The Spectrum of Cervical Glandular Neoplasia and Issues in Differential Diagnosis

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The diagnosis of “in situ” and invasive endocervical adenocarcinoma and their distinction from various benign and malignant mimics may be a challenge for the practicing pathologist, considering the different morphologies these tumors may have and the overlapping features with other benign and malignant glandular lesions from and outside the cervix. In this review, the spectrum of histopathologic appearances of endocervical glandular neoplasia is discussed, emphasizing morphologic key features and immunohistochemical markers useful in its differential diagnosis.

ADENOCARCINOMA IN SITU

Adenocarcinoma in situ (AIS) is a well-known precursor of invasive cervical adenocarcinoma. It is related to high-risk human papilloma virus (HPV) (more frequently type 18) and typically occurs in women in their fourth decade of life, 10 to 15 years earlier than invasive adenocarcinoma. At the time of diagnosis most patients are asymptomatic and the lesion is detected either on screening Papanicolaou smear or incidentally during clinical evaluation of a cervical squamous intraepithelial lesion, as in 30% to 60% of patients they occur simultaneously. If symptomatic, the most common presentation is abnormal vaginal bleeding. On colposcopic examination, when detectable, AIS has a nonspecific appearance.

Diagnostic Criteria

Adenocarcinoma in situ is characterized by a set of well-established architectural and cytologic features (Figure 1, A and B). The former include: (1) preservation of normal glandular architecture (intraglandular papillae or cribriforming may occasionally minimally be present); (2) partial or complete involvement of endocervical glands; and (3) abrupt transition to normal endocervical epithelium (Figure 1, A). Glands involved by AIS typically do not elicit a stromal response. Cytologically, the neoplastic cells: (1) have variable cytoplasm with little or no mucin (mucin depleted) or, less frequently, abundant mucin; (2) are variably stratified, crowded, enlarged, with hyperchromatic nuclei; (3) have inconspicuous to small single or multiple nucleoli; (4) have frequent mitoses, particularly in an apical location; and (5) have apoptotic bodies (Figure 1, B).

Location and Extent of Cervical Involvement

Adenocarcinoma in situ is typically located at the transformation zone, although it may be present high up in the endocervical canal (between 20 and 30 mm, measured from the maximal convexity of the portio vaginalis). Adenocarcinoma in situ usually involves both endocervical glands and surface epithelium; however, it may be limited to endocervical glands (33%), being a potential source of sampling error, or infrequently, to the surface epithelium (3%). The latter is prone to be overlooked as it is often very focal, appears to have less-pronounced cytologic atypia, and fewer mitoses and apoptotic bodies. It has been hypothesized that involvement of only surface epithelium is an early form of AIS, as it occurs in a younger
age group (mean, 26.8 years). Adenocarcinoma in situ may be multicentric in up to 15% of patients. Definitions used in the literature for multicentric disease include: (1) finding of greater than 2 mm of uninvolved mucosa in between 2 foci of AIS (“skip lesions”)10,11 or (2) complete normal radial section in between 2 adjacent sections involved by AIS.8,9 These 2 features of AIS, namely, endocervical location and multicentricity, highlight the importance of submitting the entire specimen for histologic evaluation.15 Reported data related to extent of involvement by AIS (focal versus diffuse) have been contradictory owing to the use of different or imprecise definitions (number of microscopic fields versus number of blocks versus number of quadrants involved).8,11,12,16,17

Subtypes

Although the architectural and cytologic features described above are shared by all AIS subtypes, the overall morphologic appearance may vary, reflecting the histologic spectrum of this entity.14,16 The 3 most frequent AIS subtypes are endocervical (usual), intestinal, and endometrioid, while tubal, stratified, mucin-producing intraepithelial lesions, and adenosquamous subtypes are uncommon to rare (Figure 2, A through D).12,14,19-22 Precursor lesions to clear cell endocervical carcinoma, albeit reported, are not well characterized.12,23,24 Although no differences in behavior exist among most AIS subtypes, awareness of their different morphologies allows one to establish the correct diagnosis and potential associated risks.14

Endocervical (usual) AIS is the most frequent subtype12,25 and can be pure (58%) or admixed with intestinal (29%) or endometrioid (16%) AIS.12 Although it has a resemblance to normal endocervical glands,12 cells typically have less intracytoplasmic mucin (“mucin depleted”) (Figure 2, A).12 Intestinal AIS is defined by the presence of variable number of goblet cells and less commonly, neuroendocrine and Paneth cells.12,20,26,27 It typically shows less nuclear pseudostratification and appreciable cytologic atypia (due to abundant intracytoplasmic mucin displacing nuclei to a basal location) and much lower mitotic rate than usual endocervical AIS (Figure 2, B).20,28,29 Intestinal AIS has been reported to be infrequent as a pure form, being more common admixed with usual AIS.7,11,12,20,30 However, the finding of CDX2 expression in areas morphologically identical to usual type (more eosinophilic cytoplasm) as manifested by CDX2 positivity.33

Intestinal AIS occurs in an older age group when compared to usual type (45 versus 32 years) and most are related to HPV 18. Nevertheless, a small subset is HPV 18 unrelated and shows an even more pronounced age difference with usual AIS (62 versus 32 years). These differences suggest, at least in some intestinal AISs, an alternative pathogenesis that is HPV unrelated.32 Finally, intestinal AIS has been associated with a higher rate of progression to invasive adenocarcinoma than usual subtype.20 Endometrioid AIS is rare and characterized by cells with dense eosinophilic cytoplasm and no visible intracytoplasmic mucin (small amounts of mucin staining along the luminal border are allowed) and marked nucleus pseudostratification, resembling to some extent proliferative-type endometrial glands.12,14,29,34 However, its distinction from usual subtype (if mucin depleted) may be sometimes arbitrary owing to their overlapping morphologic appearance.12,22 Tubal AIS refers to the replacement of preexisting endocervical glands by ciliated and intercalated cells, with nuclear stratification and mucin loss (Figure 2, C).22 It may occur alone or admixed with other subtypes. Most tubal AISs have been described to be in continuity with tubal metaplasia showing an increased gradient of nuclear atypia and mitotic activity as a step-wise progression (atypical tubal metaplasia).22,35 Some tubal AISs may contain glands with a more endometrioid appearance with apical cytoplasmic “blebs/snouts” (as occur in tubal metaplasia frequently seen transitioning to tuboendometrial metaplasia and endometriosis).22 Adenosquamous carcinoma in situ has rarely been reported in the literature and is defined as having both glandular and squamous cell elements that are juxtaposed on histologic examination.16,17 The stratified mucin-producing intraepithelial lesion (SMILE) is an infrequent and relatively recently described variant of AIS characterized by the following architectural features: (1) stratified epithelium resembling squamous dysplasia at low power; (2) rounded borders at the epithelial-stromal interface, and (3) absence of gland formation. Cytologic features include: (1) polyhedral to columnar cells, (2) abundant clear or vacuolated cytoplasm throughout the thickness of the epithelium, often showing intracellular mucin creating even spacing of nuclei in middle and lower layers; and (3) nuclear hyperchromasia (Figure 2, D).21 By immunophenotype (cytokeratin CK 14

Figure 1. Adenocarcinoma in situ (AIS) (usual type). A, The preexistent architecture is typically preserved with partial involvement of glands and abrupt transition from normal endocervical epithelium to AIS. B, Nuclear pseudostratification, crowding, and hyperchromatism with brisk mitotic activity in apical location and numerous apoptotic bodies are seen (hematoxylin-eosin, original magnifications ×100 [A] and ×200 [B]).
negative and p63 negative or only weakly positive), SMILE is best classified as a variant of endocervical columnar cell neoplasia.21 SMILE has been reported by some investigators to represent a poorly differentiated variant of AIS that should be reported as poorly differentiated or stratified AIS.21,36 Finally, even though minimal deviation adenocarcinoma has no well-characterized in situ precursor, it has been postulated to have a link with lobular endocervical glandular hyperplasia with atypical features or AIS with gastric phenotype (see below).31

Differential Diagnosis

Recognition of AIS and its distinction from various benign mimics and invasive adenocarcinoma is not always straightforward. Moreover, morphologic characterization of endocervical glandular atypia that does not fulfill AIS criteria is not well defined. To highlight the most common problems and pitfalls in the differential diagnosis of AIS, the following topics will be addressed: (1) AIS versus benign mimics; (2) AIS and its relation to endocervical glandular dysplasia; (3) AIS versus early invasive adenocarcinoma; and (4) AIS versus squamous lesions. Even though mucosal cervical extension of endometrial adenocarcinoma may also be misinterpreted as AIS, distinction between endocervical and endometrial adenocarcinoma is discussed later on, under the section “Invasive Endocervical Adenocarcinoma” but most of the aspects discussed there also apply to AIS.

Adenocarcinoma In Situ Versus Benign Mimics.—Not infrequently, benign glandular lesions of the cervix cause concern for malignancy. Familiarity with their histopathologic features is essential for their recognition and distinction from AIS. The following pseudoneoplastic lesions are discussed: (1) reactive/reparative glandular atypia; (2) mitotically active endocervical glands; (3) tubal/tuboendometrioid metaplasia; (4) endometriosis; (5) mesonephric remnants; (6) intestinal metaplasia; (7) Arias-Stella reaction; and (8) atypical oxyphilic metaplasia.

Reactive/Reparative Atypia.—Reactive/reparative atypia shows a spectrum of changes37–40 that occasionally may be misinterpreted as AIS when the following features are present: (1) nuclear atypia with large hyperchromatic nuclei; (2) nuclear stratification (reserve cell hyperplasia or tangen-
tional sectioning may simulate nuclear stratification; (3) mitotic figures; (4) intraepithelial lymphocytes (interpreted as apoptotic bodies); and (5) tufting and short micropapillary processes (especially when prior biopsy or curettage). Some of these alterations may or may not be accompanied by a background of inflammation. General features that help in this differential diagnosis include: (1) preservation of the nuclear to cytoplasmic ratio; (2) round nuclei with nucleoli but evenly distributed chromatin; (3) degenerative-type atypia (smudge chromatin); (4) absent to rare mitoses (present in a basal location); and (5) no apoptotic bodies.37–40 Other helpful features pointing toward the reactive nature of the endocervical glands, especially in the setting of a previous curettage/biopsy, include: (6) cells with squamoid or hobnail appearance; (7) surface erosion associated with fibrinoid material; and (8) stromal vascu-
larization, hyalinization, and fibrosis.39

Radiation-induced atypia of endocervical epithelium may be observed weeks to years after treatment and occasionally may cause marked cytoplastic changes that can be misinterpreted as AIS, especially if the prior clinical history is not known to the pathologist. Worsome findings include: (1) large cells displaying dense eosinophilic, often vacuolated cytoplasm; (2) loss of nuclear polarity; (3) large, clear to vesicular to smudgy nuclei; and (4) prominent eosinophilic nucleoli. However, the correct diagnosis can be achieved as (1) endocervical epithelium is frequently denuded; (2) endocervical glands are typically fewer when compared to normal endocervical glandular architecture; (3) dilated glands are often present and a complex architecture is absent; (4) nuclear stratification, marked increased nuclear to cytoplasmic ratio, mitoses, and apoptotic bodies are lacking; (5) atypical cells are interspersed with normal-appearing endocervical cells; and (6) stromal fibrosis/hyalinization, intimal thickening of vessels, and atypical stromal cells are often seen.38,41

