Hormone-producing tumors of the ovary

G Olt and R Mortel
Milton S Hershey Medical Center, Penn State University School of Medicine, Hershey, Pennsylvania 17033, USA
(Requests for offprints should be addressed to G Olt)

Introduction
Hormone-producing tumors of the ovary are extremely uncommon and are thus unfamiliar to most practicing gynecologists. Because of this it would seem ideal to organize this review by presenting signs and symptoms. Unfortunately, patients may have similar tumors but very different clinical manifestations depending on their age. Furthermore, many tumors may produce either estrogens or androgens. Therefore, for clarity, we have chosen to organize the review by histopathology, placing all tumors into either sex cord-stromal or germ cell classification. A summary organized by tumor type is presented in Table 1 and by reproductive status and presentation in Table 2.

Diagnosis of hormone-secreting tumors is usually straightforward as most ovarian masses can be palpated during pelvic examination. Additionally, vaginal ultrasound can be very helpful in identifying very small, non-palpable ovarian masses. For extra-ovarian masses, computed tomography or magnetic resonance imaging can detect very small lesions. Rarely, ovarian tumors such as hilus cell tumors may be undetectable. In these very rare instances, ovarian vein catheterization with measurement of selective venous samples has been reported to be of benefit. However, this procedure requires great expertise to be successful and should rarely be necessary.

Sex cord-stromal tumors
This category of ovarian neoplasms includes tumors containing granulosa cells, theca cells, Sertoli cells, Leydig cells, or ovarian stromal cells singly or in combination. They account for, in total, 8% of ovarian tumors. However, those that produce hormonal manifestations represent less than one-half of this group. The most common hormonally active sex cord-stromal tumors in decreasing order of frequency are granulosa cell tumors, thecomas, Sertoli cell tumors, and Sertoli-Leydig cell tumors.

Granulosa cell tumors
Granulosa cell tumors of the ovary are uncommon, comprising 1-2% of ovarian neoplasms. Although most patients are diagnosed at an early stage, either early or late recurrences can occur and, therefore, granulosa cell tumors are considered to represent a low grade malignancy. Granulosa cell tumors found in young women tend to recur within several years following diagnosis while recurrences in older patients may be found 10-20 years later. Because of their notable differences in behavior and histology, these tumors are frequently subdivided into adult and juvenile categories. The adult form is much more common, representing 95% of all granulosa cell tumors. Although juvenile granulosa cell tumors are usually found in young women and children they may also rarely occur in older patients.

Adult granulosa cell tumors
Adult granulosa cell tumors are the most common estrogen-secreting ovarian neoplasms. They occur most frequently in peri- or postmenopausal females with a mean age at presentation of 50 years and a usual range of 40-70 years of age (Pankratz et al. 1978). Thus, approximately one-half of patients are premenopausal and one-half are postmenopausal. As
<table>
<thead>
<tr>
<th>Tumor</th>
<th>Usual age range (years)</th>
<th>Hormone produced</th>
<th>Malignant potential</th>
<th>Presenting signs/symptoms</th>
<th>Bilaterality</th>
<th>Incidence</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult granulosa cell tumor</td>
<td>40-70</td>
<td>Estrogens, rarely androgens</td>
<td>Low</td>
<td>Vaginal bleeding, mass, rarely virilization</td>
<td>5%</td>
<td>1-2% of ovarian neoplasms</td>
<td>Recurrences may occur 10-20 years following primary. Associated with endometrial hyperplasia and cancer</td>
</tr>
<tr>
<td>Juvenile granulosa cell tumor</td>
<td>Newborn-30</td>
<td>Estrogens, rarely androgens</td>
<td>Low</td>
<td>Pseudoprecocity pelvic mass</td>
<td>2%</td>
<td>5% of all granulosa cell tumors</td>
<td>Associated with Ollier’s and Maffucci’s syndromes</td>
</tr>
<tr>
<td>Thecoma</td>
<td>50-70</td>
<td>Estrogens</td>
<td>None</td>
<td>Postmenopausal bleeding</td>
<td>Rare</td>
<td>0.5-1% of ovarian neoplasms</td>
<td>—</td>
</tr>
<tr>
<td>Sertoli-Leydig cell tumor</td>
<td>Usually &lt;30 (2-75)</td>
<td>Androgens, rarely estrogens</td>
<td>Low</td>
<td>Virilization (30%)</td>
<td>1-2%</td>
<td>0.5% of ovarian neoplasms</td>
<td>Most common virilizing tumor</td>
</tr>
<tr>
<td>Sertoli cell tumor</td>
<td>Reproductive (7-79)</td>
<td>Androgens, estrogens</td>
<td>Very low</td>
<td>Menometrorrhagia, amenorrhea, precocious puberty, virilization</td>
<td>None</td>
<td>0.1% of ovarian neoplasms</td>
<td>Associated with Peutz-Jegher’s syndrome</td>
</tr>
<tr>
<td>Hilus cell tumor</td>
<td>Peak 6th decade</td>
<td>Androgens</td>
<td>Extremely rare</td>
<td>Virilization</td>
<td>Rare</td>
<td>Very rare</td>
<td>—</td>
</tr>
<tr>
<td>Struma ovarii</td>
<td>Peak 5th and 6th decades (6-74)</td>
<td>Thyroxine</td>
<td>Very low</td>
<td>Pelvic mass, rarely hyperthryoidism</td>
<td>Rare</td>
<td>&lt;3% of mature cystic teratomas</td>
<td>Frequent co-existing thyromegaly</td>
</tr>
<tr>
<td>Carcinoid</td>
<td>30-80</td>
<td>Serotonin</td>
<td>Very rare</td>
<td>Carcinoid syndrome (30%)</td>
<td>Rare</td>
<td>Very rare</td>
<td>Insular (midgut) carcinoids associated with carcinoid syndrome</td>
</tr>
<tr>
<td>Chorocarcinoma</td>
<td>50%</td>
<td>Chorionic gonadotropin</td>
<td>All</td>
<td>Precocious puberty</td>
<td>Rare</td>
<td>Very rare</td>
<td>—</td>
</tr>
<tr>
<td>Gonadoblastoma</td>
<td>&lt;30</td>
<td>Androgens</td>
<td>None, unless associated with dysgerminoma</td>
<td>Amenorrhea, virilization</td>
<td>40%</td>
<td>Rare</td>
<td>Associated with gonadal dysgenesis</td>
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Table 2  Hormone-producing ovarian tumors by reproductive age and symptomatology.

