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Original Article

Carcinoma of Extrahepatic Bile Ducts and Gallbladder Metastatic to the Ovary: A Report of 16 Cases

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Summary: Information on ovarian metastasis of carcinoma of the extrahepatic bile ducts and gallbladder is limited. Sixteen examples are reported; 3 primary tumors were hilar cholangiocarcinomas, 5 common bile duct carcinomas, and 8 gallbladder carcinomas. The patients ranged from 21 to 87 years (mean, 59 years); 7 presented to gynecologists with nonspecific pelvic symptoms similar to primary ovarian neoplasms. The primary tumor was identified before the detection of the ovarian lesions in 5 cases, was simultaneously detected with the ovarian metastases in 9, and was diagnosed postoperatively in 2. All but one case had bilateral ovarian involvement. The thirty-one ovarian lesions included twenty-nine grossly abnormal ovaries that were enlarged (range, 3.0–16.5 cm, mean, 9.4 cm) and 2 ovaries with only microscopic involvement. The sectioned surface was solid in 9, solid-cystic in 15, and multicystic in 5. Microscopically, ovarian surface implants were seen in 66%, multinodular growth in 58%, and infiltrative stromal invasion in 81%. Mucinous epithelial differentiation was seen in 81%, sometimes with foci of benign-like or borderline-like epithelium simulating primary ovarian mucinous neoplasia. Cystadenoma and cystadenofibroma of non-mucinous type was even mimicked strikingly in some cases because of flattening of epithelium lining glands and cysts. Signet ring cells were present in sufficient quantity for a diagnosis of Krukenberg tumor in four tumors. Colloid-type carcinoma was observed at least focally in 3 tumors. Nonmucinous carcinomatous components included adenocarcinoma with high-grade endometrioid-like morphology in 2 cases, papillary adenocarcinoma simulating mixed müllerian epithelial adenocarcinoma in 1, and undifferentiated carcinoma in 2. Immunohistochemical studies in 8 cases showed a positive reaction for cytokeratin 7 in all and for cytokeratin 20 in 4 cases. The high rate of bilaterality, surface involvement, multinodular growth, and heterogeneity of patterns were the most helpful features for indicating a metastatic nature, with signet ring cells also being helpful in the minority of cases in which they were present. Although the diagnosis of a metastatic tumor to the ovary is possible in most of the cases based on standard diagnostic criteria, problems in the differential diagnosis may be posed by morphologic patterns that overlap strikingly with primary ovarian neoplasms, benign, borderline, and malignant, as discussed herein. **Key Words:** Ovary—Metastasis—Cholangiocarcinoma—Extrahepatic bile duct carcinoma—Gallbladder carcinoma—Krukenberg tumor.

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Metastatic tumors to the ovary originating in the biliary system are uncommon. In 1990, one of us and Dr. Robert E. Scully reported 6 cases; 5 were gallbladder carcinomas and 1 a bile duct carcinoma (1). In that report, the prior literature was reviewed, and historically interesting aspects such as the presence of 7 cases in Schlagenhaufer's seminal article on the Krukenberg tumor (2) and the observations of Rupert A. Willis (3) were noted. We will not repeat that information here but rather explore the topic and literature since that time, a 17-year interval that has seen a surge of interest in the topic of metastatic tumors to the ovary, including greater appreciation of their propensity to exhibit remarkable differentiation in the ovary. In the subsequent literature, there have been only case reports with, in some instances, little description of pathologic details, resulting in limited data on the histopathologic features of these tumors (4–12). Most of the reported primary tumors were in the gallbladder with fewer examples of extrahepatic bile duct carcinoma (1,4–7). Having recently reported our experience with ovarian spread of carcinoma of the intrahepatic bile ducts (13), this article serves as a companion to that article, exploring as it does ovarian spread of tumors of the extrahepatic bile ducts and gallbladder.

MATERIALS AND METHODS

Nine cases of metastatic carcinoma to the ovary of extrahepatic bile duct and gallbladder origin were retrieved from the surgical pathology files of the Chiang Mai University Hospital between January 1992 and December 2006, and 7 previously unreported cases were retrieved from the departmental files of the Massachusetts General Hospital and the consultation files of Dr. Robert E. Scully from the same period. Tumors of intrapancreatic bile duct origin were excluded as, from the practical perspective, they fall under the rubric of pancreatic primaries. Eight of the Chiang Mai University cases were included in previous studies on metastatic tumors to the ovary but were not reported in detail (14,15). The diagnosis of an ovarian metastasis was based on standard diagnostic criteria (16–19). The clinical features and intraoperative findings were determined from the medical records. Available preoperative and postoperative radiologic materials were reviewed. Determination of the primary tumor site was based on review of the intraoperative findings and radiologic investigations. The primary tumor was available for histologic examination in 4 cases of gallbladder carcinoma. Metastatic involvement of intra-abdominal tissues other than the ovaries was confirmed by histology in all except 1 case.

Hematoxylin and eosin–stained sections of ovarian and nonovarian specimens were reviewed. A total of 31 metastatic ovarian lesions was evaluated. The average number of sections per ovary was 5 (range, 1–16). Immunohistochemical staining using antibodies against cytokeratin (CK) 7 (DAKO, Carlsbad, CA, 1:200) and CK20 (DAKO, 1:200) was performed on the ovarian lesions in 8 cases. Additional immunostains were selectively performed in two cases, including CK AE1/AE3 (DAKO, 1:300), epithelial membrane antigen [(EMA) DAKO, 1:100], CAM5.2 (ZYMED, Carlsbad, CA, 1:200), chromogranin A (DAKO, 1:200), vimentin (DAKO, 1:1000), and desmin (DAKO, 1:100). The sections for all immunostains were subjected to heat-induced antigen retrieval using either microwave or pressure cooker. The staining was considered positive when at least 5% of neoplastic cells were immunoreactive. Positive staining was considered diffuse when at least 50% of neoplastic cells were immunoreactive and focal when less than 50% of the cells stained.

RESULTS

Clinical Features

The patients ranged from 21 to 87 years (mean, 59 yr). There was no history of cancer before the detection of either bile duct/gallbladder or ovarian neoplasms in any patient. The primary tumors, using the World Health Organization classification (20,21), included 3 hilar cholangiocarcinomas, 5 common bile duct carcinomas, and 8 gallbladder carcinomas (Table 1). Seven patients presented to gynecologists with nonspecific pelvic symptoms. One patient had emergency surgery because of symptoms of acute appendicitis; this was found to be caused by metastatic involvement of the appendix and resulted in the detection of ovarian masses. Jaundice was noted at presentation in 5 patients with bile duct carcinomas and 1 with gallbladder carcinoma. The primary tumor was identified before the ovarian tumor in 5 cases (range, 2 weeks–23 months). The primary tumors and ovarian masses were simultaneously detected by preoperative radiologic studies and/or exploratory laparotomy in 9 cases. In the remaining two cases, the primary tumors were diagnosed by follow-up investigations after ovarian resection (range, 3 weeks–2 months). Sites of distant extra-abdominal metastases included the lung in

