16 Pathology of Malignancies Metastatic to the Ovary and of Synchronous Ovarian and Endometrial Carcinoma

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Abstract

Metastases to the ovary, particularly when mucinous, are treacherously difficult to distinguish from primary ovarian neoplasms. In routine clinical practice, this remains among the commonest and worst misdiagnoses in gynecological pathology and one that pathologists and clinicians alike can easily make. The error can have especially dire clinical consequences when metastasis from a silent extraovarian primary presents as an apparent low-stage ovarian carcinoma, but can equally be made, to the detriment of management, in an ovarian neoplasm with a known other primary.

Over the last three decades or so, a volume of literature has appeared emphasizing the features of primary and metastatic ovarian tumors for correct distinction. There are many general clinical, gross, and histological features that are helpful, apart from features specific to metastases from particular types and sites of primary tumor. Metastatic tumors tend to be bilateral, relatively small in size, and show surface involvement and vascular invasion, though exceptions occur. Some histological patterns, such as signet ring carcinoma, colloid carcinoma, and tumors associated with pseudomyxoma peritonei, are essentially exclusive to metastases. Specific tumor types are discussed individually in the chapter.

The vast majority of cases can be accurately diagnosed with due attention to morphological features, with or without the help of immunohistochemistry, and it is only a tiny minority whose true nature may not become apparent till after a period of clinical follow-up.

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Pathology of Malignancies Metastatic to the Ovary

Introduction

It is well recognized that metastases to the ovary may be difficult to distinguish from primary ovarian neoplasms. This is particularly the case with mucinous neoplasms where the possibility of metastasis must be actively considered and excluded. The need for robust MDT correlation with all the clinical, radiological, and biochemical tumor marker information cannot be overemphasized in these situations. The pathological distinction of primary versus metastatic tumors to the ovary has been the subject of many historic and recent papers [1–9]. It is evident that a substantial proportion of tumors previously thought to be primary ovarian neoplasms are likely to have been metastatic, such as those associated with pseudomyxoma peritonei and widely disseminated mucinous carcinomas. Despite this increasing awareness among histopathologists, the distinction remains problematic in current clinical practice.

There are several reasons why this is a particular problem in ovarian pathology. Firstly, the ovary is a site of such a vast array of primary tumors that almost any type of metastatic tumor has an identical ovarian counterpart or a close mimic thereof. Secondly, the ovary, despite its small size, is a vascular organ and, particularly in reproductive life, appears to provide a good soil for metastasis for reasons that are incompletely understood; ovarian metastases are found in 30 % of women dying of cancer [10]. The consequences of this are that tumors metastatic to the ovary are not only common, comprising 6–7 % of all ovarian masses, but often large, dwarfing any manifestations of a primary elsewhere. Overall the incidence of discovering an ovarian metastasis prior to the primary tumor is 1 %, but this varies with primary site; while this may occur in around 1.5 % of breast tumors [11], around 10 % of colorectal metastases [3] and 60–70 % of Krukenberg tumors arise from hitherto undiscovered primaries [12]. Thirdly, metastatic tumors growing within the ovary are often cystic, irrespective of the nature of the primary, exaggerating both the difference from the primary tumor and the similarity to an ovarian neoplasm.

Certain histological appearances complicate interpretation. Ovarian metastases are notorious for demonstrating the phenomenon of "maturation" whereby the metastatic tumor appears better differentiated in part or whole than the primary, making it more difficult to relate the ovarian mass to the primary and also increasing the resemblance to a primary ovarian tumor, where background mimics of benign or borderline elements may be seen. Metastatic solid tumors often demonstrate follicle-like spaces, resembling those seen in a variety of primaries. Stimulation of the background ovarian stroma also produces unique conundrums: the extreme stromal proliferation seen in some Krukenberg tumors may mask the presence of the metastatic carcinoma cells themselves. In addition, metastatic mucinous tumors commonly elicit hormonal manifestations by inducing stromal luteinization leading to sex hormone production and causing clinical and morphological suspicion of a primary neoplasm [13].

The distinction of a metastatic tumor from a primary ovarian neoplasm is paramount as it will influence subsequent patient management. This is of particular importance in certain circumstances.

- In centers where frozen sections are carried out, a pathologist may be asked to make this distinction in order to decide whether to proceed to cytoreductive surgery and staging and occasionally prior to catheter placement for intraperitoneal chemotherapy.
- In certain situations, as when the patient is too ill for major surgery or has a history of a previous malignancy, it is imperative to make the correct diagnosis on a core biopsy so that appropriate treatment can be instituted.
- Accurate diagnosis is required for targeted therapy which may be in the context of a clinical trial.
- Accurate diagnosis enables the patient and her family to obtain correct prognostic information and appropriate counseling.

General Characteristics of Metastatic Ovarian Tumors

There are many general clinical, gross, and histological features that are helpful in this distinction, apart from the features specific to metastases from particular types of primary neoplasms detailed below. These features are discussed below and summarized in Table 16.1. Immunohistochemistry as an adjunct has a definite role in the distinction of a primary ovarian carcinoma from a metastatic tumor; the immunophenotype of mucinous ovarian tumors is summarized in Table 16.2 [14–18]. Most cases, however, can be confidently diagnosed on routine H&E preparations, with adequate clinical history including all the information obtained at a gynecological oncology MDT. A minority of cases remain after thorough workup, further sampling, immunohistochemistry, and, when indicated, clinical investigation that are labeled as carcinoma of unknown primary site [2, 14].

Clinical Features

The diagnostic process should begin before pathological examination. As mentioned above, robust MDT discussion, including a history of previous malignancies, is imperative and if present should prompt careful consideration of the possibility of ovarian metastasis. Metastases to the ovary can arise from any body site, but most commonly these are from the large bowel, elsewhere in the female genital tract, stomach, pancreaticobiliary tract, and breast. Of the various primary sites, those most likely to masquerade as primary ovarian tumors of mucinous type are gastrointestinal, pancreatic or biliary tract, and endocervical adenocarcinomas, while tumors with an endometrioid appearance may represent colorectal metastases. In the presence of an endometrial primary, the diagnosis of metastasis is complicated by distinction from independent endometrioid tumors developing synchronously at both sites; this topic is dealt with separately later in this chapter. With mucinous tumors, the extent of disease is also of value. With rare though significant exceptions, the majority of primary mucinous ovarian carcinomas are usually FIGO stage I or II at presentation, and in broad terms, a widely metastatic mucinous carcinoma is far more likely to be a non-ovarian primary. With very rare exceptions of examples arising in association with teratomas, ovarian tumors in the syndrome of pseudomyxoma peritonei are metastatic, usually from the appendix. Other clinical features which may be helpful are symptoms related to the primary tumor rather than the ovarian mass, such as abdominal pain, rectal bleeding, dyspeptic symptoms, or jaundice. It should be noted that a raised serum CA125 is nonspecific and may occur in significant numbers of cases of metastatic ovarian tumors. Similarly hormonal manifestations, although common in primary ovarian neoplasms, can occur with metastatic tumors.

Gross Features

Laterality: Bilaterality is a strong pointer to metastasis in ovarian carcinomas other than those of serous morphology (Fig. 16.1). Primary endometrioid and mucinous carcinomas are rarely bilateral and if so should prompt consideration of the possibility of metastasis. It should be noted though that metastatic tumors are not invariably bilateral – around 70 % of all metastases are bilateral (WHO) (i.e., 30 % are not), and, conversely, 10 % of bilateral ovarian masses are metastatic tumors [5].

Tumor size: In general, primary mucinous carcinomas are larger than metastatic mucinous carcinomas. One of the widely held reasons for this is the apparent origin of primary mucinous carcinomas from benign and borderline mucinous neoplasms which tend to be the largest ovarian masses overall. Metastatic tumors are usually smaller though they may attain large sizes, and this feature on its own should be regarded as having "soft" significance [2, 5].

Size and laterality: Algorithms have been proposed combining size and laterality in predicting the primary versus metastatic nature of mucinous ovarian masses, particularly at frozen section. These classify bilateral tumors as metastatic, with or without an added size criterion of <10 cm favoring metastasis and > or = 10 cm favoring a primary [5]. This correctly distinguished 84 %

Table 16.1 Features useful in distinction of metastatic and primary ovarian tumors

Feature	Primary	Metastatic	Comment
Laterality	Unilateral	Bilateral	Enlargement in bilateral metastases may not be symmetrical, thereby appearing unilateral on imaging and macroscopic appearance (e.g., in signet ring carcinoma)
Size	Maximum tumor diameter >12 cm	Maximum diameter <10 cm	About 15 % of metastatic tumors will not be correctly assigned on size and laterality criteria; cutoff points of 12 and 13 cm have been published, offering marginally better prediction; it has also been suggested that unilateral tumors 10–15 cm should be considered indeterminate
Extensive intra-abdominal spread (mucinous tumors)	Unlikely in primary ovarian mucinous carcinoma	More likely to be metastatic than primary	An alternative primary site may not be found in all such cases; rare true disseminated ovarian mucinous primaries have been reported
Multinodular growth pattern with intervening normal parenchyma	Not usual	Characteristic	
Surface involvement	Not usual, except in background endometriosis and tumors arising thereof	Characteristic	
Hilar involvement	Absent/not typical	Typical in tumors that have metastasized through hematogenously	
Patterns specifically favoring primary or metastatic carcinoma	Associated benign, borderline, and malignant appearing areas*; complex papillary architecture; association with background changes: endometriosis (seromucinous and endometrioid tumors), Brenner tumor, mature cystic teratoma, Sertoli–Leydig cell tumor, adenofibroma	Signet ring carcinoma; pseudomyxoma peritonei (ovarii); colloid carcinoma; infiltrative pattern of small glands with desmoplastic reaction, single-cell infiltration	*Maturation of ovarian metastases may result in a deceptively similar gradation of features
Extensive vascular invasion	Not usual	Favors metastasis	

of all tumors in two studies [4, 19]), but can be refined by increasing the size cutoff to 12 or 13 cm, the last correctly categorizing 98 % of primary tumors, 82 % of metastases, and 87 % overall [19]. It should be remembered, however, that 10–15 % of tumors will be incorrectly categorized using this approach alone, and all clinicopathological parameters should be carefully evaluated. The most common outliers to a size and laterality algorithm are metastatic colorectal carcinoma, which continues to be diagnostically challenging to the pathologist, and metastatic endocervical carcinoma. When these two diagnoses are in the differential diagnosis, greater vigilance is required when applying this algorithm [19]. Fortunately, as detailed later in the section on individual entities, these are the two primary sites most easy to identify with the help of immunohistochemistry. Pancreatic metastasis may also be problematic, and the use of the algorithm

Table 16.2 Immunohistochemistry in mucinous tumors of the ovary [14–18]

Marker	CK7	CK20	CEA	CA19.9	CDX2	CA125	ER	DPC4/SMAD4	P16	PAX8	Beta-catenin
Ovary, intestinal type	Diffuse, may be focal	Focal, rarely diffuse	Focal or diffuse	Diffuse	Focal	Negative	Negative	Diffuse	Negative or focal	Usually negative	Sometimes positive
Ovary, Mullerian type	Diffuse	Negative	Negative	Negative or focal	Negative	Diffuse	Diffuse	Diffuse	Negative or focal	Positive, usually diffuse nuclear	Sometimes positive
Colorectal	Negative (rectal cancers may be positive)	Diffuse	Diffuse	Diffuse	Diffuse	Negative	Negative	Diffuse	Negative or focal	Negative	Positive
Appendix	Negative, may be positive	Diffuse	Diffuse	Diffuse	Diffuse	Negative	Negative	Diffuse	Negative or focal	Negative	Usually positive, may be negative
Pancreas and biliary tract	Diffuse, may be focal	Negative, may be focal	Diffuse or focal	Diffuse	Focal	Negative	Negative	Negative in about 50 %	Negative or focal	Negative	Variable
Stomach	Diffuse, may be focal	Negative, may be focal	Diffuse or focal	Diffuse	Focal	Negative	Negative	Diffuse	Negative or focal	Negative	Positive
Cervix	Diffuse	Negative, may be focal	Diffuse or focal	Negative	Negative or focal	Diffuse	Negative or focal	Diffuse	Diffuse	Positive	Variable

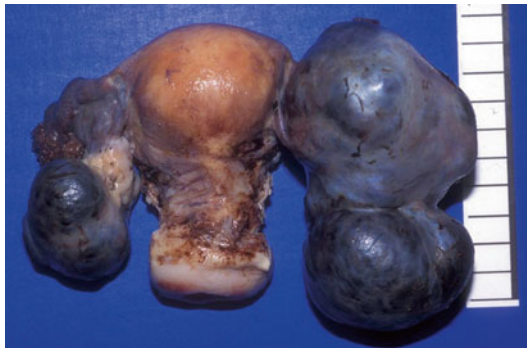

Fig. 16.1 Bilateral involvement of the ovaries is a pointer to metastasis (Courtesy of Dr Nafisa Wilkinson, St James's Hospital, Leeds, UK)

alone may be unhelpful in establishing a definitive diagnosis without adequate clinicopathological correlation.

Surface involvement: In addition to direct spread, tumors metastasize to the ovary via transcoelomic, transtubal, as well as blood-borne and lymphatic routes. Transcoelomic and transtubal spread typically result in surface deposits with characteristic microscopic features detailed below. Serous tumors also involve the surface and this parameter should be evaluated in the light of the histological subtype. Tumors arising via the blood or lymphatics do not involve the surface but manifest other histological features.

Gross features that are not discriminatory: It is important to note that several features on gross examination were found *not* to be of diagnostic value in distinguishing primary from metastatic carcinomas in one study [6] – a cystic gross appearance, the mucinous or non-mucinous appearance of cyst contents, the presence of solid or papillary areas, and the presence of hemorrhage or necrosis.

Histological Features

Bilaterality: While this feature is suggestive of metastasis in non-serous neoplasms, it may not be apparent on gross inspection as metastatic involvement can be disproportional within the two ovaries with histological examination required to confirm the presence of metastasis in an apparently "normal" ovary.

Surface involvement: Surface involvement too may not be conspicuous to the naked eye but only visible on histological examination. The microscopic appearance of the surface nodules, believed to arise from tumor cells directly implanting on the ovarian surface via transcoelomic spread or through the tubes, is characteristic. These often protrude over the ovarian capsular surface. They elicit a florid desmoplastic reaction, which may cause them to appear as depressed foci with surrounding fibrosis. Serous tumors and tumors associated with endometriosis may also involve the surface but do not elicit a desmoplastic reaction or the other features described below. The histological presence of mucin on the ovarian surface is also suggestive of metastasis [6].

Nodular growth pattern: A characteristic finding in metastatic tumors is a multinodular growth pattern within intervening areas of normal ovarian anatomy. Often the individual nodules vary not only in size but also in their histological and cytological content with single-cell infiltration, glandular areas, and cystic areas which may appear deceptively mature. Primarily emphasized in mucinous tumors, but equally applicable to non-mucinous tumors, a nodular growth pattern or a combination of features, described as "heterogeneous nodularity," is strongly suggestive of metastasis [2].

"Maturation": This is a phenomenon observed in metastatic mucinous tumors, whereby the epithelial cells display a range of appearances from highly atypical to bland, mirrored in architectural differences, with the more mature areas appearing more cystic. The appearance results in a dissimilar appearance from the tumor at the primary site and also an impression of carcinoma developing in the background of a benign or borderline tumor [1].

Infiltrative pattern: A widely variable morphological pattern of infiltration with histological features including small glands or tubules as well as single-cell infiltration favors metastasis. Primary mucinous carcinomas with foci of destructive stromal invasion may occasionally show some of these features, but the overall infiltrative pattern is not usually as heterogeneous as that encountered in metastases.

Vascular invasion: This is a distinctly uncommon feature in primary ovarian neoplasms but is found in carcinomas metastatic to the ovary. Involvement of the ovarian hilum and, in particular, hilar vessels is also a feature of blood-borne metastases.

Histological patterns almost exclusively associated with metastasis: Some histological subtypes are almost diagnostic of secondary involvement, namely, signet ring carcinoma, colloid carcinoma, and ovarian tumors associated with pseudomyxoma peritonei. Other than in exceptionally rare cases, usually in association with teratomas and, in the case of signet ring carcinoma, a few unusual mimics, these patterns are virtually diagnostic of metastasis, and relevant investigations should be encouraged.

