial carcinomas and rarely cause a problem. Endometrioid carcinomas of endocervix have a more fibrous stroma whereas an endometrial type stroma is more common around those of endometrial origin. The presence of adjacent endocervical glandular atypia or in situ carcinoma would favor an endocervical origin. Expression of CEA is more common in endocervical adenocarcinomas. Nonetheless, it is sometimes practically impossible to make a distinction. The location is the hysterectomy specimen is often helpful. Some lesions, however, appear to originate at the junction in the lower uterine segment with subsequent extension into both directions. Metastatic ovarian carcinoma is the next most common genital tract tumor, while metastatic tubal carcinoma is very rare. Extranidal tumors that metastasize to the cervix include breast, colorectal and gastric carcinoma.

Special Studies

Approximately 25% of endocervical adenocarcinomas express ER or PR, but this feature does not appear to have any prognostic significance (Fujinara et al, 1997). Ploidy levels correlate with prognosis in stages I and II disease. Tumors that have triploidy or greater DNA content are associated with a worse prognosis. Elaboration of CA125 has been associated with a worse prognosis in a small number of cases studied. Regardless of its prognostic value, CA125 may be useful in monitoring progression of the disease and response to therapy.

Prognostic Features

Survival of the patients depends on the interaction of various factors such as stage, histologic type, and size of the tumor. Tumor stage is a most important feature for prognostic purposes. Most tumors are in stages I or II at the time of diagnosis. The five-year survival depends on the stage ranging from 60 to 91% for stage I and 11 to 60% for stage II disease. For stages III and IV, the 5-year survival is dismal and only 0 to 10% in past reports; with adjuvant combination chemotherapy, a 39% 5-year survival has been reported for some stage III carcinomas. The frequency of lymph node metastases is directly related to the tumor stage, and inversely to survival.

Among histologic subtypes, glassy cell carcinoma, adenoid cystic and neuroendocrine carcinomas are associated with a more aggressive course. The papillary and endometrioid types are associated with a better prognosis. The impact of tumor grade is not well established. Depth of invasion has significance. Approximately 90% of patients whose tumors are less than 5 mm are cured. If the tumor is 3 cm in diameter, however, half of the patients have metastases. There is a significant difference in survival for stage Ib (76%) and stage IIb (49%) at 5 years. Tumors with less than 2 mm invasion almost never have nodal metastases, whereas 57% of those with invasion in excess of 1 cm have nodal metastases. Recurrences may develop, however, even with 3 mm of invasion. The concept of microinvasion has not
been well established for endocervical adenocarcinomas. This is due to the fact that identification and measurement of what constitutes early invasion is extremely difficult. Vascular/lymphatic invasion portends a more aggressive behavior regardless of the nodal status. Mucin leakage into the stroma is also associated with elevated incidence of nodal metastases.

Treatment for invasive adenocarcinomas depends on the stage at presentation. Generally, radical hysterectomy and pelvic lymphadenectomy for early stage disease. An alternative approach is to use radiation therapy as the initial treatment followed by simple hysterectomy.

REFERENCES

Adenocarcinoma


### Adenoma Malignum (Minimal Deviation Adenocarcinoma)


### Minimal-Deviation Endometrioid Adenocarcinoma


### Villo glandular Papillary Adenocarcinoma


### Adenoid Cystic Carcinoma


2. Ferry JA, Scully RE. Adenoid cystic carcinoma and adenoid basal carcinoma of uterine cervix: a study of 29


**Mesonephric Adenocarcinoma**


CASE 6

History (Case #6 – Acc. 28375)
A 22-year-old Caucasian female presented with irregular uterine bleeding and an abnormal Pap smear. Pelvic examination showed a fungating cervical mass. Patient’s past medical history was unremarkable. She had used BCP at age 16 for several months and was on Triphasil (combination BCP containing levonorgestrel and ethinylestradiol) for nine months prior to her presentation. A hysterectomy was performed. The anterior and lateral cervical walls were replaced by a fungating papillary mass. (Contributed by Fattaneh Tavassoli, M.D.)

Diagnosis: Villoglandular Adenocarcinoma of the Cervix

Pathologic Findings: Biopsy of the tumor showed numerous branching papillary projections composed of thin fibrovascular cores covered by a single layer of columnar epithelial cells. The biopsy was interpreted as a well-differentiated papillary adenocarcinoma and a radical hysterectomy was performed. Gross examination of the hysterectomy specimen showed an exophytic, fungating mass measuring 4.5 x 3.0 x 3.0 cm in the endocervix and occupying the anterior and right lateral portions of the cervix.

The biopsy and the hysterectomy specimen showed identical histology. The cervix was replaced by an arborizing papillary lesion. The papillae were supported by a fibrovascular core and covered by stratified columnar epithelial cells. Most of the epithelial cells had an endometrioid appearance with a mildly eosinophilic cytoplasm, but a few cells had intracytoplasmic mucin, which was confirmed by mucicarmine stain. The nuclei of the epithelial cells were oval with indistinct nucleoli. Mild cytologic atypia was present throughout with some variation in nuclear size and shape. Mitotic figures were present in the epithelial cells with about three to four mitotic figures per 10 high power fields. Neutrophils were sparsely distributed within the papillary stalks, gland lumens, and in the cervical stromal surrounding the tumor. No epithelial tufts or psammoma bodies were identified. The papillary stroma displayed variable fibroblastic proliferation around small vessels.

The tumor was basically exophytic with only superficial invasion of the cervical stroma. A few foci of early stromal invasion characterized by small groups of cells and individual cells extending from the surface and invading into the papillary stroma were identified. The invasive cells generally displayed a more rounded contour and a more eosinophilic cytoplasm. Vascular and lymphatic space invasion were not identified. The endometrium was in late secretory phase and displayed no involvement by the cervical carcinoma.

Immunohistochemical stains were performed on paraffin embedded tissue. The tumor cells stained positive for cytokeratins AE1/ AE3, CAM 5.2, polyclonal carcino-embryonic antigen (CEA) and progesterone receptor. The tumor stained negative for estrogen receptors and for HPV 6,11,16,18,31,33, and 35 (in situ hybridization).

Bilateral external iliac and obturator lymph nodes were removed at the time of surgery and showed no evidence of metastatic tumor. The patient is free of disease 12 months after surgery.

DISCUSSION

While assumption of a papillary growth pattern by cervical adenocarcinoma has been well recognized for a long time, villoglandular papillary adenocarcinoma of the cervix was first described as a distinct entity in 1989 (Young and Scully). About 45 cases of villoglandular papillary adenocarcinoma of the cervix have been reported in the literature. After the description of the first 13 cases by Young and Scully, twenty-four cases were reported by Jones et al, four by Costa et al, three by Hopson et al, and a single case in a pregnant patient was reported by Hurteau et al.

The etiology of VPA of the cervix has not been well established. An association between oral contraceptive use and
been and bulbous of adenofibroma have been encountered in the cervix. The papillae in VPA are typically atypia, included in the There these typical papillary endocervical resemble VP A that most biopsy must always be interpreted cautiously with a strong suspicion for malignancy. Chronic cervicitis papillary projections similar to VP A. A few cases of Mullerian papilloma, a rare lesion with an tumor . The overlying epithelium shows only mild to moderate present .

On physical examination, almost all reported women with VPA have grossly visible exophytic lesions protruding out of the endocervical canal; the tumors ranged from 0.5 cm to 8 cm. Microscopically, VPA is composed of multiple elongated papillary processes with delicate to relatively prominent fibrovascular cores. Varying amounts of acute and chronic inflammatory cells are present within the papillary cores and in the cervical stroma along the periphery of the tumor. The overlying epithelium shows only mild to moderate cytologic atypia, and increased mitotic activity may be present. The epithelial cells vary from predominantly mucinous (endocervical or intestinal) to mainly nonmucinous columnar cells.

Villoglandular (papillary) adenocarcinomas occur in a younger age group than cervical adenocarcinomas in general. The age range of the reported patients with VPA is 22 to 61 years, with an average of 35. In comparison, the average age for adenocarcinoma of the cervix ranges between 47 to 58 years.

The diagnosis of VPA can be difficult on small biopsy specimens. The differential diagnosis of VPA includes mainly typical papillary endocervical adenocarcinoma and serous papillary carcinoma. Typical endocervical adenocarcinomas can show a minor villoglandular component but generally display more cytologic atypia. The diagnosis of VPA should only be made when the villoglandular pattern is the exclusive or almost exclusive pattern (3). Villoglandular papillary adenocarcinoma differs from serous papillary carcinoma by the lack of marked nuclear atypia, epithelial tuffing, and detached epithelial fragments.

There are a few infrequently encountered benign lesions that may demonstrate a papillary pattern and should be included in the differential diagnosis of VPA. The presence of cytologic atypia, albeit mild, distinguishes VPA from these benign lesions. It must be emphasized, however, that the finding of an extensive papillary pattern on a cervical biopsy must always be interpreted cautiously with a strong suspicion for malignancy. Chronic cervicitis may show papillary projections similar to VPA. A few cases of Mullerian papilloma, a rare lesion with an architecture closely resembling VPA that most commonly occurs in the vagina of children, have been reported in the cervix. Rare cases of adenofibroma have been encountered in the cervix. The papillae in VPA are typically thinner than the broad fronds and bulbous configuration of those in an adenofibroma. Two cases of villous adenoma of the uterine cervix have been reported. However, in both of these cases, invasive adenocarcinoma was found elsewhere in the same cervix.
Behavior and Treatment

Villoglandular papillary adenocarcinoma has an extremely good prognosis compared to other variants of cervical adenocarcinoma. Invasion, when present, does not generally extend beyond the inner third of the cervical stroma. Of the 45 previously reported cases, 10 were purely exophytic lesions with no invasion of the cervical stroma, 26 showed invasion confined to the inner third of the cervical wall, and 5 cases were described as showing invasion to greater than a third of the cervical wall. The amount of invasion was not described in the 4 cases reported by Costa et al, but all 4 tumors were reported as clinical stage I. All previously reported cases were confined to the cervix except for one that showed extension into the lower uterine segment and another that had extension into the lower uterine segment and myometrial invasion. Neither vascular nor lymphatic invasion was identified in our case or any of the 45 previously reported cases.

Treatment of VPA has varied from radical hysterectomy (26 patients) to simple hysterectomy (9 women) and even a cone biopsy in 6 patients. Four of the patients who were treated by simple hysterectomy received subsequent radiation therapy. All of the 45 previously reported women were surviving without recurrence at the time reported with follow-up periods ranging from 8 months to 14 years. This includes six patients who had only a cone biopsy. In the case of VPA in a pregnant patient reported by Hurteau et al, the tumor was noted at 20 weeks gestation age, and the patient was followed until 32 weeks gestational age when she underwent a Cesarean section and radical hysterectomy. Pelvic and periaortic lymphadenectomies were performed one week later. The patient was alive and well 14 months later. In contrast, adenocarcinoma of the cervix has an overall five-year survival rate of around 50% with a five-year survival rate of 60-83% for stage I disease.

The good statistical outcomes and the young age of the patients with VPA have led some to advocate conservative therapy when feasible. Considering the excellent prognosis of these tumors, which may be due to the limited depth of invasion in most cases, radiation and chemotherapy are probably of limited value. However, the number of reported cases is still relatively small, and the current standard of treatment is to regard these lesions as a carcinoma. Furthermore, the large size of many of these lesions, as also noted in our case, often necessitates more extensive surgery in order to completely excise the tumor.

REFERENCES

CASE 7

History (Case #7 – Acc. 28376)
A 14-year-old female presented with weight loss and fever of unknown origin. On physical examination, the uterus was enlarged and fixed to surrounding tissues. At laparotomy, a massive tumor involved the uterus and extended to the upper vagina and parametrium. (Contributed by Fattaneh Tavassoli, M.D.)

Diagnosis: Inflammatory myofibroblastic tumor

DISCUSSION

A vast majority of mesenchymal lesions of the uterus are smooth muscle or endometrial stromal in nature. Rarely, however, a variety of other benign and malignant mesenchymal tumors occur in the uterus. Inflammatory myofibroblastic tumor (IMT) is a distinctive pseudosarcomatous appearing lesion that occurs in the soft tissue and viscera of children and young adults. Some cases have been multifocal. Despite its often ominous microscopic appearance, it has a benign clinical course with recurrences developing in a proportion of cases. Originally described in the lung and designated as an inflammatory pseudotumor, a variety of subsequent designations have been proposed including plasma cell granuloma, plasma cell pseudotumor, pseudosarcomatous myofibroblastic proliferation, inflammatory fibrosarcoma, and inflammatory myofibrohistiocytic proliferation reflecting the divergent viewpoints concerning the pathogenesis of this lesion and its level of malignancy. A histologically similar lesion, inflammatory fibrosarcoma, has been reported to have a metastatic rate of 11% (Mies and Enzinger 1991). Inflammatory fibrosarcoma is morphologically similar to IMT, except for the presence of large inclusion-like nucleoli in some tumor cells and focal atypia. In the current WHO classification of soft tissue tumors, inflammatory fibrosarcoma and IMT are used synonymously; a statement follows that it is unclear whether the lesions present at multiple sites reflect multifocal disease or distant metastases.

IMT occurs in both sexes. Patients have ranged in age from 3 months to 86 years. The mean and median age of the patients in one of the largest series of extrapulmonary IMT (Coffin et al, 1995) was 9.7 and 9 years respectively. Patients most commonly present with a mass associated with fever, pain, weight loss, malaise, and nonspecific GI and abdominal symptoms. Sometimes the mass is detected during physical examination or imaging studies for unexplained fever or weight loss. More than a third of the patients have anemia, generally of normo- or hypochromic, microcytic type.