Cautery artifact (mostly thermal related) is a common consequence of widespread loop electrosurgical excision procedure (LEEP) use and characteristically shows markedly stratified, compressed, strikingly elongated epithelial cells with hyperchromatic nuclei and smudged chromatin and stroma with marked eosinophilia. These changes may preclude accurate assessment of morphologic evaluation in specimens with AIS. However, closer inspection demonstrates lack of mitoses or apoptosis.34,42,43

In problematic cases, a panel of antibodies, including p16, MIB1, and ProExC, may assist in this differential diagnosis (Table 1). Adenocarcinoma in situ is almost always diffusely and strongly p16 positive (with rare exceptions),34,35,56 with MIB1 and ProExC showing positivity in greater than 30% and 50% of tumor cells, respectively.51,59 Even though there may be overlap in this immunohistochemical profile, as AIS may only show focal MIB1 and ProExC expression,51,52,54,57–60 and rare cases of reactive atypia display diffuse ProExC positivity (>67%),57 Moreover, MIB1 results must be interpreted with caution if there is a history of recent biopsy, because the regenerative activity of the endocervical epithelium is accompanied by a high MIB index.51,59 Even though there is scant literature on carcinoembryonic antigen (CEA) staining frequency of reactive endocervical glands, it is worth mentioning that radiation-induced atypia often shows focal cytoplasmatic and luminal border positivity and this can be misconstrued as evidence of AIS, which is known to show not only luminal but also cytoplasmic CEA positivity.35,50,53

Mitotically Active Endocervical Glands.—Even though the presence of mitoses in the endocervical epithelium always raises concern for AIS, this finding is not diagnostic. In rare instances, cytologically unremarkable endocervical glands may show some mitotic activity; however, mitoses do not have an apical location and they are not associated with nuclear stratification, cytologic atypia, or apoptotic bodies.

Tubal/Tuboendometrioidal Metaplasia.—Tubal/tuboendometrioidal metaplasia (TEM) is characterized by replacement of preexisting endocervical-type epithelium by cells closely resembling those seen in the fallopian tube (tubal metaplasia) or, less commonly, endometrium (tuboendometrioidal metaplasia) (Figure 3, A through E). It has been reported in

Table 1. Summary of Histochemical and Immunohistochemical Profiles of Benign Mimics of Adenocarcinoma In Situ of the Cervixa

<table>
<thead>
<tr>
<th>Glands</th>
<th>AIS</th>
<th>Endometriosis</th>
<th>Tuboendometrioidal Metaplasia</th>
<th>Reactive Atypia</th>
<th>Mesonephric Remnants</th>
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<td>ProExC</td>
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Abbreviations: AIS, adenocarcinoma in situ; CEA, carcinoembryonic antigen; CRBP-1, cellular retinol-binding protein–1; ER, estrogen receptor; IMP3, insulin-like growth factor–II mRNA-binding protein 3; PR, progesterone receptor; +, diffuse positivity; −, focal positivity; −, negative; ...not relevant in differential diagnosis or not tested.

a For exceptions to the most common patterns of staining compiled in this Table see text.
up to 69% of postconization cervices and, in those instances, interpreted as a metaplastic process following injury. TEM is frequently an incidental finding observed in the upper endocervix in cone/hysterectomy specimens (21%–62%) from premenopausal women. Not infrequently, these patients have a previous cervical smear with atypical glandular cells that may be interpreted as atypical glandular cells or suspicious for AIS. It may involve the overlying surface epithelium or, more commonly, the glandular epithelium (Figure 3, A), being usually confined to the superficial third of the cervical wall. The metaplastic glands usually are evenly spaced with preservation of the preexisting architecture, with glands totally or partially lined by pseudostratified epithelium consisting of ciliated, nonciliated, and intercalated cells, with uniform bland nuclei and rare to absent mitoses (Figure 3, B) in most cases. TEM may raise concern for usual-type AIS if pathologists are not familiar with some of the following unusual features: (1) variability in gland size and shape, including branching and prominent cystic dilatation; (2) focal gland crowding or haphazard distribution of glands; (3) segmental glandular involvement with abrupt transition from normal to metaplastic epithelium; (4) prominent nuclear pseudostratification, columnar cytoplasm, and relatively high nuclear to cytoplasmic ratio; and (5) absence of or minimal cilia, conferring a monotonous appearance to the cells (in contrast to typical admixture of various cell types seen in tubal metaplasia or TEM). Even more, the findings of frequent periglandular stromal alterations seen as hypercellular, edematous (Figure 3, A), or myxoid stroma, or involved glands present deeply in the cervical wall (including outer third), may cause concern for invasive adenocarcinoma (see “Minimal Deviation Endometrioid Adenocarcinoma”). Distinction from AIS should rely on a set of findings rather than a single finding, with the diagnosis of TEM favored in the absence of severe cytologic atypia, mitotic activity, and apoptotic bodies. Moreover, on close inspection, at least some cells have cilia and those with a more endometrioid appearance show apical cytoplasmic snouts/blebs. However, it

Figure 3. Tubal metaplasia. Cells show abundant cilia and glands are characteristically surrounded by edematous stroma (A), and may have some nuclear stratification and mitotic activity (arrow) (B). Immunophenotypically, it shows focal patchy p16 (C), diffuse cytoplasmic bcl-2 (D), as well as vimentin (E) positivity (hematoxylin-eosin, original magnifications ×100 [A] and ×400 [B]; original magnifications ×200 [C], ×400 [D], and ×100 [E]).
should be noted that a spectrum of endocervical glandular dysplasia up to AIS may occur in metaplastic tubal-type epithelium. 52,53

Even though distinction between AIS and TEM usually relies on morphology, in equivocal cases, a panel of antibodies, including a combination of p16, CEA, bcl2, MIB1, ProExC, PAX2, and vimentin may be useful (Table 1). Almost all endocervical-type AISs exhibit diffuse and strong p16 nuclear positivity, with or without cytoplasmic positivity (with rare exceptions), 45,46,54 in contrast to TEM, which often only displays focal patchy positivity44–56 (Figure 3, C). Of note, rare examples of TEM have been reported to be diffusely p16 positive. 54,47,48 Endocervical-type AIS typically shows diffuse cytoplasmic (with or without luminal border) positivity for CEA,56,62,63 while TEM is typically negative 44; this is not a very reliable immunohistochemical marker in this differential diagnosis as up to 67% of AISs have been reported to be negative 52,57 and 39% of TEM cases have been reported to be CEA positive (no specific mention about luminal versus cytoplasmic positivity or polyclonal or monoclonal CEA in the latter). 67 TEM displays diffuse bcl2 luminal versus cytoplasmic positivity or polyclonal or monoclonal CEA-positive (no specific mention about CEA positivity). In AIS, 56,62,63 endocervical-type AIS typically is usually negative or only focally positive. 54,47,48 Endocervical-type AISs exhibit diffuse and strong cytoplasmic positivity, 44,45,46,54,55,71,72 while AIS is typically negative or only focally positive. 54,47,48 Adenocarcinomas in situ usually have a higher MIB1 proliferative index (>30% of cells) 44,48,53,55,56,59,60 in contrast to the low MIB1 index (<10%) seen in TEM. 44,48,53,55,59 However, this marker should be used with caution as lower MIB1 rates can be seen in AIS (<30%, or less frequently, <10% positivity) 44,53,54 and higher MIB1 expression may be observed in TEM (>10%, or less frequently, >20%). 54,55,59 ProExC, initially proposed as a HPV-related marker and recently as a proliferative marker, is usually positive in greater than 50% of neoplastic cells in AIS, 51,57,60 whereas TEM is usually negative or only focally positive (<10%), 44,45,48,53,55,56,59,71,72 but similarly to MIB1, overlap may occur. 51,57,60 Vimentin has proved useful in the distinction of TEM from AIS as the former typically exhibits diffusely cytoplasmic staining (Figure 3, E) and AIS is negative with rare exceptions. 50,67,73 Of note, normal endocervical glands may show minimal vimentin expression confined to the basal cytoplasm along with delicate lateral staining of the cell borders. 55 Estrogen receptor (ER) and progesterone receptor (PR) also typically show positivity in TEM but their expression is absent or minimal in most AISs. 64,74 A recent study 52 has shown promising results using PAX2, a transcriptional protein involved in urogenital tract differentiation, showing negativity in all AISs (6 cases tested) but with strong and diffuse positivity in all TEM cases (8 tested). IMP3 (insulin-like growth factor–II mRNA–binding protein 3 demonstrated in a number of carcinomas, including endometrial and ovarian, has been reported in 1 study to be positive in 41 of 44 AISs (93%) (cytoplasmic staining), being negative in all TEM cases tested (19 of 19). The authors concluded that this marker is more specific but less sensitive than p16 in the diagnosis of AIS. 44 In specific instances, HPV studies may also be helpful in this differential diagnosis. 54,59,76,77

Endometriosis.—Endometriosis may be present either superficially or deep in the cervical wall, the latter usually associated with pelvic endometriosis. 78,79 Although the cervix is an uncommon location for endometriosis, 80 higher incidences (43%–46%) have been reported for patients with a history of prior trauma (curettage, biopsy, conization, cautery, or vaginal delivery). 54,79,82 It is usually an incidental finding in women of reproductive age, but patients may present with abnormal uterine bleeding or abnormal cervical/vaginal smear. 78,81,83 Colposcopic appearance may be unremarkable or may show a nonspecific friable, granular, erosive, or thickened mucosal area. When typical it appears as a red/purple/hemorrhagic punctuate or cystic lesion that enlarges and becomes congested and apparent before or during menses. 78,80,83,84 Microscopically, endometriosis is often found in the superficial stroma subjacent to squamous epithelium (ulcerated or not) or in between endocervical glands, being almost always confined to the inner third of the cervical wall 78,81,83 (Figure 4, A through C). In typical cases, glands resemble proliferative or inactive endometrium, and endometrial stroma is readily identified (sometimes only after serial sections are performed) with (1) loose and cellular appearance with periglandular distribution, which contrasts with the fibromuscular and less cellular cervical stroma; (2) characteristic small arterioles sometimes engorged with erythrocytes and/or accompanied by hemorrhage; and (3) pigmented histiocytes. 54,78,79,82,84 However, the diagnosis of endometriosis can be challenging and not infrequently misinterpreted as AIS. At low power, the “dark-staining” nature of endometriosis causes concern for AIS (Figure 4, A and D). At high power, potential confusing morphologic “epithelial” features include: (1) scant nonnuclearectoplasm; (2) “cytologic atypia,” as nuclei are pseudostratified, vesicular, sometimes hyperchromatic, and may have conspicuous nucleioli (as often seen in normal proliferative endometrium) 78,85; (3) mitotic activity which may be brisk, especially in young women 44,78,79; and (4) metaplastic changes including ciliated, eosinophilic, hobnail, mucinous, clear cell metaplasia, and occasionally in pregnant woman, secretory changes that may include Arias-Stella reaction (the latter may cause confusion with clear cell carcinoma). 79 In such cases, the key feature for the diagnosis of endometriosis is always the identification of endometrialtissue stromal atypical stromal into which the cervix may potentially progress to hyperplasia and carcinoma and, in these cases, will be associated with architectural complexity as well as cytologic atypia. 79