Histological findings favoring a primary tumor: It is worth listing at this point some general features that favor a diagnosis of a primary tumor. Although these findings are predominantly relevant to mucinous tumors, they are of some utility in other subtypes. Primary mucinous tumors tend to have an expansile invasive pattern in which the neoplastic glands are arranged back to back with no intervening stroma [20]. Other patterns favoring primary tumors are a complex papillary pattern, microscopic cystic glands, and necrotic luminal debris [6] and the presence of mural nodules which are solid areas of a cyst wall that may contain anaplastic carcinoma or sarcomatous components. Background changes that favor origin of the tumor within the ovary are the presence of endometriosis, a mature cystic teratoma, an adenofibroma, a Brenner tumor, or a Sertoli–Leydig cell tumor. In many studies, the presence of benign-appearing and borderline-appearing areas has also been stated to favor primary tumors; but this feature requires cautious distinction from the phenomenon of maturation seen in some many metastases to the ovary.

Histological findings that do not help in the distinction of primary and metastatic tumors: Finally, it is useful to list features that are of no diagnostic value as they may be seen in both primary tumors and metastases. These are the presence of stromal mucin resulting in a pattern described as "pseudomyxoma ovarii," cribriform, villous, or solid growth patterns; focal areas resembling typical colonic carcinoma; and the presence of goblet cells. Tumor grade also does not distinguish between primary and metastatic tumors [6].

Specific Features of Metastases from Different Sites

Krukenberg Tumors

Definition

This classical type of ovarian metastasis is described first. The term Krukenberg tumor should be reserved for tumors showing its classical morphology: these are carcinomas composed of an appreciable component of signet ring cells, arbitrarily defined as occupying >10 % of the tumor [2]. The presence of a prominent stromal component as described in historic papers, although typical, is not considered necessary, as this component is highly variable and its presence and amount are clinically irrelevant. Other tumors composed of cells that may show signet ring morphology, principally clear cell carcinoma and goblet cell carcinoid, should be excluded. The term Krukenberg tumor is often loosely used to describe any metastatic tumor, but this term should be reserved for metastatic signet ring cell carcinoma. Tumors with these features should be regarded as metastatic in every instance. In two-thirds of cases, the primary tumor is not clinically manifest and may be difficult to detect even when specifically sought [12]. Cases of so-called primary Krukenberg tumor are vanishingly rare, and this should be a diagnosis of exclusion [21].

Clinical Features

Krukenberg tumors most commonly metastasize from the stomach. Their incidence in the ovary depends on the incidence of gastric carcinoma, and these are most common in Japan. Gastric signet ring cell carcinoma is reported to be four times more likely to metastasize to the ovary than any other cancer in the body. This may be because of its high propensity for vascular spread and the fact that these tumors occur in younger women when the ovary is more vascular. The average age

of patients is 45. Clinically these manifest with signs of an ovarian mass or, especially in pregnant women, with hormonal manifestations due to stromal luteinization and hormone production; often the hormonal manifestations are androgenic. In other cases presentation may be due to metastasis to sites other than the ovary. Notably in approximately 30 % of cases, the patient does not have obvious signs or symptoms relating to the primary tumor. In terms of origin three-fourths of Krukenberg tumors originate from gastric primaries. The remainder arise from the large bowel (11 %), breast (4 %), appendix (3 %), biliary tract (3 %), and rarely other sites. These tumors have a poor prognosis [22].

Pathology

Grossly, these tumors are typically bilateral, solid masses with a smooth but bosselated surface. About 80 % of cases are macroscopically bilateral while in the remainder the involvement of the apparently normal ovary may only be detected on histological examination; a factor that can be misleading during frozen section evaluation. The average size is 10 cm. The cut surface varies with the relative amounts of extracellular mucin and stromal proliferation. Typically, the cut surface is solid, firm, and white, but nodularity, cystic change, a soft consistency, and a yellow appearance due to luteinization may occur. Often the periphery of the tumor is firm and dense producing a peripheral rind with a softer center.

Signet ring cells have a characteristic appearance in that they are round or polygonal cells with an eccentric nucleus that is compressed to the periphery by a large pale mucin-filled vacuole (Fig. 16.2). Although most cases show cells with these characteristic appearances, there are variations. Sometimes the cytoplasm is not pale but densely eosinophilic (Fig. 16.3). In other instances, the vacuole contains a targetoid inclusion (Fig. 16.4). In some cells the nuclei may be central rather than eccentric, resulting in a strong resemblance to clear cell carcinoma. There are usually large numbers of cells which have very little or no mucin. The tumor cells are in solid sheets but may appear nested or seen in strands or singly separated by stroma.

It is important to note that although a diffuse pattern of signet ring cells is pathognomonic, it is seldom seen in pure form. A degree of gland formation is often present (Fig. 16.5). This is in the form of small- and medium-sized tight tubules lined by cuboidal or flattened cells (Fig. 16.6). Occasionally, larger glands and cysts may also be seen (Fig. 16.7). It is also not uncommon to see nests of tumor cells containing goblet cells, identical to those seen in goblet cell carcinoids

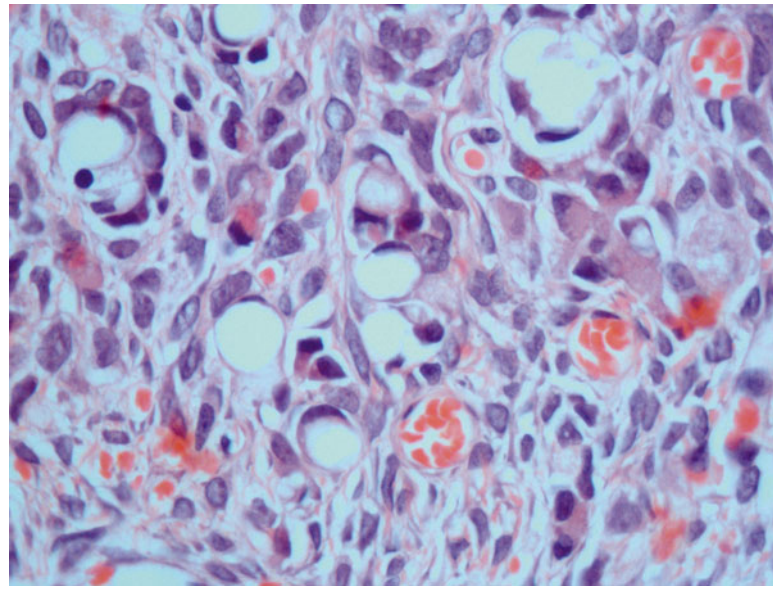

Fig. 16.2 The characteristic appearance of signet ring cells: these are round with an eccentric nucleus that is compressed to the periphery by a large pale mucin-filled vacuole

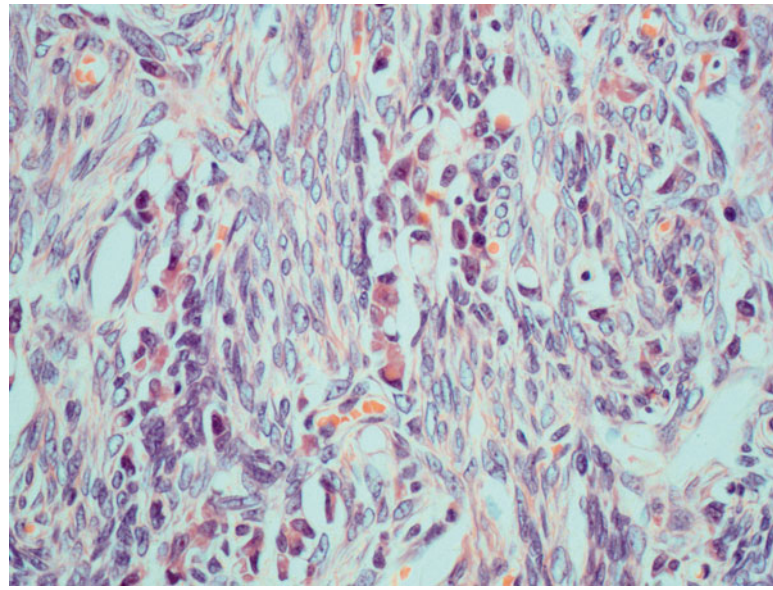

Fig. 16.3 Sometimes cells in signet ring carcinoma may show densely eosinophilic cytoplasm

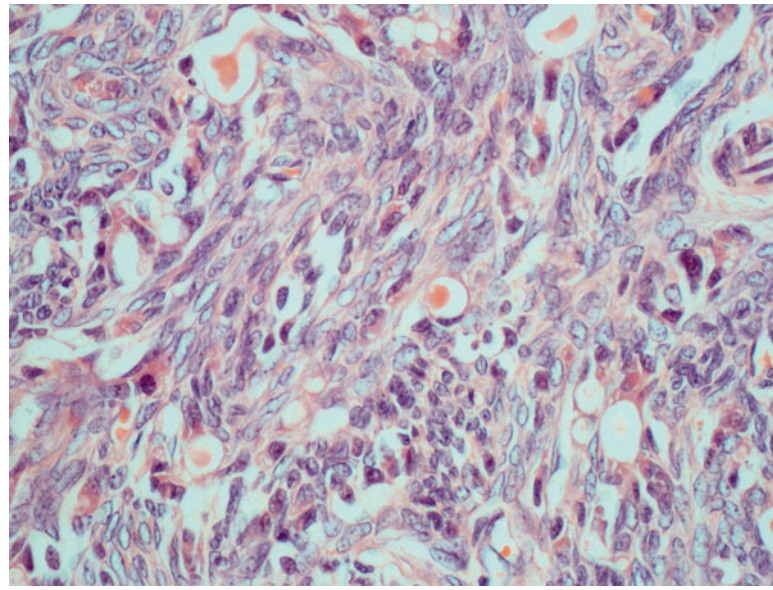

Fig. 16.4 Signet ring cell with eosinophilic targetoid inclusion

of the appendix. These are usually negative for neuroendocrine markers or may show focal positivity which does not preclude the diagnosis of Krukenberg tumor.

A characteristic feature of Krukenberg tumors is the stromal proliferation. The frequent prominence of this component led to its first description as "*fibrosarcoma ovarii mucocellulare* (mucinous sarcoma)" whereby the stroma was considered to be one component of a biphasic tumor. It was soon recognized that the stroma is reactive and very variable in amount and histological pattern. The stroma may be markedly prominent to the point of almost obscuring the single pale tumor cells; this is a known diagnostic pitfall (Fig. 16.8). In such cases, the stroma is cellular and shows a storiform arrangement of cells which are not atypical, resembling cellular fibroma. The combination of a cellular stroma with bland-appearing glandular structures may

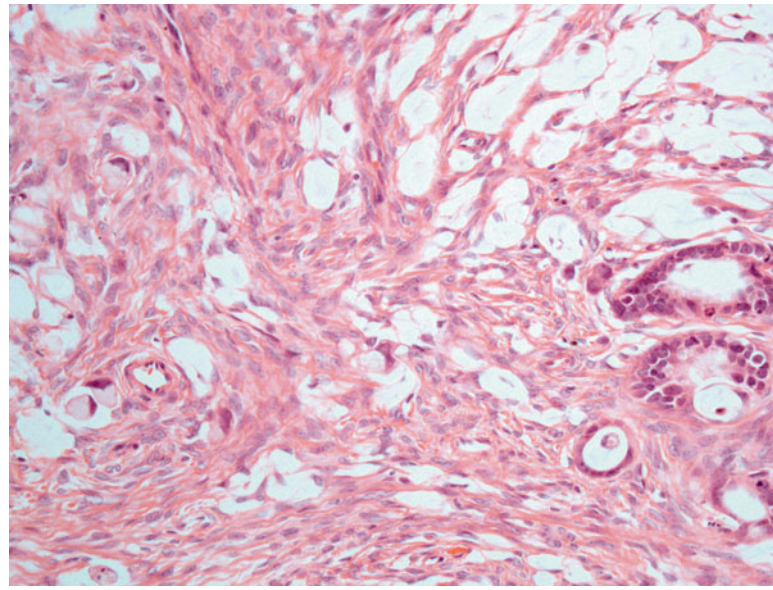

Fig. 16.5 Krukenberg tumor – it is common for the diffuse pattern of signet ring cells to be accompanied by glands and tubules; in some tumors the majority of the architecture may in fact be glandular

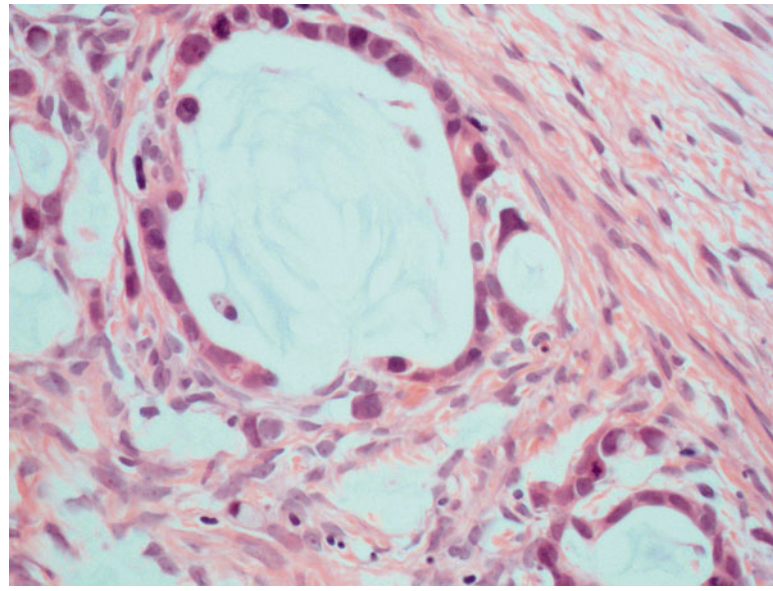

Fig. 16.6 Glands and tubules in Krukenberg tumors are often lined by a flattened, cuboidal, and deceptively bland epithelium

result in a pattern resembling an adenofibroma. In other cases the stroma is less cellular and may be markedly edematous, with small pale groups of tumor cells at the periphery, another pitfall. Alternatively, it may be in the form of strands separating the tumor cells and producing a pseudolobular pattern. In some cases thin wispy strands of stroma enclose extravasated mucin or compressed mucin-filled tumor cells resulting in a "feathery" appearance (Fig. 16.9). Finally, the appearance of the stroma may vary from one area to another in the same tumor, and it is common for the peripheral subcapsular areas to be more fibrous and dense with the central areas being more cellular and rich in tumor cells. In some tumors the stroma is inconspicuous. Another feature of the stromal proliferation seen most commonly in pregnant women is the presence of luteinized stromal cells, singly or in aggregates.