The tumors may be massive, ranging in size from 1 cm to over 20 cm; the median size is around 6.0 cm. Multiple nodules are present in 15% of cases. The nodules may be contiguous in close proximity of each other. The mass is white to tan on cut surface with a fleshy or myxoid consistency. Foci of hemorrhage, necrosis, and calcification occur in a minority of cases. Central scarring is evident in some cases.

Microscopically, three patterns have been described; these may be present simultaneously and in variable proportions in any given tumor:

1. The first pattern is that of loosely arranged, stellate to plump spindle cells in an edematous to myxoid background. An irregular network of delicate blood vessels produces a granulation tissue-like appearance that resembles nodular fascitis. Some of the stromal cells may have abundant eosinophilic cytoplasm and vesicular nuclei reminiscent of rhabdomyoblasts; cross striations are not evident, however. Mitotic figures may be abundant, but there are no abnormal figures. An inflammatory infiltrate composed of polymorphs, lymphocytes, neutrophils and eosinophils permeates the lesion.

2. In the second pattern, a more compact proliferation of spindle cells is evident forming solid, confluent areas or distributed in a patchy fashion within a densely collagenous background. Either a fascicular or storiform pattern may be evident simulating fibromatosis, a myogenic, or fibrohistiocytic neoplasm. The inflammatory infiltrate
consists of aggregates of plasma cells and lymphoid follicles. The proliferating cells may protrude into vessels or form a cuff around them.

3. The least proliferative pattern shows extensive densely collagenous zones that resemble a desmoid or scar with entrapped isolated plasma cells and lymphocytes. Punctate calcifications and metaplastic bone formation may be encountered.

Rarely recurrences develop a more undifferentiated or histiocytoid appearance with locally aggressive behavior (Coffin, 1995).

Immunohistochemical Features and other Special Studies

About 90% of the cases show immunoreaction for actin (muscle specific or smooth muscle actin). Almost 100% are positive for vimentin. About 70% show positivity for desmin. Interestingly, a third have a positive reaction with cytokeratin and about 25% have KP1 positive cells.

IMT is not aneuploid and does not have a clonal expansion of either T or B lymphocytes (Broughan, et al 1993). A translocation involving chromosomes 2 and 9 has been reported (Treissman et al, 1994).

Recent cytogenetic studies have demonstrated clonal chromosomal abnormalities lending support to a neoplastic proliferation.

Behavior and Treatment

About 15% to 20% of patients develop recurrences or die of the disease. The few patients who have died of the disease have had extensive disease with contiguous growth into adjacent structures, but no evidence of distant metastases even at autopsy. Recurrence and aggressive behavior appears to be related to site, proximity to vital structures, and multinodularity, all of which compromise complete excision of the tumor. Significantly, several tumors that were only biopsied subsequently regressed and recurrences are successfully managed by local excision (Coffin et al 1993).

A vast majority of patients are treated by excision only, while some have had only biopsy and others have also received chemotherapy. The multinodular lesions and those with contiguous growth in the retroperitoneum, omentum or mesentery are more difficult to excise completely and are associated with recurrences in 25% of cases. The constitutional symptoms and laboratory abnormalities regress within a few days after resection of the lesion. Chemotherapy or radiation therapy do not appear to have a role in management of IMT (Day et al 1986; Tang et al, 1990; Coffin et al, 1995).

Consideration of this entity in the differential diagnosis of spindle cell tumors that simulate a malignant process particularly in children and adolescents is important to avoid over treatment and a malignant diagnosis.

The pathogenesis and etiology of this lesion remain unknown.

REFERENCES


CASES 9 & 10

History (Case #9 – Acc 18101)
A 42-year-old gravida 5, para 5, Caucasian female presented with an enlarging pelvic mass of several months' duration. Recent Pap smear was negative. Menses had been irregular for the last six months. Physical examination revealed an abdominal mass, 24-26 weeks in size, in the left adnexal area. TAH-BSO was performed. The 1400 gram left ovary was 30 x 25 cm. The external surface was smooth and gray with no excrescences. The cut surface showed a soft yellow to tan lobulated tumor mass with a few small foci of hemorrhage and a few small cysts. (Contributed by Avrum Jacobson, M.D.)

Diagnosis: Granulosa cell tumor, adult type

Diagnosis (Case #10 – Acc. 22614)
A 5-year-old female presented with a six-month history of breast enlargement and development of axillary hair. She also had an abdominal mass that filled the abdomen. Preoperative plasma FSH was less than 1.0 ml U/ml (normal 0 to 6 ml U/ml), luteinizing hormone 2.6 ml U/ml (normal 0 to 6 ml U/ml). HCG was non-detectable. Total estrogen was 27 mcg. 24-hour urine was composed of Estrone 7 mcg/24-hours, Estradiol 5 mcg/24-hours, and Estriol 15 mcg/24-hours (normally trace amounts only in prepubertal females). Plasma Estriol was 1.1 mg/ml (normal less than 0.2 mg/ml). At laparotomy, a smooth, firm, well-encapsulated, freely mobile tumor replaced the left ovary. The 14 x 12 x 10 cm mass had a soft, variegated red-yellow, and finely cystic cut surface, marked by interlacing narrow fibrous bands. (Contributed by T. J. Cosgrove, M.D.)

Diagnosis: Gonadal stromal tumor, c/w anaplastic granulosa cell tumor

Note for Case 10: Composed of a compact proliferation of atypical spindle cells that have abundant cytoplasm and some very atypical nuclei and easily identifiable mitotic figures, this tumor lacked morphologic features of any epithelial or germ cell tumor. Immunohistochemical evaluation showed no elaboration of germ cell markers or classic epithelial reactions. The cells did show intense reaction with inhibin confirming a gonadal stromal type lesion. Furthermore, among gonadal stromal tumors, the type of atypia evident in this tumor is most often, though still rarely, seen in granulosa tumors.

DISCUSSION

Accounting for 1.5% of all ovarian tumors, granulosa cell tumors occur in a wide age range; cases have been reported in newborn infants as well as postmenopausal women. About 5% occur prior to puberty, while almost 60% occur after menopause. Predominantly associated with evidence of hyperestrinism, a rare unilocular thin-walled cystic variant is often androgenic when functional (Norris and Taylor, 1969; Nakashima et al, 1984). Tumors that occur prior to puberty differ morphologically from the usual granulosa cell tumors encountered in adults (adult granulosa cell tumor) and often display a distinctive morphology designated as juvenile granulosa cell tumors.

ADULT GRANULOSA CELL TUMOR

Clinical Features

The neoplastic granulosa cell is capable of producing or storing a variety of steroid hormones and may produce either estrinizing or virilizing effects. The hormonal activities of these tumors may produce clinical symptoms in up to three-quarters of the patients. A majority have clinical manifestations related to estrogenic type hormones, but androgenic activity has also been well documented. The nature of the symptoms and the clinical presentation varies depending on the patient's age and reproductive status. In prepubertal girls, granulosa tumors frequently induce...
isosexual precocious puberty - accounting for 10% of cases of precocious puberty. In women of reproductive age, the tumor may be associated with a variety of menstrual disorders related to hyperestrogenism including menometrorrhagia, oligomenorrhea and even prolonged amenorrhea. In post-menopausal women, irregular uterine bleeding due to various types of endometrial hyperplasia is the most common manifestation of hyperestrogenism. Other women present with abdominal swelling or pain; acute abdomen due to rupture and hemoperitoneum occurs in up to 10% of the cases. The tumor is usually palpable on pelvic or abdominal examination, but in about 10% of the patients the tumor is clinically occult (Fathalla, 1967).

Pathologic Features

Granulosa cell tumors are generally unilateral; less than 5% are bilateral. Commonly encapsulated, they have a smooth or lobulated surface and show tremendous variation in size. Approximately 50% are over 10 cm, and only 10% are 5 cm or smaller; the average size is around 12 cm (Norris and Taylor, 1968; Fox et al, 1975; Stenwig et al, 1979). Cross-section of the tumor shows a yellow to white solid neoplasm in a majority of cases. A high proportion have focal cystic areas, and a small percentage are totally cystic. Hemorrhage is seen in larger tumors; necrosis is focal and uncommon.

Microscopically, there is proliferation of granulosa cells with or without a stromal component of fibroblasts, theca cells or lutein cells. The cells are small, round to spindle-shaped with small amount of cytoplasm. Their nuclei are ovoid or spindle shaped with a longitudinal groove and occasional small nucleolus. Mitotic activity is generally limited and rarely exceeds 1 or 2 per 10 HPF. When luteinized, the cells develop abundant pink or vacuolated cytoplasm and the nuclei become round and lose their characteristic groove. In about 2% of cases, multinucleated or mononucleated cells with bizarre nuclei are found; the presence of these cells does not have any adverse effect on the prognosis. The cells grow in a variety of patterns; two or more patterns commonly coexist in the same tumor. The best known pattern is the microfollicular pattern characterized by the presence of Call-Exner bodies. The follicular content varied from an eosinophilic secretion with nuclear debris to basophilic mucinous secretion. A macrofollicular pattern characterized by large spaces lined by layers of granulosa cells is much less common. Insular, trabecular and diffuse patterns are relatively common; the trabecular pattern is not infrequently mistaken for a carcinoid tumor. In the insular and trabecular patterns there are islands and broad anastomosing bands of granulosa cells. The moire silk pattern shows thin winding cords with more diffuse arrangement compared to the trabecular variant. The typical diffuse pattern forms sheets of cells of round, oval or slightly spindle shaped cells assuming a “sarcomatoid” appearance.

A variable amount of thecomatous or fibromatous component surrounds the granulosa cells; these cells are rarely the dominant cell population comprising 40% to 60% of the tumor.

Differential Diagnosis

Moderately differentiated endometrioid carcinomas may display abundant rosette-like arrangement of nuclei mimicking Call-Exner bodies. The readily identifiable mitotic figures in this setting are an important clue to their carcinomatous nature; granulosa tumors with abundant Call-Exner bodies rarely display more than 1 or 2 mitotic figures per 10 HPF. Undifferentiated carcinomas and poorly differentiated adenocarcinomas are often confused with the sarcomatoid variant of granulosa cell tumors. Many of these have already extended beyond the ovary and may be bilateral at presentation. Granulosa cell tumors are almost always unilateral and Stage I. The absence of nuclear grooves is an important feature that helps distinguish all varieties of carcinoma from granulosa tumors. Thorough sampling is helpful in identifying mullerian type glands of mullerian type in carcinomas with a diffuse growth pattern.

Some endometrioid carcinomas grow in discrete nests and lack significant atypia or mitotic activity. These may be confused with the insular pattern of a granulosa cell tumor. The presence of squamous metaplasia in endometrioid tumors is a helpful feature.

As mentioned earlier, the insular and trabecular patterns of granulosa tumor are not infrequently mistaken for a carcinoid tumor and vice versa. Carcinoid tumors uniform round nuclei that lack the nuclear grooves typical of granulosa cells, however. Furthermore, special stains (Churukian-Schenk) or immunostains for chromogranin will
demonstrate neuroendocrine granules in the carcinoid tumors establishing the diagnosis. Furthermore, primary carcinoid tumors of the ovary are usually associated with other teratomatous elements, while the metastatic ones are generally multinodular and bilateral.

The diffuse pattern of granulosa cell tumors may be confused with a thecoma particularly when there is luteinization. A reticulum stain is often helpful since granulosa cells typically grow in sheets or aggregates bound by reticulin fibers, while thecomas and fibrothecomas contain an abundance of intercellular fibrils. The almost exclusive spindle cell nature of the cells in fibrothecomas is also unusual for a granulosa cell tumor.

Another frequently problematic lesion is the aggressive small cell carcinoma, which occurs in children and young women and is often associated with paraneoplastic hypercalcemia. Morphologically, it is easily confused with a granulosa cell tumor. Dissemination beyond the ovary is evident in 20% of these small cell carcinomas at presentation, a feature that is most unusual for a granulosa tumor. The presence of necrosis on gross and microscopic evaluation associated with significant cytologic atypia, lack of nuclear grooves, and abundant mitotic activity in the carcinomas are additional features that can help. Presence of mucinous epithelium in 10% of cases and clusters of larger cells in almost all small cell carcinomas provide further support. Finally, immunostains for inhibin are positive in granulosa tumors, but completely negative in the carcinomas.

**JUVENILE GRANULOSA CELL TUMOR**

**Clinical Features**

Encountered predominantly during the first two decades of life in the female gonad and during infancy in the male gonad, the juvenile granulosa cell tumor (JGT) has distinctive microscopic features that differ from those of the well-known forms of granulosa cell tumor encountered in older patients. In prepubertal girls, approximately eighty percent of these tumors are associated with isosexual pseudoprecocity. Association of juvenile granulosa cell tumors with Ollier's disease (Tamini and Bolen, 1984) and Maffucci's syndrome (Velasco-Oses et al, 1988; Vassal et al, 1988). JGT presents almost always in stage I; less than 5% are bilateral.

