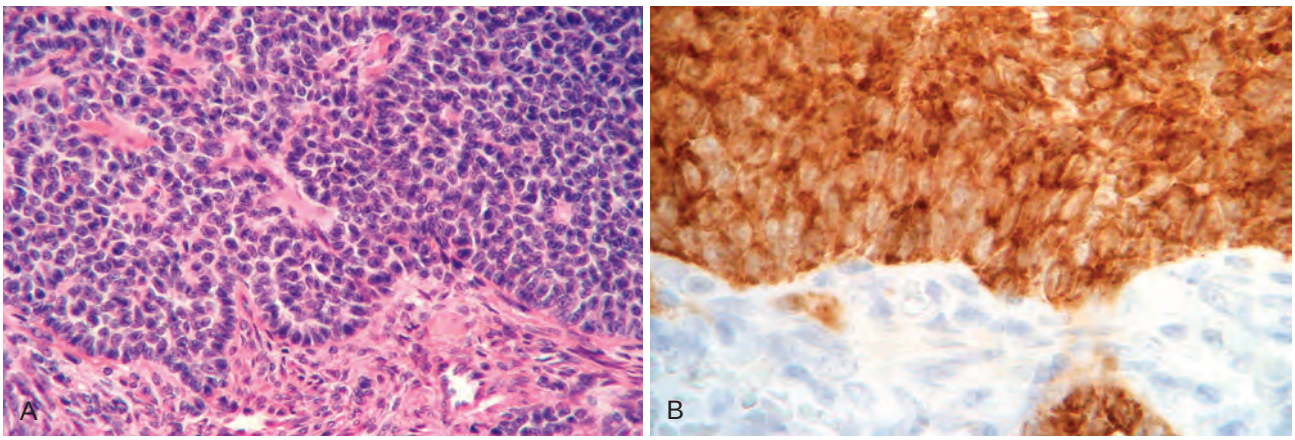

Figure 22-43 Granulosa cell tumor. **A,** The tumor cells are arranged in sheets punctuated by small follicle-like structures (Call-Exner bodies). **B,** Strong immunohistochemical positivity with an antibody to inhibin characterizes these tumors.

- The remainder occur in young women and children; in these age groups, malignant tumor dominate.
- Immature teratomas are distinguished from mature teratomas by the presence of immature elements, most often consisting of primitive neuroepithelium.
- Germ cell tumors show various lines of differentiation toward oogonia (dysgerminoma), extraembryonic yolk sac (yolk sac tumors), placenta (choriocarcinoma), or multiple germ layers (teratoma).

Sex Cord-Stromal Tumors

These ovarian neoplasms are derived from the ovarian stroma, which in turn is derived from the sex cords of the embryonic gonad. The undifferentiated gonadal mesenchyme eventually produces specific types of cells in both male (Sertoli and Leydig) and female (granulosa and theca) gonads, and tumors resembling all of these cell types can be identified in the ovary. Moreover, because some of these cells normally secrete estrogens (granulosa and theca cells) or androgens (Leydig cells), their corresponding tumors may be either feminizing (granulosa/theca cell tumors) or masculinizing (Leydig cell tumors).

Granulosa Cell Tumors

Granulosa cell tumors are composed of cells that resemble granulosa cells of a developing ovarian follicle. They are broadly divided into adult and juvenile granulosa cell tumors largely based on the age of the patient, but also on morphologic findings. Collectively, these neoplasms account for about 5% of all ovarian tumors and adult granulosa cell tumors make up 95% of all granulosa cell tumors. Although they may be discovered at any age, approximately two thirds occur in postmenopausal women.

MORPHOLOGY

Granulosa cell tumors are usually unilateral and vary from microscopic foci to large, solid, and cystic encapsulated masses. Tumors that are hormonally active have a yellow coloration to their cut surfaces, due to intracellular lipids.

The granulosa cell component of these tumors has many histologic patterns. The small, cuboidal to polygonal cells may grow in anastomosing cords, sheets, or strands (Fig. 22-43*A*). In occasional cases, small, distinctive, glandlike structures filled with an acidophilic material recall immature follicles (**Call-Exner bodies**). When these structures are evident, the diagnosis is straightforward. Occasionally, there is a predominant thecoma component that consists of clusters or sheets of cuboidal to polygonal cells (see later). In some tumors, the granulosa or theca cells may appear plumper and have ample cytoplasm characteristic of luteinization (i.e., luteinized granulosa-theca cell tumors).

Granulosa cell tumors are of clinical importance for two reasons: (1) they may elaborate large amounts of estrogen, and (2) they may behave like low-grade malignancies. Functionally active tumors in prepubertal girls (juvenile granulosa cell tumors) may produce precocious sexual development. In adult women they may be associated with proliferative breast disease, endometrial hyperplasia, and endometrial carcinoma, which eventually develops in about 10% to 15% of women with steroid-producing tumors. Occasionally, granulosa cell tumors produce androgens, masculinizing the patient.

All granulosa cell tumors are potentially malignant. It is difficult to predict their biologic behavior from histology. The likelihood of malignant behavior (recurrence, extension) ranges from 5% to 25%. In general, malignant tumors pursue an indolent course in which local recurrences may be amenable to surgical therapy. Recurrences within the pelvis and abdomen may appear 10 to 20 years after removal of the original tumor. The 10-year survival rate is approximately 85%. Tumors composed predominantly of theca cells are almost never malignant.

Elevated tissue and serum levels of *inhibin*, a product of granulosa cells, are associated with granulosa cell tumors. This biomarker may be useful for identifying granulosa and other sex cord-stromal tumors, and for monitoring patients being treated for these neoplasms (Fig. 22-43*B*). Recent studies reported mutations of the *FOXL2* gene in 97% of adult granulosa cell tumors. Although details remain to be worked out, *FOXL2* encodes a transcription