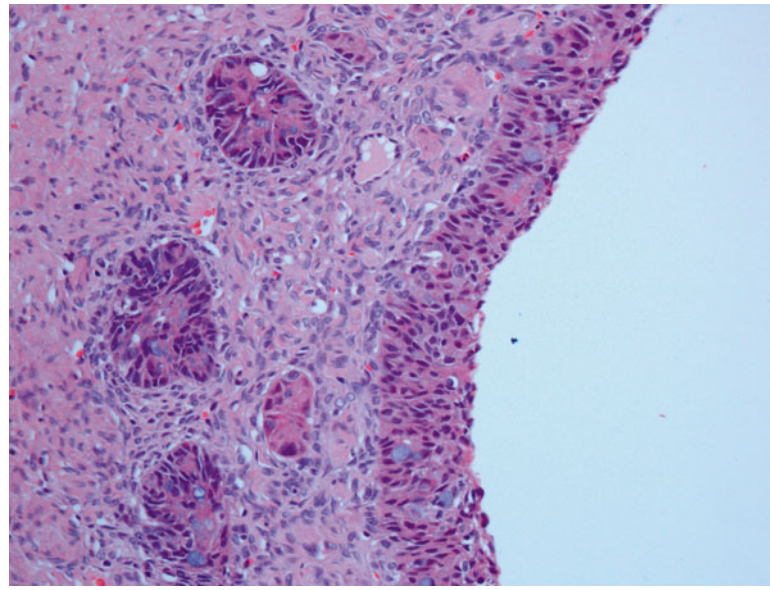

Fig. 16.7 Cystic areas are rarely present in signet ring carcinomas

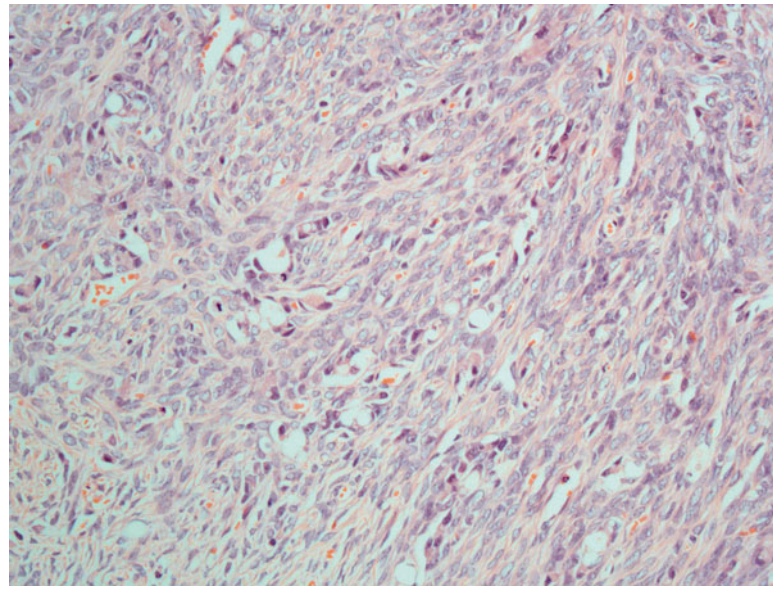

Fig. 16.8 Krukenberg tumor with markedly cellular stroma; this may sometimes obscure the scattered pale malignant cells

Other features are the common presence of lymphatic and vascular invasion, especially at the periphery of the tumor, the ovarian hilum, and at extraovarian sites such as the fallopian tubes and the uterus. Signet ring carcinoma is believed to metastasize hematogenously or by retrograde lymphatic spread, and surface involvement is not as common as in other metastases.

The diagnosis can be confirmed by positive staining for cytoplasmic mucin, using PAS after diastase digestion or mucicarmine. A panel of immunohistochemical markers should be used (see Table 16.2) although subclassification of the gastrointestinal primary tumor by immunohistochemistry is often unhelpful, and endoscopic examination together with an informed review by the radiologist at MDT can usually identify the site of primary origin. In general, gastric tumors are positive for CK7 in 55 % cases and CK20 in 70 %; therefore, dual marker profile expression is

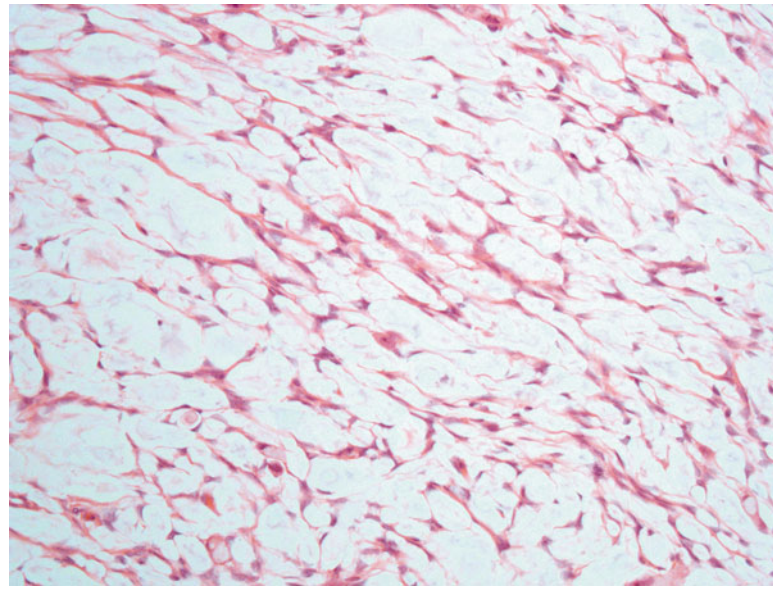

Fig. 16.9 Krukenberg tumor with thin wispy strands of stroma enclosing extravasated mucin or compressed mucin-filled tumor cells resulting in a "feathery" appearance

not uncommon (CK7+/CK20+). In addition they are CDX2 and Hep Par 1 positive and negative for estrogen receptor (ER). Tumors of colorectal origin are usually CK7−/CK20+ and also positive for CDX2, MUC2, and MUC5AC and negative for MUC1, Hep Par 1, and ER. Appendiceal tumors are usually CK7−/CK20+ or may show a CK7+/CK20+ profile and are otherwise similar to colorectal primaries. Tumors metastatic from the breast are positive for CK7, MUC1, and ER.

Differential Diagnosis

Clinicopathologically Krukenberg tumors can mimic sex cord–stromal, particularly Sertoli–Leydig cell tumors. This is because of the similar age incidence, frequent androgenic manifestations, and morphological overlap. Sertoli–Leydig cell tumors show a tubular component and, in case of heterologous differentiation, may have goblet cell containing glandular elements. Prominent stromal luteinization in Krukenberg tumors may be indistinguishable from a Leydig cell component. Furthermore, Sertoli–Leydig cell tumors can have cells resembling signet ring cells although these are invariably seen in association with goblet cell carcinoid-like neuroendocrine areas in cases with heterologous differentiation. The distinction between these tumors is by demonstration of a diffuse mucin-containing epithelial cell component and the greater atypia which may occur in Krukenberg tumors. Other non-epithelial mimics are sclerosing stromal tumors and signet ring stromal tumors; both of these can be distinguished by their other typical features and by the presence of positive lipid and negative mucin stains. Dysgerminoma also falls in the differential diagnosis of a solid tumor in a young woman, and this can on occasion show cells with eccentric nuclei resembling signet ring cells; however, these are negative for mucin stains and show other characteristic morphological and immunohistochemical features.

A few epithelial tumors may resemble Krukenberg tumor, most commonly clear cell carcinoma. Clear cell carcinomas can have signet ring cells, and conversely Krukenberg tumors may show cells with central rather than eccentric nuclei, resembling clear cells. Mucin stains are useful in distinction as the defining feature of Krukenberg tumors is intracytoplasmic mucin. Mucin may be seen in clear cell carcinoma; however, this is never intracytoplasmic, but seen within glandular lumina or over the cell surface. Clear cell carcinoma with cells resembling signet ring cells always shows areas with more typical morphology. Papillary architecture, seen frequently in clear cell carcinoma, never occurs in Krukenberg tumors. Serous, endometrioid, and

undifferentiated carcinomas may also show signet ring cells, but these are rarely frequent enough to cause a diagnostic problem. Rare examples of primary mucinous ovarian neoplasms containing signet ring cells have been reported, but the features of these differ from those of the usual Krukenberg tumor; it is recommended that these should be classified according to the underlying background neoplasm with a notation concerning the signet ring cell component, rather than being labeled as "primary Krukenberg tumors" which are exceedingly rare. Primary goblet cell carcinoids may show abundant signet ring cells and can be diagnosed by widespread neuroendocrine differentiation on immunohistochemistry. Tumors of mesothelial origin, including adenomatoid tumor and malignant mesothelioma, may show signet ring cells, but these are usually accompanied by other typical features, and epithelial mucin stains as well as immunohistochemistry for mesothelial markers can help in distinction.

Metastases from Colorectal Carcinoma Including Appendiceal [23] and Intestinal-Type Gastric Carcinoma [24]

Clinical Features

Tumors of colorectal origin top the list of ovarian metastases that can be mistaken for a primary ovarian tumor [25]. Overall ovarian metastasis occurs in about 7 % of colorectal cancers. In about half of these, the ovaries are involved as part of widespread peritoneal involvement while in the remainder the ovarian metastasis is the sole or predominant site of metastatic disease. A history of previous colorectal cancer is present in about 75 % cases; from this perspective one study has shown that an ovarian mass developing in a patient with a known history of colorectal cancer will turn out to be metastasis in 57 %, benign in 26 %, and a new primary ovarian malignancy in 17 % of cases [26]. In about 10 % of cases in the literature and in up to one-third of cases in some series [27], the ovarian mass may be the first clinical manifestation of a bowel cancer, and due vigilance by the pathologist is required to make the correct diagnosis. There are significant clinical differences between ovarian metastases developing in women with a known history of bowel carcinoma and a silent bowel primary. In comparison with women with metastasis from a known colorectal primary, those with no previous history have a greater likelihood of being significantly younger, presenting with symptoms and signs related to the ovarian mass and without any features related to the primary bowel tumor, having elevated CA125 levels, occasionally having large apparently unilateral tumors which may be mucinous, and show a CK7+/CK20+ immunophenotype [28]. In most cases the primary is discovered intraoperatively or following correct diagnosis of the ovarian mass, while in a small minority of cases, the colorectal tumor becomes apparent some months to years after the ovarian mass is removed.

There is a wide age range at presentation in the reported literature of 12–85 years [3, 27]. A few patients have hormonal manifestations such as abnormal uterine bleeding or breast tenderness, related to stromal luteinization. About 80 % of all metastases arise from primary tumors situated in the rectum or sigmoid, the remainder being within the descending colon, ascending colon, and cecum. Excluding tumors associated with pseudomyxoma peritonei, described below, metastases of appendiceal origin show broadly similar features to other intestinal tumors; it is important to note that the appendix in such cases is often firm and thickened but not grossly enlarged by a discrete mass and is therefore a classical silent primary [23]. A small number of intestinal metastases are from the small bowel. The routes of spread to the ovary are direct, transcoelomic, hematogenous, and retrograde lymphatic.

Pathology

On gross examination these tumors more often appear unilateral to the naked eye than Krukenberg tumors. They are large masses with an average size of 10 cm and may be ruptured or show surface involvement. These are solid necrotic masses with a minor cystic component and not mucinous in the majority of cases.

Histologically, metastases from the colon usually have an endometrioid appearance

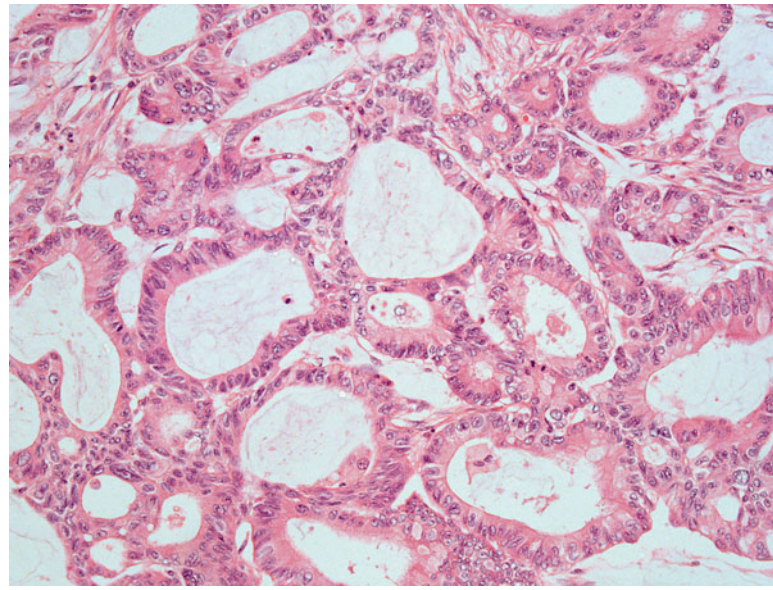

Fig. 16.10 Metastatic colorectal carcinoma often closely resembles primary endometrioid carcinoma

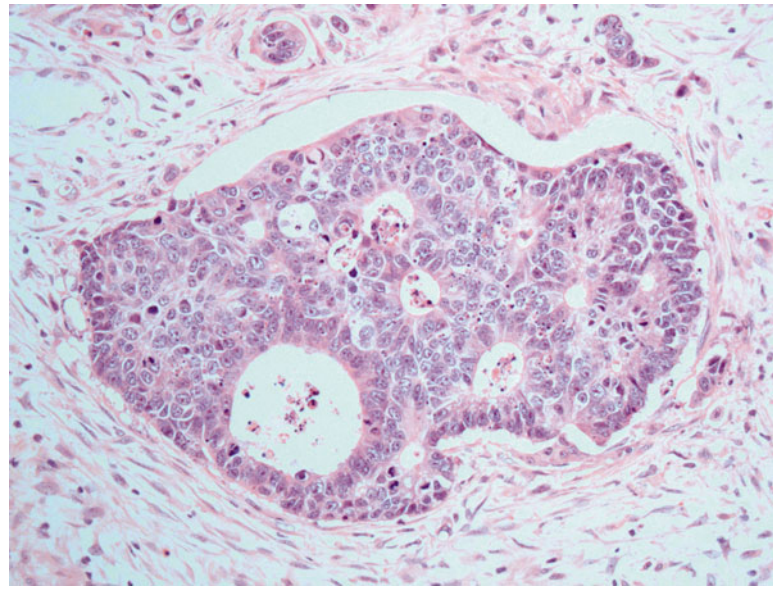

Fig. 16.11 On close inspection, despite the superficial resemblance to endometrioid carcinoma, metastatic colorectal carcinomas show a strikingly greater degree of nuclear atypia than would be seen in an endometrioid carcinoma of the corresponding architectural grade

(Fig. 16.10) [25]. Only a minority of cases are mucinous, rarely have a clear cell appearance, or may show a combination of these patterns. The endometrioid-like differentiation resembles endometrioid ovarian adenocarcinoma, with glands lined by stratified epithelium which does not show conspicuous mucin secretion. These tumors are composed of glands of varying sizes lined by non-mucinous columnar cells which show marked cytological atypia and frequent mitoses (Fig. 16.11). Two characteristic histological features have been described which must be applied judiciously as they may be seen occasionally in primary ovarian tumors. These are a "garland pattern" in which cystic glandular structures containing necrotic debris are surrounded by round tubular glands, arranged in a cribriform pattern, and "dirty necrosis" consisting of necrotic material with karyorrhectic debris (due to breakdown of carcinoma cells)

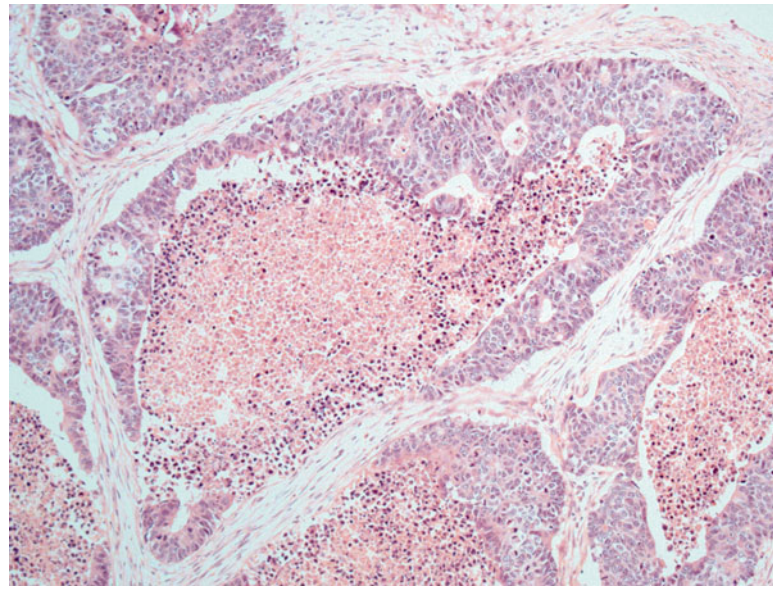

Fig. 16.12 Metastatic colorectal carcinoma exhibiting a "garland pattern" of cribriform glands with "dirty necrosis" consisting of necrotic material with karyorrhectic debris

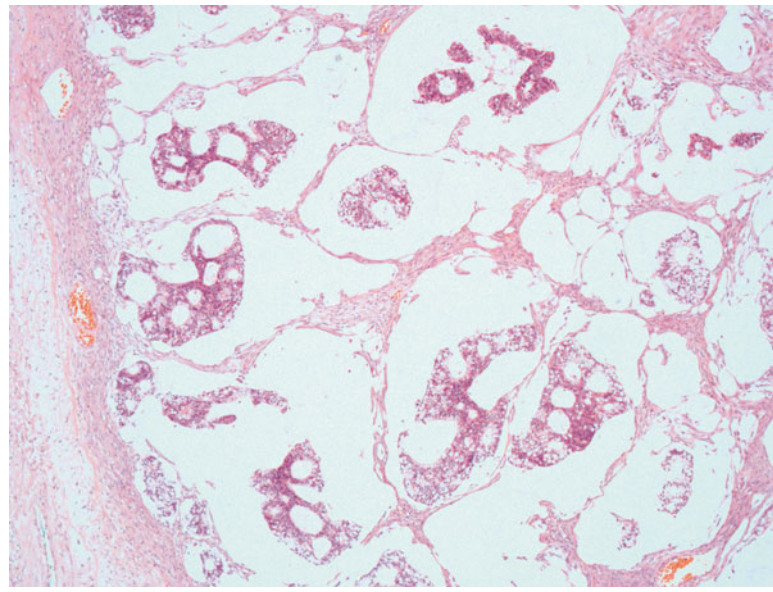

Fig. 16.13 Metastatic carcinoma with colloid carcinoma pattern characterized by malignant epithelium and glands within large pools of extracellular mucin

which can be seen within garlands and neoplastic glands (Fig. 16.12). In metastatic tumors with endometrioid differentiation, the absence of squamous metaplasia, adjacent endometriosis, or an adenofibroma may help make the distinction from primary endometrioid carcinomas. Also helpful are scattered cells with goblet cell morphology or cytoplasmic mucin secretion which are often present in metastatic colorectal carcinomas.