**Pathologic Features**

The macroscopic appearance is not distinctive and is similar in its spectrum appearances to the adult granulosa cell tumor. Microscopically, JGT is characterized by a nodular or diffuse cellular growth punctuated by follicles of varying sizes and shapes. The follicles, though large, rarely attain the size of those encountered in the macrofollicular form of adult granulosa cell tumor. The cell population is predominantly composed of granulosa cells, but theca cells are also present, generally dispersed in an edematous stroma. The granulosa cells have hyperchromatic nuclei and there is abundant mitotic activity. The cells lack nuclear grooves. Extensive luteinization is common in the theca cells but also the granulosa cells. Cytomegalgy with macronuclei, multinucleation, and bizarre multilobulated nuclei are occasionally observed. Lesser degrees of atypia are evident in approximately 15% of cases. Despite the abundant mitotic activity and occasional presence of atypical nuclei, only about 5% of these tumors behave aggressively.

**Differential Diagnosis**

While a variety of tumors may occasionally have a remote resemblance to JGT, it is only the small cell carcinoma that poses significant diagnostic problem. The presence of follicle-like structures in small cell carcinoma along with the young age at which it occurs are responsible for confusing it with a JGT. The differences may be rather subtle with more eccentric nuclei in small cell carcinomas. JGT shows a positive immunoreaction with inhibin, whereas small cell carcinoma is negative.

**Clinical Behavior and Treatment**

All granulosa tumors have a potential for aggressive behavior. There is no single histologic feature, however, that would separate the benign lesions from the malignant ones. An older study had suggested that the sarcomatoid
pattern is associated with a more aggressive behavior, but more recent studies do not support any particular association between the pattern of growth and clinical behavior of the tumor.

The most important prognostic factor is the stage of the tumor and the presence of extraovarian spread. In a recent study, 17% of those with stage I died of their lesion compared to 75% of those with stages II to IV. Approximately 17% of patients with stage I disease eventually die of the disease compared to 75% of those with stages II to IV. Almost 90% of granulosa tumors are stage I, however, and it is the prediction of behavior of this group of neoplasms that is most difficult. Factors related to a relatively poor prognosis include age over 40 years at the time of diagnosis, solid and large tumor, bilaterality, numerous mitotic figures, and atypia. There is, however, disagreement on the significance of some of these factors.

When preservation of reproductive functions is a major concern, unilateral salpingo-oophorectomy is justifiable when there is no extension beyond the ovary and the opposite ovary appears uninvolved. Hysterectomy and bilateral salpingo-oophorectomy are the treatment of choice otherwise. Recurrences may develop as late as 3 decades after the initial diagnosis. Therefore, long-term follow-up is required. Surgical resection, radiation, or a combination thereof has been used in managing recurrences that generally develop in the pelvic peritoneum.

The 1-year survival varies from 60% to over 90%. With longer periods of follow-up, a progressive decline in survival has been documented. The overall prognosis for juvenile granulosa tumor is good with a 1.5% mortality associated with stage IaI tumors; but it is poor in stage II tumors (Young et al, 1984).

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**TABLE 8**

Classification of Sex Cord-Stromal Tumors

A. **GRANULOSA-STROMAL CELL TUMORS**

1. Granulosa cell tumor
   a. adult type
   b. juvenile type

2. Tumors in the thecoma-fibroma group
   (a) thecoma
      1. typical
      2. luteinized
   (b) fibroma-fibrosarcoma
      1. fibroma
      2. cellular fibroma
      3. fibrosarcoma
   (c) sclerosing stromal tumor
   (d) unclassified

B. **SERTOLI-LEYDIG CELL TUMORS (ANDROBLASTOMAS)**

1. Well differentiated
2. Of intermediate differentiation
3. Poorly differentiated
4. With heterologous elements
5. Retiform

C. **GYNANDROBLASTOMA**

D. **SEX CORD TUMOR WITH ANNULAR TUBULES**

E. **UNCLASSIFIED**
REFERENCES

CASE 11

History (Case #11 – Acc. 28378)
A 24-year-old Caucasian female presented with a pelvic mass. The right ovary was enlarged on physical examination. At laparotomy, a 17 x 14 x 8 cm right ovary was removed. It weighed 1100 grams. The cut surface was yellowish, solid with focal cystic areas and a 4.0 cm area of necrosis. There was no gross peritoneal or omental seeding. Three months earlier, the patient had had a C-section; at that time, both ovaries and tubes appeared normal.

(Contributed by Fattaneh Tavassoli, M.D.)

Diagnosis: Small cell carcinoma, hypercalcemic type

Microscopic Features: A diffuse compact proliferation of cells was dominant in the lesion. In addition, focal areas displayed nests or cords of tumor cells. A small number of irregularly shaped or rounded follicle-like spaces were dispersed throughout the lesion; these spaces were either empty or contained an eosinophilic secretory material. The predominant proliferating cells were small and rounded with scanty cytoplasm. Round to oval nuclei with minimal variation in size displayed moderate hyperchromasia. Mitotic figures were readily apparent. Small aggregates of cells with more abundant pale to lightly eosinophilic cytoplasm were present in some tissue section.

The tumor cells were immunoreactive with CAM5.2 and chromogranin, but failed to react with inhibin.

DISCUSSION

First described in 1982, small cell carcinoma is a rare and distinctive type of undifferentiated carcinoma that is often associated with hypercalcemia. A tumor that occurs mainly in younger women, the patients range in age from 9 to 45, with an average of around 25 years. Familial clustering of small cell carcinoma has been observed in several reports. In one report it occurred in three sisters. More than half of the tumors have already spread beyond the ovary at the time of presentation.

The tumors are generally large (often exceeding 10 cm) at presentation. Cut surface is solid with cystic areas; rarely, it is predominantly cystic.

Generally composed of compact proliferation of small cells with scant cytoplasm, occasional cases are composed of large cells with abundant cytoplasm. In almost half of the cases, a second population of cell with more abundant eosinophilic cytoplasm is present in small islands throughout the tumor. Far less frequently (in about 10% of cases) mucinous cells are present in small clusters. Mitotic figures are abundant. Follicle-like structures filled with eosinophilic secretory material are present in 80% of the tumors. The tumor cells may also arrange in cords, trabeculae, and small islands. The minimal stroma evident in some cases may appear edematous or myxoid.

The undifferentiated appearing tumor cells are positive for epithelial markers and vimentin; immunostains for chromogranin have been reported as positive in only a small number of cases. By flow cytometric evaluation, these tumors are almost always diploid. At the ultrastructural level, the tumor cells characteristically show abundant rough endoplasmic reticulum, but generally no dense core granules.

Differential Diagnosis

The two most important lesions in the differential diagnosis are juvenile granulosa tumor and small cell carcinoma of the pulmonary type. The morphologic appearance of the tumor with the follicle-like spaces and the young age of most patients result in misinterpretation of a good proportion of these tumors as juvenile granulosa tumor. The
distinction is now facilitated by the use of immunostain for inhibin, which is positive in granulosa tumors, but negative in small cell carcinomas. The next lesion in the differential is small cell carcinoma of the pulmonary type. Small cell carcinomas of the pulmonary type are not associated with hypercalcemia, occur mainly in peri- and postmenopausal women; they are bilateral in close to half of the cases.

Microscopically, they are composed of islands and trabeculae of round to spindle shaped small cells with scant cytoplasm. The nuclei are hyperchromatic with rare nucleoli and a stippled chromatin. Argyrophilic granules and chromogranin positivity is observed in a small number of cases. Most tumors are aneuploid, but some are diploid.

A more remote possible source of confusion is with lymphomas. The epithelial growth pattern of small cell carcinomas and the immunostaining characteristic can easily differentiate it from a lymphoma.

Behavior and Treatment

Small cell carcinoma of the hypercalcemic type is a very aggressive tumor with a poor prognosis. A majority of patients die within two years after the diagnosis. Tumor that occur in women older than 30 years of age, lack hypercalcemia, are less than 10 cm, and do not contain the islands of larger cells are associated with a more favorable outcome. Even in stage I, only about a third of the women are disease free with follow-up ranging from 1 to 13 years (average of 5.7 years). Adjuvant chemotherapy and radiation therapy have been disappointing, though occasionally result in improved survival. Rare survival beyond 5 years has been observed among patients with higher stage tumors after intensive chemotherapy.

| TABLE 9 |
|-----------------|-----------------|-----------------|
| **Small Cell Carcinomas of the Ovary** |
| Hypercalcemia   | Small cell ca, HCT | Small cell ca, PT | Juvenile Granulosa Tumor |
| Age (yr)        | 60%              | absent           | absent                   |
| Bilateral       | 10-42 (mean 23)  | 28-85 (mean 59)  | 80% prepubertal         |
| Follicle-like spaces | Common         | Rare            | 2%                      |
| Large cells     | 40%              | Rare            | Common                  |
| Nuclear chromatin | Clumped         | Evenly dispersed | 15%                     |
| Nucleoli        | Single, uniform  | Inconspicuous   | Clumped                 |
| Mucinous Epithelium | 10%            | 10%             | Single, small           |
| Inhibin         | Negative         | Negative        | Rare                    |
| EMA             | Occasionally +   | Occasionally +  | Positive                |
| RER on EM       | Abundant         | Some            | Some                    |
| Dense Core Granules | Absent          | Present         | Absent                  |
| DNA content     | Diploid          | Aneuploid in 65%| Aneuploid in 40%        |

**Abbreviations**: HCT = hypercalcemic type; PT = pulmonary type
REFERENCES


CASE 12

History (Case #12 – Acc. 22743)
A 32-year-old Caucasian female presented with severe lower quadrant pain and accompanying backache. Physical examination revealed a cystic mass of the right ovary. An emergency TAH-BSO was performed. (Contributed by Horace Spear, M.D.)

Diagnosis: Consistent with Carcinoid tumor, metastatic type

Note: While the morphologic features are typical of carcinoid tumors, the tumor cells were negative for neuroendocrine granules with Grimelius stain and chromogranin immunostain. The bilaterality, involvement of endometrium, myometrium and a lymph node along with the absence of any teratomatous elements further support a metastatic carcinoid. Neuroendocrine granules were documented at the extra structural level.

DISCUSSION

Clinical Features

Primary carcinoid tumors are the second most common type of monodermal teratoma of the ovary. Predominantly a tumor of postmenopausal women, carcinoid tumor also occurs during the reproductive years. Patients typically present with a pelvic mass. Less than a third of the patients with primary ovarian carcinoid tumor have the carcinoid syndrome which disappears after removal of the tumor. The carcinoid syndrome occurs more often in women over 50 years of age that have tumors over 7 cm in diameter.

Pathologic Features

Primary carcinoid tumors are unilateral, but a cystic teratoma, Brenner tumor, or mucinous tumor has been reported in the contralateral breast in 15% of the cases. A majority of primary carcinoid tumors arise in a teratoma. The carcinoid component appears as a solid nodule with predominantly solid yellow-tan cut surface. The carcinoid tissue is typically firm, tan to yellow, predominantly solid, and variably fibrous in texture. Cysts filled with clear fluid are occasionally present, rarely the tumor is predominantly cystic. Approximately 75% of the tumors are mixed with other teratomatous elements. It may also be mixed with struma forming strumal carcinoid.

Microscopically, carcinoids form either insular and trabecular patterns. Pure carcinoid tumors, strumal carcinoids and mucinous carcinoids. The insular pattern is characterized by discrete cellular masses and nests separated by a scant to abundant fibromatous stroma resembling midgut carcinoids. The peripheral cells of the islands contain coarse reddish-brown granules. Small acini lined by columnar cells with copious cytoplasm and filled by an eosinophilic secretory material are dispersed between the cellular islands. The tumor cells have round uniform nuclei containing coarse chromatin; mitotic figures are rare.

Long, parallel ribbons of cells separated by a scant to abundant fibromatous stroma characterize the trabecular pattern that resembles foregut and hindgut carcinoids (44). The tumor cells are columnar with oblong nuclei and moderate amounts of eosinophilic cytoplasm that typically contains argyrophilic granules. The nuclei contain finely dispersed chromatin; mitotic figures are sparse. An insular pattern is observed as a minor feature in about 20% of the cases.

Strumal carcinoids show an intimate admixture of both struma and carcinoid; either component may predominate. The carcinoid component may exhibit either the trabecular, insular, or both patterns. The thyroid component may appear as normal thyroid tissue or a follicular adenoma. Neuroendocrine granules are demonstrable in the cells forming carcinoid trabeculae and thyroid follicles with immunostain for chromogranin or Chunukian-Schenk stain. On ultrastructural examination, neuroendocrine-type granules are present within the trabecular cells and are admixed with the thyroid epithelium lining the follicles in transitional zones.
Mucinous carcinoids (goblet cell carcinoids) resemble those of appendiceal origin. They usually occur in pure form, but may be associated with a mature teratoma or epidermoid cyst. They consist of small nests or gland composed of varying numbers of goblet cells and argentaffin cells, some of which may also be argentaffinic; their nuclei are uniform, small, and round to oval. Small pools of mucin may lie within cystically dilated glands or within the stroma. More poorly differentiated cells, often of signet-ring type, may invade the stroma, singly or in small nests. Irregular dense core granules have been identified on ultrastructural examination in some cases. Rare ovarian carcinoids include those of spindle cell type resembling their pulmonary counterparts and those with nonspecific, sometimes poorly differentiated patterns.

Differential Diagnosis

In the absence of teratomatic elements, primary carcinoids may be difficult to distinguish from metastatic carcinoids. Evidence favoring or establishing the diagnosis of metastatic disease includes the presence of a definite or probable carcinoid in the small bowel or elsewhere, extraovarian metastases, bilateral involvement, intraovarian growth as multiple nodules, and persistence of the carcinoid syndrome after removal of the ovarian tumor. Most of the above features may be equally useful in differentiating a mucinous carcinoid with a prominent signet-ring component from a metastatic signet-ring carcinoma.

