

releasing hormone agonist therapy and three-dimensional architecture of the ectopic endometrium. Ovarian and extra ovarian endometriosis can be classified into superficial, hemorrhagic and deeply infiltrating. Adhesions are classified laparoscopically and an evaluation of their age (fibrosis) and nerve proliferation can be requested from the pathologist.

Tissue on either frozen or permanent sections may be altered by artifact and clinical information is, therefore, essential. For instance, tubal fimbriae and mesothelial hyperplasia are difficult to distinguish from papillary serous proliferations. In ovarian biopsies, theca external cells may mimic a primary stromal tumor. In leiomyomas, as well as in samples of ovarian stroma, the cellular vacuolization that results from electrosurgery can be confused with mucin droplets ("signet-ring like cells"). The presence of the pathologist in the operating room is important in difficult cases, particularly in borderline tumors of the ovary. Experienced gynecologic pathologists may have some initial difficulty, since examination with the naked eye differs from the video image due to the magnifying effect of the lens.

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Mucinous borderline tumors

Mucinous borderline tumors (MBTs) are almost as common as serous borderline tumors and constitute 40-50% of all mucinous malignant tumors (1) and 71% of those that are stage I (4). Recently, MBTs have been subclassified into two different clinicopathological forms: the most common form is composed of intestinal-type epithelium and has been designated MBT of the intestinal type (IMBT). A second and less common variant of MBT contains endocervical-type epithelium and has been named MBT of the endocervical type (EMBT) (5).

IMBT (85% of MBTs), occur most frequently in the fourth to seventh decades of life with an average age of 41 years (4, 5). Most of them (80-90%) are stage I and less than 10% are bilateral (4, 5). It should be realized that metastatic mucinous tumors in the ovary often mimic primary ovarian mucinous neoplasms, particularly adenocarcinomas of the pancreas and large intestine (6, 7). The metastatic tumor may appear deceptively "benign", "borderline" or malignant. Bilaterality is exceptional in stage I ovarian mucinous tumors; consequently, tumor involvement of both ovaries should arouse the suspicion of metastatic carcinoma.

Grossly, these tumors average 19 cm in diameter and are usually multilocular (4). They cannot be distinguished from mucinous cystadenomas and cystadenocarcinomas. These tumors should be sampled extensively since variations in the degree of epithelial proliferation and nuclear atypia (from benign to borderline, and to carcinoma) are common within an individual neoplasm. Microscopically, IMBTs are composed of cysts and glands lined by atypical epithelium of intestinal type. The cysts may contain papillae, which are typically thin and branching. The lining epithelium almost always contains goblet cells. The epithelial cells are usually stratified to two or three layers, nuclear atypia is mild to moderate and mitotic figures vary from few to numerous.

The criteria used to distinguish IMBTs from mucinous carcinomas have varied, resulting in considerable confusion in the literature. In the classification of the World Health Organization (WHO) (8), the former were defined as showing a degree of epithelial proliferation greater than that seen in benign cystadenomas, but lacking "destructive" stromal invasion. Nevertheless, the morphological evaluation of stromal invasion is more difficult for these tumors than for stromal borderline tumors (SBTs); the stroma, instead of being desmoplastic, may resemble ovarian stroma, and in cystadenomas, the irregular distribution of the glands in the stroma may suggest that invasion has occurred. To resolve this problem, Hart and Norris (9) proposed that noninvasive carcinoma should be diagnosed when the lining epithelial cells show a nuclear stratification of four or greater. Subsequently, Hart (4) added other cytologic and architectural criteria to support the diagnosis of noninvasive carcinoma. These criteria included malignant features of the epithelial cells, an obvious cribriform pattern and the presence of solid cellular papillae without fibrovascular cores. Using these criteria, these authors were able to distinguish accurately between IMBT, which had an excellent prognosis (96% 10-year survival for stage I tumors) and mucinous carcinomas, which were associated with only a 67% survival (9). These "Hart-Norris" criteria became widespread in the United States but many pathologists elsewhere followed the WHO criteria. Because of this disparity in criteria, the cumulative data in the literature does not allow reliable conclusions to be drawn about which of the two sets of criteria (WHO vs. Hart-Norris) better distinguishes IMBT from noninvasive carcinomas (10). Nevertheless, the comparative analysis of some series in which

Recent advances in mucinous tumors

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Mucinous tumors account for 10-15% of all ovarian tumors (1). Approximately 75% are benign, 10% are borderline and 15% are carcinomatous (1). Although they generally occur in older women (mean ages 51-54 years); mucinous borderline tumors and carcinomas are more common in the first two decades of life than analogous serous tumors (1).

Some mucinous tumors may be of germ cell origin but neometaplasia of the ovarian surface epithelium is an alternative explanation for their development (1). Mucinous ovarian tumors may be associated dermoid cysts, Brenner tumors and mucinous tumors of other organs such as the uterine cervix and the appendix (1). Mucinous tumors are among the most common non endocrine ovarian tumors associated with hormonal manifestations (2). The serum level of alpha-inhibin is considered to be a tumor marker for mucinous borderline tumors and carcinomas (3).

both diagnostic approaches were used has shown no difference in survival whether or not the noninvasive "carcinomas" of Hart and Norris were included in the borderline category (11). Such tumors appear to be of low malignant potential and do not behave like invasive mucinous tumors (10).