Some examples of colorectal metastases are frankly mucinous, with cystic and glandular structures lined by mucin-secreting epithelium, as with other mucinous metastases. There is one pattern of mucinous carcinoma which occurs almost exclusively in metastatic carcinoma, usually of colorectal origin: this is the so-called colloid carcinoma pattern. This is characterized by malignant epithelium and glands within large pools of extracellular mucin (Fig. 16.13). Such

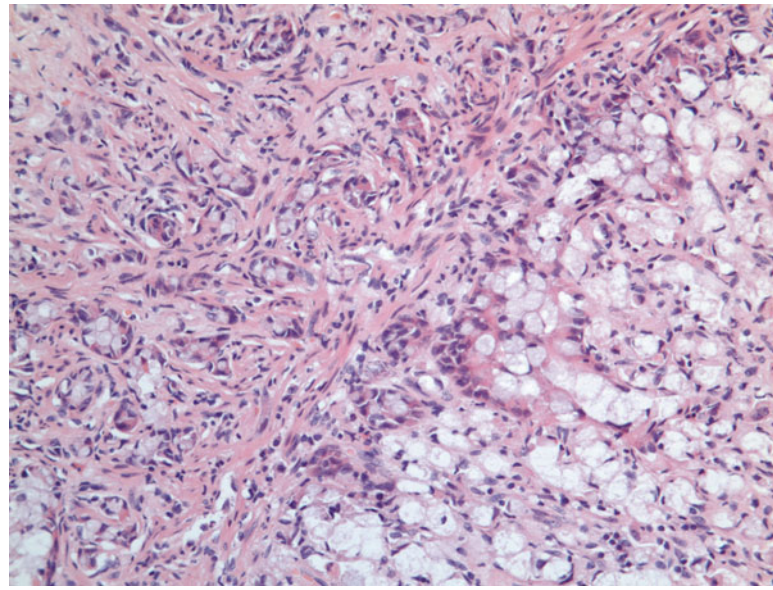

Fig. 16.14 Malignant metastatic goblet cell carcinoid (mixed adenoneuroendocrine carcinoma) in the ovary (Courtesy of Dr Nafisa Wilkinson, St James's Hospital, Leeds, UK)

a pattern is rare in primary mucinous ovarian tumors and metastasis, including one of appendiceal origin, and should be vigorously excluded.

Colorectal tumors can also present as classical Krukenberg tumors with signet ring cell morphology or a combination of signet and intestinal-type differentiation. Those of appendiceal origin may show prominent tubular differentiation, prompting a consideration of goblet cell carcinoid though it should be remembered that true appendiceal goblet cell carcinoids rarely metastasize to the ovary [3] (Fig. 16.14).

A small minority of colorectal tumors metastatic to the ovary may show clear cell morphology, resembling clear cell carcinoma or a secretory variant of endometrioid carcinoma. The presence of bilaterality, focal mucinous differentiation, and colloid-like secretion within gland lumina and the lack of characteristic features of clear cell and endometrioid carcinoma, as well as confirmatory immunohistochemistry, should help to establish the true nature of the tumor.

In all types of tumors, the stroma may be edematous or cellular, and stromal luteinization may be seen.

On immunohistochemistry, colorectal origin is easier to distinguish with immunohistochemistry showing CK7−/CK20+/CDX2+ pattern of reactivity in the majority of cases. It should be noted that while the majority of tumors show a CK7−/CK20+ immunophenotype, this is not specific for colorectal tumors and may be seen with gastric and other primaries as discussed above. The CK7−/CK20+ phenotype is dependent on tumor location and grade of the colorectal primary; while one study has reported this pattern to be more likely to be seen overall with left-sided and better-differentiated tumors [29], another study has reported that rectal tumors are CK7+ in 74 % cases [30]. Around 70 % of gastric carcinomas [29] and 50 % of appendiceal carcinomas [23] are CK7 positive. Other markers such as beta-catenin and P504S and many others have been reported to improve specificity but are not in routine laboratory usage [14, 31–33]. Differential expression of mucins, particularly MUC2 and MUC5AC, is also reported to be useful [34].

Differential Diagnosis

For reasons already emphasized, the most important differential is with primary epithelial ovarian carcinoma, particularly endometrioid. Primary endometrioid carcinomas are usually unilateral, unlike metastatic carcinomas. These arise in a background of endometriosis or may show an associated adenofibromatous component. The carcinoma often shows focal squamous metaplasia which is not a feature of colorectal

tumors. These three features, namely, endometriosis, adenofibroma, and squamous differentiation, have been stated to be a classical triad of confirmatory endometrioid differentiation which should prompt one to favor a primary over a metastasis. Apart from these associated changes, the most helpful feature is the greater atypia and mitotic activity seen in metastatic colorectal tumors; the glandular architecture undoubtedly bears a superficial and sometimes strong resemblance to endometrioid carcinoma, but the nuclear atypia and mitosis are often out of proportion to that usually expected in a low-grade (gland-forming) endometrioid carcinoma. This appearance should prompt a search for mucin secretion which may be subtle and focal.

Tumors of colorectal origin with an endometrioid pattern can be distinguished from ovarian endometrioid carcinomas using ER, CA125, CK7, CK20, CDX2, and CEA [14]. Colorectal tumors are generally diffusely and strongly positive for CK20 and negative for CK7; this pattern is highly specific but not diagnostic of colorectal origin [29]. These are positive for CEA and CDX2 and negative for ER and CA125. Endometrioid ovarian carcinomas on the other hand are diffusely positive for CK7, as well as ER and CA125 and negative for CK20 and CEA. CDX2 staining may be present in endometrioid carcinoma, and it is useful to note that squamous morules are often positive. Staining for CEA should be interpreted carefully in tumor cells as necrotic debris and inflammatory cells may be positive.

Immunohistochemistry is less helpful in metastatic colorectal tumors with mucinous morphology as these show much greater overlap with primary ovarian tumors which usually have an enteric phenotype (see Table 16.2). Primary mucinous intestinal-type ovarian tumors are usually diffusely positive for CA19-9 and may be focally or less often diffusely positive for CEA, CDX2, and CK20; alternatively, they may be negative for these markers. CK7 staining tends to be *diffusely* positive in ovarian primaries and this is a useful discriminant, as most colorectal tumors are negative or at most focally positive, although this is dependent on the location and differentiation of the primary tumor [14, 29]. It should be remembered that a proportion of colorectal metastases may show a CK7+/CK20+ profile, and rare examples may be negative for both markers. Furthermore, 19 % of gastric carcinomas may be CK7−/CK20+ in common with tumors from other locations, such as the biliary tract. Mucinous tumors with a colloid carcinoma pattern are almost always metastatic.

The distinction of the rare metastatic colorectal carcinomas with a clear cell pattern has been mentioned above.

Mucinous Ovarian Tumors in the Presence of Pseudomyxoma Peritonei

Definition and Clinical Features

Pseudomyxoma peritonei (PMP) is a clinical term describing the presence of abundant mucoid or gelatinous material within the pelvis and abdominal cavity surrounded by fibrous tissue [10], which is caused by rupture, leakage, or metastasis of a mucinous neoplasm within the abdomen. It is now well accepted that this is almost always of appendiceal origin with secondary ovarian involvement and does not occur with primary ovarian mucinous neoplasms with the exception of rare cases in association with teratomas [8, 35].

Pathology

The appendiceal tumor is typically a low-grade mucinous neoplasm which may not show obvious invasion (Figs. 16.15 and 16.16). There are associated bilateral or right-sided large multicystic ovarian mucinous tumors, which develop secondarily after incorporation of mucin and mucinous epithelium from the cortical surfaces into the ovarian parenchyma. The presence of mucin over the ovarian capsular surface is characteristic. On cut section the ovaries resemble bags of viscid mucin.

Histologically the cysts are lined by very tall columnar cells bulging with mucin which leaks out of the luminal surface of the cells (Fig. 16.17). The cells have a bland or only mildly atypical appearance. Dissection of mucin into the ovarian stroma results in *pseudomyxoma ovarii* (Fig. 16.18); while it is

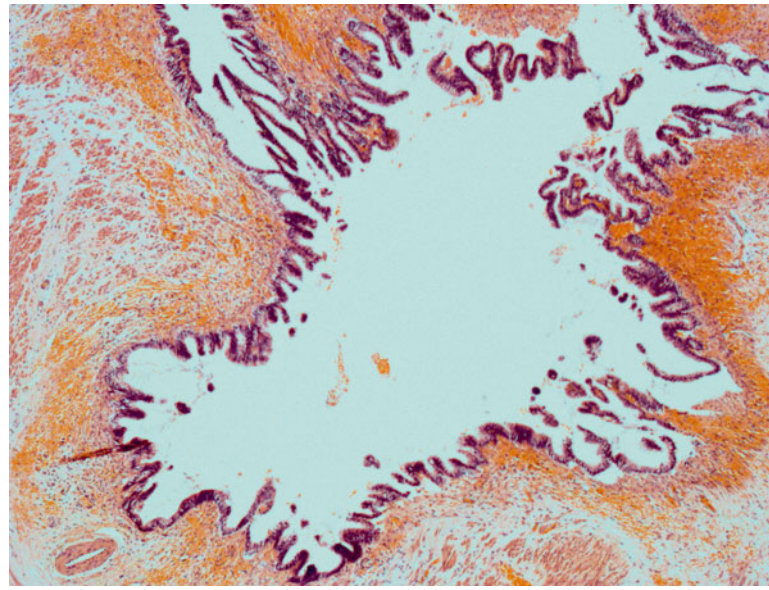

Fig. 16.15 The appendiceal tumor in cases of pseudomyxoma peritonei is typically a low-grade mucinous neoplasm which may not show obvious invasion

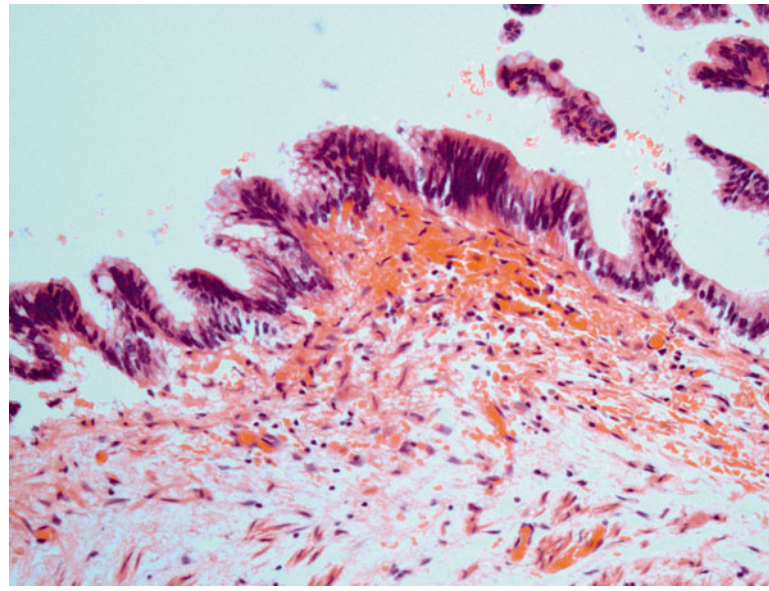

Fig. 16.16 Lining epithelium of low-grade appendiceal mucinous neoplasm shows relatively bland nuclear features

generally felt that this feature should strongly suggest metastasis, a study comparing numerous histological features in primary and metastatic mucinous ovarian carcinomas found it to be of no value in this distinction [6]. There is a variable amount of stroma between the cysts. The presence of mucin on the capsular surface may be confirmed histologically and it may or may not be associated with a desmoplastic reaction (Fig. 16.19).

Differential Diagnosis

Distinction from a primary ovarian neoplasm may be necessary. Primary ovarian mucinous neoplasms may cause mucinous ascites or PMP; these always occur in the context of mature cystic teratomas. Accurate diagnosis requires removal and histological examination of the entire appendix. This may show features of a mucocele, a frank neoplasm, or, in some instances, appear completely normal to the naked eye. Like the

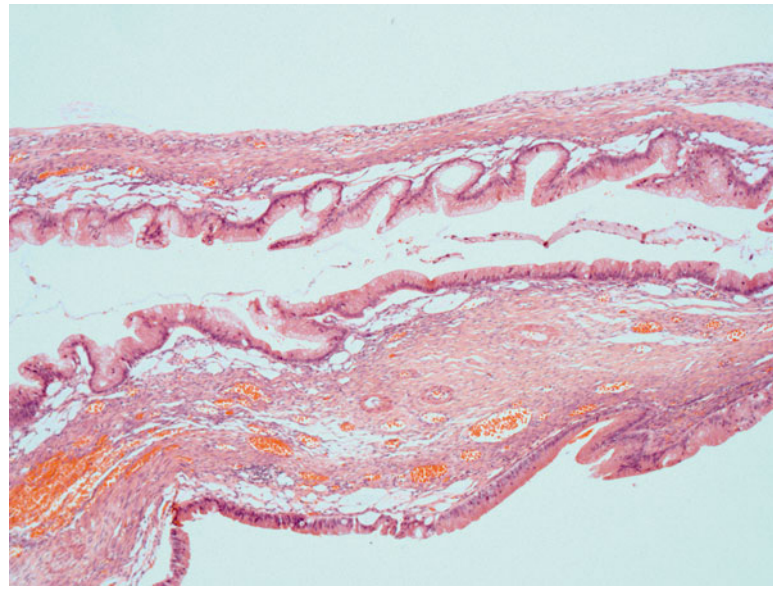

Fig. 16.17 Ovarian tumors in pseudomyxoma peritonei show mucin-filled cysts lined by very tall columnar cells bulging with mucin

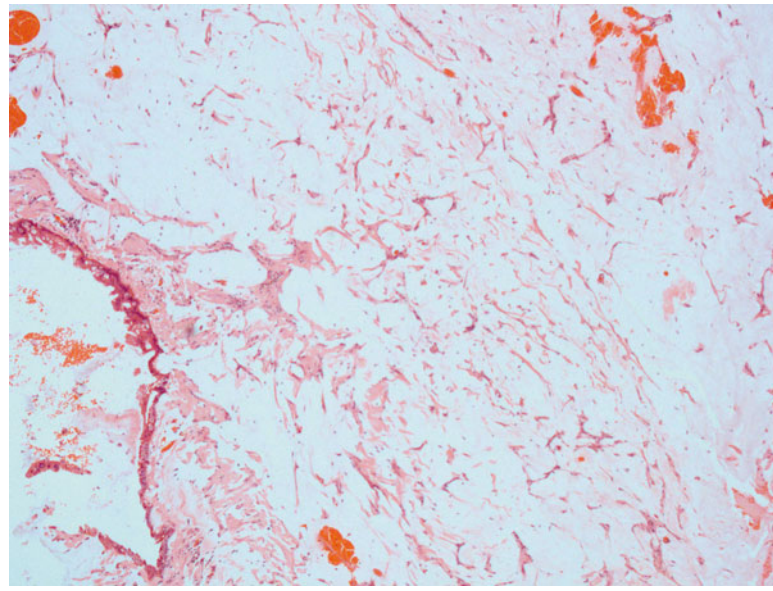

Fig. 16.18 Mucin extravasation in pseudomyxoma peritonei

tumor in the ovary, the appendiceal tumor is low grade and is composed of tall columnar cells bulging with mucin. There may be frank infiltration of the wall of the appendix with mucin on the serosal surface, but some cases do not show these features; it is postulated that sites of previous rupture may have been sealed off by fibrosis in these cases [36, 37].