Despite their distinctive microscopic characteristics, ovarian carcinoids can be confused with several other primary ovarian tumors, especially the granulosa cell tumor, the Sertoli-Leydig cell tumor (SLCT), and the Brenner tumor. In contrast to the acini of a carcinoid, the Call-Exner bodies of the granulosa cell tumor have irregular margins and contain watery eosinophilic material and occasional shrunk nuclei. The granulosa cells surrounding a Call-Exner body lack the copious cytoplasm that separates the nuclei from the lumen of a carcinoid acinus and typically have pale, grooved nuclei that are haphazardly oriented in relation to another and the lumen. The cords of Sertoli cells in SLCTs of intermediate differentiation tend to be shorter, less uniform, and more sparsely distributed than the elongated trabeculae of a trabecular carcinoid; in addition, several other distinctive patterns of SLCT may be present to facilitate the diagnosis. The epithelial cells of Brenner tumors, in contrast to those of carcinoid tumors, have a distinct urothelial appearance with grooved nuclei. Additionally, the acini within the Brenner nests are often lined by mucinous cells unlike those of a carcinoid acinus.

Strumal carcinoid has been most frequently misdiagnosed as thyroid carcinoma arising in struma. The latter exhibits the typical patterns of a papillary or follicular thyroid carcinoma, and lacks the trabecular pattern and argyrophil and argentaffin granules of the strumal carcinoid.

REFERENCES

CASE 13

History (Case #13 – Acc. 28166)
A 42-year-old, gravida I para 1, female presented with a right ovarian mass. Right salpingo-oophorectomy was performed. The specimen consisted of a 38 gram, moderately firm mass that measured 6.5 x 4.0 x 3.8 cm. The external surface was bosselated and pink-white. The cut surface was solid pink-white with areas of light gray softening and focal cystic changes beneath the capsule. (Contributed by Arthur Koehler, M.D.)

Diagnosis: Endometrioid tumor of low malignant potential

DISCUSSION

Tumors of low malignant potential (LMP), alternately referred to as borderline tumors, of the ovary show a more florid epithelial proliferation compared to that seen in benign tumors of the same cell type but an absence of destructive invasion of the stroma. Despite this lack of invasiveness within the ovary, these tumors can implant on peritoneal surfaces and the implants may invade the underlying tissue; rarely, they spread via lymphatics and, exceptionally, through blood vessels. The diagnosis, however, is based on morphologic features of the primary ovarian tumor regardless of the presence or absence of tumor spread beyond the ovary.

The distinction of LMP tumors from frank carcinomas is one of the commonest problems in ovarian tumor pathology. Borderline tumors are also designated carcinomas of low malignant potential but the term borderline tumor is preferable because it avoids having "carcinoma" in the diagnosis and is less likely to lead to overly aggressive therapy.

Endometrioid tumors of low malignant potential are uncommon. Patients range in age from 26 to 79 years. The tumors present as solitary, unilateral, predominantly solid masses that range from 2 to 40 cm in size. Microscopically, two types have been identified. One has a prominent fibrous component being basically an adenofibroma. The second and far less common variant is basically epithelial in composition with minimal fibrous stromal component. The epithelium in both variants resembles either the endometrium in atypical hyperplasia with low mitotic activity or low-grade carcinomas. There is no destructive infiltrative growth. Almost 25% of the tumors are associated with pelvic endometriosis, and 10% are associated with endometrial adenocarcinoma.

Because of the rarity of borderline endometrioid adenofibromas, as well as those with microinvasion, and the clinically benign behavior of the relatively few reported cases in these categories, recognition of features that may predict a malignant behavior requires additional experience with these tumors. For the present, the gynecologist should be aware of the apparently excellent prognosis associated with all these neoplasms.

When an intracystic papillary villoglandular tumor is lined by atypical endometrioid epithelium we designate it borderline with epithelial atypia but if the epithelium is malignant, we diagnose borderline with intraepithelial carcinoma.

Microscopic Features

Benign Endometrioid Tumors

Endometrioid cystadenomas are rare. They are lined by stratified, typically non-ciliated, non-mucin-containing epithelium, underlying endometrial-type stroma, pseudoxanthoma cells containing hemofuscin, hemosiderin, or both, and the distinctive stroma containing small spindle-shaped fibroblasts that often develops in the wall of an endometriotic cyst are absent. Extensive sampling of a cyst of this type, however, may reveal foci where these stromal findings are present, establishing the diagnosis of an endometriotic cyst.
The endometrioid adenofibroma is characterized typically by glands lined by stratified non-mucin containing epithelium within a predominant fibromatous stromal component. Occasionally, the epithelium is simple columnar, cuboidal or flat, creating a problem in differentiation from a serous adenofibroma.

Squamous differentiation in the form of morules, which may exhibit central necrosis, may be present within variable numbers of the glands. The morules occasionally excite a myxoid fibroblastic response in the adjacent stromal component, which should not in itself be regarded as evidence of borderline malignancy. Very rare intracystic polyloid and papillary tumors containing bland-appearing endometrioid epithelium also belong in the benign endometrioid category.

**Serous Tumor Of Low Malignant Potential**

The most common of the category of tumors of low malignant potential, serous low malignant potential tumors (SLMP) account for from one-quarter to one-third of malignant serous tumors. They are most common in the fourth and fifth decades. Approximately 70% are confined to the ovary (Stage I); the remaining tumors have spread within the pelvis (Stage II) or upper abdomen (Stage III). One-third of the tumors are bilateral. Rather than discussing the characteristic gross and microscopic features of SBT, which are well discussed in many standard texts, we will focus on specific diagnostic problems and recent data.

**Pseudoinvasion**

SLMPs often exhibit a complex glandular and papillary proliferation. The glands often invaginate into the stroma and, particularly when sectioned tangentially, it may appear as if invasion has occurred. This pseudoinvasion differs, however, from the destructive stromal invasion of a carcinoma. The stroma in areas of pseudoinvasion is identical in its appearance to the stroma elsewhere and the glands are orderly arranged. In a carcinoma there is typically a desmoplastic stroma and the distribution of the neoplastic glands in the stroma is more disorderly. On rare occasions, SLMP shows auto-implants and may have the desmoplastic stroma usually seen in extraovarian implants.

**Micropapillary Serous Carcinoma (MPSC)**

Recently, a variant of well differentiated ovarian carcinoma that does not display destructive infiltrative growth (carcinoma in situ), but manifests aggressive behavior has been described and designated MPSC. Its microscopic features include highly complex micropapillae, high nuclear-to-cytoplasmic ratio and numerous mitotic figures. Most MPSC contain areas of SBT, indicating that the former probably arose from the latter. Of a series of 26 of these tumors 17 were noninvasive and nine contained areas of invasion ranging from minimal to extensive. Eight of the 26 tumors were stage I, and none of those patients developed recurrence. In contrast, half of the 16 women with stage II disease or higher either died of carcinoma or were alive with disease. In these eight patients the ovarian tumors were associated with invasive peritoneal implants, which per se carry a poor prognosis. In Stage I tumors, however, there is no objective evidence that the micropapillary, solid, and cribriform patterns equal frankly invasive carcinoma in terms of prognosis.

In our experience, MPSC should be designated as a carcinoma not otherwise qualified only areas of frank invasion are identified; otherwise, they should be designated as SLMP or serous intraepithelial neoplasia, low grade or high grade depending on the cytologic features. Extensive sampling is indicated.

**SLMPs with Microinvasion**

Otherwise typical SLMPs may contain foci of microinvasion. In the first series of 18 cases of these tumors reported from AFIP described, 12 were Stage I and 6 were Stage II or III. Only one patient died of disease, and she had Stage III tumor. All the other patients were alive and well without evidence of disease from 2.5 to 5.5 years after presentation. In a subsequent series, composed of 21 cases, follow-up was available for 17 patients. Sixteen of them were alive and well without evidence of disease from 1 to 11 (average 5.2) years after presentation. One patient developed recurrent SLMP with microinvasion in the contralateral ovary almost 3 years after diagnosis and was well 6 months later. These tumors do not differ grossly from typical SLMPs. Microscopically, they show foci (under 3 mm in greatest dimension) of single cells, nests and small clusters of cells, which often have abundant eosinophilic cytoplasm, in the stroma. They are unassociated
with a significant stromal reaction. Occasionally, foci of lymphatic invasion may be present. This finding does not appear to have altered the prognosis to date. The results in these two studies indicate that SLMPs with microinvasion have a prognosis similar to that of SLMPs without this feature and conservation of the contralateral ovary and uterus may be acceptable therapy in young women, so as to preserve fertility. Microinvasion is easily overlooked and may not be rare as suggested by a review of 36 consecutive SLMPs in which it was found in 4 cases after careful search.

The distribution of the basement membrane components laminin and type IV collagenase has been investigated in a series of serous tumors of the ovary, including SLMPs with microinvasion. Benign serous cystadenomas and SBTs with microinvasion showed a continuous basement membrane; in contrast, invasive carcinomas had frequent disruptions and extensive areas lacking basement membrane. Early invasion in borderline tumors was characterized by complete absence of laminin and type IV collagen around clusters of microinvasive cells. Type IV collagenase, an enzyme that initiates the degradation of type IV collagen, could not be demonstrated in cystadenomas, whereas in invasive carcinomas the reactivity for type IV collagenase was moderate to intense. Type IV collagenase immunoreactivity was also found in SLMPs in noninvasive cells with abundant eosinophilic cytoplasm, as well as in the foci of microinvasion.

SLMPs with Peritoneal Implants

Peritoneal implants are found in 30 per cent of SLMPs. Implants are seen with greater frequency in patients with tumors that have an exophytic component compared to those which do not. Peritoneal implants may vary greatly in their histologic appearance. They most often appear similar to the primary ovarian tumor showing slight to moderate cytologic atypia, no or only a modest stromal reaction and no destructive invasion. In some cases, however, the implants appear more atypical or less atypical than the primary tumor. In the first instance there may be severe cytologic atypia and invasion of the involved tissues producing a picture similar to that of infiltrating serous carcinoma. In the second instance the foci of serous epithelium are benign or minimally atypical and are indistinguishable from what is designated endosalpingiosis in patients who do not have an ovarian serous tumor. When a patient has a SBT it is possible that many foci of "endosalpingiosis" represent mature implants (endosalpingiosis, however, usually lacks papillae and cell stratification). A frequent finding in maturing implants is numerous psammoma bodies; as the implants mature they appear to undergo obsolescence and are replaced by psammoma bodies.

The peritoneal implants of SLMPs have been classified into non-invasive and invasive categories with the former being further subdivided into epithelial and desmoplastic subtypes. In some non-invasive implants, papillary proliferations of atypical cells are present on the surface of the peritoneum or in smoothly contoured subperitoneal invaginations or invasions between lobules of omental fat. The cytologic atypia in these cases usually approximates that in the parent ovarian tumor and there is little or no significant stromal reaction to the tumor. In contrast, the desmoplastic subtype of non-invasive implant is characterized by a predominant stromal reaction to the tumor that is layered upon serosal surfaces. The stromal reaction exceeds quantitatively the epithelial component of the implant. In these foci single cells, small glands, and papillae formed and lined by atypical serous cells as well as psammoma bodies are entrapped by proliferating fibroblastic tissue that is often infiltrated by acute and chronic inflammatory cells. Necrosis with surface fibrin deposition and hemorrhage are often present. Invasive implants are characterized by an irregular infiltration of normal tissues, such as the omentum. They resemble histologically a low-grade serous adenocarcinoma; marked cytologic atypia may be present.

Some studies of SLMPs associated with peritoneal implants have shown that separation of the implants into invasive and non-invasive categories has important prognostic implications. In one report, 56 patients were studied (Kennedy and Hart, 1996). When followed for four years or more, or until death, 94 percent of patients with non-invasive implants had no progression of disease, in contrast to only 17 percent of those with invasive implants. Severe nuclear atypicity and mitotic activity in the implants were independently correlated with a poor prognosis. In another study, which included 19 Stage II-III tumors, the only four patients who died of tumor had invasive aneuploid implants (Klaman et al., 1986). Although correlation between DNA ploidy of the primary ovarian tumor and survival was not statistically significant, three of the four patients who died of tumor had aneuploid ovarian tumors. On the basis of these results we do not consider chemotherapy indicated for non-invasive implants of SLMPs but, on the other hand, think it appropriate for patients with invasive implants. It should be noted that other studies have failed to show a difference in prognosis between patients with invasive and non-invasive implants, but they may have included lesions that others would consider desmoplastic non-invasive implants, in the invasive implant category.
Another study also has emphasized the relatively favorable prognosis of patients with extra-ovarian spread of SLMPs. Disease-free survival rates for 82 patients were 95% at five years and 91% at ten years. It should be noted that almost all these patients received adjuvant therapy. It is also noteworthy that five patients in that series died of acute myelogenous leukemia as a complication of the adjuvant therapy they received. A conservative approach to the management of borderline tumors in general is currently preferred; in some cases even cystectomy may be appropriate.