TABLE 1. *Summary of clinicopathologic data (current study)*

No.	Age (yr)	Primary site	Clinical presentation at time of ovarian metastasis	Chronology of primary and ovarian tumors (interval)	Laterality and size (cm)	Epithelial differentiation
1	51	Hilum	Pelvic mass	Simultaneous	R 3.0	Mucinous*
					L 16.5	Endometrioid-like and mucinous
2	58	Hilum	Pelvic mass	Ovarian first (3 wk)	R 7.0	Mucinous*
					L <7	Mucinous
3	66	Hilum	Acute appendicitis	Ovarian first (2 mo)	R 6.0	Mucinous*
					L 3.8	Mucinous*
4	21	CBD	RUQ pain†	Simultaneous	R 8.5	Papillary nonmucinous
					L 5.0	Papillary nonmucinous
5	52	CBD	Jaundice	Primary first (6 mo)	R 4.5	Mucinous
					L 7.0	Mucinous
6	59	CBD	Jaundice	Simultaneous	R 16.0	Mucinous
					L 13.0	Mucinous
7	42	CBD	Jaundice	Simultaneous	L 0.22	Mucinous and nonspecific
8	87	CBD	Incidental finding on CT scan†	Primary first (23 mo)	R 10.5	Mucinous, nonspecific, and focal colloid carcinoma-like
					L 7.0	Mucinous, nonspecific, and focal colloid carcinoma-like
9	47	Gallbladder	Abdominal distension	Simultaneous	R 15.0	Endometrioid-like
					L 14.0	Endometrioid-like
10	51	Gallbladder	Pelvic mass	Simultaneous	R 7.0	Colloid carcinoma-like
					L 0.5	Mucinous
11	63	Gallbladder	Pelvic pain	Primary first (14 mo)‡	R 5.0	Mucinous and nonspecific
					L 16.0	Mucinous, nonspecific, and undifferentiated
12	68	Gallbladder	Vaginal bleeding†	Primary first (10 mo)	R 16.0	Undifferentiated
					L 6.5	Undifferentiated
13	76	Gallbladder	Hematochezia, nausea	Simultaneous	R 6.0	Mucinous and nonspecific
					L 16.0	Mucinous and nonspecific
14	83	Gallbladder	Unknown	Primary first (2 wk)	R 4.0	Mucinous and nonspecific
					L 4.0	Mucinous and nonspecific
15	48	Gallbladder	RLQ pain	Simultaneous	R 16.0	Mucinous and nonspecific
					L 12.0	Mucinous and nonspecific
16	68	Gallbladder	Unknown	Simultaneous	R 10.1	Mucinous and nonspecific
					L 8.5	Mucinous and nonspecific

*Krukenberg tumor; †Jaundice noted but was not the major presenting symptom; ‡The presence of gallbladder carcinoma was not recognized before the diagnosis of ovarian metastasis.
CBD indicates common bile duct; R, right; L, left; CT, computed tomography; RLQ, right lower quadrant; RUQ, right upper quadrant.

2 cases and vertebrae in 1 case, the latter occurring in 1 of the patients with pulmonary metastases.

Liver function tests performed at the time of detection of the ovarian metastases showed elevation of alkaline phosphatase in 7 cases of bile duct carcinoma and 2 cases of gallbladder carcinoma (range, 128–1,344 U/L; reference range, <100 U/L). Alkaline phosphatase levels were normal in 2 other patients with gallbladder carcinoma. The serum carbohydrate antigen (CA) 19-9 level, available for 7 patients, was elevated in 3 cases of bile duct carcinoma and 2 cases of gallbladder carcinoma (range, 119–820 U/mL; reference range, <37 U/mL), and was normal in 2 other gallbladder cases. Elevated carcinoembryonic antigen (CEA) levels were found in 3 patients with bile duct carcinoma and one patient with gallbladder carcinoma (range, 12.9–1,760 ng/mL; reference range, <5.0 ng/mL); it was normal in 1 patient with gallbladder carcinoma. The serum CA125 was elevated in 5 patients (range, 54.6–730 U/mL; reference range, <35 U/mL) and normal in one.

All patients except one underwent bilateral salpingo-oophorectomy with or without hysterectomy; 1 patient with microscopic ovarian disease had a unilateral oophorectomy. Peritoneal carcinomatosis was observed in 15 of 16 patients, and ascites in 8 patients. Multiple hepatic metastases were detected in 4 cases. Intraoperative frozen sections of the ovarian masses were requested in 6 cases; 5 had intraoperative diagnoses of adenocarcinoma consistent with metastasis, and 1 case was diagnosed as a mucinous cystadenoma.

Only 2 patients are known by us to have received postoperative chemotherapy. One had progression of the disease and was lost to follow-up after 12 months,

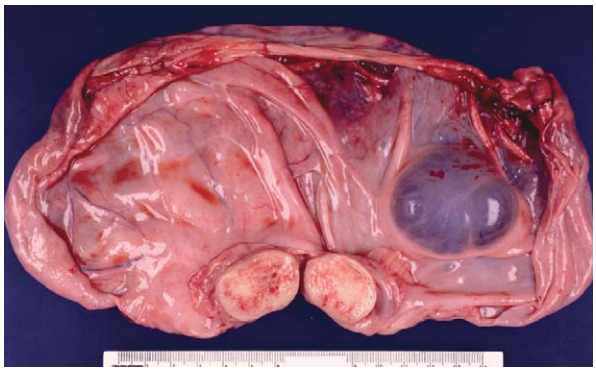

FIG. 1. Sectioned surface of multicystic ovarian mass with one large dominant locule shows a 3.2-cm well-circumscribed nodule of solid white-tan tissue with central necrosis.

and the other had partial response but died of subarachnoid hemorrhage after 5 months. All remaining patients had disease progression and were dead of disease or were lost to follow-up after short intervals.

The initial pathologic diagnosis of the ovarian lesions was primary mucinous adenocarcinoma in one case and mucinous cystic tumor of borderline malignancy in one. In the other cases, metastatic tumors were either diagnosed (n = 13) or favored (n = 1). One primary gallbladder carcinoma was initially not appreciated pathologically but was diagnosed after the ovarian metastases cast suspicion on the previously resected gallbladder.

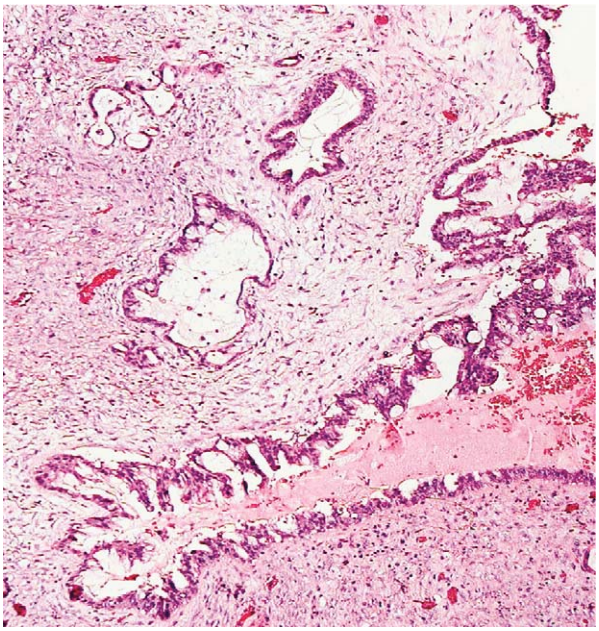

FIG. 2. A focus of invasive low-grade adenocarcinoma in a cystic tumor is characterized by irregular glands with low-grade nuclear atypia.

