

8. Emmert-Buck MR, Chuaqui R, Zhuang Z et al. *Molecular analysis of synchronous uterine and ovarian endometrioid tumors*. *Int J Gynecol Pathol* 1997; 16: 143-148.
9. Fujita M, Enomoto T, Wads H et al. *Application of clonal analysis. Differential diagnosis for synchronous primary ovarian and endometrial cancers and metastatic cancer*. *Am J Olin Pathol* 1996; 105: 350-359.
10. Catusus LI, Machin P, Lerma E et al. *Microsatellite instability in endometrial carcinomas. Clinicopathologic correlations in a series of 42 cases*. *Hum Pathol* 1998; 29: 1160-1164.

Recent advances in sex cord-stromal tumors

I. Macedo Pinto

Dept. of Pathology Portuguese Institute of Oncology Porto, Portugal.

Sex cord-stromal tumors of the ovary are rare, making up approximately 8% of all ovarian tumors. Granulosa cells, theca cells and their luteinized derivatives, Sertoli cells, Leydig cells and fibroblasts of gonadal stromal origin, in pure or combined forms and in variable degrees of differentiation, may be present.

Fibromas, which are almost never associated with endocrine manifestations, are the most frequent subtype, accounting for half of sex cord-stromal tumors; most of the other subtypes are granulosa cell tumors.

Granulosa cell tumors comprise two different subtypes, with distinct clinical settings and microscopic appearance: adult and juvenile types. Adult-type granulosa cell tumors occur more often in postmenopausal women and are the most common clinically estrogenic ovarian tumor. Granulosa cells grow in a wide variety of patterns, which are very commonly admixed. The better differentiated tumors typically have microfollicular, macrofollicular, insular, trabecular, solid or hollow-tubular patterns. The less well differentiated forms include watered-silk and gyriform diffuse (sarcomatoid) pattern alone or in combination. Whatever the histologic pattern may be, the best morphological markers of adult-type granulosa cell tumors are the presence of small cavities similar to Call-Exner bodies and cells with pale nuclei and prominent grooves.

Juvenile granulosa cell tumors usually occur in the first three decades of life. The microscopic appearance is that of a solid neoplasia with focal follicle formation. In contrast to the adult type, neoplastic cells have abundant cytoplasm and round nuclei, usually without grooves. Nuclear atypia varies from slight to severe and the mitotic rate may be high. Despite these histological features, stage is the only reliable prognostic factor in these tumors.

Sertoli-Leydig cell tumors are another interesting group of gonadal sex cord-stromal tumor. They usually occur in young women, most of them under 30 years of age and about one-third of the patients develop signs of virilization.

Different histological subtypes are described: well differentiated, of intermediate differentiation and poorly differentiated, with heterologous elements and retiform pattern. Well-differentiated tumors have a nodular architecture with fibrous bands intersecting lobules of neoplastic cells, arranged in hollow or solid tubules. Nuclear atypia is usually absent or minimal and mitotic figures are rare.

Tumors of intermediate differentiation are composed of Sertoli and Leydig cells with varying degrees of immaturity, growing in dif-

fuse sheets, nests, solid tubules and thin cords resembling the sex cords of the embryonic testis. Poorly differentiated Sertoli-Leydig cell tumors have been classified as sarcomatoid because, in addition to the presence of specifically diagnostic elements, they resemble sarcomas.

Retiform pattern, present in 15% of these tumors is characterized by a network of irregularly branching tubules and cysts into which papillae or polypoid structures may project.

In approximately 20% of these tumors of intermediate or poor differentiation, the presence of heterologous elements such as glands of intestinal-type epithelium and foci of carcinoid, cartilage, hepatocytes, embryonal rhabdomyosarcoma, retinal, as well as other tissues, is described.

Differential diagnosis

Pathological diagnosis of sex cord-stromal tumors is one of the most difficult problems in ovarian pathology. Extensive sampling of the specimen is mandatory but sometimes it is not enough to provide an accurate diagnosis.

Endometrioid carcinomas (Sertoliform type) and metastatic adenocarcinomas (tubular Krukenberg's tumor) may simulate Sertoli cell tumors, Sertoli-Leydig cell tumors and granulosa cell tumors, which are of the well-differentiated type.

Carcinoid tumors, especially those of trabecular pattern, may be confused with intermediate Sertoli-Leydig cell tumors. The retiform pattern of Sertoli-Leydig cell tumors has to be distinguished from endodermal sinus tumors, serous cystadenoma of borderline malignancy, serous or endometrioid carcinoma and mesodermal mixed tumors.