<table>
<thead>
<tr>
<th>Reproductive stage</th>
<th>Symptom</th>
<th>Tumor type</th>
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<tbody>
<tr>
<td>Prepubertal</td>
<td>Virilizing</td>
<td>Sertoli-Leydig cell tumor</td>
</tr>
<tr>
<td></td>
<td>Feminizing</td>
<td>Juvenile granulosa cell tumor</td>
</tr>
<tr>
<td>Reproductive</td>
<td>Dysfunctional uterine bleeding</td>
<td>Granulosa cell tumor</td>
</tr>
<tr>
<td></td>
<td>Virilizing</td>
<td>Sertoli-Leydig cell tumor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hilus cell tumor</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>Postmenopausal bleeding</td>
<td>Granulosa cell tumor</td>
</tr>
<tr>
<td></td>
<td>Virilizing</td>
<td>Thecoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hilus cell tumor</td>
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would be expected, the symptoms of estrogen overproduction differ depending on the patients' menstrual status.

Postmenopausal women with granulosa cell tumors most frequently complain of vaginal bleeding. Conversely, premenopausal patients most commonly describe menorrhagia, irregular menstruation, or amenorrhea (Fox & Agrawal 1975, Evans et al. 1980). Endometrial findings in patients with granulosa cell tumors are variable, and may demonstrate proliferation, atrophy, hyperplasia, or adenocarcinoma. The reported incidence of co-existing endometrial adenocarcinoma ranges from 5 to 25% (Stenwig et al. 1979, Evans et al. 1980). However, when endometrium from all patients included in a series was evaluated utilizing strict criteria for the diagnosis of endometrial adenocarcinoma, the incidence was less than 5% (Stenwig et al. 1979). It appears that carcinoma is about twice as common in postmenopausal patients (Gusberg & Kardon 1967). Additionally, as many as 50% of patients with granulosa cell tumors may have associated endometrial hyperplasia.

Non-specific findings are similar to those of patients with other ovarian malignancies. Abdominal bloating, distension, or pain are frequently noted. Occasionally, patients may complain of breast tenderness. Interestingly, patients who present with fatigue or weight loss have a very high disease-associated mortality within the first year of diagnosis (Pankratz et al. 1978). Pelvic examination will reveal a palpable mass in 80-85% of patients. Ascites is present in roughly 10% and rarely a pleural effusion is found. On occasion, cystic granulosa cell tumors may rupture resulting in an acute abdomen secondary to hemoperitoneum or the enlarged adnexa may tors (Fox & Agrawal 1975, Bjorkholm & Pettersson 1980, Young & Scully 1987a).