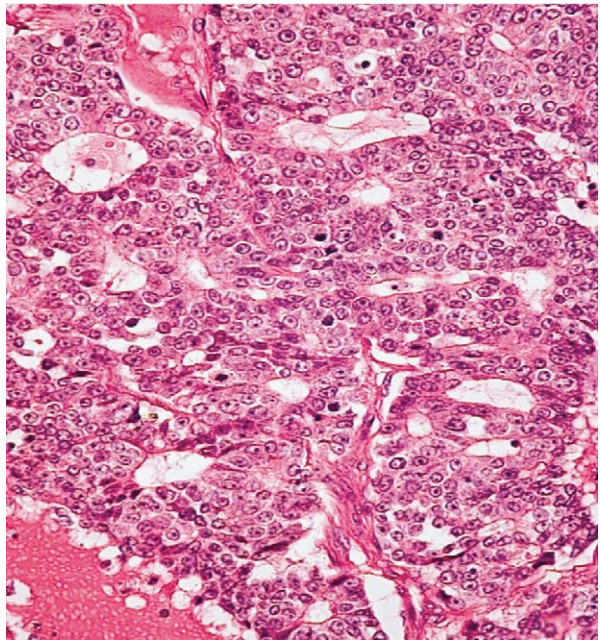

FIG. 3. Gland-forming adenocarcinoma with large round nuclei simulates high-grade endometrioid adenocarcinoma.

Pathologic Features

Gross Pathology

Bilateral involvement was present in all but 1 case. A total of 31 metastatic ovarian lesions included 29 ovaries grossly involved by tumor (range, 3.0–16.5 cm; mean, 9.4 cm) and 2 ovaries with microscopic involvement (0.5 cm and 0.22 cm) (Table 1). The appearance of the external surface was recorded for 24 tumors and was noted to be smooth in 11 tumors, irregular in 4 tumors, with adhesions or fibrinous exudate in 4 tumors, ruptured in 3 tumors, focally hemorrhagic in 1 tumor, and studded with tumor nodules in 1 tumor. Cut surfaces were predominantly solid in 9 tumors, solid-cystic in 15 tumors (Fig. 1), and multicystic in 5 tumors. The cyst contents were recorded as mucoid in 13 tumors. In 1 tumor, a 3.2-cm well-circumscribed, oval, solid nodule with central necrosis was present in the wall of a mostly cystic tumor (Fig. 1). Necrotic areas were recorded in 5 tumors.

Microscopic Pathology

The thirty-one ovarian tumors were analyzed individually. All the tumors, to varying degrees, had foci that viewed in isolation were indistinguishable from, or closely simulated, primary surface epithelial neoplasms (Figs. 2–6). However, they all also had 1

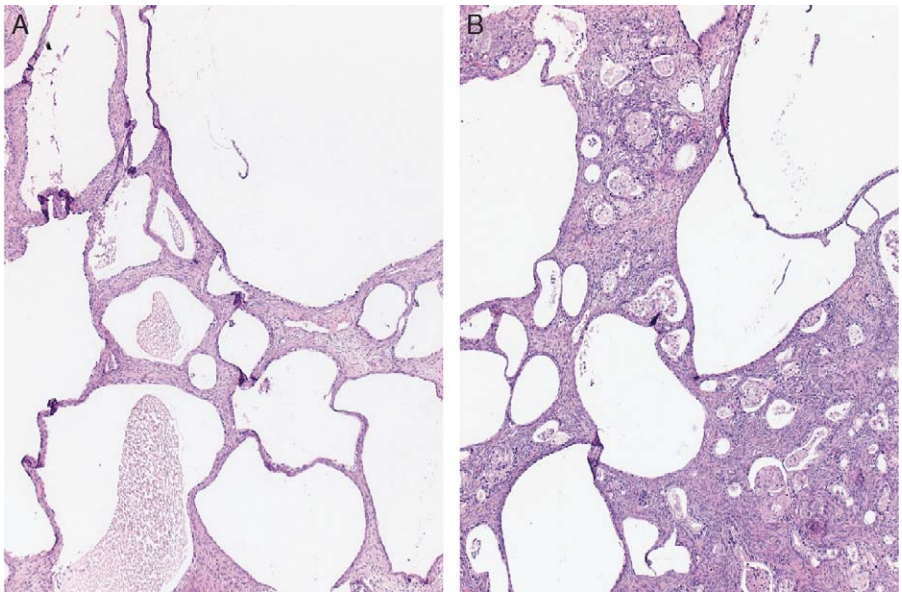

FIG. 4. A, Striking cysts lined by flattened epithelium and with scant intervening stroma mimic a cystadenoma. B, Two discrete foci of infiltrative adenocarcinoma are a major clue to the cystic component being differentiated carcinoma.

or more features characteristic of metastatic neoplasia in the ovary (Figs. 7–9).

Multinodular growth was seen in 18 tumors (58%), which all demonstrated foci of uninvolved ovarian tissue between the tumor nodules. Ovarian surface implants were observed in 19 (66%) of 29 tumors for which sections of the external surface were available (Figs. 7, 9). The surface implants were typically composed of irregularly infiltrating glands within a desmoplastic, sometimes hyalinized, stroma. In 1

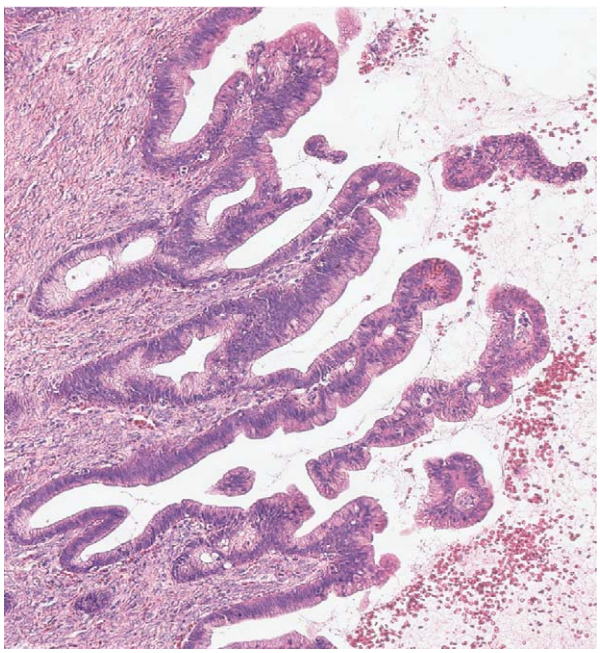

FIG. 5. Mimicry of primary mucinous tumor of borderline malignancy.

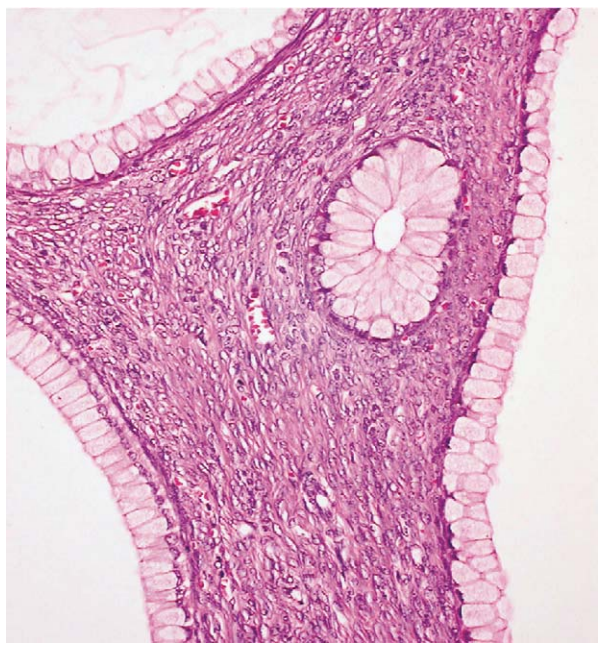

FIG. 6. Bland-appearing mucinous epithelium lining gland and cysts with intervening fibromatous stroma.