SLMPs in Lymph Nodes

Benign epithelial inclusions are present in pelvic and periaortic lymph nodes in up to 14 percent of women; it is therefore not surprising that occasionally proliferative changes, including borderline tumors, occur in this epithelium. When this happens in a patient with a SBT of the ovary, the relationship of the borderline neoplasia in the lymph nodes and ovaries is problematic. Sometimes the borderline neoplasia in the nodes is a focal finding in a case in which there are numerous foci of benign inclusions and it is logical to interpret the lymph node proliferation in these cases as simultaneous neoplasia. On the other hand, in some cases there is involvement of vascular sinuses at the periphery of the node suggesting spread to the node. In addition, in some of these cases foci of lymphatic invasion are seen in the primary ovarian tumor. Whether the lymph node involvement in these cases is synchronous neoplasia or true metastatic disease, this finding should not, in the opinion of some investigators influence the treatment of these cases.

Management of SLMP

Standard surgery consists of bilateral salpingo-oophorectomy and omentectomy along with peritoneal washings. Conservative surgery - of unilateral salpingo-oophorectomy and omentectomy along with peritoneal washings - is an alternative for stage Ia tumors in young women who have not completed their family. The efficacy of adjuvant chemotherapy remains to be shown; it has been suggested for patients who have infiltrative implants.

REFERENCES

Endometrioid tumors of low malignant potential

Serous tumors of low malignant potential


CASE 14

History (Case #14 — Acc. 28379)
A 63-year-old female presented with a pelvic mass. A 7 x 5 x 2 cm, partially cystic left ovarian mass was removed along with the contralateral ovary, uterus, omental segment, and para-aortic lymph nodes. (Contributed by Fattaneh Tavassoli, M.D.)

Diagnosis: Serotransitional Cell Carcinoma

DISCUSSION

It has recently been recognized that a subset of surface-epithelial carcinomas histologically resemble transitional cell carcinoma (TCC) of the urinary bladder, but are not associated with a recognizable benign Brenner tumor as are malignant Brenner tumors. Such neoplasms have been classified as transitional cell carcinoma (TCC) of the ovary.

Microscopically, TCCs are characterized by blunt papillae extending into spaces that are largely free of necrotic debris. The papillae are lined by multiple (often over 15 to 20 layers) layers of polygonal cells that show substantial cytologic atypia. In solid areas, the tumor infiltrates the stroma as irregular nests of similar cells. TCCs often coexist with more typical forms of ovarian carcinoma in the ovarian neoplasm, most frequently a serous carcinoma. Ovarian TCCs may metastasize as either pure TCC or as TCC mixed with other cell types with either predominating. The seminar case had focal areas of admixture with a serous type differentiation that is represented in your slide.

It has been noted that TCCs are more frequently high stage at presentation and have a worse prognosis than malignant Brenner tumors. It has also been suggested in a series of articles from investigators at the M.D. Anderson Hospital that patients with TCC and peritoneal spread of tumor have a much better response rate and longer survival interval after treatment with platinum containing chemotherapy than patients with other histologic subtypes of high grade, high stage ovarian carcinomas. These investigators have noted that patients with primary ovarian TCC whose metastatic tumor is composed purely or predominantly of TCC have a better prognosis than those whose metastatic tumor is of another histologic subtype or in which TCC is only a minor element.

The distinction between these tumors and undifferentiated carcinoma is difficult, and to some extent, subjective. Features that may aid in separating the two tumor types are that TCCs usually contain cystic areas with papillae resembling papillary TCC of the bladder, and the tumor cells infiltrate the stroma as nests, whereas undifferentiated carcinomas are usually solid proliferations of large sheets of cells. Cytologically, the cells of TCCs tend to be less pleomorphic and anaplastic appearing than those of undifferentiated carcinoma.

Primary TCC of the ovary must also be distinguished from the very rare cases of ovarian metastases from TCC of the urinary tract. In our experience, this distinction is a very difficult one. Features that favor metastatic TCC include deep invasion by the urinary tract TCC, metastasis to other sites at the time of ovarian involvement, bilaterality or multilocularity of the ovarian tumors, or lymphatic or blood vessel invasion or both in either the ovarian or urinary tract tumor. Features that favor independent primary tumors are a long interval between the detection of the ovarian and urinary tract tumors, dissimilarity in their histological features, an absence of invasion or only superficial invasion of the urinary tract tumor, the absence of metastasis to other sites, coexisting benign Brenner tumor and an absence of extraneous tract tumor for three years or more after treatment of the ovarian tumor. Immunoreaction with CK 20 would favor a urinary tract TCC, but focal CK 20 Positivity is rarely evident in ovarian transitional cell tumors also.

Pathologic Findings

Macroscopically, the tumor is often multiloculated on cut surface. The variably sized cysts are filled with blood-tinged serous fluid. Papillary and knobby excrescences are evident lining the cyst walls.
Microscopically, the lesion displays solid and papillary growth. The papillae and solid areas were composed of proliferation of spindled atypical transitional cells resembling grade 2-3 (out of 4) transitional cell carcinomas of the urinary bladder. Some nuclei have longitudinal grooves. In the seminar case, numerous spaces were present among the solid neoplastic areas; some of these contained a granular secretory material. These areas resembled the filigree pattern of serous carcinoma.

Discussion

Urothelial epithelium has been long recognized in ovarian neoplasms such as benign, proliferative, and malignant Brenner tumor as well as in non-neoplastic Walthard nests in the adnexal region. Urothelial differentiation also occurs in a variable extent in 9 to 12% of ovarian carcinomas and there are carcinomas that are composed purely of transitional cells. Transitional cell carcinomas differ from malignant Brenner tumors by the lack of a benign Brenner component. So defined, transitional cell carcinomas appear to be more aggressive than malignant Brenner tumors. The similarity of the epithelium in these lesions to the normal and neoplastic epithelium of the urinary bladder is mainly at the level of morphologic appearance. There are functional differences between the lesions that display transitional cell morphology in the ovary and those that occur in the urinary tract. At the ultrastructural level, a well-developed nuclear groove is apparent. The cells have distinct cell borders, complex interdigitating projections and well developed desmosomes. In contrast to urinary tract transitional cell tumors, expression of cytokeratin 20 is rare and very focal, if present at all, in ovarian transitional cell lesions. They do express cytokeratin 7, however, as do other epithelial tumors of the ovary. We have observed apparent derivation of Brenner tumors from both the surface epithelium and the rete ovarii. Brenner tumors occur most frequently in women between ages of 40 to 60. The proliferative and malignant Brenner tumors account for less than 5% of the cases even in consultation practice. Transitional cell carcinomas are rare with a majority encountered among women between 50 and 70 years of age. It accounts for far less than 1% of the surface epithelial derived carcinomas.

Brenner tumor variants

The typical Brenner tumor is a fibroepithelial tumor composed of multiple nests of benign transitional cell epithelium within a prominent ovarian type stroma. The epithelial cells are rounded to polyhedral with “coffee-bean” shaped nuclei. Small cysts lined by mucinous epithelium are found in the center of some epithelial nests. Squamous metaplasia may be present. The stromal cells sometimes appear luteinized. Brenner tumors are generally incidental findings and rarely exceed 2 cm in maximum diameter. About 10% are bilateral.

First described by Roth and Sternberg in 1971, proliferative Brenner tumors present as a solid and cystic mass that shows significant epithelial proliferation of the urothelial cells within a background stroma identical to that found in benign Brenner tumors. In contrast to the generally small size of benign Brenner tumors, proliferating Brenner tumors tend to be large, with a median diameter of 16 cm in one series (Miles and Norris), and 20 cm in another (Roth et al). Patients generally present with an abdominal mass, enlarging abdomen, or abdominal pain. The women range in age from 30 to 87 years; the average age has been reported as 50, 66, and 70 years in various studies. Cysts often develop within these tumors and the epithelium forms papillary processes composed of urothelial epithelium and areas of squamous metaplasia. Focal, mild atypia may be seen, but the proliferating cells are generally quite uniform and lack characteristics of highly malignant cells. The appearances are similar to a low grade (Grade 1-2) papillary transitional cell carcinoma of the urinary bladder. The papillary tumor may be partially or totally inverted. Mucinous epithelium lines some of the cysts. Typical benign Brenner tumor is always present in the adjacent area.

Some proliferative Brenner tumors display nuclear atypia and mitotic activity resembling grade 3 transitional cell carcinoma of the urinary bladder or squamous carcinoma in situ; the designation of Brenner tumor of low malignant potential has been used for these tumors. The clinical features and gross appearances are similar to those of proliferative Brenner tumor.

None of the well-documented proliferative Brenner tumors have either recurred or metastasized. Tumors designated as borderline or of low malignant potential have also had an excellent prognosis. Whether or not there is any
difference in the biologic behavior justifying separation of these unusual variants will require study of a large number of cases with long-term follow-up.

Malignant Brenner tumor displays small cysts or solid nests lined by cells that appear cytologically malignant and show stromal invasion. Intimate association with one of the benign patterns of Brenner tumor is required. These tumors are often large with an average size of 15 cm. Typically, they show both cystic and solid areas.

Transitional Cell Carcinoma

Transitional cell carcinomas present in advanced stages (III-IV) more frequently (69-100%) than malignant Brenner tumors (11-19%). Furthermore, a higher proportion of patients with malignant Brenner tumor are free at last contact (69%) compared to women with transitional cell carcinoma (24%).

These differences persist even when tumors are compared within the same stage. About 43% of patients with stage IA transitional cell carcinoma are alive and well at last contact compared to 88% of women with stage IA malignant Brenner tumor. Since a majority of either tumor type is grade 2 or 3, histologic grade does not appear to be responsible for the differences in behavior. It is possible that TCC could have arisen from a Brenner tumor and overgrown resulting in complete obliteration of the benign precursor areas. This probably does occur in some instances, but at least some transitional carcinomas are independent de novo lesions. Aside from the fact that TCC is more aggressive than MBT stage for stage, distinct areas of calcification are present in a majority of MBT and common in benign Brenner tumors, but absent in ovarian TCC. The development of transitional cell differentiation among ovarian tumors may be explained by the proximity of the gonadal ridge to the mesonephros in the early coelom and the common mesothelial covering of the two. The gonadal ridge arises at the ventral border of the mesonephros and is covered by mesothelium that is continuous over the mesonephros. The mesonephros differentiates to form the mesonephric ducts, the ends of which become incorporated in a portion of the urogenital sinus that is destined to be the bladder. Continuous with both the genital ridge and mesonephros, the coelomic mesothelium retains the potential to form similar-appearing neoplasms in each location.

Of great importance is recent data suggesting that some ovarian tumors with a pure or predominant transitional cell component display a better response to chemotherapy and show improved survival when compared to non-urothelial tumors of the same stage and grade. These tumors were subjected to similar chemotherapeutic regimens and had comparable amounts of residual tumor after primary resection. Silva and colleagues have suggested that among patients with ovarian carcinoma who receive chemotherapy, the predominance of a transitional cell pattern (>50%) is a favorable prognostic factor. Gershenson et al compared response to cisplatin-based chemotherapy in 62 patients with transitional cell carcinoma with matched serous carcinoma patients. The surgical complete response rate for women with transitional cell carcinoma was 37% compared to 11% for those with serous carcinoma. The survival time was 52.3 months for those with transitional cell carcinoma compared to 22.0 months for women with serous carcinoma. They concluded that transitional cell carcinoma is significantly more chemosensitive resulting in better survival compared to the more common serous carcinomas.

Classification of epithelial neoplasms of the ovary includes those with a transitional cell type. The distinction between MBT and TCC may have therapeutic and prognostic implications and some women with extra-ovarian spread of TCC appear to benefit from adjunctive therapy.

REFERENCES

CASE 15

History (Case #15 – Acc 10286)

A 59-year-old Caucasian female presented with lower abdominal pain and a 15 pound weight loss over a three-month period. Pelvic exam revealed a large mass. Bilateral oophorectomy, pelvic exploration and multiple biopsies of the peritoneum were done. The right ovary was replaced by a 219 gram globoid mass. Its cut surface consisted of a latticework of slimy glistening gray-tan tissue exuding mucoid material. The left ovary measured 4 x 2 x 2.5 cm, and had similar lacy-looking tumor present in its central portion. (Contributed by John Gilrane, M.D.)

Diagnosis: Krukenberg tumor

DISCUSSION

Metastatic tumors to the ovary are responsible for significant diagnostic problems in the assessment of ovarian neoplasms. The ovaries are involved in 29 to 37% of women succumbing to malignant disease; in 60% of the patients with ovarian metastases, there is no obvious lesion on gross inspection of the ovary. In the adult women, the most common sources of metastatic carcinoma to the ovary include the gastrointestinal tract and breast. The incidence is variable depending on the origin of the primary tumor. Ovarian metastases occur in 50% of women with gastric carcinoma, 44% of those dying of breast carcinoma, 30% of women with colonic cancer, and 16% of those with malignant melanoma. Ovarian involvement is noted in 1% to 40% of women with cervical carcinoma, and 0 to 50% of those with endometrial carcinoma. It is therefore, important to distinguish primary and metastatic ovarian carcinoma.

How tumors spread to the ovary

There are multiple pathways by which tumors spread to the ovary. These include:

1. Direct spread: Direct extension from a tubal, endometrial and colonic carcinoma is facilitated by presence of adhesions.

2. Surface Implantation: Implantation occurs from widespread carcinoma in the peritoneum and through the fallopian tube from endometrial carcinoma.

3. Lymphatic spread: Because of the rich lymphatic network in the pelvis, this is a common mechanism of spread to the ovary. Breast and even gastric carcinoma may spread to the ovary in this manner. The lumbar lymphatics connect the lymphatic channels of the upper GI tract and those of the ovary.