Rarely, androgen-secreting granulosa cell tumors have been reported, accounting for less than 3% of adult granulosa cell tumors (Nakashima et al. 1984). The majority of these patients exhibit masculinization, most frequently clitoromegaly and hirsutism and less frequently deepening of the voice, male escutcheon, and male pattern balding. Most patients with androgenic granulosa cell tumors have elevated serum testosterone levels.

At exploration, the appearance of granulosa cell tumors is quite variable. The average size is about 12 cm in diameter but ranges from tumors which nearly fill the entire abdomen to those only microscopically detectable (Dockerty & MacCarty 1939, Fox & Agrawal 1975). Only rarely are both ovaries involved with greater than 95% noted to be unilateral and equally distributed between both ovaries. Tumors may be predominately cystic, solid, or mixed. Interestingly, androgenic granulosa cell tumors are more frequently associated with predominately cystic tumors (Nakashima et al. 1984). When cut, they range from yellow to gray depending on intracellular lipid content and may be soft or firm in consistency depending on the amount of fibrothecomatosus stroma present (Young & Scully 1987a). The most frequent finding is a mixed solid and cystic tumor with the cystic cavities filled with hemorrhage.

Microscopic evaluation of well-differentiated adult granulosa cell tumors may show numerous patterns, including microfollicular, macrofollicular, insular, trabecular, solid-tubular, and hollow-tubular (Young & Scully 1987a). Call-Exner bodies, which are small cavities containing eosinophilic fluid and
resembling developing ovarian follicles, are frequently present. Watered-silk, gyriiform, or diffuse patterns are more often seen in less well-differentiated tumors. Nuclei are usually oval, pale, and grooved (coffee bean appearance) which aids in differentiating granulosa cell tumors from undifferentiated carcinomas, adenocarcinomas, and carcinoids. It is important to identify these tumors correctly as their prognosis and treatment differ greatly.

Surgical treatment of patients with adult granulosa cell tumors is similar to that undertaken for other ovarian cancers. The FIGO staging classification for epithelial ovarian cancers is currently applied to these tumors as well and is helpful since stage is one of the most important prognostic factors. However, although surgery is the primary therapy for granulosa cell tumors, the extent of surgery required remains controversial. Because most patients are stage I and bilateral ovarian involvement is very rare, it seems reasonable to preserve uninvolved organs in women with unilateral ovarian disease and who desire to maintain reproductive potential. Several large series have retrospectively compared survival of patients undergoing bilateral versus unilateral adnexectomy with conflicting results (Anderson et al. 1971, Pankratz et al. 1978, Evans et al. 1980, Ohel et al. 1983). Unfortunately, accurate staging was not accomplished in all patients and thus the role of ovarian preservation remains undefined. Because of the rarity of these tumors and their proclivity for late recurrences, a prospective randomized trial comparing unilateral versus bilateral adnexectomy is unlikely. If a hysterectomy is not performed, a dilation and curettage should be undertaken to rule out co-existing endometrial pathology. Patients with advanced disease or those who are peri- or postmenopausal should undergo bilateral salpingo-oophorectomy.

Radiotherapy has been utilized as adjunctive therapy and to treat recurrences with mixed results. In a series of 61 patients, 48 patients received postoperative irradiation with a slight but not statistically significant improvement in survival (Pankratz et al. 1978). These patients varied in their surgical treatment as well as extent of radiotherapy and thus the effect of adjuvant irradiation is unclear. In another study, patients who received postoperative radiotherapy had a higher recurrence rate (Evans et al. 1980). Therefore there are presently few data to support the use of adjuvant postoperative radiotherapy. Radiotherapy for recurrent disease has been helpful but reports of long-term responses are unusual. Patients who are considered for radiation therapy should be selected for sites of recurrence as well as their ability to undergo other treatment modalities, such as surgery or chemotherapy. The major role for the use of radiotherapy of recurrent disease may be in the palliation of symptoms.

Chemotherapy is usually reserved for patients with advanced or recurrent disease. Complete responses have been reported with single agent Cytoxan or melphalan or with combinations such as cisplatin, Adriamycin, and Cytoxan or vincristine, Adriamycin, and Cytoxan. However, response is usually of short duration. The Gynecologic Oncology Group studied actinomyycin D, vincristine, and Cytoxan and found a 20% partial response rate (Slayton et al. 1985). More recently greater success has been achieved with vincristine, bleomycin, and cisplatin or etoposide, bleomycin, and cisplatin. There is no evidence to support the use of adjuvant chemotherapy to prevent recurrence.