A panel of antibodies, including a combination of p16, CEA, MIB1, ProExC, and PAX2 may assist in this differential diagnosis (Table 1). Adenocarcinoma in situ is typically diffusely p16 positive (Figure 4, E) in contrast to endometriosis that demonstrates at most focal positivity in most cases (Figure 4, B). 44,48,51,56,74,87 Endocervical-type AIS characteristically shows diffuse cytoplasmic (with or without luminal border) CEA staining, whereas endometriosis is usually negative or at most only focally positive. 44 As occurs in the differential diagnosis with TEM, endometriosis shows diffuse bcl2 cytoplasmic positivity, 44,45,48,53,55,72,88 while AIS is typically negative (with rare exceptions). 44,45,48,53,55,72,88 MIB1 proliferative index is high (>30% of cells) in AIS (Figure 4, F), 56,51,53,58,89 while endometriosis usually shows less than 10% positivity (Figure 4, C). 44,51 However, overlap may occur as occasionally AISs have lower proliferative index (<30%, or less frequently, <10%), 44,51,53,54 and endometriosis may show higher proliferation index (>10%). 44 ProExC shows parallel results to those reported for MIB1, as it usually shows positivity in greater than 50% of neoplastic cells in AIS, while endometriosis is usually negative or only focally positive for this marker (<10%). 51,57,64 but may show some overlap. 44,51,53,54,60 There is a significant loss of ER and PR expression in AIS compared to benign mimics, including..
endometriosis. PAX2 has been reported to show negativity in AIS (6 tested) but strong and diffuse positivity in almost all examples of endometriosis (22 of 24). Additionally, the following markers have been reported to be useful in the distinction between endometrial and endocervical stroma, thus helping in the diagnosis of endometriosis: (1) reticulin shows a fine network around individual stromal cells in endometrial-type stroma in contrast to cervical stroma that lacks reticulin fibers; (2) trichrome shows thick blue collagen bands in cervical stroma in contrast to scant and thin red fibers in endometrial-type stroma; (3) CD34 in combination with CD10 demonstrates a CD34+/CD10− profile in endometriotic stroma and a CD34−/CD10+ staining pattern in endocervical stroma. However, some authors have found that cervical stromal cells, especially around glands, are CD10 immunoreactive. Cellular retinol-binding protein-1 (CRBP-1) may appear to be a more specific marker for endometrial stromal cells as it has shown negativity in endocervical stromal cells. If necessary, HPV studies may also be performed.

Mesonephric Remnants.—Mesonephric remnants occur in the lateral walls of the cervix in up to 22% of women of reproductive and postmenopausal age and they are always an incidental finding. Histologically, mesonephric remnants are characterized by: (1) small collections of tubules arranged in well-circumscribed lobules with or without a central duct; (2) single layer of cuboidal cells with scant cytoplasm and bland nuclei lining the tubules; (3) absent...
mitotic activity; and (4) bright pink to red hyaline, periodic acid-Schiff (PAS)–positive, diastase-resistant intraluminal contents.59,77 Distinction between mesonephric remnants and mild mesonephric hyperplasia may be arbitrary and a cutoff of 6 mm has been used.59,98 Mesonephric remnants may rarely cause problems in the differential diagnosis with AIS owing to their nonmucinous and scant cytoplasm and p16 immunoreactivity that may be strong and diffuse.59,98 However, in mesonephric remnants, nuclear atypia, mitotic activity, and apoptotic bodies are absent.59 To AIS (bcl2, PAX2, and CD10 negative)44,45,46,53,55,72,75,88,103 they are characterized by low (5%) MBI expression,53,99 no staining for monoclonal CEA,53,100 diffuse Bcl2 and PAX 2 expression, and often, focal CD10 positivity (Table 1).53,75

Intestinal Metaplasia.—Intestinal metaplasia has been rarely reported in otherwise unremarkable endocervical glands.27 However, some investigators20 advocate that the finding of intestinal metaplasia in the cervix is always indicative of a premalignant or malignant lesion. Intestinal differentiation is frequently seen in AIS (mixed and pure intestinal)7,11,12 and occasionally in benign lesions (villous adenoma [abundant goblet cells] and lobular endocervical glandular hyperplasia [rare goblet cells])102,103 and invasive adenocarcinoma.26,22 Thus, the diagnosis of intestinal metaplasia in benign endocervical glands should be made (if ever) with caution.50,28,29,38

Arias-Stella Reaction.—Arias-Stella reaction is discussed in detail in the section “Invasive Endocervical Adenocarcinoma” as this lesion typically causes problems in differential diagnosis with clear cell carcinoma.104–106

Atypical Oxyphilic Metaplasia.—Atypical oxyphilic metaplasia is a rare incidental metaplastic change seen in isolated superficial endocervical glands. Cytologically, the presence of variable nuclear atypia, with enlarged, hyperchromatic, and multilobulated nuclei (multinucleated cells may be present) and prominent nucleoli may cause concern for AIS. However, affected cells have abundant, dense, eosinophilic, and focally vacuolated cytoplasm, rarely with apical snouts and absence of nuclear stratification, apoptotic bodies, and mitotic figures, in contrast to AIS.105 Immunohistochemistry may not be useful in this setting as only 3 cases have been tested for CEA, all negative.105

Adenocarcinoma In Situ Versus Squamous Metaplasia/Dysplasia/Carcinoma In Situ (SMILE).—SMILE shares with immature squamous metaplasia the finding of stratified epithelium and mucin-containing cells (Figure 2, D). However, in contrast to the latter, in which mucinous cells are confined to the upper or at most, upper and middle layers, in SMILE, mucin-producing cells are present throughout the epithelium. However, mucin may not be apparent on routine hematoxylin–eosin examination, and the diagnosis of SMILE should be suspected by the finding of abundant cytoplasm in the cells and spacing of the nuclei in middle and lower layers.21 Presence of mitoses and nuclear hyperchromasia also points toward this diagnosis. In problematic cases, MBI, p16, and mucicarmine may be helpful as, unlike squamous metaplasia, SMILE shows a high proliferation index, is usually diffusely and strongly p16 positive, and has a diffuse distribution of mucicarmine-positive cells.21,25

SMILE can also be mistaken with a high-grade squamous lesion, as both have stratified epithelium, and squamous lesions may contain preexistent mucinous cells (Figure 2, D). However, in contrast to high-grade squamous lesions, at low power, SMILE has a more “pink” appearance as cells have more cytoplasm. At higher magnification, mucinous cells are seen throughout the epithelium and can be evidenced by distribution of mucicarmine (in squamous lesions mucin is only present on the surface or within the center of the endocervical glands), negative staining for keratin-14, and overall reduced p63 staining (positivity present only in basal cells and absent on columnar, suprabasal cells).21

Colonization of endocervical glands.—Colonization of endocervical glands by squamous dysplasia/carcinoma in situ may mimic AIS. However, in the former, there may not be a sharp transition to normal endocervical epithelium and cells tend to have: (1) more abundant cytoplasm; (2) disorganization of nuclei (not as pseudostratified as in AIS) that show vesicular chromatin; and (3) no apical mitoses or basally located apoptotic bodies (personal observation). p63 may be useful in this differential diagnosis as it typically shows negativity in AIS and positivity in squamous lesions (mild dysplasia showing positivity in basal and parabasal cells and more severe lesions displaying positivity in the middle and upper layers). However, potential pitfalls include: (1) poorly differentiated AIS, which may exhibit basal cell p63 positivity (parabasal cells are negative); and (2) positive residual normal reserve cells not replaced by AIS.108

Adenocarcinoma In Situ and Its Relation to Endocervical Glandular Dysplasia.—Endocervical glandular dysplasia (EGD), which refers to endocervical glandular abnormalities not associated with inflammation that display some but not all features of AIS, is a poorly characterized and controversial entity. Various diagnostic criteria3,109,110 have been proposed for this putative precursor lesion of AIS without widespread acceptance, with some authors66,111–114 questioning the existence of this entity. Findings supporting EGD as a precursor of AIS include: (1) high frequency of EGD adjacent to AIS or invasive adenocarcinoma;12,13,109,115–117,119–121 (2) presence of high-risk HPV as detected in AIS4,116, (3) high proliferative activity4,120, and (4) similar lectin profile between EGD and AIS.105,122 Findings against it include: (1) infrequent coexistence of EGD and AIS113,115; (2) low frequency of oncogenic HPV DNA26,31,118,16, (3) existence of HPV-negative glandular atypia (and thus presumably not a Precursor) with high proliferative index123; and (4) great overlap in lectin profile between EGD and normal endocervical epithelium.122 Overall, it is accepted that differences in the reported frequencies of these lesions are most likely related to different thresholds used in the diagnostic criteria of AIS.10,112,113 Essentially, it is important to keep in mind that the appearance of AIS can vary, some lesions being subtle, if very focal,15 or when dealing with some AIS subtypes,20,32 and that benign endocervical glandular lesions may show a wide spectrum of reactive cytologic changes. In both instances, the histologic findings may greatly overlap with EGD, making this entity a nebulous one and difficult to reproduce. Moreover, as the biologic significance attributed to EGD remains unproven, in our opinion and according to some authors,13,14,31,130,113 it is best at the present time to avoid the use of this term, and thus we do not make a diagnosis of EGD.

Adenocarcinoma In Situ Versus Early Invasive Adenocarcinoma.—The definition of early invasive adenocarcinoma (EIA) is a controversial issue in gynecologic pathology. Furthermore, distinction of EIA from florid AIS, and accurately determining the depth of invasion at which patients have increased risk of recurrence/metastases, represent important problems in daily pathology. Establishing morphologic criteria to address these issues has been the
aim of many studies as they will determine a patient’s treatment and prognosis. Early invasive adenocarcinoma is defined by most authors by a depth of invasion of less than 5 mm, measured as the greatest distance between the base of the surface epithelium and the deepest infiltrating neoplastic glands (tumor thickness), while others have used limits between 1 and 3 mm. Still, some authors advocate the use of tumor volume (500 mm³) as a better predictor of pelvic lymph node metastases and recurrence. The current International Federation of Gynecological Obstetrics (FIGO) defines stage IA tumors as “invasive cancer identified only microscopically. Invasion is limited to...” Obstetrics (FIGO) defines stage IA tumors as “invasive cancer identified only microscopically. Invasion is limited to...” FIGO further subdivides stage IA tumors into 2 categories: stage IA1 with measured stromal invasion of no greater than 3 mm in depth and stage IA2 as “measured invasion of stroma greater than 3 mm but no greater than 5 mm in depth.” However, the Society of Gynecological Oncologists suggests that “microinvasive carcinoma” be defined as “a microscopic invasive cancer with a maximum depth of invasion of 3 mm and in which lymphatic or blood vessel involvement is not demonstrated.” In the rare event when invasion does not occur from the surface or crypts, the maximum depth of invasion should be measured from the gland (s) where the tumor appeared to originate or from the base of the nearest nonneoplastic surface epithelium.