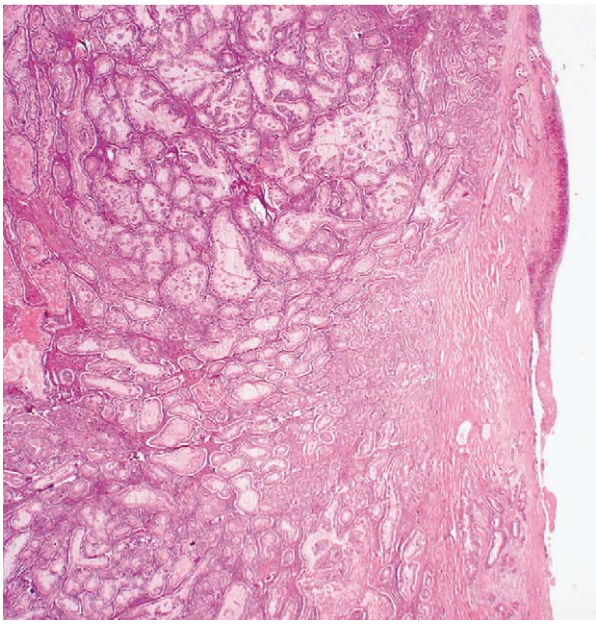

FIG. 7. Plaque-like surface involvement by adenocarcinoma with hyalinized stroma (middle right) overlies crowded neoplastic glands with focal papillary projections that simulate the appearance of ovarian mucinous tumor of borderline malignancy.

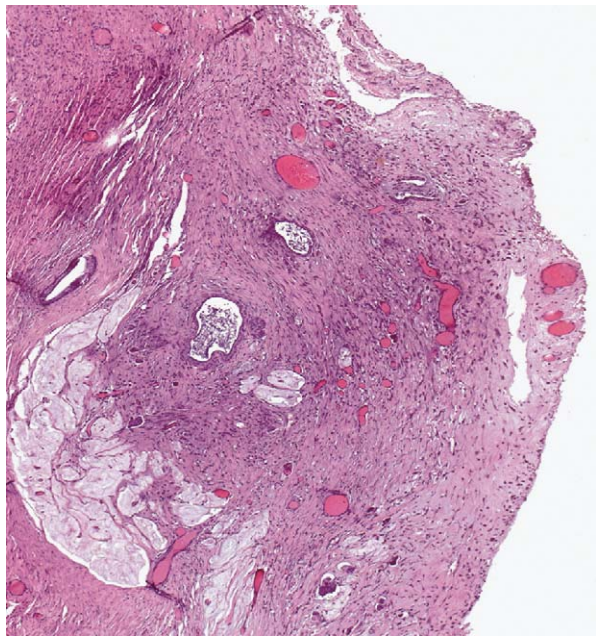

FIG. 9. Typical surface implant.

case, there were surface pools of mucin. Hilar involvement was seen in fifteen (52%) of 29 tumors with hilar sampling.

Somewhat dilated and occasionally markedly cystic (Fig. 4) glands set in a variable amount of stroma represented the dominant morphologic pattern in

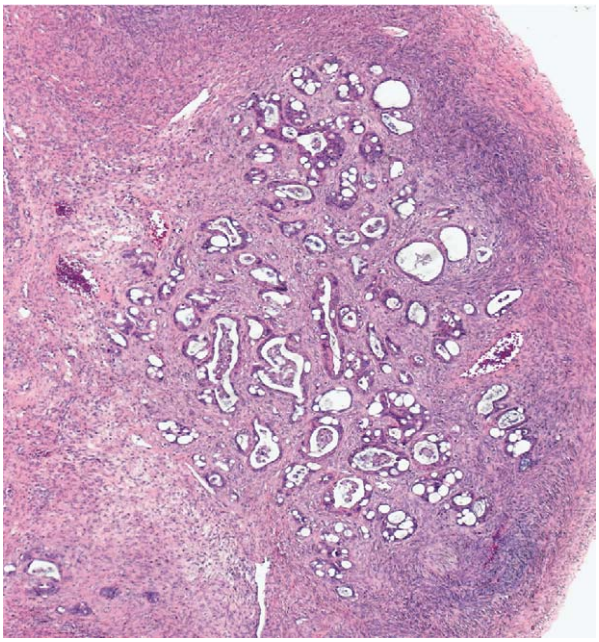

FIG. 8. Discrete nodular focus of carcinoma in superficial cortex separated from another smaller focus of carcinoma (lower left) by nonneoplastic stroma.

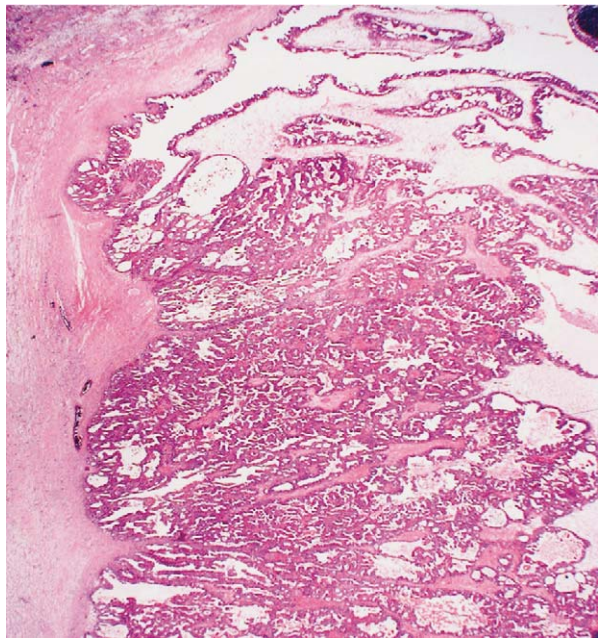

FIG. 10. Complex papillary structures project into a large cystic space without infiltrative stromal invasion. The stroma of the papillae is occasionally edematous.

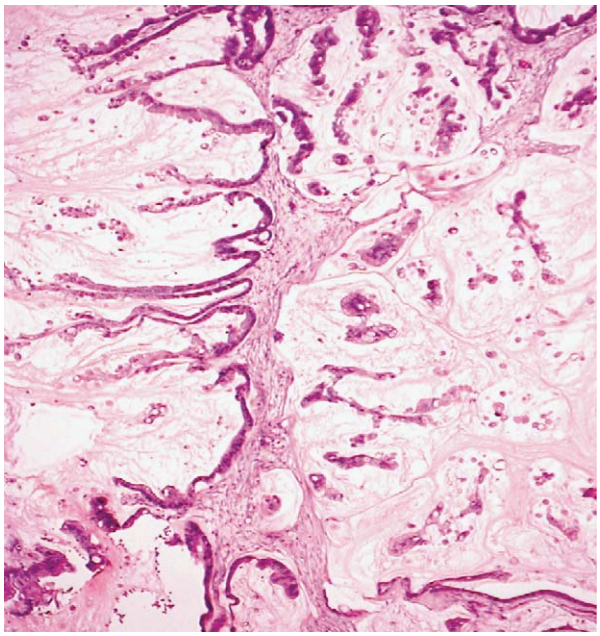

FIG. 11. Component of colloid adenocarcinoma adjacent to conventional cystic adenocarcinoma.

many tumors. Infiltrative foci consisting of angulated tubular glands (both mucinous and nonmucinous), irregular tumor cell nests, or single tumor cells were seen in 25 tumors (81%); these foci were often multiple and extensive. Papillae were seen in 15 tumors (48%), mostly within glands and cysts, but they were generally inconspicuous. Complex papillary structures indicative of expansile invasion (Fig. 10) were prominent in both tumors in 1 case. An admixture of the aforementioned features was usual and resulted in a particularly varied appearance, even in individual slides.