4. Hematogenous Spread: This is a common mode of tumor spread to the ovary.

Characteristics of Metastatic Carcinomas

A high proportion (60%) of the tumors are bilateral. They may persist as diffuse enlargement of the ovaries, as multiple discrete solid nodules, as partly cystic, or even entirely cystic lesions. Areas of hemorrhage and necrosis are common. Features supporting metastatic involvement include abundant necrosis, multifocality and vascular invasion.

Krukenberg Tumor

The classic Krukenberg tumor is usually a bilateral tumor characterized by the presence of mucin-filled signet ring cells, typically lying within a cellular stroma derived from the ovarian stroma. The source of Krukenberg tumors in from 70 to 100% of reported cases is a gastric carcinoma, usually arising in the pylorus. Carcinomas of the large
intestine, appendix and breast are the next most common primary sites; the gallbladder, biliary tract, pancreas, cervix, and urinary bladder are rare sources of these tumors. Saphir demonstrated in an autopsy study that signet ring cell carcinomas of various organs are more often associated with ovarian metastasis than carcinomas of other histologic types by a ratio of about 4 to 1. More recent studies have supported his observation. Gastric signet ring cell carcinomas metastasize to the ovary in 41% of the cases whereas intestinal-type carcinomas of the stomach do so in only 17%. Signet ring cell carcinoma of the colon also metastasizes to the ovaries more frequently than does the usual colonic adenocarcinoma.

The frequency of the Krukenberg tumor varies with that of gastric carcinoma in the population analyzed ranging from 39% of ovarian metastases at the radium remett to very large proportion in countries such as Japan, with a high prevalence of gastric carcinoma and a low prevalence of primary ovarian carcinoma. The average age of patients with Krukenberg tumors is about 45 years. From one-quarter to almost half of the patients have been under 40 years, and only slightly more than 10% of them have been over 60 years. This age distribution is related in part to the disproportionate frequency of gastric signet ring cell carcinomas in young women as well as the greater vascularity of the ovary in young women. In one study 10% of women 35 years or younger with this tumor had ovarian metastases at presentation.

Almost 90% of patients with Krukenberg tumors have symptoms related to ovarian involvement, the most common of which are abdominal pain and swelling; occasionally, there is abnormal uterine bleeding and rarely overt signs of excess hormone production such as virilization. The remainder of the patients have gastrointestinal or miscellaneous symptoms, or are asymptomatic. A history of prior carcinoma of the stomach or, rarely, another organ can be obtained in 20 to 30% of the cases. The interval between the diagnosis of a gastric carcinoma and the subsequent discovery of ovarian involvement is usually six months or less, but periods as long as 12 years have been reported. In most cases, the diagnosis of the gastric carcinoma is made preoperatively, during the operation for the ovarian metastasis, or within a few months thereafter. Often, the primary tumor is too small to be detected at operation, and radiographic examination of the upper gastrointestinal tract may also fail to reveal evidence of a tumor even after the diagnosis of Krukenberg tumor has been established. Rarely, the gastric carcinoma may not be detected until five or more years after discovery of the ovarian metastatic tumor.

Most tumors with the microscopic features of the Krukenberg tumor are metastatic, but very rare examples may be primary. It is well known that mammary and gastric carcinomas may remain silent for many years. In some cases of Krukenberg tumor, the primary gastric carcinoma may not become apparent until over five years after the ovarian tumor had been removed. Thus, clinical dormancy of the primary tumor probably accounts for some of the cases of Krukenberg tumor with long survival. As poorly differentiated primary mucinous carcinoids of the ovary may have extensive foci of signet ring cell proliferation, it is possibly that some of the “primary Krukenberg” tumors in the literature reflect mucinous carcinoid tumors.

Gross Features

Krukenberg tumors typically cause diffuse ovarian enlargement or may form rounded, firm, white masses that may be bosselated and may attain a large size. The cut surfaces are usually yellow or white but areas of purple, red, or brown discoloration and extensive hemorrhage are also encountered. The consistency is characteristically firm but fleshy, gelatinous, or spongy areas are common.

Microscopic Features

Microscopic examination of a Krukenberg tumor reveals mucin-laden, signet-ring cells strewn individually and in small clusters within a cellular ovarian stroma; occasionally the stroma has a storiform pattern. Frequent variations from the classical appearance include small glands, a prominent tubular architecture, mucin-poor tumor cells in trabecular and large masses, abundant collagen formation, marked stromal edema, and cell-free pools of mucin in the stroma. Occasionally, small or large cysts lined by minimally atypical appearing mucinous epithelium forms a conspicuous component of the tumor, with more characteristic areas lying between the cysts. The cytoplasm of the signet ring cells is occasionally granular and eosinophilic rather than pale and vacuolated; the cytoplasm sometimes has a bull’s-eye appearance, containing a large vacuole with a central eosinophilic body. As with metastases in
general, blood vessels and lymphatic invasion is common. Lutein cells are occasionally present in the stroma, particularly if the patient is pregnant.

**Clinical course of the disease**

Almost all the patients die within a year of the diagnosis of ovarian metastasis, with an average duration of seven months from diagnosis to death, but a rare patient has survived, apparently free of tumor, for as long as six years after gastrectomy and bilateral oophorectomy. Such a result, even though exceptional, justifies removal of both the stomach and the ovarian metastases for possible cure in cases in which the tumor appears limited to those organs. It is also prudent for the surgeon to remove the ovaries routinely in menopausal and postmenopausal women having a gastric resection for carcinoma to prevent the later complication of ovarian metastasis and avoid another operation.

**Differential Diagnosis**

The Krukenberg tumor may resemble a fibroma or any other type of solid ovarian tumor on gross examination. Its appearance may also occasionally be deceptive on frozen section or low-power examination but should be readily diagnosable on high-power microscopic examination, especially with the aid of mucin stains. A frequent misdiagnosis is a Sertoli-Leydig cell tumor, particularly when a prominent tubular component and a luteinization of the stroma are encountered in a Krukenberg tumor; signet ring cells, however, are not a feature of Sertoli-Leydig cell tumors except for occasional tumors of heterologous type. The sclerosing stromal tumor may contain cells resembling signet cells as well as a proliferating fibroblastic component, but such cells contain lipid rather than mucin. The rare signet ring stromal tumor also may enter the differential but the signet ring cells in that tumor also fail to react with mucin stains. In clear cell carcinomas, the clear cells contain glycogen; mucin, when present, is typically luminal and extracellular. In rare cases portions of the tumor contain aggregates of signet ring cells but the presence of other characteristic features of this tumor permit its identification. Mucinous carcinoid tumors that contain large numbers of signet ring cells are distinguished from Krukenberg tumors by their additional component of carcinoid, the presence of which can be confirmed by argyrophil staining. These tumors are discussed further in the section on metastatic carcinoid tumor. Finally, the rare non-neoplastic lesion, mucinocarminophilic histiocytosis, which is caused by injection of substances containing polyvinylpyrrolidine is characterized by signet ring-like cells and may involve numerous tissues and organs including the ovaries. Although these cells are stained by mucicarmine, they are PAS-negative.

**REFERENCES**


CASE 16

History (Case #16 – Acc. 25047)

A 72-year-old Caucasian female presented with complaints of indigestion, urinary frequency, and swelling of the right lower extremity of a few days duration. A large mass was palpable, filling both lower abdominal quadrants. At laparotomy, a cystic and solid mass was removed. The 9 cm cystic mass had soft, red-brown, polypoid masses filling it. The outer surface was smooth to slightly wrinkled. The wall averaged 0.2 to 0.4 cm in thickness, with solid tan areas in the wall up to 3.0 cm in diameter. The patient had undergone hysterectomy and removal of right and left fallopian tubes and right ovary twenty-six years previously for endometriosis. (Contributed by Edward Klatt, M.D.)

Diagnosis: Clear cell carcinoma of ovary with oxyphilic type differentiation

Note: The oxyphilic differentiation was focal.

Histologic Findings: The tumor displays a papillary, tubulocystic and solid growth pattern. The papillae are lined by cells with vacuolated, granular or homogeneous eosinophilic cytoplasm. Architecturally, the eosinophilic cells line many papillae. Definite glandular differentiation is present in some areas, and dilated tubules are focally present. Scattered throughout the tumor are markedly pleomorphic cells with large hyperchromatic nuclei. Stromal vascularity is not prominent. Glassy eosinophilic basement membrane-like material surrounds many of the tumor cell nests and glands. This is especially well seen in PAS-stained sections that also focally show a moderate amount of intracytoplasmic glycogen deposits. Mucicarmine stain shows only a rare intraluminal mucin deposit. Immunostains are strongly positive for AE1-3, EMA and CD15 (Leu-M1) and are negative for S100, vimentin and inhibin.

DISCUSSION

Scully proposed the name “clear cell carcinoma” for the group of neoplasms originally described and designated as mesonephroma by Schiller. More than half of the patients in Scully’s study had pelvic endometriosis, and many of the carcinomas developed from the lining of endometriotic cysts leading to the conclusion that clear cell carcinoma is related to endometriosis. It is now accepted that clear cell carcinoma develops from the surface epithelium of the ovary and in a minority of cases (15%) from endometriosis. It accounts for 6-7% of ovarian carcinomas. Clear cell carcinomas of the female genital tract (and urethra) have numerous distinctive architectural and cellular patterns. The most common architectural patterns are solid, glandular, tubular or tubulocystic and papillary. Less common are the trabecular (Sertoliform), adenofibromatous and parvilocular patterns. About 80% of tumors have a mixture of patterns. The neoplastic cells classically have abundant clear or vacuolated cytoplasm that contains glycogen. Clear cells are usually most abundant in the solid and glandular patterns, but are found to some extent in practically all clear cell carcinomas. In the tubular and tubulocystic patterns, flat, cuboidal and so-called hobnail cells are especially prominent. These features are well known. Less well known are tumors in which the cells have abundant eosinophilic cytoplasm. We found these eosinophilic cells to be present in greater numbers than clear cells in 43% of a series of 29 ovarian clear cell carcinomas. Young and Scully proposed the term “oxyphilic clear cell carcinoma” for tumors in which these cells are especially prominent.

Oxyphilic clear cell carcinomas have the same general clinical features (age, clinical presentation, etc.) and gross appearance as clear cell carcinomas in general. The importance of recognizing this histologic variant is its distinction from other primary and metastatic ovarian tumors with an abundance of eosinophilic cells. The differential diagnosis includes the following primary tumors: steroid (lipid) cell tumors, oxyphilic variant of endometrioid carcinoma, luteinized sex cord-stromal tumors, yolk sac tumors and the extremely rare hepatoid carcinoma. The most common metastatic tumors that must be considered in the differential diagnosis are melanoma and renal cell carcinoma. Parenthetically, it is also worthwhile knowing that the more typical clear cell carcinoma may be mimicked by ovarian metastases from the uncommon primary clear cell carcinoma of the small and large intestines.
Cells with large pleomorphic nuclei are very common in all clear cell carcinomas. Also the presence of homogeneous glassy eosinophilic basement membrane-like material around glands or within papillae always suggests a diagnosis of clear cell carcinoma. Other patterns and cell types of clear cell carcinoma should be searched for to confirm the diagnosis. Oxyphilic endometrioid carcinomas usually have more diagnostic areas with branching complex glands or squamous differentiation. Renal cell carcinomas rarely metastasize to the ovary. They are characteristically hemorrhagic tumors with a rich vascular network.

In some particularly difficult cases especially when considering a lipid cell tumor or melanoma, immunostains may be helpful in the differential diagnosis. Cytokeratins AE1/AE3, CD15 (Leu-M1) and EMA are typically strongly positive in clear cell carcinomas, while steroid cell tumors have been reported to be uniformly negative for CD15, positive for EMA in only a small minority of cases (0 to 8%) and generally have only focal cytokeratin positivity. Melanoma is negative for the various epithelial markers but positive for HMB45 and/or S100. Furthermore, lipid cell tumors show intense and diffuse positivity with inhibin. Clear cell carcinomas may also show focal positivity with inhibin.

Clear cell tumor of low malignant potential account for 5 to 8 percent of clear cell neoplasms, but the accuracy of these figures is questionable because of a lack of a uniform definition of these tumors. Approximately 28 cases of clear cell tumors of LMP have been reported in the literature; the 19 cases described in detail had the pattern of adenofibromas with atypical, proliferating epithelium of clear cell type (CCLMP). The peak frequency of these tumors has been in the 7th decade.

CCLMPs are solid or solid with small cysts, resulting in their designation by Schiller as “parvilocular cystomas”. Most reported cases have been confined to the ovaries; bilateral ovarian involvement was present in only one case. Microscopic examination reveals widely spaced or crowded glands, small cysts or smoothly contoured solid nests of epithelial cells embedded in a fibromatous stroma without evidence of destructive stromal invasion. The epithelial cells show the cytologic features of low-grade malignancy (grade 1 of 3). In such tumors, the glands are lined by one to three layers of hobnail or polygonal cells with clear or occasionally eosinophilic cytoplasm and slightly pleomorphic nuclei containing irregularly clumped chromatin and prominent nucleoli. The cells within the solid nests are also slightly atypical and contain abundant clear cytoplasm. Papillae have been absent in all of the well described cases. Most of the tumors also contain areas of benign-appearing clear cell adenofibroma. These features are similar to those described by Roth and coworkers; however, Russell includes tumors with higher grade epithelial proliferation in the absence of stromal invasion in the borderline category. Because clear cell adenofibromatous foci are often associated with invasive clear cell carcinoma, the former diagnosis should not be rendered unless the specimen has been extensively sampled.