Tumors associated with PMP may be metastatic from other sites, usually the large bowel. These tend to show greater atypia than those arising from the appendix.

Metastatic Tumors of Pancreatic and Biliary Tract Origin

Clinical Features

Tumors of the pancreas may metastasize to the ovary; an autopsy series showed this to be the third commonest site of primary disease following gastric and breast carcinoma [38]. In clinical

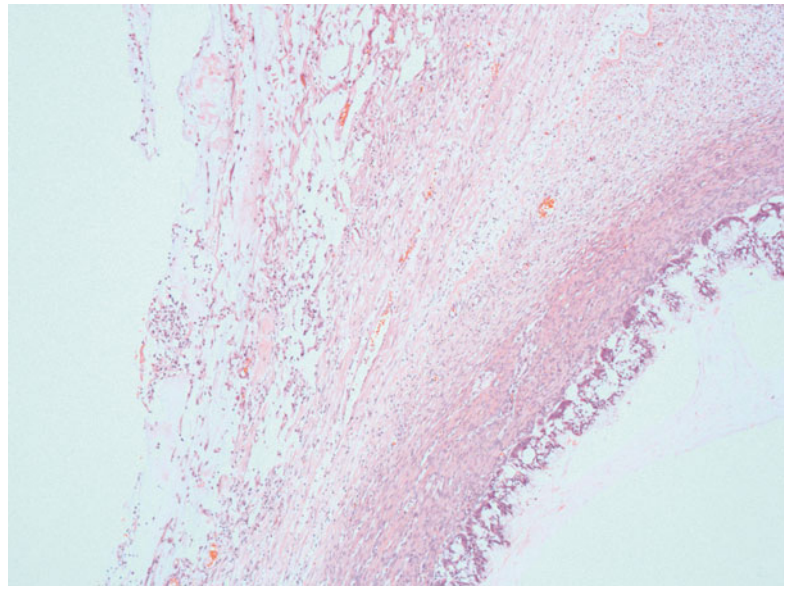

Fig. 16.19 Surface mucin in pseudomyxoma peritonei or other forms of metastatic mucinous carcinoma may be seen histologically, applied to the surface with or without a desmoplastic reaction, even when not macroscopically obvious

practice, these account for 7 % of nongenital tract and 19 % of tumors of gastrointestinal tract origin metastasizing to the ovary. Most of the metastases are from pancreatic ductal carcinomas, with other tumor types more rarely encountered. Metastases from the gall bladder and extrahepatic biliary tree are generally considered rare, although accounting for a significant number of cases in countries such as Thailand where there is a higher incidence of cholangiocarcinoma. Pancreaticobiliary tumors can be difficult to distinguish from primary ovarian mucinous carcinomas owing to significant morphological and immunohistochemical overlap.

These have been encountered in women aged between 21 and 87 years with a mean age of 59 years. In 6 % of cases in a series of pancreaticobiliary tumors [39] and in as many as 31 % of a series composed solely of gallbladder and biliary tract metastases [40], the ovarian tumor was detected prior to the detection of the primary. In most cases the primary tumor was detected at the same time as that in the ovary. Where follow-up was available, the majority of patients had died of disease after a mean period of 9 months. The correct diagnosis is therefore of importance because of the vastly different clinical outcomes. The majority of primary mucinous ovarian neoplasms behave in a clinically benign fashion.

Pathology

About 90 % of cases are bilateral, although in a minority of cases involvement of the second ovary may be only identified on histological examination. These tumors show an average size of approximately 10 cm, but range from 2 to 21 cm, and may be solid, solid–cystic, or multicystic. Capsular surface involvement is seen in 40 % of cases and in 66 % on microscopic examination. Around 60 % of tumors show a multinodular growth pattern, either grossly or histologically.

On histological examination, the tumors are usually mucinous and show a variation in histological patterns. Areas resembling borderline tumor and/or a cystadenofibromatous pattern are seen in almost 70 % of cases. An infiltrative growth is seen at least focally in 80 % of cases (Fig. 16.20). Other patterns which may be encountered are an endometrioid-like pattern, a small gland pattern (especially in metastasis from intrahepatic cholangiocarcinoma (Fig. 16.21) [41]), colloid carcinoma, Krukenberg tumor, or undifferentiated carcinoma [3, 40, 41]. A papillary growth pattern closely simulating a primary Mullerian malignancy has also been present on rare occasion [40].

On immunohistochemistry the tumor cells are always positive for CK7 and coexpress CK20 in

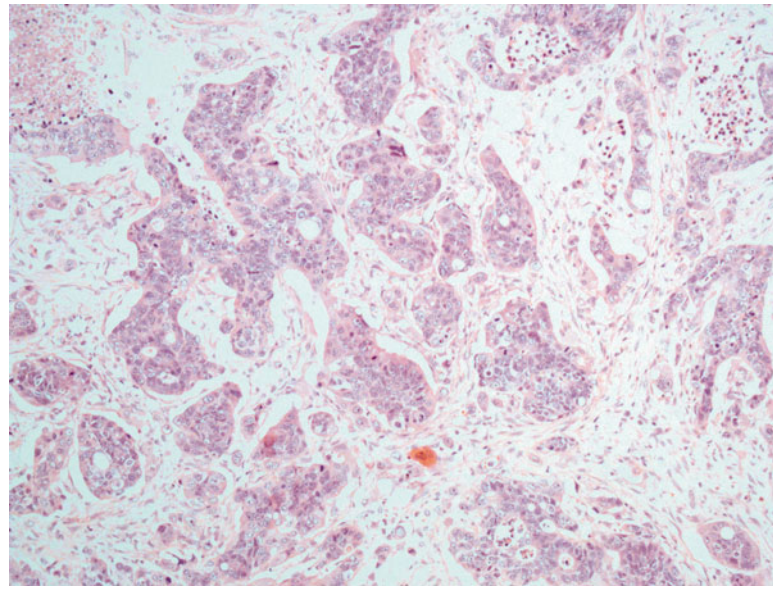

Fig. 16.20 An infiltrative growth pattern in a mucinous ovarian neoplasm, even if focal, is a strong pointer to metastasis

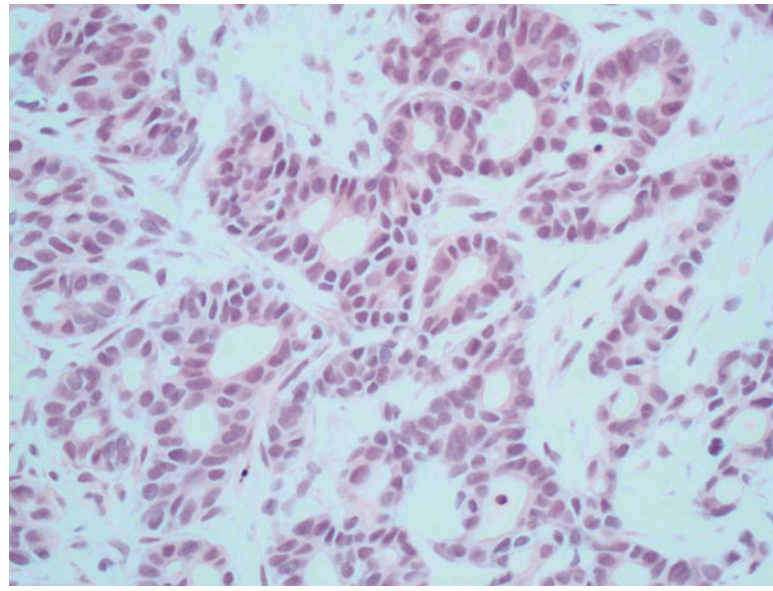

Fig. 16.21 A small gland pattern often seen with metastatic cholangiocarcinoma, though not exclusive to this source

about half of the cases. One of the most useful markers is loss of DPC4 expression [42] which occurs in 61 % of metastatic pancreaticobiliary carcinomas [39].

Differential Diagnosis

As has been emphasized in the introductory section and summarized in Table 16.1, distinction from primary ovarian mucinous tumors can be very difficult. Bilaterality, a nodular growth pattern, surface involvement, and infiltrative areas are all singly or in combination strongly suggestive of metastasis, and radiological or intraoperative exploration of a primary should be recommended. The distinction in individual cases can be difficult as the primary tumor may be clinically silent and presentation is with pelvic signs and symptoms due to the ovarian mass, ovarian involvement is unilateral in 10 % cases, and surface involvement may be absent. Almost

all reported cases show cystadenoma-like or borderline-appearing areas, and in 20 % of cases in the largest reported series, these were the sole patterns with no infiltrative growth seen [39]. On the other hand, severe nuclear atypia and intraepithelial carcinoma-like areas were seen in the vast majority, and peritoneal involvement was present in almost all cases reported. It is also widely reported that there is marked variation in morphology in different areas of the tumor and sometimes even on a single section, which should prompt the pathologist to exclude a metastasis. Immunohistochemistry is of limited value with the exceptions of CK17 positivity [43] and loss of expression of DPC4 which favor pancreaticobiliary origin; 55 % of pancreatic tumors and 10–50 % of biliary tract tumors show loss of DPC4 expression, while this is retained in 98 % of ovarian tumors [40].

Metastases from the Breast

Clinical Features

Metastases from breast carcinoma may be encountered in the ovary; these are not usually diagnostically problematic. After the gastrointestinal tract, the breast is the commonest source of nongenital tract ovarian metastases. This is reported in 10 % of cases in autopsy series and up to 50 % in therapeutic oophorectomies [3]. The incidence of metastatic breast carcinoma in risk-reducing salpingo-oophorectomies is very low at 1 % [44]. From a clinical perspective, an ovarian mass in a patient with a known history of breast carcinoma was found to be benign in 50 %, a new ovarian/tubal primary in 36 %, and metastatic breast carcinoma in 13 %; a malignant tumor in this scenario is therefore three times more likely to be a new primary than metastasis from the known breast cancer [45]. There are very rare reported instances of metastatic breast cancer presenting as an ovarian pathology prior to detection of the primary lesion [46]; in current clinical practice, this problem is virtually nonexistent.

Women with breast cancer metastatic to the ovaries were found to be more likely to be premenopausal with a genetic predisposition and suffering from tumors which are hormone-receptor positive, involving both breasts and showing lobular differentiation. The tumors were largely asymptomatic and discovered at a median interval of 5 years after diagnosis of the primary. Median survival was 3 years with significantly improved outcomes following optimal debulking surgery [47].

Pathology

Depending on the indication for oophorectomy, the ovaries may or may not be enlarged. There is often surface involvement, and this may appear papillary. The metastatic involvement has a multinodular appearance.

Histologically, lobular carcinoma has a greater propensity than ductal carcinoma to metastasize to the ovaries; in practice however most metastases are of ductal type (Fig. 16.22). The tumors may show a tubular/ductal/glandular pattern or show single-cell infiltration including a signet ring cell morphology. Rarely a papillary architecture may be encountered simulating an ovarian primary epithelial carcinoma. In such cases a review of the previous breast tumor and comparison with the metastasis to the ovary usually resolves the diagnostic dilemma.

Stromal luteinization is not a common feature. Vascular invasion is usually prominent.

Differential Diagnosis

Depending on the pattern, metastatic breast carcinomas may simulate a new high-grade ovarian primary, especially when detected after chemotherapy. A diffuse lobular pattern can resemble a granulosa cell tumor or small cell ovarian carcinoma. Tubular or insular patterns may simulate carcinoid tumors. Breast carcinomas at times can show a signet ring pattern reminiscent of a metastasis from the stomach, but this is usually not seen as a sole morphological pattern.

Immunohistochemistry is of value in distinguishing breast from ovarian carcinomas. A panel of WT1, CA125, and GCDFP is useful in this distinction [48], with breast tumors typically showing negative immunoreactivity for WT1 and CA125 and positive immunoreactivity for GCDFP. More recently, it is reported that the addition of PAX8 to this panel increases its

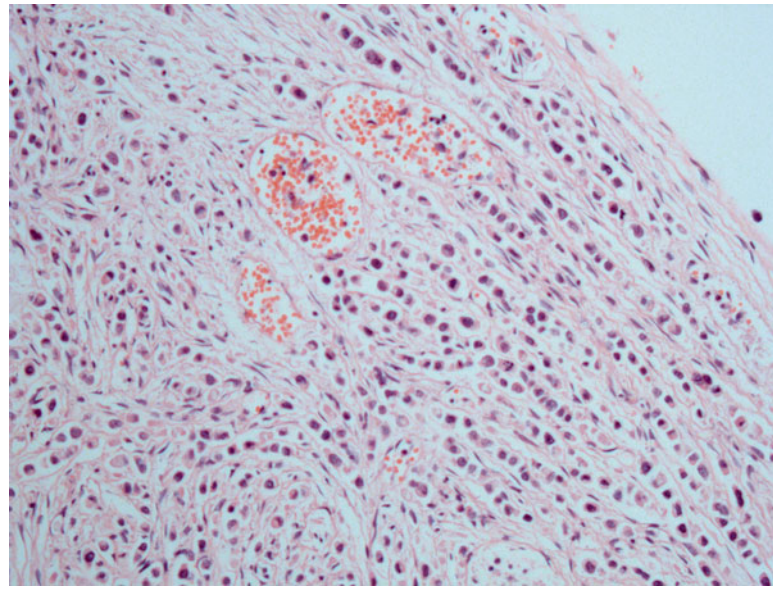

Fig. 16.22 Metastatic lobular carcinoma of the breast showing tumor cells in "Indian-file" arrangement

specificity as GCDFP is only positive in 43 % of breast carcinomas, and non-serous ovarian tumors do not express WT1 [18].

Metastases from Endometrial Carcinoma

Clinical Features

After the gastrointestinal tract, the endometrium is the commonest source of ovarian metastases, accounting for about 15–20 % of all cases. Spread may be transtubal, directly from serosal involvement or via lymphovascular invasion [49]. There are two problems in the differential diagnosis of ovarian metastases from endometrial carcinoma: the first is to distinguish a metastasis from an independent simultaneous primary tumor occurring in both the uterus and ovary; this is dealt with later in this chapter. The second is to distinguish high-grade uterine serous carcinoma from one of tubo-ovarian origin in cases involving both sites, as these are distinct entities in terms of their genetic abnormalities and response to chemotherapy [50].

For these reasons, it is difficult to describe the clinical features of metastatic endometrial carcinoma; these vary considerably with the type of the tumor. Synchronous tumors occur at a relatively younger age and have a more favorable prognosis than endometrial tumors metastatic to the ovary. In both groups clinical presentation is usually the result of signs related to the endometrial tumor, and it is unusual for an endometrial cancer to manifest first as an ovarian metastasis.

Pathology

Endometrioid tumors metastatic from an endometrial primary tend to share morphological characteristics, although the ovarian metastases tend to show a greater degree of nuclear atypia (Figs. 16.23, 16.24, and 16.25). Features useful in supporting metastatic spread, as opposed to an independent primary, are a higher grade and stage of the endometrial primary, including the presence of deep myometrial invasion, cervical stromal invasion, cornual involvement, or vascular invasion. The presence of surface involvement should be interpreted cautiously in this context as endometriosis often occurs over peritoneal surfaces and can be the source of a primary endometrioid ovarian adenocarcinoma; this feature therefore carries less weight in supporting metastasis than other features [3]. Immunohistochemistry is of no use in this regard as both metastatic and synchronous endometrioid tumors exhibit the same immunoreactivity.