Several tumor markers, urinary and serum estrogen, serum inhibin, and follicle regulatory protein, have been evaluated in patients with granulosa cell tumors. Estradiol levels are elevated in some patients and levels usually fluctuate in relation to disease. However, the lack of sensitivity and wide range of normal values limit its clinical use. Furthermore, the production of estradiol by granulosa cells requires the production of testosterone by adjacent theca cells which may be sparse in some granulosa cell tumors and are always absent in metastases. More recently, inhibin, a peptide hormone which is produced by granulosa cells, has been studied in the sera of patients with primary and recurrent disease (Lappohn et al. 1989, Jobling et al. 1993). Inhibin levels appear to be elevated in most patients with granulosa cell tumors and levels correlate well with disease status. Furthermore, elevations of serum levels have been reported 2 years prior to clinical detection of recurrence. In a similar fashion, follicle regulatory protein may be helpful as well, although few data are presently available (Rodgers et al. 1989).
Juvenile granulosa cell tumors

Juvenile granulosa cell tumors are a histological subtype which are most frequently found in young women and children. Although they are occasionally diagnosed in postmenopausal patients, 97% occur in the first three decades (Young et al. 1984). Age at the time of diagnosis ranges from newborn to the seventh decade.

Because of the marked developmental differences in females of this age range, presenting symptoms are dependent on the age and menstrual status of the individual. Roughly one-third of all juvenile granulosa cell tumors occur prior to the age of 8 years and 80% of these patients manifest symptoms of sexual pseudoprecocity including uterine bleeding, vaginal discharge, or the development of secondary sex characteristics (Young et al. 1984). Following puberty, abdomino-pelvic masses, pain or swelling are the usual presenting symptoms. Menstrual abnormalities such as menometrorrhagia or amenorrhea may occur as well. Juvenile granulosa cell tumors have, on occasion, been associated with Ollier's disease (enchondromatosis) or Maffucci's syndrome (enchondromatosis and skin hemangiomatosis) (Tamimi & Bolen 1984, Young et al. 1984). Androgenic manifestations, primarily clitoromegaly, may be present; however, this is a rare finding present in less than 5% of patients.

At exploration, juvenile granulosa cell tumors may be cystic, solid, or mixed. Tumors are rarely bilateral and are usually confined to the ovary but may be adherent to the omentum, bowel or pelvic structures. The surface is usually smooth and size ranges from 5 to 30 cm in diameter. Ascites is rare, but when present may be bloody. When cut, solid portions of the tumor are tan or gray. Cysts are filled with serous or sero-sanguinous fluid and areas of hemorrhage or necrosis may be present.

Microscopically, juvenile granulosa cell tumors exhibit solid areas of granulosa and theca cells with intermixed mucin containing follicles of various sizes. However, Call-Exner bodies (uniform microfollicles) are rare (Young et al. 1984). The theca cells which are present often appear luteinized. Granulosa cells have abundant eosinophilic cytoplasm and nuclear atypicality which is usually mild to moderate but may be marked. Mitotic rate ranges from less than 1-30 mitosis/10 high power fields. Juvenile granulosa cells are differentiated from their adult counterparts by the abundant luteinized cytoplasm and round nuclei which lack grooves.

Treatment of juvenile granulosa cell tumors is similar to that of the adult form. As these tumors often occur in young women, care should be given to preservation of contralateral adnexa and the uterus. Chemotherapy for advanced disease is usually bleomycin, etoposide, and cisplatin. A majority of patients retain their reproductive ability after such therapy.

Thecoma

Thecomas are estrogen-producing tumors which contain lipid-laden stromal cells resembling theca cells. They occur about one-third as commonly as granulosa cell tumors and typically are found in an older population (Bjorkholm & Pettersson 1980). Most tumors are diagnosed between the ages of 50 and 70 and uncommonly before age 30. Thecomas occur rarely, if ever, before puberty. Because the majority of patients are postmenopausal, the most common presenting complaint is postmenopausal bleeding which was reported in approximately 75% of this group (Bjorkholm & Pettersson 1980). Premenopausal patients noted irregular bleeding or amenorrhea in 50% of cases. Other frequent complaints for both groups included abdominal distension or pain.

At exploration, thecomas are usually 3-10 cm in diameter and are infrequently bilateral. The overwhelming majority of tumors are FIGO stage Ia. When sectioned, tumors appear yellow and are usually solid with cysts and hemorrhage is rarely noted.

Microscopic evaluation reveals oval cells with bland oval- or spindle-shaped nuclei and cytoplasm containing moderate to abundant amounts of lipid. Mitoses are infrequent but most tumors exhibit notable hyaline plaques. Reticulum staining demonstrates extensive reticulum fibrils surrounding individual cells in contrast to granulosa cell tumors.