The diffuse and/or sarcomatoid pattern of granulosa cell tumors may resemble an endometrial stromal sarcoma, an undifferentiated carcinoma or a small cell carcinoma of the hypercalcemic type.

Steroid cell tumors (NOS) may be confused with other neoplasms, particularly luteinized granulosa cell tumors and thecomas, clear cell carcinomas, metastatic renal cell carcinoma and malignant melanoma.

Sex cord-stromal tumors have a rather nonspecific immunohistochemical profile. Their expression of intermediate filaments is quite variable and this variability is misleading when making a differential diagnosis. The absence of epithelial membrane antigen in these tumors has diagnostic value, since most of the histologic look-alikes of granulosa and Sertoli-Leydig cell tumors, such as metastatic and primary carcinomas, are positive to epithelial membrane antigen.

Recent reports have emphasized the importance of the immunodetection of inhibin in sex cord-stromal tumors in providing a reliable differential diagnosis with epithelial neoplasms, melanoma, lymphoma and soft tissue tumors.

Inhibin is a glycoprotein produced by granulosa cells, theca cells and Sertoli cells. Immunostaining by antibodies against alpha-inhibin has been strongly positive in granulosa cell tumors, Sertoli cell tumors, and consistently negative in carcinomas, germ cell tumors, melanomas and lymphomas. Antibodies against the alpha-subunit of human inhibin may also be useful in identifying, late metastases of granulosa cell tumors, especially when the previous diagnosis is unknown.

Furthermore, inhibin appears to be a sensitive serological marker of the presence or progression of these tumors and their metastases. It may be valuable in assessing response to chemotherapy or in predicting recurrent disease. Serum inhibin level evaluation

should be incorporated into large-group trials of therapy for sex cord-stromal tumors.

Prognosis

The behavior of these tumors has not been easy to define because they may have a long clinical course with late recurrences and metastases. Prognosis is closely related to stage and degree of differentiation. In stage I Sertoli-Leydig cell tumors, only those of intermediate differentiation (11%), poor differentiation (59%) and those with heterologous elements (19%) have been clinically malignant. The retiform pattern also seems to be associated with more aggressive behavior. In contrast to granulosa cell tumors, recurrences of Sertoli-Leydig cell tumors usually occur early, in the first year after diagnosis.

Granulosa cell tumors are characterized by indolent growth with a significant capacity to recur many years after an apparent clinical cure.

Several pathological features have been evaluated as prognostic factors. Nuclear atypia, high mitotic rate, high Ki67 PI and the absence of Call-Exner bodies seem to be pathologic predictors of recurrence.

Other studies have investigated biological and molecular parameters by means of immunohistochemistry (c-myc, p21-ras, c-erbB2, p53), but results have been inconsistent.

DNA ploidy, percent S-phase fraction, proliferative index and morphometric studies have been performed in series of granulosa cell tumors. Aneuploidy, S-phase fraction >10%, large nuclear area and nuclear perimeter seem to be adverse prognostic factors. Nevertheless, using these clinical, pathologic or biological parameters, it is difficult to predict early recurrences and impossible to predict late recurrences.

Trisomy of chromosome 12 has frequently been described in various neoplasms, particularly in tumors of the female genitourinary tract. Recently, this chromosomal abnormality has been found in a large proportion of sex cord-stromal tumors, including thecoma-fibromas, granulosa cell tumors and Sertoli-Leydig cell tumors. The prognostic significance of trisomy 12 in these tumors is unknown.

Sex cord-stromal tumors of the ovary may present in a wide variety of morphological pictures, creating serious problems of differential diagnosis with other neoplasia. Recent advances have provided key markers to facilitate the correct diagnosis. The behavior of these tumors remains somewhat unpredictable, especially because of the lack of prognostic factors in early stage disease.

Further studies are needed to go deeper into the pathogenesis of these fascinating tumors.