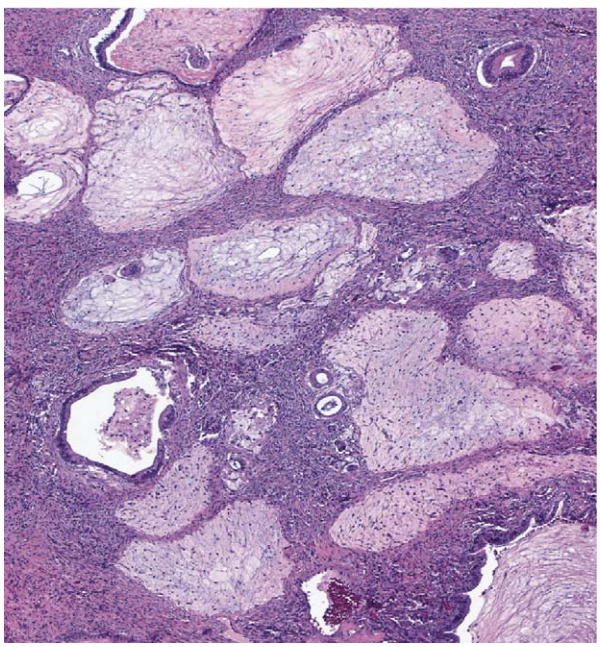

FIG. 12. Pools of mucin dissect within ovarian stroma (pseudomyxoma ovarii).

The neoplastic epithelium demonstrated variable mucin production. Mucin-producing cells of nonsignet ring-type were observed at least focally in 25 tumors (81%) (Table 1). They were usually tall and columnar with abundant intracytoplasmic mucin (Fig. 6). Goblet cells were identified in 16 tumors (52%). Signet ring cells comprised greater than 10% of the neoplastic cell population in 4 tumors (13%) from 3 patients, warranting a diagnosis of Krukenberg tumor in those instances. In a few other cases, sporadic signet ring cells were identified. Three tumors (10%) contained colloid carcinoma-like areas (Fig. 11), with epithelium floating within mucin; in 1 tumor, this change was extensive. In the other 2, broad regions of acellular dissecting mucin with a pseudomyxomatous pattern (Fig. 12) were also present. Areas resembling a mucinous tumor of borderline malignancy (Fig. 5), with or without intraepithelial carcinoma, were observed in 13 tumors (42%). Bland-appearing single-layered mucinous epithelium (Fig. 6) was seen in 11 tumors (35%).

Nonmucinous epithelium was present in 20 tumors (65%) (Table 1) and had 3 main appearances: 1) nonspecific cuboidal or columnar epithelium lining glands and cysts with a variable degree of nuclear atypia in 14; 2) gland-forming adenocarcinoma with a cribriform pattern or focal cord-like infiltration mimicking high-grade endometrioid adenocarcinoma in 3 (Fig. 3); and 3) undifferentiated carcinoma in 3 (Fig. 13). The undifferentiated carcinoma formed a well-circumscribed, mural nodule-like mass within the wall of a large cyst in one case. The undifferentiated component was located adjacent to areas of better differentiated tumor consisting of small, superficially banal tubular glands in a fibromatous stroma that mimicked an adenofibroma (Fig. 13). Review of the previously resected gallbladder in this case revealed both undifferentiated carcinoma and well-differentiated mucin-producing adenocarcinoma. In another case, both ovaries were diffusely involved by undifferentiated carcinoma with focal spindle cell areas.

One ovary that was not grossly abnormal had a small surface implant abutting a 0.5-cm cyst in the cortex lined by malignant-appearing mucinous epithelium. The other case with microscopic disease was notable for a 0.22-cm focus of infiltrative

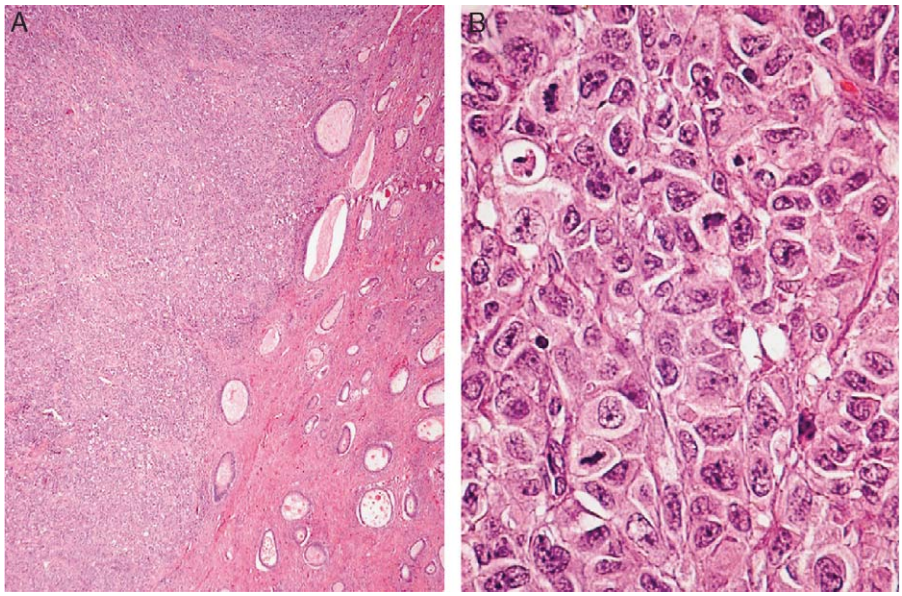

FIG. 13. A, Well-circumscribed nodule composed of solid sheets of undifferentiated carcinoma (left) and adjacent adenofibroma-like component with differentiated glands (right). B, Undifferentiated malignant cells show pleomorphic medium to large nuclei containing distinct nucleoli.

adenocarcinoma in the cortex, adjacent to an 8.0-cm serous cystadenoma.

The nature of the stroma and its prominence varied greatly, both within individual tumors and among the ovarian tumors as a group. Fibromatous stroma was present in 20 tumors (65%), desmoplastic stroma in 11 (35%), and hypocellular to hyalinized stroma in 7 tumors (23%). Luteinized stromal cells were seen in 5 tumors (16%). Although the stromal component was typically overshadowed by the glandular proliferation, in occasional cases the presence of superficially banal glands and cysts within expanded fibrous stroma led to a remarkable mimicry of a primary ovarian adenofibroma or cystadenofibroma. In tumors with a less prominent stromal component, the relatively bland cysts mimicked a cystadenoma on