The mean age at presentation is intermediate between that of AIS and “clinically” invasive adenocarcinoma (39–46 years). Patients are often asymptomatic but abnormal uterine bleeding, pain, or discharge may occur. Colposcopy is frequently unremarkable and Papanicolaou smear findings, detected in 66% of the patients, are similar to those detected in AIS. Most EIAs are localized at or proximal to the transformation zone, but may be extending higher in the endocervical canal as occurs in AIS. It appears that maintaining EIA as an independent category within the group of invasive adenocarcinomas is helpful as there is increasing evidence of excellent prognosis of patients with stage IA (following FIGO definitions) endocervical adenocarcinomas, as evidenced in a review of 1170 patients with these tumors who had 98.5% survival. In this study, only 15 of 531 patients (<2%) who underwent pelvic (with or without para-aortic) lymphadenectomy had 1 or more positive lymph nodes, and 11 of 15 (73.3%) had an adverse outcome. In the same study, among 98 patients who underwent conization as mainstay of treatment (up to 10% also received adjuvant radiation or had pelvic lymphadenectomy), no recurrences were reported. Although Östör et al reported multicentricity in 25% of EIAs, true “skip” lesions (foci separated by more than 3 mm) were not identified, and thus residual disease does not seem to be a problem if conservative treatment is considered as long as cone margins are uninvolved by carcinoma. However, Östör also reported that only one-third of patients are eligible for this treatment, as frequently margins are positive. From the low frequency of lymph node metastases, and relative significant frequency of chronic leg edema related to node dissection in these patients, other authors have advocated for less radical surgery approaches. From the pathologic point of view, it appears that endometrioid histology may be associated with late recurrence and worse survival in EIA.

Histologic assessment of early stromal invasion and thus distinction of EIA from extensive AIS may be very difficult, especially when an expansive as opposed to an overtly infiltrative growth pattern is present. Indeed, in approximately 20% of cases, the pathologist may be uncertain about the presence of stromal invasion. Glands involved by AIS may show architectural patterns that should not be misinterpreted as invasion: (1) occasional glands closely packed together; (2) papillary infoldings; (3) outpouchings/exophytic budding of glands into the stroma (a pattern also seen occasionally in normal endocervical glands); and/or (4) cribiform pattern (limited to isolated glands). It is important to emphasize that the normal overall endocervical glandular architecture is preserved in AIS when compared to EIA and that the abnormal glandular proliferation should be always compared to the distribution of preexisting endocervical glands, which may greatly vary from cervix to cervix.

Diagnostic features of stromal invasion are depicted in Figure 5, A through C, and include: (1) fragmented/ragged glands with tiny fingerlike processes extending into the stroma and/or detached cell clusters/isolated cells; (2) stromal response, including edema, chronic inflammatory infiltrate, or desmoplastic reaction; (3) extension of the neoplastic glands beyond the deepest normal endocervical crypts; and (4) lymphovascular involvement. Close proximity of glands to thick-walled blood vessels (thickness less than or equal to that of the vessel wall) seems to be a useful feature in the diagnosis of invasive adenocarcinoma. Two patterns have been described: (1) “circumferential” with multiple glands circumferentially involving a vessel and (2) “molded” in which 1 or more distorted glands mold around a vessel. Cytologically, cells in these early invasive glands may have more cytoplasm and larger nuclei with more prominent nucleoli than cells of adjacent AIS, imparting a “squamous” or “anaplastic” appearance. However, many EIAs do not display the above features. In those instances, features that may be helpful in raising suspicion for early invasion include: (1) confluent architecture of the involved glands that exceeds that accepted for AIS (lack of lobular architecture of crypts involved by AIS/absence of normal overall endocervical glandular architecture) or (2) complex architecture that may include glandular branching, small solid glands, or marked papillary or cribiform arrangement (Figure 5, A). A definitive diagnosis of EIA can only be made on cone or hysterectomy specimens, but not in biopsy samples. In addition, these specimens must be extensively sampled to assure accurate size of the neoplasm and assessment of margins.

Little is known about the molecular and immunophenotypic alterations associated with invasion in endocervical carcinomas. Although laminin-5 γ2 chain may facilitate assessment of early invasive tumor buds that show cytoplasmic positivity (AIS glands are usually negative), it should not be used in isolation to establish a diagnosis of early invasion. Stewart and colleagues have recently addressed the immunophenotypic changes associated with epithelial-mesenchymal transition in endocervical adenocarcinomas and their correlation with tumor morphology (including growth patterns). Epithelial-mesenchymal transition is a biologic process through which an epithelial cell acquires a mesenchymal phenotype, including enhanced migratory capacity, invasiveness, elevated resistance to apoptosis, and increase production of extracellular matrix components. This process is completed with the degradation of underlying basement membrane and migration from the epithelium of origin of the newly formed mesenchymal...
cell. Activation of an epithelial-mesenchymal transition program is now considered an important mechanism for the acquisition of malignant phenotype by epithelial cancer cells including cervical carcinomas.\textsuperscript{144,145} Invasive endocervical adenocarcinomas show immunophenotypic changes consistent with epithelial-mesenchymal transition, namely, positivity for vimentin (few cases), nuclear and cytoplasmic cyclin D1, fragmented or incomplete membrane E-cadherin, and incomplete or absent membrane β-catenin staining. This aberrant expression occurs typically at the tumor invasive front, where cytologic alterations, including loss of cell polarity and cytoplasmic eosinophilia, are observed. Therefore, these immunohistochemical markers can potentially be helpful in the distinction of EIA from AIS by highlighting morphologic subtle invasive foci.\textsuperscript{48,55,142}

**INVASIVE ENDOCERVICAL ADENOCARCINOMA**

The frequency of cervical adenocarcinoma among all cervical neoplasias has increased in the last decades, from less than 10% to up to 27%, owing not only to a real increase in annual incidence but also to a decrease in frequency of invasive squamous cell carcinoma.\textsuperscript{146–150} Most

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**Figure 5.** Early invasive adenocarcinoma. Diagnostic features include stromal response with chronic periglandular inflammatory infiltrate (A), cribriform architecture (B), and ruptured glands with detached cellular clusters (C) (hematoxylin-eosin, original magnifications ×100 [A and B] and ×200 [C]).

**Figure 6.** A, Usual-type endocervical adenocarcinoma with microcystic pattern may have a flattened lining epithelium with bland appearance mimicking tunnel clusters; however, a complex chaotic architecture is typically present. B, On the other hand, type B tunnel clusters, a potential mimic of endocervical adenocarcinoma, may have focal atypia. C, A lobular architecture and admixture with type A tunnel clusters favors a benign nature of the glandular proliferation (hematoxylin-eosin, original magnifications ×40 [A], ×100 [B and C], and ×400 [inset B]).
cervical adenocarcinomas are HPV related. Interestingly, HPV 16 and 18 are detected with equal prevalence in most subtypes, except in endometrioid and well-differentiated villoglandular adenocarcinomas where HPV 16 is the predominant type, and minimal deviation adenocarcinoma and mucinous adenocarcinoma with gastric phenotype, which seem to be HPV unrelated. Unlike squamous cell carcinomas, adenocarcinomas have been linked to obesity, excessive estrogens, and oral contraceptives but do not appear to be related to cigarette smoking. The mean age at presentation is 50 years in most series but the percentage of women younger than 35 years has increased in recent years. The most common presenting symptom is abnormal vaginal bleeding. The gross appearance of cervical adenocarcinoma is variable, ranging from nonapparent, especially in early stages (although some deeply invasive tumors can be grossly deceptively) to mass forming (polypoid, papillary, nodular, sessile, ulcerated, or diffuse thickening of cervical wall). Pure endocervical adenocarcinomas may be classified as follows: (1) usual, including (1A) well-differentiated villoglandular papillary adenocarcinoma; (2) endometrioid, including (2A) minimal deviation endometrioid adenocarcinoma; (3) mucinous, including (3A) gastric, (3B) minimal deviation mucinous adenocarcinoma, and (3C) intestinal, including signet ring cell adenocarcinoma; (4) clear cell; (5) serous; and (6) mesonephric. Individualization of the most common form, usual-type endocervical adenocarcinoma, from mucinous-type endocervical adenocarcinoma represents a change to World Health Organization classification and is based on the observation that most cervical adenocarcinomas have little or no intracytoplasmic mucin on hematoxylin-eosin and mucin staining. Tumors containing more than 10% of a mucinous component are designated as “mixed” adenocarcinomas (proportion of each component should be recorded). Patients with adenocarcinoma are more likely to present with early-stage disease when compared to squamous cell carcinoma; however, 5-year survival is lower when compared stage by stage. Five-year survival stratified by stage is as follows: 84.8% (IB1), 68.3% (IB2), 45.5% (IIA), 46.3% (IIB), 15.6% (IIIA), 20.3% (IIIB), 8% (IVA), and 9.4% (IVB). Potential pathologic prognostic factors include: (1) histologic type and grade; (2) vascular and paracervical invasion; (3) depth of invasion; (4) resection margins; and (5) lymph node metastasis.

**Subtypes and Differential Diagnosis**

**Usual Type.**—Usual type endocervical adenocarcinoma is the most common among cervical adenocarcinomas (>80%). Histologically it is characterized by (1) randomly arranged, widely spaced, or closely packed medium-sized glands, often angulated and with complex architecture, including branching, cribriform, and papillary patterns; (2) glands lined by cells with eosinophilic to amphophilic cytoplasm containing variable amount of mucin (usually mucin depleted) and basally located atypical nuclei; (3) numerous mitotic figures; (4) acute inflammatory cells in gland lumens and stroma (often); (5) desmoplastic stromal reaction (+/−); and (6) simultaneous AIS or squamous dysplasia. Most of these tumors are moderately differentiated. Usual-type endocervical adenocarcinomas may occasionally cause diagnostic difficulties, especially if papillary, villoglandular, and microcystic patterns (uncommon) are present.