References

- Bogges JF, Soules MR, Gaff BA et al. *Serum inhibin and disease status in women with ovarian granulosa cell tumors.* Gynecol Oncol 1997; 64: 64-69.
- Coats MJ, Ames PF, Walls J et al. *Inhibin immunohistochemistry applied to ovarian neoplasms: A novel, effective, diagnostic tool.* Hum Pathol 1997; 28: 1247-1254.
- Fleming P, Wellmann A, Maschek H et al. *Monoclonal antibodies against inhibin represent key markers of adult granulosa cell tumors of the ovary even in their metastases. A report of three cases with late metastases, being previously misinterpreted as hemangiopericytoma.* Am J Surg Pathol 1997; 19: 927-933.
- Haba R, Miki H, Kobayashi S et al. *Combined analysis of flow cytometry and morphometry of ovarian granulosa cell tumor.* Cancer 1993; 72: 3258-3262.
- King LA, Okagaki T, Gallup DG et al. *Mitotic count, nuclear atypia, and immunohistochemical determination of Ki67, c-myc, p21-ras, c-erbB2, and p53 expression in granulosa cell tumors of the ovary: Mitotic count and Ki67 are indicators of poor prognosis.* Gynecol Oncol 1996; 61: 227-232.
- Kommoas F, Oliva E, Bhan AK et al. *Inhibin expression in ovarian tumors and tumor-like lesions: An immunohistochemical study* Mod Pathol 1998; 11: 656-664.

- Matias Guiu X, Pans C, Prat J. *Mullerian inhibiting substance, alpha-inhibin, and CD99 expression in sex cord-stromal tumors and endometrioid ovarian carcinomas resembling sex cord-stromal tumors.* Hum Pathol 1998; 29: 840-845.
- Miller BE, Barron BA, Wan JY et al. *Prognostic factors in adult granulosa cell tumor of the ovary.* Cancer 1997; 79: 1951-1955.
- Persona DL, Hartmann LC, Herath JF et al. *Fluorescence in situ hybridization analysis of trisomy 12 in ovarian tumors.* Am J Clin Pathol 1994; 102: 775-779.
- Riopel MA, Perlman EJ, Seidman JD et al. *Inhibin and epithelial membrane antigen immunohistochemistry assist in the diagnosis of sex cord-stromal tumors and provide clues to the histogenesis of hypercalcemic small cell carcinomas.* Int J Gynecol Pathol 1998; 17: 46-53.
- Rishi M, Howard LN, Brattauer GL et al. *Use of monoclonal antibody against human inhibin as a marker for sex cord-stromal tumors of the ovary.* Am J Surg Pathol 1997; 21: 583-589.
- Roush GR, el Naggat AK, Abdul Karim FW. *Granulosa cell tumor of ovary: A clinicopathologic and flow cytometric DNA analysis.* Gynecol Oncol 1995; 56: 430-434.
- Shashi V, Golden WL, von Kap Herr C et al. *Interphase fluorescence in situ hybridization for trisomy 12 on archival ovarian sex cord-stromal tumors.* Gynecol Oncol 1994; 55: 349-354.
- Taruscio D, Carcangiu ML, Ward DC. *Detection of trisomy 12 on ovarian sex cord-stromal tumors by fluorescence in situ hybridization.* Diagn Mol Pathol 1993; 2: 94-98.

Neuroendocrine tumors of the ovary

J. Kupryjanczyk

Dept. of Molecular Biology, The Maria Skłodowska-Curie Memorial Cancer Center and Dept. of Pathology, Brodnowski Hospital, Warsaw, Poland.

Neuroendocrine tumors are a heterogeneous group of separate clinicopathological entities, which have a common characteristic, *i.e.*, expression of endocrine differentiation potential. In order to diagnose endocrine differentiation within a tumor, we should first see the histological characteristics suggesting such differentiation and apply special studies only to confirm the suspicion. In the ovary, the term "neuroendocrine" relates mainly to the widely known carcinoids but it may also be applied to rare neuroendocrine carcinomas of non-small-cell type and small-cell carcinomas of pulmonary type, which have been described in recent years.

Neuroendocrine carcinomas of non small-cell type

Neuroendocrine carcinomas of non small-cell type are characterized by the presence of islands, sheets and trabeculae with little intervening stroma (organoid growth pattern) as well as by cellular homogeneity. Palisading of cells at the periphery of nests may be seen, particularly in low-grade tumors. Neuroendocrine carcinomas are higher grade than carcinoids. To date, nine such tumors have been reported and all developed in association with glandular müllerian-type component (seven mucinous-type tumors, one endometrioid carcinoma and one carcinosarcoma). Microscopically, the neuroendocrine component grew in the background of a surface-epithelial tumor but both components could be still recognized as separate. The tumor cells were medium-sized to large. Other cytological characteristics, *i.e.*, the amount of cytoplasm, chromatin and