Metastatic clear cell or serous carcinoma shows identical features in the endometrial and ovarian tumors. Uterine serous carcinomas

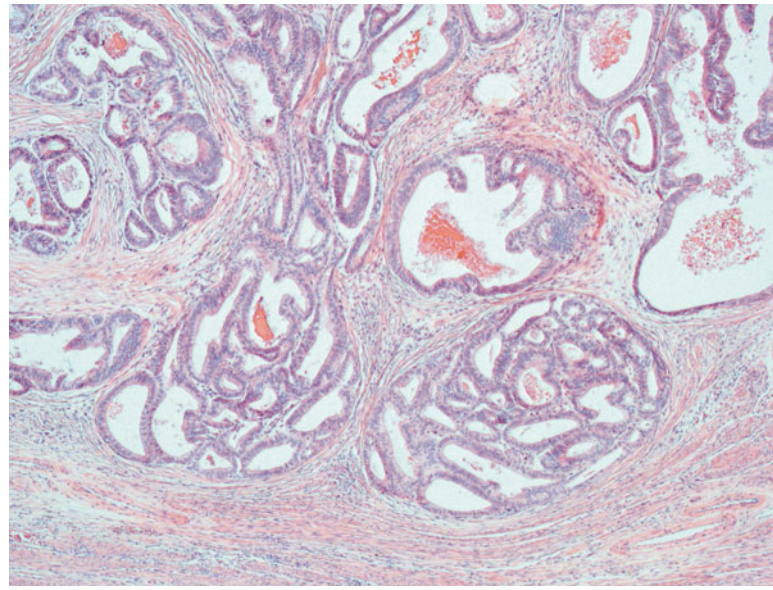

Fig. 16.23 Endometrial endometrioid carcinomas with ovarian metastasis usually show deep myometrial invasion

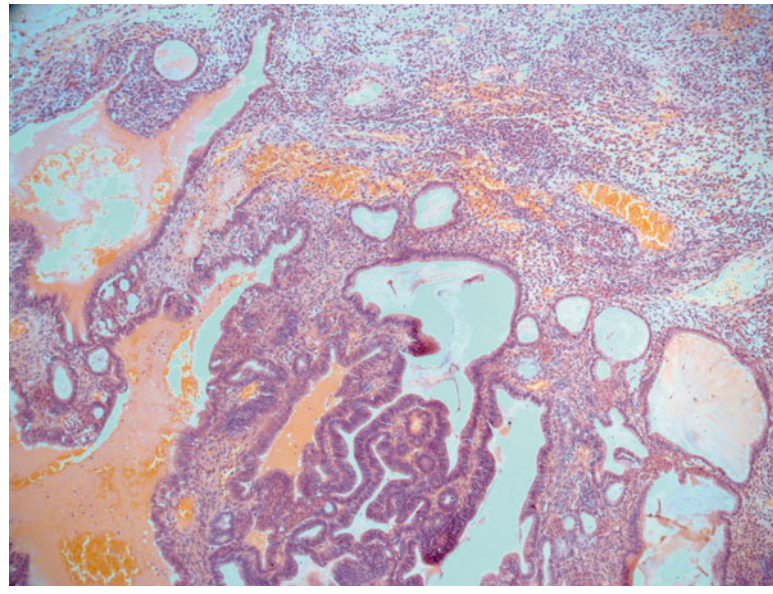

Fig. 16.24 Ovarian metastases from endometrioid endometrial carcinomas show similar morphology, but often appear to have greater nuclear atypia and may be associated with necrosis

occur in a background of an atrophic endometrium or an endometrial polyp. It is possible for these to metastasize widely, possibly by transtubal spread, without being deeply invasive at the primary site. The usual features of metastases apply when trying to establish if the tumor is primary or metastatic at this site. Ovarian involvement may be unilateral or bilateral, and surface involvement and vascular invasion are often present. In the presence of serous carcinoma involving both the endometrium and ovary, immunostaining for WT1 is valuable; this shows diffuse and strong positive immunoreactivity in tumors of tubal/ovarian origin, while there is negative or weakly and focally positive immunoreactivity in the vast majority of endometrial primaries [51]. The pattern of involvement and the site of bulky disease are invaluable in establishing the primary site of origin of the tumor.

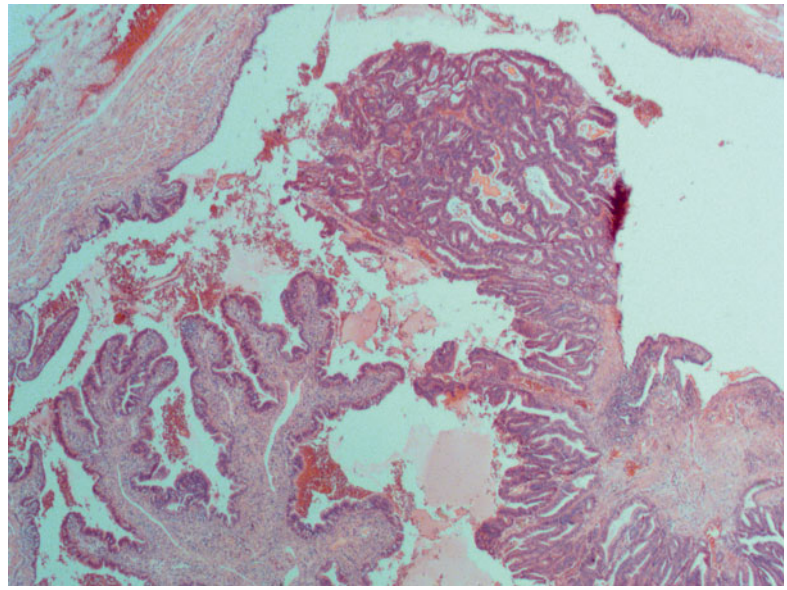

Fig. 16.25 In some instances ovarian metastases may be associated with carcinoma within the fallopian tube

Metastases from Cervical Carcinoma

Clinical Features

The cervix is the source of metastatic carcinoma to the ovary in a small number of cases. Adenocarcinomas are more likely than squamous carcinomas to metastasize to the ovary [52] and show some differences in clinical behavior as detailed below.

Carcinomas other than pure adenocarcinomas occur in young patients with a mean age of 43. In most cases the ovarian and cervical tumors are discovered simultaneously, but rarely the ovarian tumor may be the first manifestation of disease.

Metastases from endocervical adenocarcinomas may be difficult to recognize as such in both HPV-related and non-HPV-related cancers. In one large series, in 65 % cases, the cervical tumor was diagnosed concurrently or after the diagnosis of the ovarian mass, with the remaining minority of cases occurring in the context of a known history of cervical neoplasia. The knowledge of a previous cervical carcinoma does not always make the diagnosis easier because of confounding histological features that overlap with borderline ovarian tumors as described below.

Pathology

Excluding pure adenocarcinomas which are described below, cervical carcinomas metastatic to the ovaries were bilateral in 50 % cases and had an average size of 9 cm. The tumors were identical to the cervical primaries which were locally advanced and clinically evident. The histological types included squamous, adenosquamous, small cell, mixed small cell and adenocarcinoma, and undifferentiated carcinoma. As the morphological appearances of these tumors bear no resemblance to primary ovarian neoplasms, they are not diagnostically challenging to the pathologist [53]. In current practice, p16 immunoreactivity and testing for HPV by a variety of techniques can provide supportive evidence of the neoplasm being metastatic to the ovary as HPV is not found in primary ovarian tumors.

Metastatic cervical adenocarcinomas to the ovary are more problematic [54, 55]. These fall in the differential diagnostic category of metastatic mucinous carcinomas with all the difficulties described above. The simulation of primary ovarian tumors is greater than that seen with metastases from other sites due to their tendency to be large (mean size of 12 cm) and unilateral and to be detected prior to diagnosis of the cervical primary. In one series only 10 % of cases were bilateral with an infiltrative histological pattern. While the majority occur in association with an invasive cervical adenocarcinoma, in 11 of 29 cases (38 %) in this series the cervical

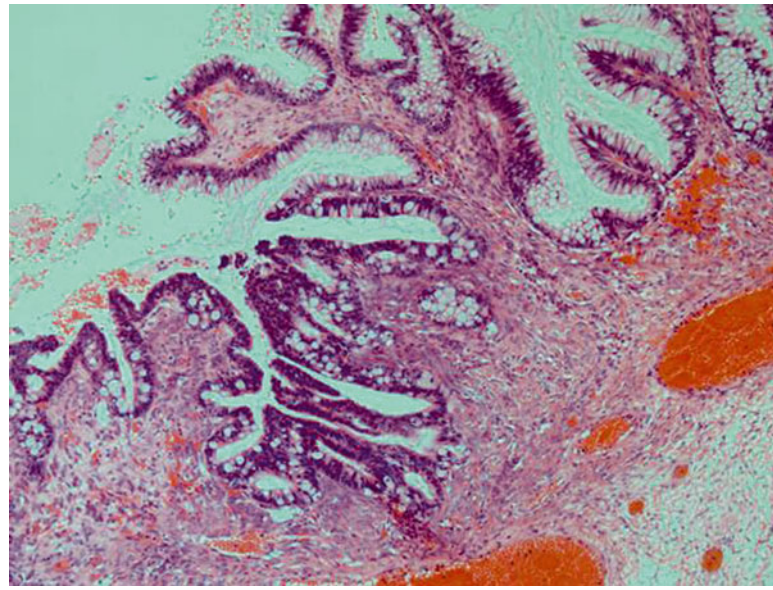

Fig. 16.26 Metastatic carcinoma from an endocervical mucinous primary may resemble a borderline tumor

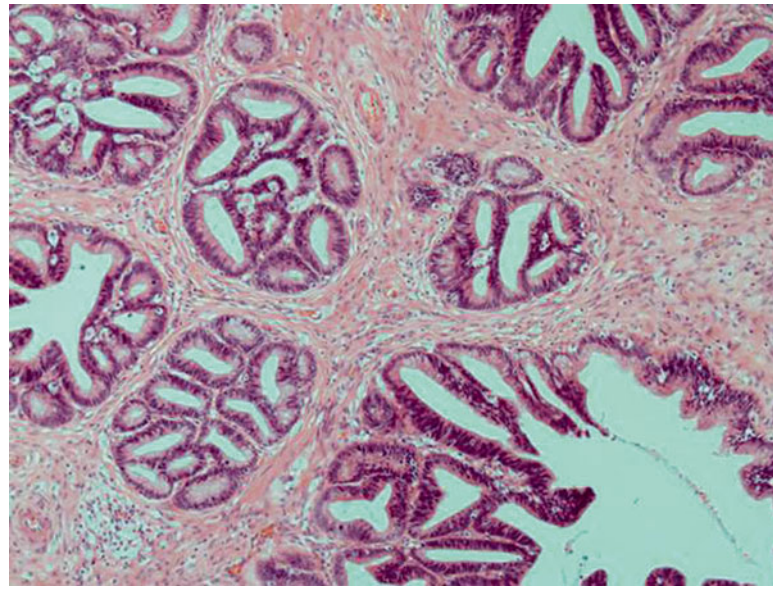

Fig. 16.27 The endocervical primary in these subtle cases often shows no or questionable invasion

primary was solely or predominantly composed of adenocarcinoma in situ with no definite invasive component. The histological patterns seen within the ovary include borderline-like confluent glandular, cribriform, and villoglandular areas similar to primary mucinous borderline tumors (Figs. 16.26, 16.27, and 16.28). Testing for HPV and immunoreactivity for p16 if diffuse and strong is valuable in HPV-related tumors [54].

Differential Diagnosis

Metastatic squamous cell carcinomas may on occasion require distinction from locally advanced tumors originating in teratomas or as a result of overgrowth of the malignant squamous component in an endometrioid carcinoma. The background elements of a mature teratoma would favor the former diagnosis while adjacent endometriosis would favor the latter.

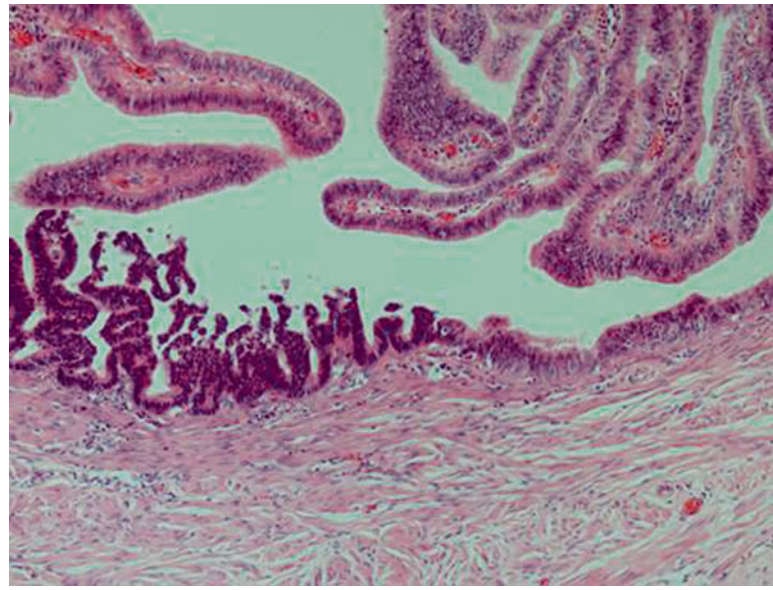

Fig. 16.28 The fallopian tube in the case illustrated in Figs. 16.25 and 16.26 showed foci of surface epithelial involvement

Metastatic mucinous tumors require distinction from primary ovarian neoplasms. This can be difficult even when there is known cervical neoplasia as this may be minimally invasive or entirely composed of adenocarcinoma in situ, and the metastasis may occur many years after treatment of the primary. It is postulated that such indolent cases may represent transtubal spread of the neoplastic cells as there is a frequent association with isthmic and endometrial involvement [55]. For HPV-related tumors p16 and HPV testing are of value.

Metastatic Malignant Melanoma

Clinical Features

Due to its protean morphological manifestations, metastasis from malignant melanoma can pose diagnostic problems at any site, and the ovary is no exception, particularly if the history of a skin or ocular melanoma is remote and/or not conveyed to the pathologist [3, 56–58]. These tend to occur in young women, and presentation is with abdominopelvic symptoms. The ovarian involvement is part of more widespread metastasis in the vast majority of cases.

Pathology

About half of all cases are bilateral and the average size is 10 cm. Only a third of cases are pigmented macroscopically, showing a black or brown color, sometimes only focally. Most tumors are predominantly solid although a significant proportion is at least focally cystic and sometimes extensively so; this may produce an appearance similar to "chocolate cysts" (Figs. 16.29 and 16.30).

Histologically about half of all cases are amelanotic. The tumors are usually composed of round cells; although these are arranged in solid sheets, the formation of follicle-like spaces is common and may impart an appearance similar to ovarian small cell carcinoma or other primary tumors. The tumors may consist of abundant eosinophilic cytoplasm and thereby resemble ovarian tumors with oxyphilic cells. Some tumors are composed of spindle cells and these may have a fascicular arrangement. Other tumors are composed of sheets of epithelioid cells, small cells, clear cells, or rhabdoid cells.