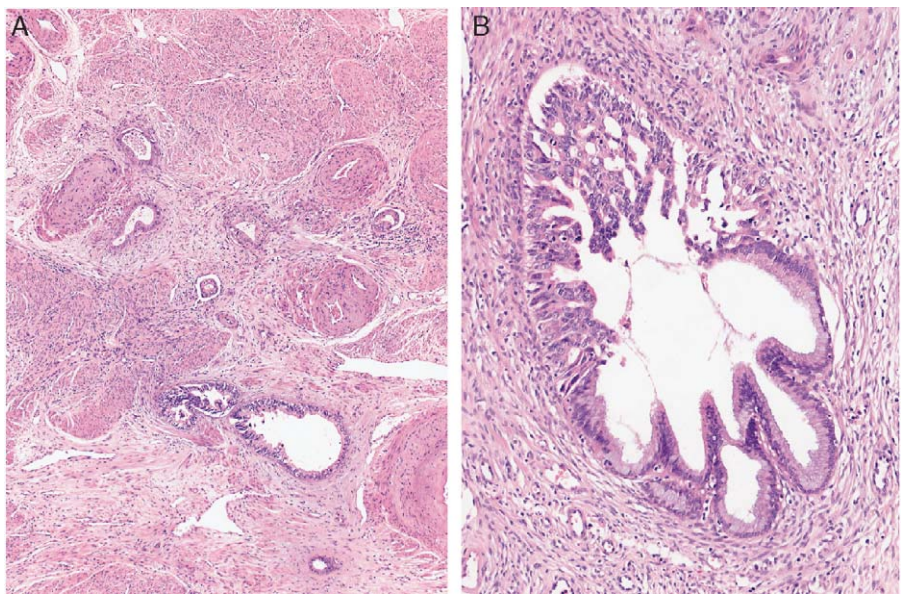

FIG. 14. Tumor metastatic to cervix. A, Irregular infiltration and lymphatic invasion typical of metastasis to cervix. B, Focal endocervical gland involvement that could potentially be misinterpreted as primary neoplasia.

TABLE 2. *Coordinate expression profiles of immunohistochemical stains for CK7 and CK20 in 8 cases*

Immunohistochemical profile	No. cases (%)
CK7+ diffuse/negative CK20	3 (38)
CK7+ focal/negative CK20	1 (12)
CK7+ diffuse/CK20+ focal	2 (25)
CK7+ focal/CK20+ focal	2 (25)

low power (Fig. 4A). Although closer inspection in these areas sometimes revealed at least focal nuclear atypia, it was overall more helpful that their merging with obvious carcinoma (Fig. 4B) made it clear that they represented differentiated foci of the metastatic cancer.

Intraluminal necrotic debris was observed in 4 tumors (13%), and 1 tumor demonstrated a garland-like pattern of cribriform epithelium around the necrosis. Broad zones of necrosis were seen in 3 (10%). Ovarian lymphatic invasion was unequivocally identified in only 2 tumors (6%), although striking involvement of paratubal lymphatics was seen in some other cases. Intracytoplasmic hyaline globules were present in rare cases.

Omental or peritoneal biopsy was performed in 13 cases. All showed metastatic involvement with features of infiltrating adenocarcinoma and one also having features of colloid carcinoma. The appendices were removed in 6 patients. Four showed metastatic involvement, accompanied by acute suppurative inflammation distal to tumor in 2 of them. One case was notable for metastatic disease to the cervix (Fig. 14) that raised concern for a synchronous primary cervical adenocarcinoma. In addition to infiltrative foci, the metastatic tumor demonstrated colonization of native endocervical glands (Fig. 14B), such that the appearance of adenocarcinoma in situ was mimicked. The colonized endocervical glands were notable for higher-grade nuclear atypia than is usually seen in endocervical adenocarcinoma in situ, however, and the infiltrative foci showed typical patterns of metastatic disease in the cervix, including prominent lymphatic invasion (Fig. 14A). The overall tumor was considered unequivocally metastatic.

Immunohistochemical stains of the ovarian tumors were available in 8 cases. The mucinous or non-specific epithelium in all 8 cases (100%) showed immunoreactivity for CK7, diffuse in 5, and focal in 3 (Table 2). Immunoreactivity for CK20 was focally observed in 4 cases (50%) (Table 2). The endometrioid-like adenocarcinoma in Case 1 was focally positive for EMA and CK7. Scattered cells were positive for chromogranin A, and a Stain for CK20. The undifferentiated carcinoma in Case 11 showed diffuse and strong positivity for vimentin with focal reactivity for CK AE1/AE3 and CAM5.2; stains for CK7, CK20, EMA, chromogranin A, and desmin were negative.

In the few cases in which the primary tumor was available for review, the morphology was typical for biliary adenocarcinoma (Fig. 15A), but of relevance

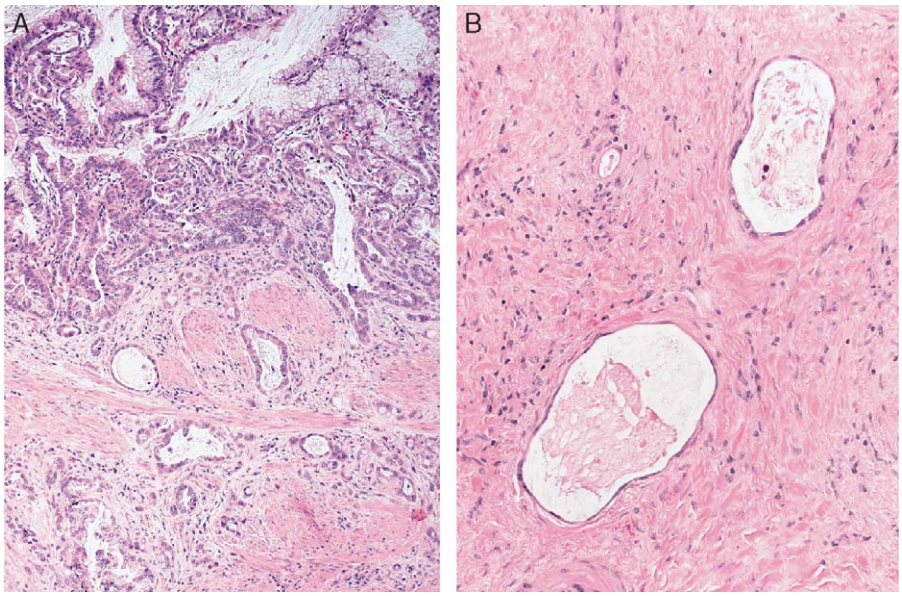

FIG. 15. Primary gallbladder carcinoma. A, Adenocarcinoma involving mucosa and infiltrating into the gallbladder wall. B, Deceptively bland-appearing but deeply invasive glands.

to the current topic was the presence of occasional glands that had a deceptively bland morphology in their more deeply invasive aspects (Fig. 15B).

DISCUSSION

Metastatic neoplasms involving the ovary continue to be the source of numerous problems in differential diagnosis for the pathologist and have been the subject of much interest in the last 2 decades (22,23). Diverse issues have been emphasized in the recent literature, including but not limited to the remarkable mimicry of primary ovarian mucinous neoplasia in some cases (17,24); the morphology of metastatic intestinal adenocarcinoma, dating in large part from the seminal observations of Lash and Hart (25); and the delineation of a wider spectrum of morphology of the Krukenberg tumor of the ovary (26) than had previously been known for the most part. Aspects of the current study overlap with the considerations just noted inasmuch as our metastatic carcinomas from the biliary system in part had a mucinous morphology, were occasionally in the Krukenberg family, and, less frequently, had an intestinal-type picture. The morphology was complicated by additional patterns that were nonspecific, but there also was the small- to medium-sized glandular pattern familiar to pathologists as being characteristic of many tumors primary in the biliary and pancreatic region. Our anecdotal experience with the varied morphology of many of these cases, which has not received much comment in the literature, and our recent study of intrahepatic cholangiocarcinoma spreading to the ovary (13), prompted us to undertake the current study to record and depict the remarkably varied histopathology of tumors of the extrahepatic biliary tree spreading to the ovary and to contrast their features with those of tumors spreading to the ovary from other sites in the gastrointestinal tract and associated structures. A comparison between ovarian metastases from intrahepatic cholangiocarcinoma and carcinoma of extrahepatic bile ducts and gallbladder showed no striking differences in the clinicopathologic and immunohistochemical (CK7/CK20) features, with the possible exceptions that there was a lower rate of bilaterality in the former group and rather greater morphologic diversity in the latter category.

