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Simultaneous carcinomas involving the endometrium and ovaries

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The simultaneous occurrence of multiple primary cancers in the upper female genital tract is well known (1-5). In fact, ovarian carcinomas may be associated with endometrial malignancies as well as with involvement of the contralateral ovary or even the cervix (6).

The occasional finding of simultaneous primary tumors in the ovaries and endometrium should not be surprising. The surface epithelium of the ovary has the same embryologic derivation as the Mullerian duct and therefore, in adults, a given carcinogenic stimulus may produce similar epithelial proliferations in both structures. Cancers developing concomitantly in these locations are not infrequently misdiagnosed as metastatic tumors (3). However, the overall survival of these patients suggests multifocal rather than metastatic

disease (3). These tumors should be separated from true metastatic carcinomas from one to another organ of the female genital tract, since each of these two categories carries a different prognosis and clinical implications.

Several clinicopathological features can be helpful for the correct classification of the into these two groups (stage, size, bilaterality and pattern of ovarian involvement, histological types and grades, presence of endometrial hyperplasia or ovarian endometriosis, myometrial, tubal, lymphatic and blood vessel invasion, as well as follow-up of the patients) (2-5). In some cases, however, it may be difficult to distinguish between metastatic and independent malignancies because the tumors may share features of both categories.

Seven years ago, we studied 18 cases of adenocarcinoma, simultaneously involving both the endometrium and the ovary, and tried to assess the importance of clinical, pathological, immunohistochemical and DNA flow cytometric parameters in the differential diagnosis (6). Of the nine cases with independent primary tumors, seven showed different immunohistochemical profiles (CAM 5.2, wide spectrum keratin, vimentin carcinoembryonic antigen, CEA 125, and CA 19.9) in the ovarian and uterine tumors but only four of the nine metastatic tumors had similar staining characteristics in both locations. In contrast, when one of the two simultaneous tumors was metastatic from the other, identical aneuploid DNA indexes were encountered (6). Therefore, in synchronous tumors with different DNA indexes, the possibility of independent primaries has to be considered. Our data indicated that immunohistochemical and DNA flow cytometric analysis may be of some value when distinguishing between metastatic and independent tumors. The differential diagnosis, however, still largely relies upon conventional clinicopathological criteria (6).

Molecular pathology techniques can also be of some help in distinguishing independent primaries from metastatic tumors. Recent studies have shown a different pattern of loss of heterozygosity on chromosome 17 in the ovary and endometrium in several cases of synchronous tumors of both locations (7, 8). Also, X-chromosome inactivation, *K-ras* mutations and mutations or allelic losses of p53 have been applied (9). Moreover, the demonstration of microsatellite instability in endometrial carcinomas and its absence in the ovarian tumors can also be taken as strong evidence of their independent origin. Indeed, we have successfully used such an approach in the evaluation of several cases of synchronous endometrioid tumors of the ovary and endometrium (10).

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Recent advances in sex cord-stromal tumors

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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