Patients with thecomas are treated with abdominal hysterectomy and bilateral salpingo-oophorectomy. Because these tumors are rarely, if ever, malignant, patients who desire to maintain reproductive potential may undergo a unilateral adnexectomy.
Sertoli-Leydig cell tumors

Sertoli-Leydig cell tumors are ovarian stromal tumors which recapitulate testicular differentiation and were originally designated as arrhenoblastomas or androblastomas indicating androgen production. Because the majority of tumors are non-functioning, the descriptive designation Sertoli-Leydig cell tumor is preferable. They contain Leydig cells, Sertoli cells, fibroblasts, and occasionally heterologous elements in varying proportions. Tumors are categorized into four groups based on WHO guidelines: well differentiated, intermediate differentiation, poorly differentiated, and with heterologous elements (Serov et al. 1973). A fifth category, retiform, has been proposed by Young & Scully (1983) as an aid in diagnosis.

While Sertoli-Leydig cell tumors may be found in women of all ages, they occur most frequently in young women. In a series of 207 patients, with ages ranging from 2 to 75 years, three-quarters of the cases were found before age 30 (Young & Scully 1985). Well-differentiated tumors occur, on average, 10-15 years later than less well-differentiated tumors.

The reported frequency of virilization associated with Sertoli-Leydig cell tumors is quite variable and dependent on each author’s definition. Virilization, as defined by clitoromegaly, deepening of voice or hirsutism, occurs in approximately one-third of patients; however, the number of patients who present with complaints of masculinization is somewhat less (Roth et al. 1981, Young & Scully 1985). Other common presenting complaints include amenorrhea, pelvic mass, pelvic pain, or postmenopausal bleeding. Rarely, Sertoli-Leydig cell tumors produce estrogenic manifestations, primarily menometrorrhagia.

The gross appearance of Sertoli-Leydig cell tumors is variable and not distinct. Well-differentiated tumors usually have smooth external surfaces while poorly differentiated tumors are more likely to be adherent or have ruptured preoperatively. The majority of tumors are solid and cystic but may be completely solid or cystic. Tumors containing heterologous or retiform components are more likely to be cystic. Nearly all tumors are unilateral (1-2% bilateral). Most range from 5 to 15 cm in diameter; however, their size tends to increase with decreasing differentiation (Young & Scully 1985). It is worthwhile to note that size alone is not an independent prognostic factor.

Microscopically, well-differentiated Sertoli-Leydig cell tumors exhibit tubular patterns with associated stromal tissue appearing as bands of mature fibroblasts. Nuclear atypia is minimal or absent and mitotic figures are rare. Crystalloids of Reinke are present in 20% of tumors (Young & Scully 1984). In tumors of intermediate and poorer differentiation, Sertoli and Leydig cells may exhibit various degrees of immaturity. Additionally, the stroma appears immature and may resemble fibrosarcoma in poorly differentiated tumors. Heterologous tumors may contain foci of intestinal epithelium, carcinoid, cartilage, or rhabdomyosarcoma. Young & Scully (1983) have described a series of Sertoli-Leydig cell tumors which contain elongated branching tubules which resemble the rete testis. This retiform pattern, which is found in 15% of less well-differentiated tumors, can be frequently misinterpreted as endodermal sinus tumor or serious adenocarcinoma.

Surgical therapy is usually hysterectomy and bilateral oophorectomy. However, in reproductive age women, unilateral oophorectomy may be considered if the disease is limited to one ovary. Sertoli-Leydig cell tumors are of low malignant potential with 5-year survival ranging between 70 and 90%. Nearly all patients are stage I (97.5%) and patients with advanced or recurrent disease usually have poorly differentiated tumors (Young & Scully 1985). For patients with advanced or recurrent disease, vincristine, Adriamycin, and cyclophosphamide combination chemotherapy has provided some response and is frequently recommended. Radiation therapy appears to be of benefit, as well, in selected cases.

Sertoli cell tumors

Sertoli cell tumors are neoplasms of gonadal stromal origin made up of Sertoli cells in a tubular arrangement within a fibrous stroma and lacking a Leydig cell component. These extremely rare neoplasms comprise less than 5% of all Sertoli stromal tumors. All patients with Sertoli cell tumors reported to date have had unilateral disease limited to the ovary. Sertoli cell tumors are of low malignant potential with recurrence occurring very rarely.

The age range of patients with Sertoli cell tumors is from 7 to 79 years with a median age of 33 (Tavassoli & Norris 1980). The majority of patients...
are of reproductive age; however, roughly 10% of patients are either prepuberal or postmenopausal.