Although the overall information on ovarian metastasis from extrahepatic bile duct and gallbladder carcinomas is limited, the phenomenon is probably more frequent than the number of reported cases would indicate. This is strongly suggested by an autopsy study from Japan in which Fujiwara et al. (27) found ovarian involvement in 7 (22.6%) of 31 women with bile duct carcinoma. The frequency with which the pathologist is confronted with a metastatic tumor of gallbladder or extrahepatic bile duct origin varies throughout the world because of the differing incidences of the primary cancers. In northern Thailand, where many of our cases were identified, this type of metastasis accounted for 7% of metastatic ovarian tumors of nongenital origin, with extrahepatic bile duct origin being more common than the gallbladder (14). Among the Boston cases in this and the prior study (1), the gallbladder was a more frequent site of origin (10/13 cases).

Since the 1990 report by Young and Scully (1), 11 additional cases have been described in the English literature to our knowledge (4–12). A summary of a total of 33 cases derived from these reports and the current study is presented in Table 3. Eighteen cases were from the gallbladder, and 15 were from extrahepatic bile ducts. The mean age at presentation of the ovarian metastases was 56 years (1,4–12). Most patients presented with nonspecific abdominal or pelvic symptoms (pain, distension, or mass). Jaundice was occasionally observed (1,10). Extra-abdominal spread at the time of ovarian metastasis was reported in 4 cases (meninges, lymph nodes, bone, and lung) (8,9). The primary tumors were identified before the ovarian metastases in 9 (27%) of 33 cases, with the interval ranging from 2 weeks to 4 years. In 5 cases (15%), the ovarian metastases were detected 3 weeks to 2 months before the primary tumors. The primary and metastatic tumors were simultaneously identified in 19 cases (58%). Serologic markers at the time of ovarian metastases were variable; alkaline phosphatase was elevated in 75% of cases tested, CA19-9 in 62%, CEA in 45%, and CA125 in 58% (4,6,7,9–11). The serum alkaline phosphatase, CA19-9, and CEA levels tended to be elevated in the bile duct carcinoma cases more frequently than in the gallbladder cases (7–11).

The clinical presentation of many tumors mimicked that of primary ovarian neoplasia. Even with preoperative radiologic investigation, the primary lesions were not always diagnosed before surgery (7,10,11). The operative findings frequently noted abnormalities in and around the primary site that raised suspicion of nonovarian origin, but in some cases, the primary tumor was not recognized or, in others, had been previously removed. In 1 case of hilar cholangiocarcinoma in this study, the primary

TABLE 3. *Reported cases of metastatic carcinoma of extrahepatic bile ducts and gallbladder to the ovary*

Reference	Age (yr)	Primary site	Clinical presentation	Chronology of primary and ovarian tumors (interval)	Laterality	Size (cm)	Epithelial differentiation
Young and Scully (1)	Range, 33–72; mean, 57	Gallbladder, n = 5 Bile duct, n = 1	Abdominal pain, n = 4 Pelvic mass, n = 1 Jaundice, n = 1	Primary first, n = 2 (1–2 yr) Simultaneous, n = 3 Ovarian first, n = 1 (5 wk)	Bilateral, n = 5 Unilateral, n = 1	2.5–13	Endometrioid-like, n = 1 Mucinous, n = 1 Other or nonspecific, n = 4
Lashgari et al. (4)	41	Bile duct	Abnormal uterine bleeding	Simultaneous	Bilateral	5 and 7	Mucinous
Sharma et al. (5)	59	Bile duct	Abdominal distension	Ovarian first (1 mo)	Bilateral	NA	Mucinous
Kim et al. (6)	59	Bile duct	Abdominal mass	Primary first (8−mo)	Bilateral	8 and 18	Mucinous
Ayhan et al. (7)	33	Gallbladder	Abdominal pain and distension	Simultaneous	Unilateral	3	Nonspecific
	73	Bile duct	Constipation and abdominal distension	Simultaneous	Unilateral	6	Nonspecific
Miyagui et al. (8)	43	Gallbladder	Confusion	Simultaneous (autopsy)	Bilateral	17 and 19	Mucinous
Garcia et al. (9)	36	Bile duct	Abdominal pain	Ovarian first (NA)	Bilateral	4.5 and 6	Mucinous
	44	Bile duct	Pelvic pain	Simultaneous	Unilateral	NA	Nonspecific
Jain et al. (10)	45	Gallbladder	Abdominal pain	Simultaneous	Bilateral	NA	Mucinous
Jarvi et al. (11)	82	Gallbladder	Abdominal pain	Simultaneous	Bilateral	NA	Nonspecific
Taranto et al. (12)	52	Gallbladder	Pelvic mass	Primary first (4 yr)	Bilateral	Up to 15	Mucinous
Present series	Range, 21–87; mean, 59	Bile duct, n = 8	Abdominal or pelvic pain/ distension, n = 4	Primary first, n = 5 (2 wk–23 mo)	Bilateral, n = 15	0.22–16.5	Mucinous, n = 5
		Gallbladder, n = 8	Pelvic mass, n = 3 Jaundice, n = 6* Acute abdomen, n = 1 Vaginal bleeding, n = 1 Hematochezia, n = 1 Asymptomatic, n = 1 NA = 2	Simultaneous, n = 9 Ovarian first, n = 2 (3 wk–2 mo)	Unilateral, n = 1		Endometrioid-like, n = 1 Nonspecific or mixed, n = 10

* Includes 3 patients for whom jaundice was not the main presenting symptom.
NA indicates not available.

tumor was not detected until 2 months postoperatively, despite repeated preoperative and postoperative abdominal computed tomographic scans. The relatively occult nature of hilar cholangiocarcinoma has been previously described in one of two examples reported by Garcia et al. (9).

As anticipated, the overall features of the cases pointed, in aggregate, to metastasis, but some comments are indicated. If one uses a size of 10 cm as an arbitrary cutoff, following the inference of a recent study (28), many tumors were "small," but 55% were large ($\geq$10 cm) (Table 3). This is relevant to note inasmuch as although a large size is more typical of primary mucinous neoplasia on average, there are so many exceptions to this observation as to make a size cutoff unreliable in any individual case. Bilateral ovarian involvement, as observed in 28 (85%) of 33 cases, is more reliable in suggesting

metastasis, although obviously primary tumors may be bilateral on occasion. As an example, primary müllerian mucinous cystadenomas are, in our experience, bilateral with appreciable frequency, and it is notable that some of our cases showed areas remarkably similar to these lesions. Surface involvement and a multinodular growth pattern were also common, both very characteristic of metastasis. Morphologic heterogeneity from area to area within an individual slide is also very typical of metastasis and was seen in many of the tumors in our study.