**Usual-Type Adenocarcinoma Versus Benign Proliferations.**—Tunnels clusters are divided into type A and B. Type A tunnel clusters are characterized by multiple small, closely packed, elongated glands lined by columnar or low cuboidal cells with amphophilic cytoplasm. They may raise concern for usual-type adenocarcinoma as they may show: (1) back-to-back arrangement of the glands; (2) cells with increased nuclear to cytoplasmic ratio; (3) cellular crowding and prominent nuclei pseudostratification; (4) degenerative atypia, including nuclear enlargement, hyperchromasia, vesicular chromatin, and prominent nucleoli; (5) stroma with edema or inflammation causing confusion with desmoplastic stroma; and (6) focally irregular glandular borders conferring a pseudoinfiltrative appearance. Type B tunnel clusters consist of closely packed cystically dilated glands lined by flat or cuboidal endocervical cells. They may mimic usual-type endocervical adenocarcinoma with microcystic pattern, as the latter may have flattened lining epithelium with bland appearance and an orderly glandular distribution. Moreover, tunnel clusters may have: (1) associated mucoid discharge or striking gross abnormality; (2) deep involvement of cervical wall; and (3) focal cytologic atypia (Figure 6, B). However, in contrast to usual-type endocervical adenocarcinoma, tunnel clusters often: (1) are an incidental finding; (2) are confined to the superficial aspect of the endocervical wall; (3) are multiple; (4) have striking lobulation (a feature only focally seen in invasive adenocarcinoma); and (5) lack cribriforming, true nuclear stratification, conspicuous and extensive cytologic atypia, mitoses, and desmoplasia (seen in many but not all invasive adenocarcinomas); moreover, (6) both types are often admixed. Microglandular hyperplasia consists of closely packed glands lined by low columnar or cuboidal cells with lumina containing mucin and inflammatory cells, particularly polymorphonuclear leukocytes. Unusual microscopic features that may cause concern for usual-type adenocarcinoma include: (1) striking gross appearance, such as an erosion, a polyp, or occasionally a prominent and friable lesion; (2) closely packed glands; (3) solid, reticular, and trabecular patterns (that may predominate); (4) variably sized and shaped glands (ranging from small and round to large and cystic); (5) myxoid, hyalinized, or edematous stroma, often infiltrated by acute and chronic inflammatory cells and sometimes with irregularly shaped groups of cells with abundant eosinophilic cytoplasm, simulating invasion; (6) unusual cell types, such as spindle shaped, clear, or hobnail, or signet ring-like cells; and (7) focal mild to moderate nuclear atypia and occasional mitoses. On the other hand, rarely, usual-type endocervical adenocarcinoma may have areas that mimic microglandular hyperplasia if it shows a striking microglandular pattern or if gland lumens contain mucinous secretions with numerous acute inflammatory cells. However, in invasive adenocarcinoma, the degree of nuclear atypia and mitotic activity exceeds that observed in microglandular hyperplasia, and desmoplasia may be observed. Furthermore, characteristic features of microglandular hyperplasia include: (1) frequent reported association (but not always) with a history of hormone therapy or pregnancy; (2) presentation as an incidental finding; (3) superficial location; (4) cells frequently with subnuclear or supranuclear vacuoles; (5) small uniform nuclei with inconspicuous nucleoli; (6) absent to rare mitotic...
Immunohistochemistry may be helpful in the differential diagnosis of usual-type endocervical adenocarcinoma and pseudoneoplastic glandular lesions, in particular with tunnel clusters and microglandular hyperplasia, as it may further help to characterize a particular lesion. However, results should always be interpreted in conjunction with the clinicopathologic findings. A panel of antibodies including p16, CEA, MIB1, ProEx C, and PAX2 has been used. p16 usually (but not always) shows strong and diffuse positivity in endocervical adenocarcinomas and negativity or only focal positivity in benign glandular proliferations, including tunnel clusters and microglandular hyperplasia. However, microglandular hyperplasia may exhibit strong p16 positivity in greater than 50% of the cells (areas of squamous metaplasia may be either negative or weakly and focally positive). Usual endocervical adenocarcinomas usually exhibit focal or diffuse cytoplasmic and luminal border CEA reactivity with some exceptions, whereas nonneoplastic endocervical epithelium is usually negative or exhibits focal positivity along the luminal border, especially if a polyclonal antibody is used. Of note, foci of squamous metaplasia in microglandular hyperplasia are CEA positive, thus, the importance of correctly interpreting positive staining within the lesion. In one study, ER was reported to be strongly and diffusely positive in 8 of 8 cases of microglandular hyperplasia, while endocervical adenocarcinomas are usually negative or only weakly and focally positive (up to 38%), especially if well differentiated. Progesterone receptor is not useful in this differential diagnosis, as both microglandular hyperplasia and usual-type endocervical adenocarcinoma are negative.

Figure 7. Microglandular hyperplasia typically consists of closely packed glands lined by cuboidal cells, with supranuclear cytoplasmic vacuoles and lumina often containing mucin and acute inflammatory cells (A). The spectrum expands to irregularly shaped glands, some cystic with abnormal stroma (B), trabecular or cribriform confluent growth (C), pseudoinfiltrative appearance associated with myxoid stroma (D and E), and solid pattern with or without signet ring cells (F) (hematoxylin-eosin, original magnifications ×100 [A, C, D, and E], ×40 [B], and ×400 [F]).
or only focally positive for this marker. To the best of our knowledge, ER or PR status has not been reported in tunnel clusters. Benign endocervical lesions characteristically have a low MIB1 proliferation index (<10%)194,195,196,197,198 in contrast to usual-type endocervical adenocarcinoma, which typically is associated with higher rates, usually above 20%194,195,196,197,198 Nevertheless, occasionally, some benign endocervical proliferations, particularly microglandular hyperplasia,199,200,201 tunnel clusters,202 and cases with a history of a recent biopsy (brisk regenerative activity)203 may have higher MIB1 scores, reaching the lower end of the spectrum seen in adenocarcinoma. ProEXC shows diffuse cytoplasmic and nuclear staining in most endocervical adenocarcinomas (usually >25% of cells) but shows negativity or only focal positivity in nonneoplastic endocervical epithelium.204,205 Occasionally, microglandular hyperplasia may have diffuse staining (>50% of cells) and endocervical adenocarcinomas may show only focal positivity (<25%)206 and thus, like other markers, ProEXC should only be used as part of a panel of antibodies. Finally, PAX2 has been reported to show strong and diffuse positivity in tunnel clusters and negativity in usual-type invasive adenocarcinomas (1 case was focally positive)207 but it has not been tested in microglandular hyperplasia, to the best of our knowledge.

**Variant: Well-Differentiated Villoglandular Papillary Adenocarcinoma.**—This is a rare variant of endocervical adenocarcinoma (<8%) that usually occurs in younger women (average age, 35–45 years), when compared to other endocervical adenocarcinomas, and has been associated with oral contraceptive use.199,208 Microscopically, these tumors are usually well circumscribed with no or only superficial stromal invasion and have 2 components: (1) papillary on the surface, often with tall and thin, or less frequently, short and broad, papillae with fibrovascular cores containing abundant inflammatory cells; and (2) infiltrating glandular component with irregular and elongated branching glands (some papillae may be present) separated by fibrous or, less frequently, desmoplastic or myxoid stroma (mostly at the deepest areas of invasion). Both components are lined by 1 or more layers of columnar cells, mostly with scant mucin, often resembling endocervical or endometrioid-type cells showing nuclear pseudostratification and scattered mitoses.199,202,203 Rare goblet cells may be present. Vascular invasion and lymph node metastasis are rare.204 Adjacent AIS and/or squamous dysplasia is often present.205,206 The diagnosis of villoglandular carcinoma should be made with caution in biopsy specimens as not infrequently they are associated with a higher-grade underlying invasive adenocarcinoma, and pure conventional cervical adenocarcinomas may have a papillary architecture.194–196 Thus, the diagnosis of villoglandular carcinoma should be reserved for tumors with pure villoglandular morphology and low-grade nuclei in the superficial and deep components, which can only be assessed in cone or hysterectomy specimens.202,207,208 These tumors if pure are associated with better prognosis than other adenocarcinoma subtypes.192,193 The absence of p53, BRCA1, c-erb-B2, and K-ras alterations, among others, may help to explain the favorable behavior of this tumor.190

**Well-Differentiated Villoglandular Papillary Adenocarcinoma Versus Benign Mimics.**—Well-differentiated villoglandular papillary adenocarcinoma may rarely be confused with papillary endocervicitis, especially in small and very superficial biopsies or when papillary endocervicitis is very florid. Both share a papillary growth and prominent inflammatory background. However, in papillary endocervicitis, papillae are covered by a single layer of mucinous cells with bland nuclear features, while well-differentiated villoglandular papillary adenocarcinoma usually has a more complex papillary architecture, cellular stratification, and more cytologic atypia than is accepted for a benign reactive lesion.209

Villoglandular adenoma can potentially enter in this differential diagnosis as both lesions are composed of delicate elongated papillae; cells may contain mucin; and goblet cells, pseudostratified nuclei, and mitoses may be present.209,210 However, villoglandular adenoma has a nonbranching architecture, cells show minimal to absent cytologic atypia, and there is no infiltration at the base.209 It should be emphasized that villoglandular adenoma of the cervix is exceptionally rare. Indeed, in our group, we never have made the diagnosis of villoglandular adenoma, and we recommend that this diagnosis not be rendered in biopsy and every cautious in resection specimens, as villoglandular carcinomas may show areas with a very deceptive morphology.

**Well-Differentiated Villoglandular Papillary Adenocarcinoma Versus Other Papillary Adenocarcinomas.**—Well-differentiated villoglandular papillary adenocarcinoma is differentiated from other cervical adenocarcinomas with papillary growth, namely, usual-type (Figure 8, A and B), serous, and clear endocervical adenocarcinomas, by the absence of other characteristic patterns and high-grade nuclear features seen in the latter tumors (Figure 8, B).202,203

**Endometrioid-Type Endocervical Adenocarcinoma.**—The use of different criteria in the diagnosis of endometrioid-type adenocarcinoma is most likely responsible for the discrepancies in the reported incidence of this tumor as pointed out by Young and Clement.162 Some investigators have reported endometrioid-type adenocarcinoma to be uncommon (<7%),196,198 while others found a much higher incidence (30%–50%).200,201 Histologically, this tumor is characterized by an endometrioid phenotype resembling its endometrial counterpart with: (1) tubular glands (some angulated and branched), frequently medium sized (can range from small to cystic) and often cribriforming; (2) glands lined by stratified columnar cells with absence to minimal intracellular mucin (may be present in luminal border) with less cytoplasm than the usual-type adenocarcinoma cells; (3) cilia in some cells; and (4) lower nuclear grade, less mitotic activity, and fewer apoptotic bodies when compared to usual-type adenocarcinoma.202