Differential Diagnosis

Distinction from a variety of ovarian primary neoplasms can be difficult in the absence of a known history. These tumors are well-known mimics of almost any tumor subtype known and in the ovary can resemble sex cord–stromal tumors of adult granulosa cell or steroid cell types or epithelial tumors of high-grade serous,

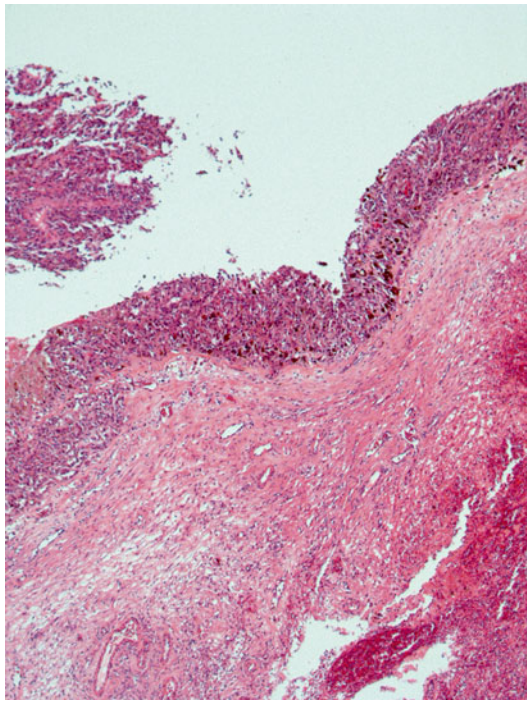

Fig. 16.29 Cystic metastases from malignant melanoma can produce a low-power appearance resembling endometriosis

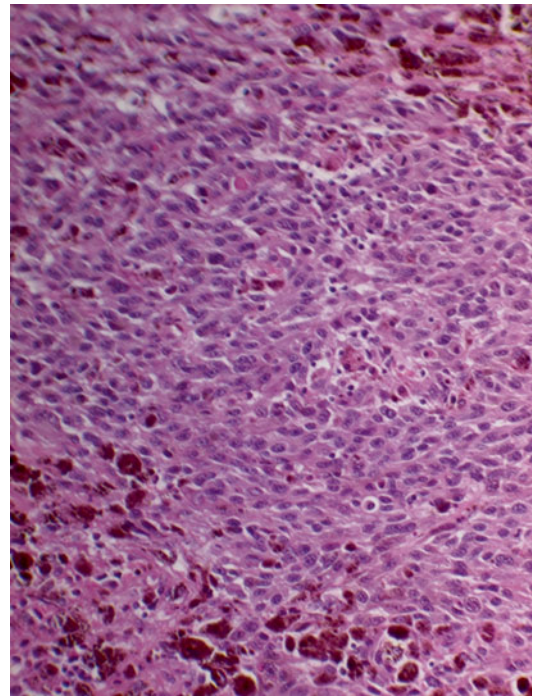

Fig. 16.30 Malignant melanoma metastatic to the ovary (Courtesy of Dr Nafisa Wilkinson, St James's Hospital, Leeds, UK)

clear cell, and undifferentiated types with a solid pattern. Other round cell tumors and spindle cell tumors may also fall in the differential diagnosis. If suspected, the diagnosis can usually be established using a panel of immunohistochemical markers including S100, HMB45, melan A, and others, together with demonstration of negative reactivity for markers of epithelial and sex cord–stromal differentiation, although focal positivity for inhibin and calretinin has been reported in melanoma. It is important for the pathologist to always consider a metastatic melanoma as a possibility in ovarian tumors which do not show features classical of a primary ovarian neoplasm.

One further issue is the distinction of metastatic melanoma from a primary ovarian melanoma which is very rare and usually encountered in association with a mature teratoma [59].

Metastatic Carcinoid Tumors

Clinical Features

Metastatic carcinoid tumor is rare in the ovary [60]. Most cases occur in women over 40 years, and the clinical features of a carcinoid tumor are present in 40 % cases. There is evidence of extraovarian disease in 90 % cases. The prognosis is poor and 75 % of cases are fatal within 5 years, in comparison with the almost uniformly benign behavior of primary ovarian carcinoids. Most arise from ileal primaries, but jejunal, cecal, pancreatic, and pulmonary origin are also recorded.

Pathology

The tumors are usually bilateral, solid, multinodular masses with a minor cystic component. Some tumors may show a yellow cut surface. Microscopically the tumors are most commonly insular and composed of large islands of neoplastic cells with a characteristic granular chromatin pattern. Acinar formation is seen at the periphery of the tumor islands, and the luminal spaces may show hyaline material or dystrophic calcification. Follicle-like spaces are often seen and may resemble primary tumors. The stroma may show hyaline fibrosis. A minority of cases show trabecular or solid patterns.

Differential Diagnosis

Metastatic carcinoids may mimic primary sex cord–stromal tumors, including Sertoli–Leydig and adult granulosa cell tumors. The presence of cell groups with acinar and follicle-like structures in a fibromatous stroma causes diagnostic confusion with a benign Brenner tumor or adenofibroma. Primary carcinoid tumors may occur on a background of a mature teratoma which may not be evident at first but should be carefully sought and excluded. Immunohistochemistry for neuroendocrine markers is useful to confirm the neuroendocrine differentiation but is of no value in establishing primary origin. It should be noted that CD56 immunoreactivity in isolation is of no use in this distinction, as this marker shows reactivity with a variety of neoplastic tumors especially those of sex cord–stromal origin; instead a panel of markers including chromogranin and synaptophysin should be applied.

Metastases from the Respiratory Tract

Clinical Features

Metastasis from lung tumors occurs at an average age of 47 years, and most cases occur in the presence of a known history of lung cancer. Significantly though, many tumors are discovered at the same time as the ovarian mass, and in 16 % of cases, the ovarian tumor was discovered 2–26 months before the lung primary [61]. In 40 % of cases the lung and ovary are the only sites of disease.

Pathology

Only a third of cases present with bilateral ovarian tumors with an average size of about 10 cm. The tumors show a solid or solid and cystic appearance with areas of necrosis. Surface involvement is uncommon. Histologically the most common subtype is small cell carcinoma, followed by adenocarcinoma and large cell carcinoma. Squamous cell carcinomas constituted a minority of all cases and are unlikely to metastasize to the ovary.

Differential Diagnosis

The morphology of these subtypes resembles that of the primary. Vascular invasion is usually prominent. Metastatic small cell carcinoma may also show follicle-like spaces which are seen with other solid tumors metastasizing to the ovary. There is overlap with many primary tumor types, and correct diagnosis depends on suspecting metastasis and confirming with specific immunohistochemical markers, including TTF-1 and napsin, as well as clinical correlation.

Metastases from the Kidney and Urinary Tract

Clinical Features

Renal clear cell carcinoma can rarely give rise to ovarian metastasis. This usually follows within 2 years of diagnosis of the primary, but can occur before its clinical manifestation, or many years after its diagnosis. Transitional cell carcinomas of the urinary tract may rarely metastasize to the ovary [3].

Pathology

Metastatic renal cell carcinoma is often unilateral and large, with a solid–cystic, yellow cut surface. The histology is very similar to primary ovarian clear cell carcinoma. Metastatic transitional cell carcinoma may be indistinguishable from a primary surface epithelial tumor.

Differential Diagnosis

In the absence of a known history of renal clear cell carcinoma, metastases can be difficult to distinguish from primary ovarian clear cell carcinomas. The primary tumors however often occur in a background of endometriosis, show a greater variation in cell morphology and architecture, and show prominent stromal hyalinization. By contrast metastatic renal clear cell carcinomas are more uniform and monotonous in their appearance. In both these tumors, i.e., renal cell carcinoma and transitional cell carcinoma, where a metastasis is being considered, a complete clinical history is essential to confirm the diagnosis.

Metastases from the Liver

Clinical Features

Excluding tumors of the intrahepatic bile ducts which have been considered above with pancreaticobiliary tumors, tumors of hepatic origin

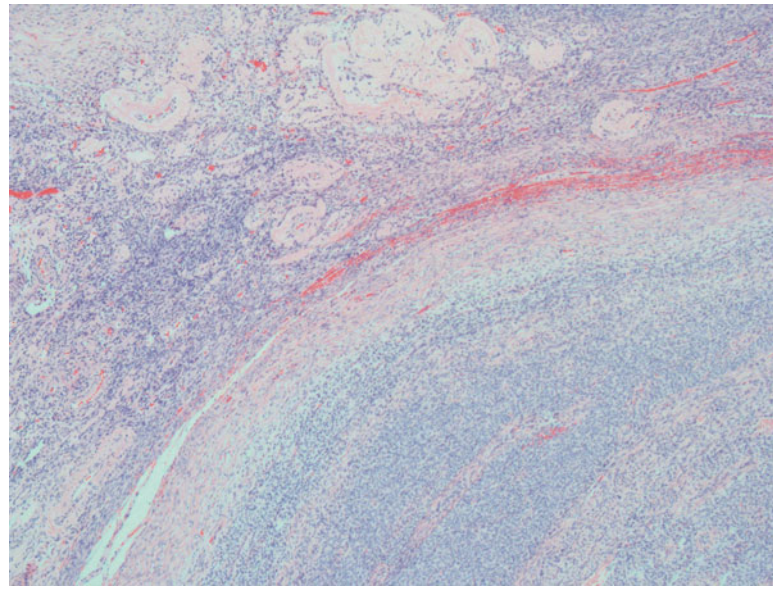

Fig. 16.31 Metastasis from low-grade endometrial stromal sarcoma many years after removal of primary

uncommonly give rise to ovarian metastases. These may occur in young individuals and present as an ovarian mass.

Pathology

These tumors may be bilateral and solid. Histologically hepatocellular carcinomas are composed of cells with abundant eosinophilic cytoplasm. Useful diagnostic features are the presence of bile in canaliculi.

Differential Diagnosis

These tumors can mimic a variety of oxyphilic tumors of the ovary including clear cell carcinoma, hepatoid carcinoma, or hepatoid yolk sac tumor. The primary tumor may be difficult to diagnose [3].

Metastatic Endometrial Stromal Sarcoma

Clinical Features

These are the most common sarcomas to metastasize to the ovary [3, 62]. This occurs in perimenopausal or postmenopausal women. A previous history of endometrial stromal sarcoma or other uterine neoplasm may be present, but as these tumors are indolent, this may be remote. They also need to be distinguished from a primary endometrial stromal sarcoma which may develop from endometriosis within an ovary.

Pathology

These tumors are bilateral solid masses with a soft yellow cut surface and at times a minor cystic component. It may be possible to appreciate the worm-like intravascular growth on naked eye examination. On microscopic examination, there is a diffuse pattern of oval cells with scanty cytoplasm (Figs. 16.31 and 16.32). Arterioles may not be conspicuous and the characteristic intravascular pattern may only be seen at the hilum if at all. There may be a prominent epithelial component and stromal hyalinization with hyaline plaque formation.

Differential Diagnosis

There is morphological overlap with sex cord–stromal tumors, principally diffuse adult-type granulosa cell tumors and fibrothecomas. Positive immunohistochemistry for CD10 is also seen in sex cord–stromal tumors, and so this marker should be accompanied by a panel of markers more specific for sex cord differentiation to avoid misdiagnosis. Endometrial stromal sarcoma can also occur as an ovarian primary often in a background of endometriosis.

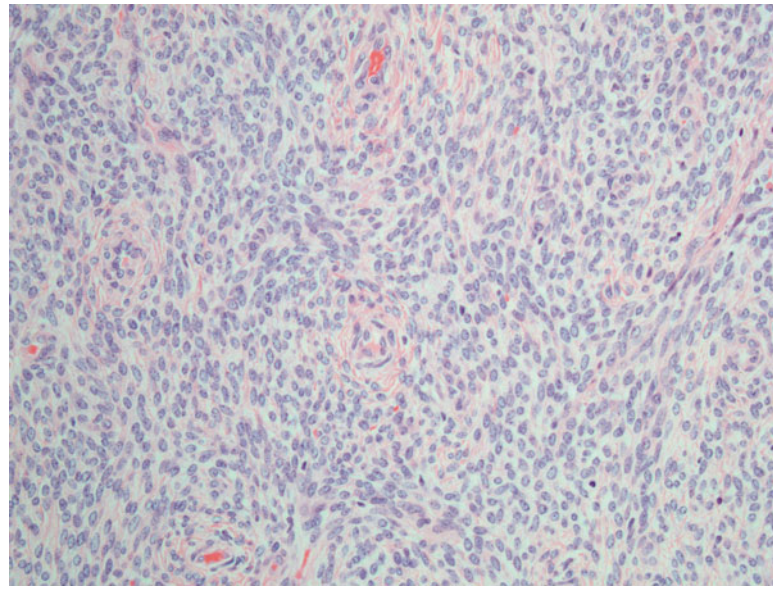

Fig. 16.32 Metastatic endometrial stromal sarcoma composed of monotonous bland elongated cells with prominent arteriolar vessels

Metastatic Gastrointestinal Stromal Tumor

Clinical Features

Gastrointestinal stromal tumors are being increasingly recognized as a diagnostic problem for gynecological pathologists. These may masquerade as primary smooth muscle tumors when they occur in the rectovaginal septum or present with ovarian metastases simulating an ovarian primary [63, 64]. These occur in middle aged to elderly women and may be discovered before or many years after the primary which is usually in the small bowel or mesentery.

Pathology and Differential Diagnosis

These tumors are cellular spindle cell masses indistinguishable from primary smooth muscle tumors or cellular fibromas. Positive immunohistochemistry for c-kit or DOG1 clinches the diagnosis if this is suspected.

Metastases from Mesothelial Tumors

Clinical Features

Malignant mesothelioma of the peritoneum may show ovarian involvement in a significant number of cases, resembling widely metastatic ovarian serous carcinoma. The patients show a wide age range of 17–92 years, and presentation with abdominopelvic symptoms including ascites and a pelvic mass [65] may be encountered. Intra-abdominal desmoplastic round cell tumor is a rare mesothelial tumor of uncertain histogenesis that can also present with ovarian involvement in young women [66].

Pathology

The majority shows an epithelial morphology with only rare cases being biphasic or sarcomatoid; a few show deciduoid features [65]. The tumor has a tubulopapillary architecture and shows prominent stromal hyalinization. The epithelial cells show monotonous nuclei with mild atypia.

Desmoplastic round cell tumor involving the ovary is composed of round cells separated by stroma in an insular pattern.

Differential Diagnosis

These tumors closely resemble primary serous tumors although the latter show more cellular stromal cores in papillary areas and greater cytological variation than the monotonous appearance in mesotheliomas. Psammomatous calcification is not as prominent in mesothelioma while this is a more common feature in serous tumors of all types. Immunohistochemistry for the mesothelial markers calretinin and D2-40 is useful [3, 65].

Desmoplastic round cell tumor resembles small cell carcinoma, sex cord–stromal tumors, and metastatic lobular carcinoma. Immunohistochemistry is essential for correct diagnosis of ovarian round cell tumors [66, 67].

Pathology of Synchronous Primary Endometrial and Ovarian Carcinomas

Introduction

About 1–2 % of all women with gynecological cancers have two or more simultaneous independent primary tumors involving the female genital tract [68–70]. The female genital tract develops from the Mullerian ducts, invaginations of the coelomic cavity. There are a number of genes involved in the differential development of various parts of the tract whose expression in turn is regulated by a variety of local and systemic influences, principally ovarian hormones as well as inflammatory and immune modulators [71]. The sensitivity of the female genital tract to such humoral influences is manifest during its development and also throughout reproductive life as cyclical and pregnancy-related changes occur. The peritoneal mesothelium appears to retain its capacity to differentiate along Mullerian lines. Endometriosis and endosalpingiosis are likely results of such aberrant or ectopic differentiation, although other theories exist for their development. Such foci, under the influence of relevant tumorigenic stimuli, could develop tumors as a result of field change. It is currently believed that many gynecological malignancies arise from the secondary Mullerian system [72].

Synchronous tumors of the endometrium and ovary account for 50–70 % of all synchronous female genital tract malignancies [68, 70]. About 10 % of women with ovarian cancer will be found to have synchronous endometrial cancer, and about 5 % of women with endometrial cancer harbor simultaneous ovarian cancer [73]. A higher incidence of synchronous tumors is reported in patients of endometrial cancer aged under 50 years [74, 75].

Clinical Features

The median age reported in various series ranges from 41 to 52 years, about a decade younger than the median age of incidence of either endometrial or ovarian cancer alone [73, 76–82]. The median age is younger for tumors with endometrioid histology than other types [73]. The median BMI is reported to be high in the largest single series from one institution [73] with a range of 15.5–53 [73, 79], and over a third of women are obese. About two-thirds of women with synchronous endometrioid tumors are premenopausal [73, 79] and roughly 40 % are nulliparous [73, 83]. The most common presentation is abnormal uterine bleeding with the ovarian carcinoma being discovered secondarily [68, 73, 76, 79, 84]. A minority of cases present with a pelvic mass, pelvic pain, or other symptoms.

Pathology

The endometrial and ovarian tumors reported in most large series are both of endometrioid type in roughly 50–70 % of cases. The remainder show mixed histology or different histology at the two sites. Owing to the common occurrence of mixed tumors at both sites, these need careful evaluation as tumors of apparently different histologies may still represent metastases with a minor component being missed at the primary site.