Prepuberal patients present with symptoms of precocious puberty including vaginal bleeding, breast development, and pubic hair growth. Several cases of precocious puberty secondary to Sertoli cell tumors have been found in association with Peutz-Jeghers syndrome. In one series of 28 patients, 36% of adults presented with menometorrhagia and 10% showed evidence of virilization including hirsutism, amenorrhea, breast atrophy, clitoromegaly, and deepening of the voice (Tavassoli & Norris 1980). Overall, 17 of 28 patients exhibited unusual hormonal manifestations.

Sertoli cell tumors are solid, smooth-surfaced neoplasms which are rarely adherent to other pelvic structures. Their size varies considerably but is typically 7-10 cm in diameter. When cut, they appear fleshy and are yellow or tan in color.

Microscopic examination usually reveals cuboidal, columnar, or round cells arranged in a tubular pattern. Nuclei are spherical or oval with distinct nuclear grooves and rarely demonstrate atypia. The appearance of the cytoplasm varies with the amount of lipid present. Some cells contain abundant lipid and are designated as lipid-rich Sertoli cell tumors.

Hysterectomy and bilateral adnexectomy is appropriate surgical therapy for peri- and postmenopausal patients with Sertoli cell tumors. Because of the unilateral and low malignant potential of these neoplasms, unilateral adnexectomy may be performed in patients who desire to maintain fertility. Limited experience in the treatment of recurrent disease limits recommendation of chemo or radiation therapy.

**Steroid cell tumors**

Steroid cell tumors are ovarian neoplasms composed entirely of cells resembling lutein, Leydig, or adrenal cortical cells which normally secrete steroid hormones (Taylor & Norris 1967). Previously termed lipid cell tumor and lipoid cell tumor, the preferred designation is steroid cell tumor (Scully 1979).

**Hilus cell tumor**

Hilus cell tumors arise from Leydig cells located in the hilus of the ovary and are morphologically identical to testicular Leydig cells. Ovarian hilar Leydig cells are found adjacent to non-myelinated nerve fibers as well as lymphatic and vascular spaces. Hirsutism and virilization are the most common manifestations associated with hilus cell tumors and occur in three-quarters of patients. Occasionally, estrogenic effects are noted and one case has been described in association with endometrial carcinoma (Huang & Holaday 1970).

Most patients with hilus cell tumors present with symptoms secondary to androgen production. Hirsutism, deepening of the voice, and male pattern balding are noted in 50-75% of patients (Dunnahoo et al. 1966). Amenorrhea occurs most frequently but patients may also describe postmenopausal bleeding or menorrhagia suggestive of estrogenic production. Infrequently these tumors are large enough to be palpated during pelvic examination. Ages reported for hilus cell tumors range from 4 to 86 with an average age of 58 years.

At exploration, tumors are small, usually 1-5 cm in diameter but may be as large as 15 cm. Hilus cell tumors are reddish-brown to yellow in color, are located in the hilum of the ovary and are rarely bilateral.

Microscopic examination reveals masses of steroid cells with abundant eosinophilic cytoplasm with prominent lipochrome pigment (Young & Scully 1987a). Crystals of Reinke are usually present and confirm the diagnosis.

Because only a single case of malignant hilus cell tumor has been reported, hysterectomy and bilateral adnexectomy is adequate therapy. For patients who desire to maintain reproductive potential, unilateral adnexectomy is appropriate.

**Adrenal cortical-type steroid cell tumors**

These extremely rare tumors are thought to arise from adrenal cortical nests within the ovary. Three cases of malignant ovarian steroid cell tumors have been reported (Marieb et al. 1983, Young & Scully 1987b). All patients had symptoms of Cushing's disease when diagnosed as well as elevated cortisol levels. At exploration all had stage III disease which was resistant to cytotoxic chemotherapy and all of them died of disease within 2 years.
Germ cell tumors

Dysgerminoma

Only very rarely are dysgerminomas associated with endocrine manifestations, primarily production of chorionic gonadotropin. The great majority of these tumors have choriocarcinomatous elements and very rare examples of pure dysgerminomas containing syncytiotrophoblastic giant cells are noted. It seems likely that the extremely rare pure dysgerminomas which produce chorionic gonadotropin may represent tumors which contain unidentified choriocarcinomatous elements or syncytiotrophoblasts. Therefore, they are not included in this discussion.

Struma ovarii

Struma ovarii are considered to represent a form of teratoma in which there is development of only thyroid tissue. Although thyroid tissue is occasionally present in mature cystic teratomas, the diagnosis of struma ovarii is made if thyroid tissue is predominantly present, if thyroid tissue can be recognized macroscopically, or if the patient exhibits symptoms of hyperthyroidism which resolve following surgery. Struma ovarii are rare and represent only 2.7% of all mature teratomas (Gusberg & Danforth 1944).