**Variant: Minimal Deviation Endometrioid Adenocarcinoma.**—Endometrioid-type minimal deviation adenocarcinoma is a rare endocervical tumor typically seen in women of reproductive age.203,204 Histologically it has a deceptively benign appearance with (1) disorderly distributed irregular glands and cysts (uncommonly may be closely packed with cribriforming or have villose papillae); (2) glands and cysts lined by simple or stratified epithelium comprising cuboidal cells with scant cytoplasm, some with cilia or apical snouts (mucin is absent); (3) mild to moderate cellular atypia; (4) infrequent mitoses; (5) at least focally desmoplastic response (in most cases); and (6) occasional association with tuboendometrioid metaplasia (Figure 9, A–C).204 Although based on small series, prognosis of these tumors seems to be better than that of “usual-type” endocervical adenocarcinoma.203,204

**Minimal Deviation Adenocarcinoma Endometrioid Type Versus Benign Mimics.**—Even though tuboendometrioid...
metaplasia (TEM) and endometriosis pose typically more problems in the differential diagnosis with AIS, on occasion, these benign glandular proliferations may cause concern for minimal deviation adenocarcinoma of endometrioid type, as glands and cysts in the latter are often lined by benign-appearing cells, occasionally containing cilia and lacking diffuse stromal desmoplastic reaction. Worrisome findings in TEM include glands extending deep in the cervical wall (including outer third) and periglandular stromal alterations (especially if edematous or myxoid).35 Even more, TEM associated with diethylstilbestrol (DES) exposure has a striking pseudoinfiltrative growth with haphazardly distributed glands mimicking even more closely the appearance of minimal deviation adenocarcinoma, endometrioid type.69 Histologic features favoring TEM include: (1) superficial location in most cases; (2) orderly arrangement of the glands similar to that of normal endocervical glands (unless metaplastic changes occur in preexistent benign lesions with closely packed glands such as tunnel clusters);35 (3) only slight variation in size and shape of glands204; and (4) stromal hypercellularity but no desmoplasia or inflammation.35

Some endometriotic lesions may have cytologic atypia and brisk mitotic activity especially in young women.64,78,79 In older women, endometriosis may have an atrophic appearance, being only represented by glands with no stroma or surrounded by elastotic stroma simulating invasion. Key features are: (1) superficial location; (2) presence of endometrial-type stroma often associated with recent hemorrhage; (3) degenerative-type atypia; and (4) common association with prior conization.64,78

Figure 8. Usual-type endocervical adenocarcinoma with villoglandular pattern. A, Slender branching papillae lined by neoplastic cells with bland cytology (inset) are seen on the surface. B, However, high-grade cytologic features are present at the deep invasive front (hematoxylin-eosin, original magnifications ×40 [A], ×200 [inset A], and ×100 [B]).

Figure 9. A, Minimal deviation endocervical adenocarcinoma, endometrioid type, shows a deceptively benign appearance at low power. B, Glands are lined by cuboidal cells with scant cytoplasm and mild to moderate cytologic atypia and infrequent mitoses. C, However, desmoplastic response is focally seen (hematoxylin-eosin, original magnifications ×40 [A], ×200 [B], and ×100 [C]).
Florid endosalpingiosis rarely may enter in the differential diagnosis of minimal deviation endometrioid adenocarcinoma owing to the randomly distributed glands with irregular contours (complex infolding and branching), marked variation in gland size and shape, and occasional nuclear pseudostratification. Helpful features in favor of florid endosalpingiosis include: (1) tubal-type epithelium with no more than mild atypia; (2) absence of mitotic activity; and (3) unremarkable stroma. Endometrioid minimal deviation adenocarcinoma has more marked variation in gland size and shape with frequent outpouchings and, at least focally, cytologic malignant features, mitotic activity, and periglandular stromal desmoplastic reaction.

Endometrioid Versus Usual-Type Endocervical Adenocarcinoma.—Endometrioid-type endocervical adenocarcinoma is a rare type of endocervical adenocarcinoma (<7%) and morphologically different from the usual type as it has (1) a predominant tubular pattern with glands lined by cells with scant cytoplasm that may occasionally be ciliated; and (2) lower nuclear grade, less mitotic activity, and fewer apoptotic bodies.

Endocervical Versus Endometrial Adenocarcinoma.—Distinction between endocervical and endometrial adenocarcinoma is usually straightforward both because the primary site of the tumor is often evident and the morphologic features of the neoplasm are usually characteristic enough to allow an accurate diagnosis. However, diagnostic difficulties between specific subtypes with overlapping histologic features may occur in both biopsy (more challenging owing to poor tumor representation) and hysterectomy specimens if there is extensive tumor involvement of both sites. Some of these tumors may represent endometrial adenocarcinomas extending to the cervix, endocervical adenocarcinomas extending upward or more rarely, independent primary tumors. This distinction is critical as it is the cornerstone for treatment options with prognostic implications. Issues can arise with the following subtypes: (1) usual-type endocervical adenocarcinoma (mucin depleted) versus endometrial endometrioid adenocarcinoma (most frequent scenario); (2) endometrioid endocervical versus endometrial adenocarcinoma; and (3) mucinous endocervical versus endometrial adenocarcinoma.

In general, features that favor an endometrial origin include: (1) tumor centered in the uterine corpus; (2) coexisting atypical endometrial hyperplasia; (3) presence of a predominant tubular pattern with glands lined by cells with scant cytoplasm (occasionally ciliated); (4) benign squamous elements; (5) no prominent nuclear pseudostratification; (6) vesicular chromatin distribution; and (7) absence of stromal foamy histiocytes. A primary endocervical adenocarcinoma is favored if the following features are present: (1) concomitant AIS or squamous dysplasia/carcinoma in situ; (2) angulated and/or branching glands; (3) nuclear pseudostratification with hyperchromatic nuclei; and (4) high nuclear grade, high mitotic activity (typically apical mitoses), and numerous apoptotic bodies. More challenging but infrequent may be the distinction between endometrioid endocervical and endometrial adenocarcinoma as both tumors are morphologically similar. The former is a rare variant of endocervical adenocarcinoma (<7%) and should only be diagnosed after a primary origin in the corpus is carefully excluded by clinical findings (volume, tumor location), fractional curettings when dealing with a biopsy, or additional sections in a hysterectomy specimen. Rarely, an endometrioid endometrial adenocarcinoma may invade deeply into the endocervical stroma to an extent that both volume and depth of invasive tumor in the cervix is more prominent than in the corpus (Figure 10, A through E). Unawareness of this pattern of cervical involvement can lead to a misdiagnosis of an independent primary endocervical adenocarcinoma especially because (1) superficially invasive endometrial glands in the cervix may simulate AIS; and (2) appearance of invasive glands in the endocervix often differs from that in the myometrium (more widely spaced, presence of either smaller or larger cystic dilated glands, and less cytologic atypia simulating appearance of endometrioid variant of minimal deviation adenocarcinoma) (Figure 10, A and B). However, in most cases, the cervix is grossly normal and superficially, invasive endometrial glands have a different morphology from AIS. Minimal deviation endocervical adenocarcinoma of endometrioid type can be excluded as: (1) it is usually seen to originate from cervical glandular epithelium; (2) glands are characteristically larger and more irregularly branched when compared to the relatively regular tubular glands of endometrial adenocarcinoma; and (3) continuity between the cervical and endometrial neoplastic glands is almost always observed (sometimes only after additional sections). Pure mucinous endometrial adenocarcinomas or endometrioid adenocarcinomas with mucinous differentiation can be difficult to distinguish from usual endocervical adenocarcinomas especially in small biopsies. Recently, a subset of mucinous endometrial adenocarcinomas has been reported to have a deceptively benign appearance and commonly to be confused with benign cervical mucinous proliferations but also with adenoma malignum. Furthermore, these mucinous adenocarcinomas of the endometrium may have a very deceptive appearance in the endometrium and thus be overlooked. When involving the cervix, the latter show low to moderate architectural complexity and minimal nuclear pleomorphism, and voluminous extracellular mucin has been found to be a common feature. The authors concluded that the presence of an endocervical-like mucinous epithelial process in association with voluminous extracellular mucin should prompt consideration for a low-grade mucinous adenocarcinoma of the uterine corpus, a feature lacking in minimal deviation adenocarcinoma of mucinous type. Furthermore, the finding of conventional areas of endometrioid carcinoma as discussed above can also be helpful in this distinction.

Immunohistochemistry may provide additional evidence of an endometrial or endocervical origin of a tumor (Table 2). A combination of vimentin, ER, PR, CEA, p16, and/or ProExC has consistently been reported to be useful in this distinction. However, it should be kept in mind when reviewing the literature that many studies do not specify immunohistochemical findings by subtype in the category of endocervical adenocarcinomas. Vimentin is strongly and diffusely expressed in most (>85%) endometrioid and mucinous endometrial adenocarcinomas in a characteristic lateral cell border or “perinuclear” pattern (Figure 10, C), although in some, especially those with mucinous differentiation, it may show only focal positivity (same pattern) or even negativity. Conversely, endocervical adenocarcinomas are usually vimentin negative or at most, focally positive (in up to 13% of tumors). Estrogen receptor and PR typically show strong and diffuse positivity in endometrioid adenocarcinomas (endometrioid and mucinous) (Figure 10, D), with PR showing stronger...
and more extensive positivity than ER, while endocervical adenocarcinomas are usually negative or only weakly and focally positive for these markers (up to 38% and 46%, respectively), especially for PR and if the tumor is well differentiated. Nevertheless, some endometrial adenocarcinomas, especially when high grade, show much less frequent positivity for ER and PR. Endocervical adenocarcinomas usually exhibit focal or diffuse cytoplasmic and luminal border CEA reactivity with the exception of endometrioid type, which more frequently may be negative, whereas endometrial adenocarcinomas are typically negative when a monoclonal antibody is used (areas of squamous metaplasia are often positive) (Figure 10, E). p16 usually shows strong and diffuse positivity in usual and endometrioid-type endocervical adenocarcinomas and negativity or focal positivity in most, but not all, endometrioid and mucinous endometrial adenocarcinomas (squamous metaplasia is typically positive). It is important to keep in mind that high-grade endometrioid and serous endometrial adenocarcinoma frequently display strong and diffuse p16 positivity and that endocervical adenocarcinoma, especially of gastric differentiation, is p16 negative. ProExC shows strong and diffuse positivity in usual and endometrioid-type endocervical adenocarcinomas, being usually negative, or at most focally positive, in endometrial endometrioid and mucinous adenocarcinomas. However, the latter may occasionally be diffusely positive, limiting the use of ProExC as a single marker in this differential diagnosis. Mammaglobin is expressed in most endometrioid endometrial adenocarcinomas (77%), but also in 31% of endocervical adenocarcinomas, and thus is not specific enough to be used alone in the distinction of these 2 tumors. Human papilloma virus may also be useful in this setting as most endocervical adenocarcinomas are HPV related, and only rare endometrial adenocarcinomas have been reported to be HPV positive. Caution should be exercised when dealing with a mucinous