As a group these tumors tend to show grade 1 or 2 endometrioid carcinoma in both endometrium and ovary with approximately 70 % concordance in grade [85]. The endometrial carcinomas tend to be grade 1 or 2 in nearly 90 % cases and are generally confined to the endometrium or show superficial myoinvasion (Fig. 16.33). Deep myoinvasion is seen in a minority of cases [73]. Vascular invasion is present in about 30 % of cases and is considered a poor prognostic sign [78]. Ovarian tumors range from <4 cm to over 10 cm in diameter; roughly one quarter of the ovarian tumors are discovered in normal-sized ovaries. These are generally solitary with no surface involvement [73] (Fig. 16.34). Associated ovarian endometriosis is seen in about 30 % of cases [85].

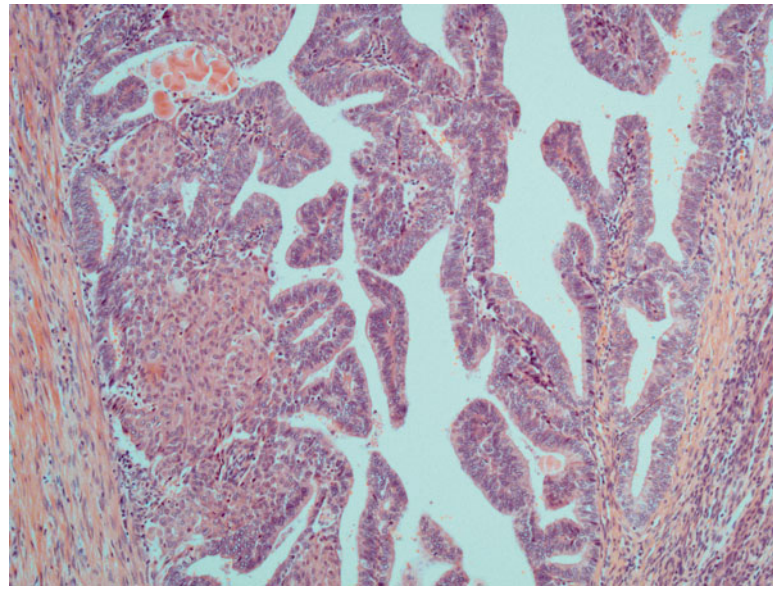

Fig. 16.33 Grade 1 endometrioid endometrial carcinoma with synchronous carcinoma in the ovary, seen in Fig. 16.34

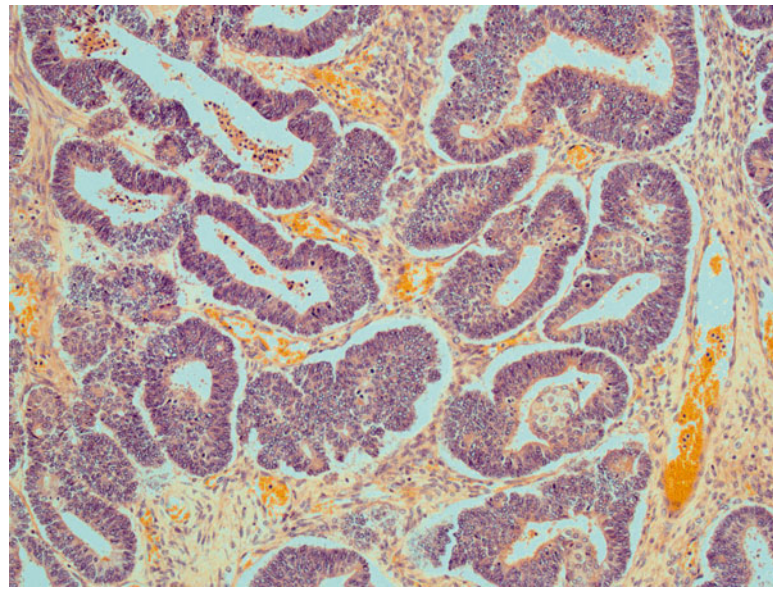

Fig. 16.34 Synchronous grade 1 endometrioid ovarian carcinoma in the case illustrated in Fig. 16.33

Differential Diagnosis

The main diagnostic consideration is exclusion of metastasis from an endometrial primary to the ovary or vice versa. Criteria for distinguishing synchronous tumors from metastases were first documented by Ulbright and Roth [86] and subsequently detailed by Scully et al. [13]. These are widely accepted and summarized in Table 16.3. Although criteria have also been laid down for ovarian carcinoma metastasizing to the endometrium [13], metastasis from the ovary preferentially to the endometrium in the absence of other pelvic involvement is an exceedingly unlikely occurrence with very exceptional cases documented in the literature [86]. Such spread would generally include involvement of the corpus from the external surface, and tumors with these features have been excluded from most series as they do not pose a diagnostic problem.

Table 16.3 Comparison of features of synchronous independent endometrial and ovarian carcinomas with those of endometrial carcinomas with ovarian metastasis

Feature	Synchronous independent endometrial and ovarian carcinomas	Endometrial carcinomas with ovarian metastasis
Histological type	Usually both endometrioid, may be entirely different histological types	Similar and consistent with endometrial primary
Histological grade	Both low grade	Similar and consistent with endometrial primary
Myometrial invasion	None or minimal	Usually deep myometrial invasion
Tumor in cervix	Absent	Often present
Tumor in Fallopian tubes	Absent	Often present
Vascular invasion	Absent	Often present
Uni-/bilateral ovarian tumors	Unilateral	Often bilateral
Ovarian endometriosis	Present	Usually absent
Pattern of ovarian involvement	Single dominant mass	Multinodular with surface involvement
Local extension	Both tumors confined with no direct extension to contiguous sites	May show large endometrial tumor with direct extension to ovaries
Involvement of other sites	Both tumors confined with no spread to sites beyond the endometrium and ovary	Involvement of other sites may be present
Molecular changes in tumors at the two sites	Typically dissimilar	Similar or identical

Molecular Changes in Synchronous Endometrial and Ovarian Tumors

It has been shown that the majority of tumors can be accurately categorized by histological evaluation as synchronous primaries or single primary with metastasis, as demonstrated by the poorer clinical outcome of the latter. Unfortunately there remain a few cases that cannot be classified with confidence, either because of widespread involvement, in which case the distinction is of academic rather than practical or prognostic significance, or, because of, more importantly, overlapping or ambiguous histological features.

Molecular analysis of synchronous endometrial and ovarian tumors has been the subject of a large number of research publications. The vast majority are aimed at finding robust molecular diagnostic tests that can complement histopathology or provide an alternative or more accurate diagnosis in difficult cases. A second approach is for studying the molecular pathogenesis of this enigmatic group of tumors. A few studies are specifically devoted to the association between microsatellite instability in the context of the association of HNPCC with the development of synchronous tumors; these are discussed in a later section.

The techniques that have been assessed for diagnosis of synchronous tumors as independent primaries range from ploidy analysis by Feulgen [87] or flow cytometry [88, 89], X chromosome inactivation studies [90], loss of heterozygosity (LOH) [91–93], microsatellite instability (MSI), mitochondrial DNA genotyping [94], beta-catenin expression, and gene-specific analysis of p53, k-ras, pTEN, and beta-catenin mutations [78, 90, 95–101]. Recent studies promote detection of multiple genetic changes in tumors to minimize the confounding effects of tumor progression and heterogeneity. The most reliable markers are generally those that are present early in tumor development. Major advances in molecular biological techniques allow detection of multiple genetic changes using gene expression and/or DNA microarrays or microsatellite analysis. In a study of 90 cases of simultaneous endometrial and ovarian cancers, it was found that histology alone provided a diagnosis in only 61 % of cases while the combination of histology and molecular diagnosis based on LOH at 22 loci and MSI was able to categorize 98 % of cases

[93]. There was 91 % concordance between histology and molecular results. In a similar study on 12 cases using these techniques together with pTEN and CTNNB1 mutations and beta-catenin expression, it was found that 5 of 8 cases diagnosed as independent primaries showed at least one different molecular alteration [101]. It was noted, however, that there was also at least one or more identical alteration in these pairs of tumors. These results are similar to those of previous studies [78, 97, 98]. An additional observation of potential routine diagnostic value is the frequent presence of CTNNB1 mutations in cases of independent primary endometrial (50 %) and/or ovarian (44 %) tumors. This is associated with nuclear as opposed to membranous expression of beta-catenin on immunohistochemical analysis. The staining pattern of beta-catenin may therefore be a valuable additional diagnostic tool in differential diagnosis as it is more likely to be associated with synchronous independent primary tumors than those occurring singly and is associated with better outcome [97, 101]. This finding, however, needs wider testing.

A second approach to identify the organ of origin has been the use of gene expression profiling. The identification of single genetic alterations is unreliable for diagnosis because of a large degree of overlap in signature genetic abnormalities in endometrial and ovarian primary endometrioid carcinomas. In a recent study gene expression profiling demonstrated 163 genes that showed differential expression in endometrioid cancers of endometrial and ovarian origin, enabling generation of a 119-gene predictive model. This showed concordance with histopathology in 11/16 cases. Further studies are needed to determine the practical utility of this technology in a prospective setting [102].

Some molecular studies have also tried to elucidate the molecular pathogenesis of synchronous tumors. These have aimed to evaluate whether this is a coincidental occurrence or whether such tumors have a different pathogenesis from sporadic cases. The most frequent molecular abnormalities underlying endometrioid carcinoma of the uterus are mutations in pTEN (30–50 %) and the beta-catenin gene (25 %), as well as microsatellite instability (MI) (20–45 %), which is due to hMLH1 promoter gene hypermethylation in sporadic cases as opposed to the specific mismatch repair gene mutations occurring in HNPCC carriers. The same abnormalities are reported in ovarian endometrioid tumors, though with different frequencies [103], and hence are not of diagnostic value. In synchronous endometrioid tumors of the endometrium and ovary, MI is reported to occur at about double the frequency seen in single tumors, together with a higher rate of pTEN and CTNNB1 mutations. It is suggested that these three mutator pathways are all of importance in the development of synchronous tumors and that the pathogenesis of these tumors is different from that of single primaries [97, 101].

Results of molecular studies should be cautiously interpreted and always together with clinicopathological findings. The finding of different genetic abnormalities may reflect tumor heterogeneity rather than evidence of separate primaries [104]. On the other hand, identical gene mutations have been detected in clearly independent primaries, probably resulting from a "field effect" of a common oncogenic stimulus [101]. Similarly loss of heterozygosity, though generally considered an early reflection of loss of tumor suppressor genes, may also appear as a late event due to genetic instability [96, 105].

Prognostic Factors

Several studies have compared outcome of synchronous primary tumors with that of endometrial cancer with ovarian metastasis as categorized by histological findings. These have consistently demonstrated vastly superior survival in cases of synchronous endometrioid primaries. This has given conclusive evidence that these tumors are indeed low-stage independent primaries, and it is advocated that such tumors, if confined to the endometrium and ovary, do not require adjuvant treatment following surgery. A large prospective GOG study that did not distinguish between synchronous and metastatic tumors but was designed to study clinical outcome found that the groups as a whole showed better survival than either

stage 3 endometrial or stage 2 ovarian cancers [85]. Within the group factors influencing survival were found to be the presence of metastasis outside the ovaries and tumor grade. Poor prognostic factors highlighted in other studies are the presence of deep myoinvasion [106], vascular invasion [107], stage of the ovarian cancer [108], positive washings, and tumor grade [109, 110].

Many studies have compared the outcome in synchronous tumors of endometrioid type with that of other subtypes. Although some showed no significant differences in clinical features or survival [79, 106, 111, 112], the majority of large studies have demonstrated significantly better outcomes in cases of synchronous endometrioid tumors as opposed to other subtypes, and many studies have excluded uterine serous and clear cell carcinoma and carcinosarcoma from their series. These "type 2" cancers are generally seen in older postmenopausal women and tend to behave aggressively. Uterine serous carcinoma even when presenting with "apparently" low-stage disease within the uterine corpus may have widely disseminated peritoneal disease. For these reasons it is unlikely that "type 2" tumors simultaneously involving the endometrium and ovaries ever represent independent primaries. Molecular studies are also confounding in these cases as there is a high degree of tumor heterogeneity and rapid progression in genetic abnormalities. Since such subtypes are treated aggressively irrespective of stage, it is unlikely that histological misinterpretation will influence management adversely.

Synchronous Endometrial and Ovarian Cancer in Young Women

It has been noted that the median age for synchronous independent endometrial and ovarian cancers is about a decade lower than that of single primaries at either site. While synchronous tumors of the ovary are reported in 5 % of endometrial cancers overall, this incidence is significantly higher in women under 50. Two studies have reported that the incidence of a synchronous ovarian tumor is 19 % in women under 50 [74] and 25 % in women aged 24–45 [75]. In 15 % of cases the involved ovaries were normal or benign appearing on radiological and/or intraoperative assessment [75]. Women with endometrial cancer who desire ovarian conservation need to be appropriately counseled, and the high risk of synchronous ovarian tumors should be discussed.

Synchronous Endometrial and Ovarian Cancer and HNPCC

The syndrome of hereditary non-polyposis colorectal cancer (HNPCC) is caused by mutations in a family of genes known as DNA mismatch repair (MMR) genes, most commonly hMLH1 or hMSH2. This results in progressive accumulation of DNA replication errors in the progeny of an abnormal cell and genetic instability; the molecular evidence of this phenomenon is the demonstration of widespread microsatellite instability. Individuals with HNPCC are at increased risk of development of a variety of cancers: endometrial, ovarian, stomach, small intestine, hepatobiliary tract, ureter, brain, and skin. A number of studies have shown that women with HNPCC are at a higher risk of developing endometrial cancer than colorectal cancer; in comparison with a lifetime risk of around 50 % for colorectal cancer, women with HNPCC have a lifetime risk of 40–60 % for endometrial cancer and 10–12 % for ovarian cancer [113]. Current guidelines recommend that patients with two HNPCC-associated cancers should undergo appropriate screening [114].

Overall MMR gene mutations account for a tiny minority of endometrial cancers [113]. Two studies devoted to identifying the prevalence of HNPCC in synchronous endometrial and ovarian cancers found these to account for 3 and 7 % of cases, even after limiting analysis to younger patients [114, 115]. This was comparable to that in endometrial cancers in general and considerably lower than that in cases of synchronous or metachronous endometrial and colorectal cancer. Both studies concluded that since this is a relatively common tumor combination to occur sporadically, genetic testing in

synchronous endometrial and ovarian cancers should be limited to cases with a suggestive family history. For the diagnostic pathologist, it is sufficient to raise this as a possibility in a multidisciplinary setting, and immunohistochemical testing for MMR gene product expression may not be indicated in all cases as the yield is likely to be low.

Summary and Practical Approach to Synchronous Endometrial and Ovarian Cancers [116]

A synchronous tumor in the ovary or endometrium is seen, respectively, in 5 % of women with endometrial cancer and 10 % of women with ovarian cancer. The distinction of synchronous endometrial and ovarian primaries from stage 3 endometrial cancer is crucial for correct patient management. The diagnosis of synchronous primaries should be made with extreme caution, if at all, in grade 3 endometrioid and type 2 endometrial cancers. For endometrioid cancers, most cases can be accurately categorized on the basis of standard histological features summarized in Table 16.3.

Molecular testing can provide valuable adjunctive information but must be interpreted with clinicopathological correlation and not in isolation. Gene expression profiling may provide specific diagnostic information for accurate staging of synchronous tumors in the future. Nuclear, as opposed to membranous, expression of beta-catenin on immunohistochemistry is reported to favor synchronous independent primaries but requires wider testing for confirmation of this observation. Poor prognostic features are tumor grade, vascular invasion, and stage-related factors: deep myoinvasion, positive peritoneal washings, and metastasis outside the uterus and ovaries. A very low percentage of women with synchronous primaries in the uterus and ovary are HNPCC patients, and genetic or immunohistochemical testing for mismatch repair gene mutations may be unnecessary in all cases, but should be carried out according to prevailing guidelines. Women under 50 are much more likely than older patients to have a synchronous ovarian tumor, and this should be taken into account if ovarian conservation is being considered.

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