In a comparative analysis of 32 IMBTs and 15 stage I noninvasive, well-differentiated mucinous carcinomas reported recently by De Nictolis et al. (12), statistically significant differences in quantitative nuclear morphology were found between IMBTs and noninvasive carcinomas. None of the 15 carcinomas produced metastases and the authors proposed that patients with stage IA, well-differentiated noninvasive carcinomas could be grouped together with stage I IMBTs as far as prognosis and treatment are concerned, providing that the patients have been adequately staged, the tumors extensively sampled and metastatic carcinoma excluded. Recently, Scully (10) and coworkers (1) have proposed maintaining the WHO diagnostic criteria and additionally have divided IMBTs into forms with epithelial atypia and variants with intraepithelial carcinoma. The latter diagnosis is based mainly on cytologic features. The term carcinoma would only be used for tumors exhibiting obvious invasion of the stroma.

Otherwise typical IMBTs may occasionally contain small foci or clusters of tumor cells with atypical nuclei within a reactive stroma. The upper size limit for microinvasion has been arbitrarily set at 10 mm² (10). Too few cases of microinvasive IMBTs have been reported to determine its significance (11, 13-15).

Mucinous intestinal cystic tumors of the ovary, whether benign, borderline or malignant, may be associated with mural nodules of various types. These intriguing nodules were initially classified as true sarcomas and sarcoma-like mural nodules (SLMNs) (16, 17). Subsequently, foci of anaplastic carcinoma were also described as nodules in the walls of mucinous cystic ovarian tumors (18). Keratin immunostaining is typically strongly positive in the nodules of anaplastic carcinoma but only focally or weakly positive in the SLMNs (19). Although the distinction between the foci of anaplastic carcinoma and true sarcomatous nodules may not prove to have prognostic significance, both types of nodule should be separated from SLMNs because of the latter's favorable prognosis (17). Over the last 20 years, several additional cases of mural nodules in cystic ovarian tumors have been reported. However, the nature of these mysterious nodules remains unclear. A surprising finding is that combinations of any of the three types of nodules can occur (20). A recent immunohistochemical study of SLMNs suggested a submesothelial origin for these lesions (21). In our experience, SLMNs appear to be self-limiting lesions; if they are well circumscribed, their presence does not influence the prognosis based on the main mucinous cystic tumor (21).

According to the annual report of the International Federation of Gynecology and Obstetrics (FIGO)(22), MBTs are confined to one or both ovaries in 82% of the cases, are stage II in 6%, stage III in 10% and stage IV in 2%. The corresponding figures for mucinous carcinomas are 49%, 11%, 29% and 10% of the cases. Almost all stage II-III IMBTs are associated with pseudomyxoma peritonei and there is convincing evidence that most of these tumors are secondary to mucinous tumors of the appendix (see below). This finding, as well as the almost 100% 5-year survival rate of stage I IMBTs, has raised the question of whether the noninvasive mucinous ovarian tumors have any malignant potential (23). Nevertheless, Scully (10) has recommended that all cases of pseudomyxoma peritonei associated with a mucinous cystic ovarian

tumor should be diagnosed as stage II or stage III ovarian tumors to avoid confusion in the clinical evaluation of these cases. However, the inclusion of these metastatic tumors in the category of IMBTs will result in overestimating their malignant potential.

While performing a frozen section, the pathologist should be aware that additional postoperative sampling of an apparently benign mucinous tumor may disclose a carcinomatous component and the surgeon should be informed that the diagnosis could be changed after examination of the permanent sections. When this is done, the surgeon is more likely to undertake appropriate staging. If there are pseudomyxoma peritonei or bilateral ovarian tumors, removal of the appendix as well as exploration of the abdomen for a possible source of metastasis are recommended.

Synchronous mucinous tumors of the appendix and the ovary associated with pseudomyxoma peritonei

In cases in which ovarian IMBTs are associated with pseudomyxoma peritonei, the appendix is also involved by a similar mucinous lesion in 60% of the cases and appears normal in the remaining 40% (10, 23-26). These findings indicate that in some cases pseudomyxoma peritonei results from a primary ovarian IMBT. The synchronous ovarian and appendiceal tumors were traditionally considered as independent primary neoplasms but there is now convincing evidence that in most cases the ovarian tumors represent metastasis from the appendiceal lesions (23-25).

The gross and microscopic evidence includes: i) simultaneous presentation of the ovarian and appendiceal tumors in cases of pseudomyxoma peritonei; ii) their histologic similarity; iii) high frequency of bilaterality of the ovarian tumors (ovarian IMBTs are usually unilateral and only occasionally associated with pseudomyxoma peritonei); iv) right-sided predominance of unilateral ovarian tumors; v) presence of pools of mucin dissecting through the ovarian stroma (pseudomyxoma ovarii), a rare finding in primary mucinous ovarian tumors; vi) unusually tall mucinous epithelium of the ovarian tumors in the presence of appendiceal and peritoneal involvement; and vii) appendiceal tumors always showing the histologic features of a primary tumor, being either adenomas or adenocarcinomas (23-25).