Vessel space invasion was surprisingly uncommon in the current series perhaps because transperitoneal, rather than vascular, spread was the likely major mode of spread to the ovary. Peritoneal carcinomatosis frequently accompanied the ovarian metastases (1,5–10), although it was absent in at least some cases (4,7). Metastasis to preexisting primary ovarian neoplasms as a "collision phenomenon" (17) was seen in 3 patients, 1 with a reported mucinous borderline tumor and the 2 with serous cystadenomas (5,11). Although spread of a metastatic tumor to an ovary independently involved by a common primary neoplasm is occasionally encountered, as the three cases just mentioned would suggest, the bias in cases of this general type should always be to consider the ovarian "primary" neoplasia actually a differentiated metastasis unless evidence to the contrary is overwhelming. Abundant recent literature points out that maturation is a remarkable feature of many tumors when they reach the ovary (18). This maturation phenomenon has, for the most part, been emphasized with regard to tumors having a mucinous morphology, but one aspect of the current series that has resonated with us is the extent to which some of the benign-appearing foci were nonmucinous and could, out of context, be considered serous cystadenomas, or cystadenomas with a cell type so indifferent as to preclude specific cell-type categorization. On the other hand, the nature of the epithelium occasionally suggested its metastatic nature. Signet ring cells were seen in several cases, occasionally in sufficient quantity to warrant a diagnosis of Krukenberg tumor. Their presence is highly suggestive of a metastatic process, although it should be noted that they have been reported in primary surface epithelial tumors, most recently by Che et al. (29) and Reichert (30).

Metastatic nonintestinal carcinoma to the ovary with a colloid carcinoma-like morphology, of which we had three examples, has received little emphasis in the literature. The morphologic features of such cases are similar to ovarian metastases from intestinal colloid carcinomas. That primary colloid carcinoma of the ovary, albeit seen, is rare and should prompt consideration of a metastasis on the basis of that feature alone. Two tumors with focal colloid carcinoma-like areas also demonstrated extensive areas of acellular, dissecting mucin resulting in a pseudomyxomatous appearance. As with the colloid carcinoma-like pattern, extensive mucin dissection is unusual in primary ovarian neoplasia and suggests the possibility of a metastatic lesion. This is a common feature of metastatic appendiceal neoplasms, but our experience with the cases in this study indicates that the biliary system is another possibility to be considered, particularly if suspicion is not otherwise drawn to the appendix.

Metastatic mucinous tumors can be very similar to primary ovarian mucinous tumors grossly and occasionally pose major diagnostic problems microscopically, particularly when there is bland-appearing epithelium or an adenofibroma or cystadenoma-like pattern. More than a third of the tumors in this series had deceptively benign-appearing, single-layered epithelium reminiscent of cystadenoma. Atypical epithelium resembling that of borderline mucinous neoplasia was seen in 42% of tumors. Viewed in isolation, these foci were not readily distinguishable from benign or borderline ovarian lesions. Fortunately, such areas were typically focal, and other regions with greater cytologic atypia and infiltrative growth were easily found and readily diagnosed as carcinoma. Even so, the presence of these bland and borderline-like areas could mislead one into concluding that the carcinoma arose out of a background primary ovarian neoplasm. Not infrequently, well-differentiated glands and cysts dispersed in prominent fibrous stroma strikingly mimicked ovarian adenofibroma, and similar well-differentiated cysts in less conspicuous stroma mimicked a cystadenoma. Similar misinterpretation of such an area as a preexisting ovarian lesion could lead one to wrongly conclude that the entire process was primary in the ovary. Awareness of this phenomenon and attention to the clinical findings, gross features, and other histologic indicators of metastatic disease as noted previously should enable one to avoid this diagnostic pitfall. It is obvious, however, that in a limited sample such as that likely to pertain in the intraoperative (frozen section) setting, this can be a particularly treacherous area.

The metastatic lesion in 1 case demonstrated overlapping features with primary ovarian adenocarcinoma of nonmucinous type because of its extensive papillary growth, serous and endometrioid-like foci,

and focal bland-appearing cuboidal epithelium. The differential diagnosis in cases that have an endometrioid-like morphology is well known and has been much discussed in recent years, dating back to the article of Lash and Hart (25). Given the emphasis this issue has received in the recent literature, we will not repeat it here, but note that a pseudoendometrioid morphology, albeit striking in one of our cases from 1990, is an uncommon feature of metastatic biliary neoplasms.

One of our tumors had a discrete nodule of undifferentiated carcinoma reminiscent of the mural nodules seen in surface epithelial primary carcinomas, most often those of mucinous type. This finding is in general more typical of a primary neoplasm (17), but illustrates that there is overlap in what may be seen in primary and secondary ovarian neoplasia. In another patient, both ovaries were diffusely involved by undifferentiated carcinoma, which represented the sole histologic pattern. A purely undifferentiated morphology is actually more common in primary ovarian carcinomas than metastatic ones. In this case, however, the ovarian tumors resembled the previously resected gallbladder carcinoma, so there was no doubt of its metastatic nature in the ovary. Such examples emphasize the importance of considering many features, both clinical and pathological, in arriving at the final interpretation. Even more unusual overall than having an appearance that resembles undifferentiated carcinoma, not otherwise specified, is to have a spindle cell morphology as in one of our cases. In context, this case was not problematic, but the phenomenon nonetheless highlights yet again the breadth of morphologic overlap between metastatic tumors in the ovary and miscellaneous other neoplasms.

The immunohistochemical profiles of CK7 and CK20 of metastatic tumors originating in the biliary tract and gallbladder overlap significantly with those of primary ovarian mucinous tumors (31,32). However, CK20 immunoreactivity, if present, may be helpful in the differential diagnosis of tumors with a nonmucinous morphology, as this finding is unusual in primary nonmucinous neoplasms of the ovary.

Recently, CK17 and Dpc4 have been reported as potential markers that may be helpful in the differential diagnosis between primary ovarianmucinous neoplasia and metastatic tumors of pancreaticobiliary origin (33,34). Immunoreactivity of CK17 was reported in 42% to 83% of pancreaticobiliary carcinomas, whereas primary ovarian epithelial neoplasms were rarely positive (34,35). Immunohistochemical expression of Dpc4 was reported in 98% of primary ovarian mucinous tumors (33) compared with only 45% to 50% of bile duct carcinomas (36,37). However, Dpc4 expression was variable along the biliary tract as it was observed in 65% to 85% of intrahepatic and hilar cholangiocarcinomas and 81% to 90% of gallbladder carcinomas (36–38). These findings limit the use of Dpc4 immunostaining in cases of metastatic carcinoma from the gallbladder and hilar bile duct.

Just as spread to the ovary may be problematic, so may spread to other sites in the genital tract. This is not the focus of this report but worthy of brief comment because of the presence in one case of spread to the cervix, which mimicked in situ neoplasia at that site. It is important to be aware of the propensity for metastatic tumors to diverse genital tract sites, such as endometrium, fallopian tube, and cervix, to be difficult or even impossible to differentiate from primary neoplasia in isolation. However, as with the evaluation of ovarian metastatic disease, when the entire picture is evaluated, it is usually possible to make a confident interpretation, as in our case in which spotty involvement of the cervix and conspicuous lymphatic invasion were typical of spread to the cervix.

In conclusion, metastatic tumors originating from extrahepatic bile ducts and gallbladder have rather heterogeneous morphology. Although the diagnosis of a metastatic tumor to the ovary is possible in most cases based on standard diagnostic criteria, problems in differential diagnosis may arise because of morphologic patterns that overlap strikingly with those of primary ovarian neoplasms, usually malignant ones but even benign ones if only a limited sample is available, such as in the intraoperative setting. Awareness of the clinical background is usually helpful, but in the occasional case in which the biliary primary is occult, knowledge of the extent to which secondary neoplasia may mimic primary neoplasia and a search for clues, both gross and microscopic, should usually raise enough suspicion for metastasis to prompt appropriate clinical evaluation.

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