The typical age of patients with struma ovarii is similar to that of mature cystic teratomas and ranges between 6 and 74 years (Nieminen et al. 1963). Roughly one-half of patients are less than 50 years of age. Most patients present with an asymptomatic mass or occasionally with pain secondary to the mass. Only rare patients exhibit signs of thyrotoxicosis, however mild symptoms may be easily overlooked. Thyrotoxicosis is estimated to occur in 5-15% of cases of struma ovarii (Emge 1940, Dalgaard & Wetteland 1956). Interestingly, struma ovarii are occasionally associated with coexisting enlargement and hyperactivity of the thyroid gland, thus suggesting similar stimulatory control mechanisms of both sites. In rare cases thyroid gland enlargement is noted following removal of the struma ovarii.

At exploration, struma ovarii are similar in appearance to mature cystic teratoma. The surface is usually smooth and without adhesions. Most tumors are less than 10 cm in diameter but, on occasion, may be considerably larger, particularly if associated with other teratomatous elements. Most struma ovarii are unilateral but the contralateral ovary may contain a cystic teratoma with thyroid elements. When cut, the tumor is frequently composed of amber-colored thyroid tissue and cystic areas with necrosis and hemorrhage occasionally present.

Microscopically, struma ovarii usually have the appearance of mature thyroid tissue. Acini, which may be quite variable in size, contain periodic-acid-Schiff’s staining colloid lined by a single layer of columnar epithelium (Talerman 1987). Occasionally, the appearance may resemble that of hyperactive thyroid gland or nodular adenomatous goiter. Rarely, struma ovarii are malignant and exhibit a follicular pattern or papillary carcinoma. Malignant struma ovarii are very rare and may be difficult to diagnose, particularly if well differentiated, unless there is metastatic malignant disease present. Peritoneal spread of mature thyroid tissue, termed benign strumosis, may occur and does not represent malignancy.

The usual therapy for patients with struma ovarii is hysterectomy and bilateral adnexectomy. In patients for whom ovarian conservation is appropriate, unilateral adnexectomy is reasonable. Because of their rarity, little information is available on the therapy of malignant struma ovarii. Postoperatively, whole body $^{131}$I (5-10 mCi) scintillation scanning may be helpful in identifying metastases. If metastasis is present, therapy with $^{31}$I (100 mCi) may be curative.

Ovarian carcinoid

Primary carcinoids of the ovary are classified as insular (arising from the midgut), trabecular (arising from the foregut or hindgut) or mucinous. Of these, only the insular form is associated with serotonin production and carcinoid syndrome and thus will be discussed. In a similar situation, strumal carcinoids, composed of thyroid tissue and carcinoid, have not been associated with specific clinical presentations and are not known to produce serotonin.

Insular carcinoid occurs rarely with approximately 70 cases reported, although more cases certainly exist. Carcinoids may be found as a component of mature cystic teratomas but 40% are pure insular carcinoids (Talerman 1984). Most tumors occur in peri- or postmenopausal patients but reported ages range from 31 to 79 years (Scully 1979).
Approximately one-third of patients with insular carcinoid tumors exhibit signs of carcinoid syndrome prior to surgery (Robboy et al. 1975). Unlike ileal carcinoids, ovarian carcinoid tumors may produce carcinoid syndrome without metastases because their secreted serotonin does not directly enter the portal system and is therefore not metabolized as rapidly by the liver. Symptoms of carcinoid syndrome, such as flushing, telangectasias, diarrhea, and bronchial constriction resolve shortly after tumor excision. Patients without carcinoid syndrome usually have complaints related to a pelvic mass.

At exploration, the tumor may range in size from microscopic to 28 cm in diameter but most are 5-10 cm (Robboy et al. 1975). Primary ovarian carcinoid tumors are nearly always unilateral and the presence of bilateral ovarian involvement indicates likely metastases from the small bowel. However, the ipsilateral ovary may contain a second cystic teratoma, mucinous cystadenoma or mucinous cystadenocarcinoma (Robboy et al. 1975). The tumor surface is usually smooth and without adhesions. Tumors associated with carcinoid syndrome are frequently predominantly solid with cut surfaces appearing tan or yellow. Those not associated with carcinoid syndrome usually have hair and sebum-containing cysts with a firm nodule in the cyst wall (Robboy et al. 1975). Larger carcinoid tumors are more likely to produce carcinoid syndrome.