Features against the secondary nature of ovarian tumors are: i) large size and presence of a benign-looking epithelial component in ovarian tumors; ii) small size, low grade or benign microscopic appearance of the appendiceal tumors with intact appendiceal wall on gross inspection or even microscopic examination; iii) occasional presentation of the appendiceal tumor months or years after the discovery of the ovarian tumor; iv) differences in the histologic grade of the ovarian and appendiceal tumors; v) discordant epithelial immunohistochemical staining in the ovarian and appendiceal tumors; and vi) more favorable clinical behavior in these patients than that expected from patients with metastatic carcinomas (24, 27).

Authors in favor of the metastatic nature of ovarian tumors have contended all of the above points and stated that the appendiceal source of the pseudomyxoma can only be excluded after adequate sampling and microscopic examination of the appendix (23-25). The appendiceal tumors may be small and rupture sites can be sealed after evacuation of mucus and retraction of the appendiceal wall (24). Differences in histologic appearance and immunohistochemical staining between appendiceal and ovarian tumors may reflect tumor heterogeneity or incomplete sampling of the neoplasms (1). Moreover, mucinous tumors metastatic to the ovary typically show a much higher degree of differentiation than

do primary neoplasms and may appear deceptively "benign" in some areas (1, 24). Concordant negative immunostaining reactions for HAM 56 and cytokeratin 7 in both tumors also support their appendiceal origin (28).

At least three molecular genetic studies have addressed this problem (29-31). An analysis of loss of heterozygosity on chromosomes 17q (nm23), 3p (VHL) and 5q in 12 cases disclosed divergent findings in ovarian and appendiceal tumors in three cases (supporting two separate primaries) and similar findings in another three (supporting a single primary tumor with metastatic spread) (29). Although genetic progression of the metastatic tumors could account for the disparity of these results, it should also be noticed that the authors of this study did not interpret the synchronous lack of loss of heterozygosity in six of their cases as concordant results.

c-Ki-raspoint mutations at codons 12 and 13 occur with increasing frequencies in benign (55%), borderline (73%) and carcinomatous (85%) mucinous tumors of the ovary (32). They appear to be an early event in mucinous ovarian tumorigenesis. Recently, we performed a clinicopathological study and a comparative analysis of c-Ki-ras mutations in six cases of synchronous ovarian and appendiceal tumor (30). Their clinicopathologic features (simultaneous presentation, bilaterality or right-sided predominance, similar histopathological findings and presence of pseudomyxoma peritonei) suggested that they were primary appendiceal tumors metastatic to the ovaries. Moreover, the concordance of c-Ki-ras mutational pattern in both tumors in each patient also suggested their clonal nature and supported that they were not separate neoplasms but originated from the same clone which, in the light of the clinicopathologic data, was most likely to be of appendiceal origin. Our results have recently been confirmed by a similar study of 16 additional cases (31).

In Rutgers and Scully's series (5), EMBTs accounted for approximately 15% of MBTs. These tumors differed in many respects from IMBTs, as shown in Table 1.

The prognosis of EMBTs is excellent and approximates that of SBTs. All the patients were alive at an average of 3.7 years of follow-up. Two patients, initially treated by a unilateral salpingo-oophorectomy, had recurrent tumors in the contralateral ovary. One-half of the patients with higher-stage tumors were treated with chemotherapy and none had tumor progression or recurrence.

Table 1. Comparative analysis of endocervical-like and intestinal mucinous borderline tumors (5).

	EMBT(a)	IMBT(b)
Average age (years)	34	41
Bilaterality (%)	40	6
Diameter (cm)	8	19
Multilocularity (%)	20	72
Gross papillae (%)	87	17
Stromal papillae	++++	+
Cellular tufting	++++	+
Goblet cells (%)	0	100
Grimelius + cells (%)	3	86
Acute inflammation (%)	100	0
Endometriosis, either ovary (%)	30	6
Stage II-III (%)	24	10
Discrete implants +/- or node mets (%)	20	0
Pseudomyxoma peritonei (%)	0	17

(a)EMBT = endocervical mucinous borderline tumors. (b)IMBT = intestinal mucinous borderline tumors.

There is no evidence that chemotherapy is helpful, even for patients with higher-stage disease (5).

Mucinous carcinomas

Recently, Hoeri and Hart (14) have summarized the clinicopathological features of these tumors as follows: i) mucinous carcinomas of the ovary are very uncommon tumors, after metastatic carcinomas and tumors associated with pseudomyxoma peritonei have been excluded; ii) they are rarely bilateral; iii) FIGO stage is the single most important prognostic factor, and stage I carcinomas have an excellent prognosis; iv) stage I carcinomas that metastasize have extensive stromal invasion; v) extensive stromal invasion is found only in tumors with intraepithelial carcinoma; vi) high-stage carcinomas invariably contain extensively invasive carcinoma and have very poor prognosis; and vii) stromal microinvasion (<1 mm) does not change the good prognosis of either carcinomas or borderline tumors at stage I.

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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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