Endometriosis was present in the ipsilateral ovary or elsewhere in the pelvis in 25 percent of the cases in one series; this increased frequency of endometriosis is similar to that observed in association with clear cell carcinomas of the ovary.

With only a small number of CCLMP tumors described, the prognosis appears excellent, with no deaths from tumor having been reported thus far. However, one patient, with a clear cell adenofibroma of borderline malignancy and foci of microinvasive carcinoma that ruptured intraoperatively and was incompletely removed, developed a pelvic mass that had the histologic appearance of a CCLMP 3.3 years later. The therapy of most patients has been total abdominal hysterectomy and bilateral salpingo-oophorectomy, but more conservative therapy may be considered in a young woman with unilateral involvement.

REFERENCES

CASE 17

History (Case #17 – Acc. 24904)
A 42-year-old Caucasian female presented with vague abdominal pain, hirsutism and irregular menstrual periods, and was found to have a 5 x 8 cm cystic periumbilical mass. Hysterectomy with bilateral salpingo-oophorectomy was performed. The specimen consisted of a 9 x 7 x 5 cm multinodular, cystic mass with a firm white capsule. The center of the cyst contained hair and yellow-white, greasy material. A 5 x 4 x 3 cm bright yellow, solid area was noted during sectioning. (Contributed by Douglas Andorka, M.D.)

Diagnosis: Lipid cell tumor (Steroid cell tumor)

DISCUSSION

Lipid cell tumors account for less than 0.1% of all ovarian neoplasms. Opinions vary, however, regarding the use of this term as a specific or generic designation. At AFIP, this term is used as a specific designation for a clinically and histologically similar group divided into Leydig (hilar) cell tumors, adrenal cortical-like tumors, and stromal luteomas. The term steroid cell tumor has been the latest designation proposed for this group of tumors; this has been justified on the basis of resemblance of the tumor cells to typical steroid hormone-producing cells. Considering the steroid-producing capability of other gonadal stromal tumors and the lack of steroid production by some of the “steroid cell tumors,” this designation is not optimal.

Clinical Presentation

Most patients with lipid cell tumors are adults with only a few tumors reported in prepubertal children. Androgenic activity and virilization are recognized as the major functional manifestation of lipid cell tumors occurring in 75 to 90% of cases. In the adult female, the majority of the patients present with progressive virilization over a 5- to 10-year period. The main virilizing symptoms are hirsutism, amenorrhea, deepening of the voice, and clitoral enlargement. The variety of hormones that are produced by this tumor include testosterone, androstenedione, dihydrotestosterone, 17-hydroxyprogesterone, progesterone, cortisol, and less frequently estrogenic hormones. Evidence of estrogenic activity is actually present in close to 25% of the patients. While production of estrogens may be responsible for some of these, it is also possible that the estrogens result from peripheral aromatization of androstenedione in adipose tissue. Features of Cushing’s syndrome have been reported in about 5 to 10% of patients, but well-documented cases are few. Diabetic glucose tolerance test, obesity, and hypertension also occur. A palpable tumor mass is a rare presenting complaint. In prepubertal girls, virilization occasionally associated with precocious puberty may develop. Removal of the tumor results in rapid regression of the hormonal effects, although some stigmata of the androgenic effects (i.e., hirsutism) usually persist.

Gross Features

These tumors are almost all unilateral, lobulated, soft, and smooth with sharply defined margin. The color varies and may be yellow, orange, tan, or brown. Areas of hemorrhage and necrosis may be present. The size varies extensively but is usually around 5 to 7 cm.

Microscopic Features

Lipid cell tumors are well circumscribed with an expansile growth margin; an infiltrating margin is rarely observed. The tumor is generally composed of two cell types that are present in varying proportions, but some are composed purely of one or the other cell type. One cell type (Leydig or hilar) is cuboidal or polyhedral with a round eccentric nucleus and a granular eosinophilic cytoplasm which may contain lipochrome or Reinke crystals (the latter is required by some for designating a cell as hilar or Leydig in type). The other cell type resembles cortical cells. It is often
larger than the hilar cells and has a rounded contour and abundant foamy or clear cytoplasm. The nuclei in these cells are generally smaller and have a more dense chromatin than those of the hilar cell. These cells do not contain lipochrome pigment. Considerable amounts of intracytoplasmic lipid may be found in either cell type, but many of the hilar or Leydig cell variants are totally devoid of stainable fat. Lipid cell tumors generally have a rich vascular network. Areas of fibrosis and hyalinization may be found but are not very common. There is no correlation between the cell type and the associated functional manifestation.

**Differential Diagnosis**

Steroid cell tumors may be confused with other neoplasms particularly highly luteinized granulosa cell tumors and thecomas, clear cell carcinomas compose entirely of either clear cells or cells with abundant eosinophilic cytoplasm, metastatic renal cell carcinomas and rarely, lipid-rich Sertoli cell tumors. The rare granulosa cell tumor or thecoma that is markedly luteinized can be distinguished from a steroid cell tumor by the focal presence of non-luteinized granulosa cells in the former and the finding of abundant intercellular reticulum in the latter. Clear cell carcinomas that are composed exclusively of clear cells have glycogen-rich cytoplasm and typically eccentric nuclei in contrast to the characteristic lipid-filled cytoplasm and central nuclei of steroid cell tumors containing clear cells. Clear cell carcinomas composed largely of cells with dense, eosinophilic cytoplasm tend to exhibit epithelial arrangements of their cells and almost always contain foci of more typical clear cell carcinoma. A very rare steroid cell tumor, however, may be difficult to distinguish from a clear cell carcinoma or a metastatic renal cell carcinoma, just as some adrenal cortical carcinomas may be difficult to distinguish from renal cell carcinomas. The distinction of a lipid-rich Sertoli cell tumor with a prominent diffuse pattern from a steroid cell tumor depends on identifying areas with a tubular pattern in the former.

Pregnancy luteomas, which are hyperplastic nodules composed of lutein cells that develop during pregnancy, may form large masses that resemble steroid cell tumors grossly and microscopically. Like the latter they may also be virilizing. Unlike steroid cell tumors, however, approximately one-third of pregnancy luteomas are bilateral and approximately one-half are multiple. Microscopic examination reveals masses of cells with abundant eosinophilic cytoplasm containing little or no lipid; mitotic figures may be numerous, sometimes up to two or three per 10 HPF. In contrast, a steroid cell tumor with minimal cytologic atypia that resembles a pregnancy luteoma usually contains only rare mitotic figures. Although it may be impossible to distinguish a lipid-poor or lipid-free steroid cell tumor from a solitary pregnancy luteoma, a lesion encountered during the third trimester of pregnancy is presumed to be the latter unless clear-cut evidence indicates otherwise.

**Behavior and Therapy**

These tumors are generally benign, but about 10 to 15% of them are associated with an aggressive behavior. Extension to contiguous pelvic structures at the time of initial operation is an ominous sign. A majority of malignant tumors have been 8 cm or larger in diameter. They may exhibit cytologic pleomorphism and increased mitotic activity or, rarely an infiltrating margin. Aggressive behavior is rare in tumors of the hilar cell type with identifiable Reinke crystals. Aside from these features, no consistent correlation of morphologic findings and behavior has been established. Unilateral oophorectomy is generally curative except for the rare malignant tumors. A standard approach to management of malignant lipid cell tumors has not been established.

**REFERENCES**


CASE 18 & 19

History (Case #18 – Acc. 17746)
A 19-year-old, gravida 0, para 0, Black female presented with vaginal bleeding, a five month history of amenorrhea and three months of rapid abdominal enlargement. IVP showed a pelvic mass with hydronephrosis. A pregnancy test was negative. At surgery, a large left ovarian mass and para-aortic nodes were noted, as well as a nodular liver. The 2600 gram left ovarian tumor was 29 x 17 x 12 cm. The tumor had multilocular cystic spaces with intervening firm, rubbery, yellow areas. There were also areas filled with greasy, gritty, keratin debris and dark black hair, as well as one area with a cartilaginous consistency. (Contributed by C. P. Schwinn, M.D.)

Diagnosis: Yolk sac tumor (endodermal sinus tumor)

History (Case #19 – Acc. 21050)
A 33-year-old Caucasian female presented with left-sided pelvic discomfort and pain. Physical examination revealed a large left adnexal mass which extended up to the umbilicus. A pregnancy test was negative. At laparotomy, the 1520 gram, 18 x 14 cm left ovary was firm, nodular and reddish-purple. The cut surface was yellow-tan, spongy and mucoid with areas of degeneration and hemorrhage. (Contributed by John Swift, M.D.)

Diagnosis: Polyembryoma with prominent hepatoid differentiation

DISCUSSION

Clinical Features
Yolk sac tumors (YSTs) account for 1% of all ovarian malignancies, but approximately 20% of malignant primitive germ cell tumors. They are the second most common ovarian malignant germ cell tumor, almost as common as dysgerminomas in females under the age of 20 years. Patients range in age from 14 months to 45 years with a median age of 19 years. It is rare over the age of 40 years. Approximately half of the patients report sudden onset of symptoms of about a week’s duration. Three quarters of the patients experience abdominal pain. A large abdominal or pelvic mass is readily detected on physical examination. Elevation of serum level of alpha-fetoprotein preoperatively is an important clinical feature of this tumor; assessment of its level is useful in monitoring the effects of therapy and detecting recurrent disease.

Gross Features
A rapidly growing and highly malignant tumor, YST is associated with extraovarian spread to the peritoneum, retroperitoneal lymph nodes, or both, in approximately one-third of the patients at presentation. Yolk sac tumors present as a large (median diameter of 15 cm), well-delineated, unilateral mass. Bilaterality is seen only in association with disseminated disease. The surface is ruptured in 25% of the tumors. Cut surface is predominantly solid admixed with cystic areas; foci of hemorrhage and necrosis are common within the friable yellow-gray solid areas. A honeycomb appearance indicates the presence of a polyvesicular vitelline component.

Microscopic
A wide range of patterns is often present in variable proportions in all YSTs. Domination of one pattern to the exclusion of others is rare. The reticular pattern is the most common characterized by a loose meshwork of spaces and channels lined by attenuated or cuboidal cells with scant clear cytoplasm; the cytoplasm contains mainly glycogen and sometimes lipid. The nuclei are irregular and hyperchromatic with prominent nucleoli. Mitotic figures are numerous. Variably sized, eosinophilic, PAS-positive, diastase resistant, hyaline bodies are common in this pattern.
The classic festoon pattern is characterized by columns and cords of primitive germ cells. A layer of columnar germ cells line simple elongated or rounded papillae with a delicate vascular core that protrude into spaces surrounded by a mantle of attenuated to hobnail primitive appearing cells (Schiller-Duval bodies); these structures are thought to recapitulate the endodermal sinuses of the yolk sac. A solid growth pattern dominates in some lesions. Hyaline bodies are found in most YST, but also only in a wide variety of tumors (Al Naffusi et al, 1993). Hyaline bodies are common in this pattern.

Among the more rare patterns that may occasionally predominate or occur in pure form is the polyvesicular-vitelline pattern. This pattern is characterized by the presence of cysts sometimes with eccentric constrictions lined by low columnar cells that become attenuated in parts of the lining. The cysts are distributed in a dense fibroblastic stroma. The cysts with eccentric constrictions simulate the division of the primary yolk sac vesicle into a large component corresponding to the vestigial yolk sac of the embryo and a smaller component, which is the forerunner of the primitive gut. A lesion that closely resembles polyvesicular vitelline pattern is the polyembryoma. Polyembryoma is an exceedingly rare primitive germ cell tumor characterized by proliferation of embryoid bodies composed of ectodermal and endodermal vesicles and resembling the normal early embryos. The embryoid bodies are widely separated by a loose myxoid stroma composed of cells with stellate nuclei. In the seminar case, there are also numerous glands lined by mucinous epithelial cells and clusters of hepatoid cells, some with bile pigment. This loose stroma is in sharp contrast to the relatively dense stroma of the polyvesicular vitelline YST. Furthermore, the ectodermal plate of the embryoid bodies has an appearance of somewhat stratified columnar cells in contrast to the more cuboidal cells of the polyvesicular vitelline pattern. The presence of trophoblastic cells and/or teratomatous elements in the polyembryoma can further assist in separating these two lesions.

One of the rarest forms is the solid pattern composed of nests and sheaths of large cells with abundant eosinophilic cytoplasm vaguely resembling hepatoblasts separated by thin fibrous bands (Prat et al, 1982). While the hepatoid variant is rare, hepatoid cell clusters are present in 15% of yolk sac tumors. Occasional YSTs are composed of or contain glands lined by a nonspecific or vacuolated cells, and in rare tumors, a predominant glandular pattern resembling that of typical or secretory endometrioid carcinoma is seen; tumors of this type have been designated “endometrioid-like” YSTs (Clement et al 1987). Enteric-type glands occur in as many as 50% of YSTs but are rarely numerous; rarely intestinal type glands predominate in the tumor (Cohen et al, 1987). These glands are lined by bland mucinous columnar cells, goblet cells, and rarely, Paneth cells. “Parietal” differentiation is characterized by small extracellular accumulations of basement-membrane material, typically within reticular foci (Ulbright et al, 1986). Nonspecific patterns that may occur in YSTs include solid, papillary and adenofibromatous. Cells with large intracellular vacuoles that displace the nucleus simulating liposarcoma are seen focally in some YSTs.