Microscopically, insular carcinoids contain nests and small acini composed of epithelial cells with abundant cytoplasm with round centrally located bland nuclei (Talerman 1984). Mitotic activity is low. The cytoplasm contains red or brown granules and electron microscopy reveals neurosecretory granules. Immunohistochemistry demonstrates the presence of serotonin.

Treatment is usually hysterectomy and bilateral adnexectomy. If ovarian conservation is appropriate, the contralateral ovary should be carefully inspected. Malignant primary ovarian carcinoid is very rare and little information is available from which to determine adequate therapy. Metastatic carcinoid has been treated with cytotoxic chemotherapy with little success.

Choriocarcinoma
Non-gestational, ovarian choriocarcinoma is exceedingly rare in its pure form. Although found more frequently in association with other germ cell elements, even mixed tumors are rare, accounting for less than 2% of germ cell tumors in children (Abell et al. 1965). This tumor has been primarily diagnosed in premenarchal children in whom a gestational origin could be excluded, and thus this young age group may be over-represented.

In premenarchal patients, symptoms of isosexual precocious puberty are frequently noted and are due to high levels of chorionic gonadotropin production. These patients may exhibit breast development, vaginal bleeding, or growth of axillary and pubic hair. Postpubertal patients usually present with symptoms related to their mass.

At exploration, the gross appearance of non-gestational choriocarcinoma is non-specific. Most cases are unilateral unless advanced disease has resulted in metastasis to the contralateral ovary. Tumors range greatly in size but are frequently very large.

Microscopically, choriocarcinoma is composed of small polygonal cytotrophoblasts and large multinucleated syncytiotrophoblasts. The syncytiotrophoblasts are responsible for chorionic gonadotropin secretion. Frequently, other germ cell tumor elements are present.

The treatment of non-gestational choriocarcinoma is primarily surgical and is usually hysterectomy, bilateral salpingo-oophorectomy, and complete surgical staging. Some gynecologic oncologists do not perform routine pelvic and para-aortic lymphadenectomy as all patients will require adjuvant chemotherapy. Radiation therapy has rarely been helpful and does not appear to play a role in the management of patients with these tumors. Some responses have been noted, however, in patients treated with vincristine, bleomycin, and cisplatin or bleomycin, etoposide, and cisplatin. However, long-term responses are unusual and most patients with advanced disease are not cured.

Gonadoblastoma
Gonadoblastoma is an unusual steroid-secreting tumor made up of both germ cells and sex cord-stromal derivatives. Sex cord-stromal derivatives consistently present are immature Sertoli or granulosa cells. Frequently, Leydig and lutein cells are noted as well. Germ cells are represented by dysgerminoma in 50% of cases and other germ cell malignancies in an additional 10%. Thus, gonado-
blastoma may be thought of as an in situ tumor within which germ cell tumors may develop (Scully 1970). Gonadoblastoma occurs in association with dysgenetic gonads and although patients are phenotypic females, most are genotypically male.

Nearly all cases of gonadoblastoma occur before 30 years of age and may induce precocious puberty. Patients may or may not be virilized. Non-virilized patients most frequently have amenorrhea which is frequently primary, but may be secondary. Virilized patients almost always have primary amenorrhea. Most gonadoblastomas are discovered incidentally during evaluation of primary amenorrhea. Because these tumors are frequently small, symptoms related to the mass are uncommon.

At exploration, tumors range in size from microscopic to 8 cm in diameter but may be much larger if overgrown by dysgerminoma (Talerman 1987). Gonadoblastomas are solid tumors which may be fleshy or hard depending on the degree of calcification. The cut surface is usually yellow or gray. Tumors are bilateral in at least 40% of cases (Scully 1970). Gonadoblastoma is not malignant and thus involvement of the pelvis and abdomen by metastatic tumor implies the presence of a malignant germ cell component.

Microscopically, gonadoblastoma is composed of nests containing a mixture of germ cells and sex cord derivatives surrounded by connective tissue (Talerman 1987). The sex cord derivatives are immature Sertoli and granulosa cells. The germ cells are larger and round and mitotic activity may be present. The stroma may contain cells which resemble Leydig or lutein cells. Calcification and hyalinization are seen in most cases. In one-half of cases there is overgrowth by dysgerminoma which is similar in appearance to pure dysgerminoma.

Treatment is primarily surgical and consists of removal of the affected gonad as well as the contralateral testis if present. If a normal-appearing uterus is present, consideration should be given for leaving it in place for potential assisted reproduction with donor oocytes. Gonadoblastoma is not malignant and no adjuvant therapy is indicated. Patients with overgrowth of dysgerminoma or other germ cell tumor should be considered for adjuvant therapy utilizing bleomycin, etoposide, and cisplatin chemotherapy.

References