Figure 10. Endometrial adenocarcinoma with secondary cervical involvement. The complex architecture and higher nuclear atypia present in the corpus component (A, hematoxylin-eosin) contrasts with the more widely spaced and cystic dilated glands with bland nuclear features present in the cervix (B, hematoxylin-eosin). In both sites the tumor is strongly and diffusely positive for vimentin (lateral cell border and “perinuclear”) (C, vimentin staining) and estrogen receptor (D, ER staining) with only luminal border carcinoembryonic antigen positivity (E, CEA staining) (hematoxylin-eosin, original magnifications ×40 [A and B] and ×200 [insets A and B]; original magnifications ×200 [C and E] and ×400 [D]).
endocervical adenocarcinoma, as some may be HPV negative, especially those with gastric differentiation.154,155

Finally, it is important to remember that mucinous-type endocervical adenocarcinomas may be associated with synchronous mucinous tumors elsewhere in the female genital tract (ovary, fallopian tube), sometimes being difficult to determine if they are primary tumors of the cervix or metastatic.215–219 If metastatic, p16 and HPV studies may be helpful.215,220

**Mucinous Type Endocervical Adenocarcinoma.**—Mucinous-type endocervical adenocarcinoma is characterized by the presence of abundant cytoplasmic mucin in more than 50% of the neoplastic cells in contrast to the mucin-poor cells of the usual-type adenocarcinoma.162

**Gastric-Type Endocervical Adenocarcinoma.**—Gastric-type endocervical adenocarcinoma is characterized by the presence of cells with a pyloric phenotype as evidenced by: (1) distinct morphologic appearance with voluminous, clear, or pale eosinophilic cytoplasm and distinct cell borders;221 (2) expression of gastric mucins (HKI1083 and MUC6)31,221; and (3) no association with HPV.154,155 A spectrum of lesions from lobular endocervical glandular hyperplasia to mucinous gastric-type adenocarcinoma, more often minimal deviation, has been observed (Figure 11, D through F).21 These tumors may also coexist with usual-type adenocarcinoma. Patients with gastric phenotype adenocarcinomas have a significantly decreased 5-year disease-specific survival rate when compared to usual-type adenocarcinoma (30% versus 77%), as they often have an overt infiltrative growth.154,21

**Variant: Minimal Deviation Adenocarcinoma (Adenoma Malignum).**—Minimal deviation adenocarcinoma (MDA) of mucinous type is uncommon (1.3%) and may be diagnosed in a wide age range (20–78 years; mean, 45 years).31,222 Minimal deviation adenocarcinoma is reported to have gastric phenotype in 75% to 100% of tumors11,103,223,228 and thus, most cases are included in the spectrum of endocervical adenocarcinomas with gastric differentiation. It may occur in the setting of Peutz-Jeghers syndrome.208,229–232

The genetic locus for this syndrome has been mapped to chromosomal region 19p13.3 with germ-line inactivation of the STK11/LKB1 gene (coding for a serine/threonine kinase).233 Interestingly, sporadic MDA has also shown loss of heterozygosity for the same region,234 with some tumors displaying STK11 mutations.235 Unlike most endocervical adenocarcinomas, HPV DNA is rarely detected, as occurs in gastric-type adenocarcinomas.151–153,235 Together, these findings suggest that MDA has a distinct pathogenetic background.151 Most common symptoms at presentation include abnormal vaginal bleeding and vaginal discharge (often mucoid).208,216,222 Imaging studies show a predominantly solid component often associated with cysts (minor component).236 Grossly, the cervix is often abnormal, firm, or indurated, with friable, hemorrhagic, or mucoid mucosa and tan-white to yellow cut surface, sometimes with cysts (measuring up to 2 cm).208 Histologically it is characterized by: (1) closely packed to widely spaced glands that are usually irregular in size (typically large but occasionally cystically dilated or small) and shape (marked abnormal branching or papillary infoldings); (2) glands lined by deceptively benign-appearing, mucin-rich, tall columnar cells with basal nuclei (nonspecific cuboidal cells may occasionally be present) and, at least focally, periglandular desmoplastic or loose edematous stromal response (usually focal); (3) deep invasion in most cases and, not infrequently, spread to the parametrium or myometrium; and (6) vascular invasion, seen in half of cases.208 Patients usually present with high-stage tumors and have a worse prognosis when compared to “conventional” endocervical adenocarcinoma.208,237

**Adenoma Malignum Versus Benign Proliferations.**—Benign mimics that may cause confusion with MDA include lobular endocervical gland hyperplasia, tunnel clusters, deep glands and cysts, diffuse laminar endocervical gland hyperplasia, endocervicosis, and endocervical-type adenomyoma. Lobular endocervical glandular hyperplasia (LEGH) may be difficult to distinguish from MDA as both share the following features: (1) patients clinically may present with watery/mucoid discharge226,230; (2) lesions are usually multicystic on radiologic examination226,235; (3) grossly, they have cysts; (4) microscopically, they may have florid proliferation of glands associated with deep cervical

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**Table 2. Summary of Helpful Immunohistochemical Profiles in the Differential Diagnosis of Most Common Adenocarcinomas Involving the Cervix**

<table>
<thead>
<tr>
<th></th>
<th>Endocervical (Usual/Endometrioid)</th>
<th>Endometrial (Endometrioid/Mucinous)</th>
<th>Endocervical (Mesonephric)</th>
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<tbody>
<tr>
<td>Vimentin</td>
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<tr>
<td>ER/PR</td>
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<tr>
<td>CEA</td>
<td>+/+ + d</td>
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<tr>
<td>p16</td>
<td>+/+ t</td>
<td></td>
<td>+/+</td>
</tr>
<tr>
<td>ProExC</td>
<td>+/−</td>
<td></td>
<td>+/−</td>
</tr>
<tr>
<td>Mammaglobin</td>
<td>−/+ +</td>
<td></td>
<td>+/+</td>
</tr>
<tr>
<td>CD10</td>
<td>…</td>
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<td>Calretinin</td>
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<tr>
<td>STK11 (LKB1)</td>
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<td>Calretinin</td>
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**Abbreviations:** CEA, carcinoembryonic antigen; ER, estrogen receptor; PR, progesterone receptor; +, diffusely positive; +, focally positive; −, negative; not useful for the differential diagnosis with AIS or not tested.

a May be focally positive or negative, especially if mucinous differentiation.
b Positivity especially with ER and in well-differentiated adenocarcinomas.
c Less positivity with high-grade adenocarcinomas.
d May be negative, especially if endometrioid type.
e Squamous metaplasia often positive.
f Some endocervical adenocarcinomas, especially gastric type, may be negative.
g High-grade endometrial adenocarcinomas frequently display strong and diffuse p16 positivity.
h Occasionally may be diffusely positive.
i More frequently negative.
involvement and poor demarcation from the surrounding stroma, involving the squamous columnar junction (Figure 11, A and B);²₂₅,₂₃₆,₂₃₈,₂₃⁹ (5) both have gastric phenotype as evidenced by positivity for MUC6 and HIK1083 (antibody specific for gastric pyloric mucin)³₁,₁₀³,₂₂₃–₂₂₈, (6) both are HPV unrelated⁷₇,₁₅₃,₂₃₅,₂₄₀; and (7) both show nonrandom chromosomal imbalances.²₃₅ Thus, although initially thought to be unrelated, the 3 latter listed features support the hypothesis of LEGH being the precursor of MDA.³₁ It is important to keep in mind that a spectrum of lesions from typical to atypical LEGH to mucinous gastric type adenocarcinoma, more often MDA, may occur (Figure 11, A through F).³₁ It has been suggested that the association may be predominantly limited to LEGH displaying gastric phenotype.⁴₁ LEGH is favored when: (1) presented as incidental finding; (2) there is a predominantly cystic pattern with an inner solid component on imaging studies; (3) grossly, the cervix is unremarkable or predominantly cystic (larger sized and more numerous cysts); and (4) microscopically, the lesion is located higher up in the cervical canal, is confined to the inner half of the cervical wall, consists of an orderly lobulated proliferation of glands lined by a single layer of tall columnar mucinous-rich epithelium with basal nuclei, and lacks malignant cytologic features, irregular stromal infiltration, or desmoplastic stromal response (Figure 11, A).²₂₅,₂₃₆,₂₃₈,₂₃⁹ Of note, the presence of glands adjacent to thick-walled vessels (≥86 μm) is a helpful marker of invasion as discussed earlier.¹⁹⁰,₁₁₆ Tunnel clusters have already been discussed in the section “Usual-Type Endocervical Adenocarcinoma Versus Benign Mimics” and

Figure 11. Endocervical glandular lesions with gastric phenotype. Lobular endocervical glandular hyperplasia LEGH shows a lobular proliferation of glands lined by a single layer of tall columnar mucinous-rich “pyloric-type” cells with bland, basally located nuclei (A). Transition from typical to atypical LEGH to minimal deviation adenocarcinoma of mucinous type is seen (B through D). Minimal deviation mucinous adenocarcinoma shows irregularly sized and shaped glands lined by deceptively benign-appearing epithelium (E) and cells with voluminous, pale eosinophilic cytoplasm and distinct cell borders alternating with glands with marked cytologic atypia (F) (hematoxylin-eosin, original magnifications ×40 [A and E], ×200 [inset A], and ×100 [B and D]).
the points touched upon in that section can also be applied herein. Endocervical glands and Nabothian cysts may occasionally extend to the outer third of the cervical wall, and the latter may be associated with a striking gross appearance, raising concern for malignancy, especially when florid. However, they lack architectural complexity, significant atypia, mitotic activity, and desmoplastic stroma.245 Diffuse laminar endocervical gland hyperplasia may morphologically cause concern for MDA as: (1) it is characterized by a diffuse proliferation of closely packed endocervical glands; (2) occasionally, glands are angulated and irregular, with intraglandular papillary tufting and bridging; and (3) stroma may have marked inflammatory response simulating invasion. Key features favoring this benign proliferation are: (1) evenly distributed glands, limited to the inner one-third of the cervical wall and sharply demarcated from the underlying cervical stroma; (2) round and regular glandular outlines (most frequent); (3) glands lined by uniform endocervical columnar cells with at most mild reactive cytologic atypia; (4) rare mitotic figures; and (5) absence of desmoplastic stroma.244 Endocervicosis consists of ectopic benign endocervical-type glands that may involve the cervix and raise concern for malignancy as (1) it presents grossly as a mass involving the outer cervical wall or paracervical connective tissue, and (2) histologically, it has an infiltrative pattern. However, endocervicosis is confined to the outer aspect of the cervix or paracervical tissue, lacks significant nuclear atypia, mitotic activity, and desmoplastic stromal response, and occasionally is admixed with other müllerian-type glands and/or endometriotic stroma.245 Endocervical-type adenomyoma may be worrisome for MDA, as it typically presents as a polypoid endocervical mass, histologically with glands surrounded by “muscle” simulating invasion. However, the correct diagnosis is achieved as: (1) it is usually an incidental finding; (2) glands often have a lobular arrangement and are lined by bland-appearing mucinous epithelium; (3) a smooth muscle component is present; (4) borders are well circumscribed; and (5) occasionally, tubal metaplasia or endometriosis may be observed.246 Of note, mucin extravasation from a ruptured gland may result in periglandular edema with the rupture of glands and LEGH.47,247 Alcian blue–PAS and HID-AB may help in distinguishing MDA from benign endocervical glands and endocervical glandular hyperplasia (not otherwise specified), which typically exhibit neutral and acid mucins equally, but not from LEGH, which exhibits almost exclusively neutral mucins as seen in MDA.253 p16 may be overexpressed in up to 30% of MDAs and even in higher percentages in LEGH,31,240,247 and occasionally, in other benign endocervical lesions including Nabothian cysts and microglandular hyperplasia.248–250,52,54,56,177 and thus, it is not helpful. Finally, MIBI is also not useful in the distinction of MDA from benign endocervical glandular proliferations as all often have a low proliferative index.25,34

Intestinal-Type Endocervical Adenocarcinoma, Including Signet Ring Type.—Intestinal-type endocervical adenocarcinomas are rare tumors, predominantly composed of cells with an intestinal appearance, including goblet, argentaffin, and rarely, Paneth cells.26,254 Less frequently, tumors have extensive extracellular mucin (colloid carcinoma)255 or a villous adenoma-like component102 (see next section for differential diagnosis). Primary signet-ring cell carcinoma of the cervix is exceedingly rare256–258 and it should always be a diagnosis of exclusion.