Immunohistochemical Features and Other Studies

Immunohistochemical findings are useful in confirming a diagnosis of YST, particularly in case of unusual tumors or those with nonspecific histologic patterns. Many of the cells in the hepatoid variant contain hyaline globules that are positive for AFP and alpha-1-antitrypsin (AAT). The cytoplasm of the tumor cells well as the luminal contents of the glands and cysts in tumors with polyvesicular-vitelline and endometrioid-like patterns as well as almost all other variants show at least focal immunoreactivity with AFP and AAT.

At the ultrastructural level, the cells of the solid (hepatoid) EST contain numerous intracytoplasmic osmiophilic bodies of various sizes and densities corresponding to the AFP and alpha-1-antitrypsin. Intracellular and extracellular canaliculi are common.

Differential Diagnosis

Historically and currently, clear cell carcinoma remains the tumor most commonly confused with YST (Klemi et al 1982). The distinctly different age distribution of these two tumors is an important and helpful feature in many cases. The loose, edematous appearance of clear cell carcinomas closely simulates the reticular pattern of a YST. Furthermore, papillary and hyaline bodies may be present in clear cell carcinomas accentuating the similarities. The papillae in clear cell carcinomas have a hyalinized core in contrast to the central delicate vessel of YSTs. Evaluation of additional tissue could help identify more recognizable solid pattern of clear cell carcinoma or areas of admixed
Endometrioid carcinoma pointing to the epithelial nature of the tumor. In contrast, identification of other germ cell tumor components would establish the diagnosis of YST. Clear cell cystadenofibromas may be confused with the polyvesicular vitelline pattern. The presence of constriction in the small cystic spaces and nuclear atypia would favor a germ cell tumor. Immunoreactivity with alpha-fetoprotein generally favors the diagnosis of YST, but a variety of carcinomas are also capable of elaborating AFP on some occasions (Zirker et al, 1989). Patient's age is also of great value in distinguishing the hepatoid YST from the rare hepatoid carcinoma of the ovary (Ishikura and Scully, 1987); the carcinoma occurs in older women with an average age of 63 years, while the germ cell tumor occurs in children, adolescent and young women. Metastatic hepatocellular carcinomas also enter the differential (Young et al, 1992). These are generally bilateral but the distinction can be very difficult without a clinical history. The primary hepatoid carcinomas have not been associated with typical foci of yolk sac.

Behavior and Treatment

Yolk sac tumor is characterized by an extremely rapid growth with evidence of spread to the peritoneum, retroperitoneum, and lymph nodes in almost one third of the patient. In the prechemotherapeutie era, 84% of the patients with stage Ia tumor died despite surgical extirpation and adjuvant radiation therapy. Combination chemotherapy has resulted in survival rates exceeding 80% in patients with stage I tumors, and over 50% in patients with higher stage tumors (Gershenson et al, 1983).

REFERENCES

CASE 20

History (Case #20 – Acc. 28380)
A 32-year-old female presented with a pelvic mass. A 7.0 x 5.3 x 4.4 cm lobulated, circumscribed right ovarian tumor was removed at laparotomy. Cut surface of the tumor was granular and tan-yellow. (Contributed by Fattaneh Tavassoli, M.D.)

Diagnosis: Mixed germ cell-sex cord stromal tumor

Additional History and Follow-up: Thirty-three months earlier, patient had presented with persistent pelvic pain. Laparoscopy showed massive pelvic adhesions believed to secondary to a healed pelvic inflammatory process. No biopsies were taken. After excision of the ovarian mass, no further therapy was given. Five years later, a large pelvic mass was noted just above the uterine fundus extending to the left adnexa. Sonography and CAT scan delineated the mass. At laparotomy, a 7 cm mass adherent to the uterine serosa and anterior abdominal wall with multiple peritoneal implants was removed along with hysterectomy, left salpingo-oophorectomy, omentectomy and lymphadenectomy. This was followed by chemotherapy (bleomycin, Cisplatin, and etoposide) with excellent response. Ten months later, the patient was free of tumor.

Microscopic Features: The primary and metastatic tumors were morphologically identical. Small cells with scanty cytoplasm and oval grooved nuclei were admixed and larger cells (germ cells) with abundant clear cytoplasm containing PAS positive material, central round nuclei and small nucleoli. A single layer of the small cells generally surrounded the cell nests that were separated from each other by bands of eosinophilic hyaline material. Up to 5 mitotic figures per 10HPF were present among the germ cells. There was no evidence of calcifications or necrosis. An epithelial element or a retiform tubular pattern was not present. The residual right ovarian tissue contained normal structures. The subsequently removed left ovary was unremarkable. The tumor differed morphologically from gonadoblastoma by the absence of calcifications and its occurrence in a normal ovary.

The patient had a normal 46XX karyotype in contrast to those with gonadoblastoma who often have mixed gonadal dysgenesis with persistent Mullerian duct structures, chromosomal mosaicism with a Y chromosome component, and gonads that resemble a differentiated testis or streaks that may show partial differentiation toward either testis or ovary.

DISCUSSION

Gonadal neoplasms containing a combination of two or more cell lines are relatively uncommon. Among those that occur, mixtures of epithelial and mesenchymal cells are relatively common. Combinations of gonadal stroma and germ cells are quite rare. Gonadoblastoma is the best known of the combined germ cells-sex cord stromal tumors and it occurs in intersex individuals (Cabanne 1971; Scully 1970). Another variant of this combination occurs in normal females and has been described by Talerman (Talerman tumor); these notably lack the nested pattern and the prominent collagen bands.

Both gonadoblastoma and Talerman tumor are basically benign. Approximately half of gonadoblastomas are overgrown by a malignant germ cell tumor, however, making early prophylactic removal of the gonads advisable in all patients. The malignant tumor is usually a dysgerminoma, but yolk sac tumor, immature teratoma, embryonal carcinoma and choriocarcinoma occur in 8% of cases (Welch and Robboy, 1981).

The present case is unique in displaying an aggressive behavior despite absence of any superimposed malignant germ cell tumor.
REFERENCES

Image Legends

Case 1. Leiomyosarcoma.  (a) At low magnification, the tumor shows a compact proliferation of spindle cells without any evidence of an epithelial component.  (b) A fascicular growth pattern and palisading of bundles of spindle cells is suggested.  There is an admixture of cells with cigar-shaped nuclei and others with ovoid and atypical nuclei.  The cells show significant nuclear atypia; mitotic figures are readily apparent.  (c) Patchy areas of hemorrhagic necrosis are scattered throughout the tumor.

Case 2. Adenocarcinoma.  (a,b) Broad polypoid fronds are covered by benign epithelial cells.  The major bulk of the polypoid structures are composed of a compact proliferation of ovoid to spindle cells most closely resembling endometrial stromal cells.  The low magnification appearance is reminiscent of phyllodes tumor of the breast.  (c) Deeper within the lesion, periglandular cuffing is characteristic of this tumor.

Case 3. Low grade endometrial stroma sarcoma.  (a,b) Irregularly shaped aggregates of a densely cellular tumor proliferate through the myometrium and protrude into vessels (b).  (c) Higher magnification shows a delicate vascular support.  The proliferating tumor cells resemble the proliferative endometrial stromal cells.  Mitotic figures are rare.  (d) Immunostain for actin shows absence of immunoreactivity in the tumor cells and intense positivity in the myometrial smooth muscle.  Immunostains for desmin were similar.

Case 4. Choriocarcinoma.  (a) Syncytiotrophoblasts form biphasic aggregates invading the myometrium and (b) vascular channels.  (c) Fibrinoid necrosis is superimposed on the proliferating tumor cells, a reflection of the therapy induced changes.

Case 5. Mucinous (colloid) adenocarcinoma of the cervix.  (a) The cervical stroma is infiltrated by distended glands containing abundant mucoid material.  (b) At higher magnification, atypical cells with abundant intracytoplasmic mucin and atypical nuclei line a gland that has ruptured with mucus dissecting into the surrounding stroma.  (c) Many cells have a signet-ring appearance.

Case 6. Villoglandular adenocarcinoma of the cervix.  (a) Long papillary projections branch out from the surface of the cervical epithelium.  (b) The papillae have abundant stromal support.  (c) The papillae are lined by columnar cells lacking significant atypia; only occasional mitotic figures are evident.

Case 7. Inflammatory myofibroblastic tumor of the uterus.  (a) The tumor is composed of a diffuse and loose proliferation of spindle cells infiltrating the myometrium; foci of calcification are evident.  (b) Higher magnification shows bland spindle cells with a paucity of cytoplasm and rather small and sometimes pyknotic nuclei admixed with plasma cells; small number of lymphocytes and even fewer eosinophils were evident in other fields.

Case 8. Sarcoma (leiomyosarcoma) with osteoclastic giant cells.  (a) A hemorrhagic tumor irregularly invades the myometrium.  (b) A large number of multinucleated giant cells containing numerous bland round nuclei are dispersed among atypical mononucleated cells that contain irregularly shaped nuclei and display frequent mitotic figures.  The giant cells have a more eosinophilic and granular cytoplasm compared to the background mononucleated cells.  (c) Immunostain for KP1 shows intense staining and confirm the histiocytic nature of the multinucleated giant cells, while the mononuclear tumor cells fail to react.

Case 9. Granulosa cell tumor, adult type.  (a) A diffuse and relatively compact proliferation of tumor cells shows mainly a cord-like or trabecular arrangement of the cells.  (b) The nuclei are relatively uniform and some have longitudinal grooves.  The cells have small amount of granular eosinophilic/amphophilic cytoplasm.

Case 10. Gonadal stromal tumor, consistent with anaplastic granulosa tumor.  (a) A solid proliferation of tumor cells alternate with edematous stroma.  (b) Higher magnification shows atypical nuclei and mitotic figures.  (c) Some cells had irregular nuclear grooves.  (d) Immunostain for inhibin shows positive reaction in the tumor cells.
Case 11. Small cell carcinoma.  (a,b) Low power magnification shows an irregularly clustered proliferation of cells with scattered ovoid follicle-like spaces filled with eosinophilic secretory material.  (c) Higher magnification shows atypical cells with cell defined margins and mitotic figures.  (d) Immunostains for cytokeratin shows patchy areas of intense immunoreactivity.

Case 12. Carcinoid tumor.  (a) The tumor is composed of a highly uniform population of cells forming irregular islands in a fibrous stroma.  Some of the islands have central spaces where the cells seem to have fallen off.  (b) The tumor cells have round uniform nuclei and a small amount of amphophilic cytoplasm.  The cells in the periphery of the islands form a more distinct layer.

Case 13. Endometrioid tumor of low malignant potential.  (a) At low power, islands of endometrioid glands without or without squamous metaplasia are found dispersed in a dense fibromatous stroma.  (b,c) The endometrioid glands are back to back or distended with extensive squamous metaplasia.  (d) The appearance of the epithelial elements is like hyperplastic endometrium.

Case 14. Serotransitional cell carcinoma.  (a) A papillary pattern is evident overlying solid areas of epithelial growth.  (b,c) At higher magnification, the solid areas display a clear and spindle cell population reminiscent of squamous epithelium.  Atypia is focally evident.  (d) Scattered through the solid areas, are spaces containing small amounts of secretory material; these areas resemble serous tumor.

Case 15. Krukenberg Tumor (Metastatic signet-ring cell carcinoma).  (a) At low power, there is simply some irregularity in the distribution of the spindle cells; areas of cellularity alternate with edematous areas.  (b) The cellular areas show aggregates of signet ring cells.  (c) Even the edematous areas contained numerous signet ring cells; immunostain for cytokeratin unmasks the abundance of the carcinoma cells permeating the ovarian stroma.

Case 16. Clear cell carcinoma.  (a,b,c). The tumor is characterized by a combination of tubulocystic and papillary growth pattern; solid areas constitute a minor component.  (d) The tumor cells have vacuolated, granular or eosinophilic cytoplasm with irregular nuclei.

Case 17. Lipid (steroid) cell tumor.  (a) A solid proliferation of cells with abundant vacuolated cytoplasm.  (b) The nuclei are uniform and lack atypia or mitotic activity; a rich vascular network is characteristic of this tumor.  (c) Some areas are composed of cells with a more granular eosinophilic cytoplasm.

Case 18. Yolk sac tumor.  (a) The tumor displays a honeycomb appearance with cysts lined by a single layer of flat cells or naked nuclei (the reticular pattern) and a loose myxoid loose reticulum.  (b,c) Some of the cystic spaces in a denser fibrous stroma show constrictions reminiscent of the polyvesicular vitelline pattern.

Case 19. Polyembryoma with prominent hepatoid differentiation.  (a) A loose myxoid reticulum supports small glands and embryoid bodies.  (b) At higher magnification, the embryoid bodies are composed of ectodermal and endodermal vesicles and are surrounded by a loose myxoid reticulum.  (c) Clusters of hepatoid cells are dispersed in the loose reticular stroma.  (d) Some cells even have bile pigment.

Case 20. Combined germ cell- sex cord stromal tumor.  (a) Rounded nests of cells are surrounded by thick basement membranes.  Rounded hyaline bodies composed of basement membrane are found within the nests.  (b) At higher magnification, the islands are composed predominantly of cells with ovoid nuclei.  Scattered among these cells are large cells with round nuclei and prominent nucleoli - germ cells.  (c) Immunostain for inhibin shows a positive reaction in the sex cord stromal cells while the germ cells fail to react with inhibin.