Intestinal-Type Endocervical Adenocarcinoma Versus Other Cervical Lesions With Intestinal Differentiation.—Intestinal differentiation has been only rarely reported in benign lesions,102,103 and thus its presence should always raise the possibility of malignancy.20,258 Goblet cells are frequently seen in AIS (mixed and pure intestinal).13,12 being its distinction from intestinal-type endocervical adenocarcinoma, based on the presence of stromal invasion.

Intestinal-Type Endocervical Adenocarcinoma Versus Metastatic Colonic Carcinoma.—Intestinal-type endocervical adenocarcinoma may raise the possibility of secondary involvement by a primary intestinal adenocarcinoma.20,259–262 Distinguishing between a primary tumor and metastasis to the cervix may be very difficult, especially on small biopsies, although it is an extremely important distinction. Pathologists should rely on clinical history, tumor markers (CEA, CA 19.9, epidermal growth factor receptor), and overall morphologic criteria indicative of metastasis: (1) growth pattern of the tumor from the external aspect of the cervical wall with little or no mucosal involvement; (2) prominent vascular involvement; (3) absence of an in situ
lesion; and (4) additional histologic features characteristic of each subtype: primary intestinal adenocarcinomas are often associated with extensive necrosis and have a higher degree of cytologic atypia and mitotic activity; and endocervical adenocarcinomas with intestinal differentiation are usually associated with areas of usual-type adenocarcinoma (except if pure, which is rare). Immunohistochemistry has proved to have limited utility in this differential diagnosis as there is great overlap for different markers including CK7, CK20, CEA, p16, and CDX2. However, if used as a panel, these antibodies may help to support a clinical and/or morphologic suspicion. CK7 typically shows diffuse positivity in intestinal-type endocervical adenocarcinomas and negativity in most primary large bowel adenocarcinomas, although some, especially those with microsatellite instability and BRAF mutations (more common in right-sided colorectal adenocarcinomas), are diffusely CK7 positive. CK20 usually shows negativity in intestinal-type endocervical adenocarcinomas and diffuse positivity in most primary large bowel adenocarcinomas, with some exceptions (right-sided colorectal adenocarcinomas presenting microsatellite instability and BRAF mutations). CDX2 usually shows strong and diffuse positivity in colorectal adenocarcinomas but intestinal-type endocervical adenocarcinomas show a spectrum of staining from negative to strongly and diffusely positive, limiting the utility of this antibody in this differential diagnosis. p16, p53, and CEA are not useful in differentiating intestinal-type endocervical adenocarcinoma from secondary involvement by large bowel adenocarcinoma as both exhibit similar immunophenotypic profiles.

**Signet Ring-Type Endocervical Adenocarcinoma Versus Other Benign Proliferations/Carcinomas Containing Signet Ring Cells.**—Microglandular hyperplasia with a solid pattern may have signet ring–like cells being potentially misconstrued as signet ring–type endocervical adenocarcinoma. However, the former is characterized by (1) cells with no cytologic atypia; and (2) presence, at least focally, of areas with the typical glandular pattern. Other malignant tumors should be considered if signet ring cells are present: (1) poorly differentiated adenocarcinoma with focal signet ring cells; (2) squamous cell carcinoma with signet ring–like cells; (3) clear cell carcinoma with signet ring cells; and (4) metastatic signet-ring cell carcinoma (more often gastrointestinal and breast origin). Clear Cell Adenocarcinoma.—This subtype of endocervical carcinoma has historically had a unique association among clear cell carcinomas of the female genital tract with intrauterine exposure to DES but can also occur outside this setting. The former (no longer seen for practical purposes since DES administration in pregnancy was banned) typically occurred in women in their late teens and early twenties. Those tumors were typically centered in the exocervix and had a better prognosis than DES-unrelated clear cell adenocarcinoma. The latter usually occur in older women (average age, 47–53 years), both in exocervix or endocervix, and have a prognosis similar to that of usual-type endocervical adenocarcinoma. Both DES-exposed and, more frequently, DES-unexposed clear cell adenocarcinoma may be HPV related, although this association is less frequent than that reported for usual endocervical adenocarcinomas. Histologically, they are characterized by the finding of the typical architectural patterns: (1) tubulocystic (most frequent) where tubules and cysts vary in size and are lined by flat or cuboidal cells, with or without hobnail cells; (2) solid growth with nests and sheets of cells; and (3) papillary growth with small round papillae, often with hyalinized cores. Cytologically, they are characterized by (1) cells with variable amounts of clear and, less frequently, oxyphilic cytoplasm that may contain hyaline globules; and (2) high-grade nuclear features but low mitotic rate. Other features that may be seen include: (1) signet ring cells; (2) abundant plasma cells; (3) scattered psammoma bodies; (4) extracellular but not intracellular mucin; and (5) occasional associated endometriosis. Clear cell carcinoma must be distinguished from other tumorlike conditions containing clear cells such as (1) Arias-Stella reaction; (2) microglandular hyperplasia; and (3) mesonephric hyperplasia; as well as (4) carcinomas containing clear cells (squamous cell carcinoma and metastatic clear renal cell carcinoma).

Clear Cell Carcinoma Versus Benign Mimics.—The Arias-Stella reaction can occur outside the endometrium, including the cervix. This benign lesion may raise concern for clear cell adenocarcinoma as both may show the following features: (1) extensive gland involvement (including deep glands) sometimes resulting in a confluent growth; (2) complex architecture with prominent intraglandular tufting, delicate filiform papillae, and cribriforming; (3) cells with hobnail, clear, or oxyphilic appearance; and (4) stratified, enlarged hyperchromatic nuclei. However, patients with Arias-Stella reaction usually have a history of recent pregnancy or hormonal therapy, and the lesion typically is an incidental finding (often in a polyp). It involves preexistent glands (preserving normal architecture) and not infrequently, there is only partial involvement of glands (Figure 12, A). Furthermore, the cells have characteristic vacuolated cytoplasm and nuclear atypia of degenerative type, with smudge chromatin often alternating with normal-appearing nuclei; mitotic activity is rare to absent (Figure 12, B) in contrast to clear cell carcinoma (Figure 12, C and D); and associated stromal fibromuscular changes are noted.

Microglandular hyperplasia consists of closely packed glands lined by low columnar or cuboidal cells with lumina containing mucin and inflammatory cells, particularly polymorphonuclear leukocytes. Microglandular hyperplasia occasionally has unusual microscopic features that may cause concern for clear cell carcinoma, including the following: (1) grossly evident lesion (erosion, polyp, or friable appearance); (2) closely packed glands; (3) solid, cystic, and tubular growths; (4) variably sized and shaped glands (ranging from small and round to large and cystic), (5) hyalinized, myxoid, or edematous stroma, often infiltrated by acute and chronic inflammatory cells and sometimes with irregularly shaped groups of cells with abundant eosinophilic cytoplasm, simulating invasion; (6) unusual cell types, such as clear, hobnail or signet ring–like cells; and (7) focal mild to moderate nuclear atypia and occasional mitoses. However, in contrast to clear cell carcinoma, microglandular hyperplasia is often associated with (1) history of hormone therapy or pregnancy; (2) presentation as an incidental finding; (3) superficial location; (4) absence of papillary growth; (5) subnuclear and supranuclear vacuoles; (6) small uniform nuclei with inconspicuous nucleoli; (7) absent mitotic activity; and (8) focal squamous metaplasia and subcolumnar reserve cell hyperplasia.

Mesonephric hyperplasia may enter the differential diagnosis of clear cell carcinoma, as it often has tubules and cysts and may have a diffuse and/or extensive growth (may reach...
cervical surface, lower uterine segment, and upper vagina); focal glandular crowding and nuclear atypia may be seen. However, mesonephric hyperplasia is further characterized by: (1) typical incidental presentation; (2) tubules lined by single layer of cuboidal cells with scant cytoplasm and bland nuclei; (3) absent mitotic activity; and (4) bright pink to red hyaline, PAS-positive, diastase-resistant intraluminal contents. Some unusual but characteristic histologic patterns, when present, may help in this distinction as they are absent in clear cell carcinoma, including: (1) slitlike anastomosing tubules resembling rete testis; (2) endometrioid appearance suggestive of epididymal differentiation; and (3) morphology similar to seminal vesicles with lipofuscin pigment deposition.

The role of immunohistochemistry as a diagnostic tool for clear cell carcinoma is limited because of the reduced number of studies in this subtype of adenocarcinoma and of the heterogeneous pattern of staining with some of the antibodies tested, not infrequently overlapping with the immunophenotype of potential mimics. A panel of antibodies, including p53, ER, PR, bcl-2, and MIB1, may be useful in specific differential diagnoses. p53 shows focal nuclear positivity (“wild-type” pattern of staining) and less frequently, negativity or diffuse positivity in clear cell carcinoma, while benign lesions, namely, Arias-Stella reaction and mesonephric hyperplasia, have been reported to be p53 negative. On the other hand, p53 immunoreactivity in microglandular hyperplasia ranges from negative to focally positive. Estrogen receptor and PR typically show negativity in clear cell carcinomas and mesonephric hyperplasia but positivity in microglandular hyperplasia and Arias-Stella reaction. Clear cell carcinoma and mesonephric hyperplasia show strong and diffuse bcl-2 positivity, while microglandular hyperplasia is almost always negative. Of note, foci of reserve cell hyperplasia in microglandular hyperplasia exhibit bcl-2 positivity. Clear cell carcinoma has been reported to show high proliferative MIB1 index (>95%) in 1 case, while Arias-Stella reaction, mesonephric hyperplasia, and microglandular hyperplasia have low indexes (<10%) with rare exceptions (some cases of microglandular hyperplasia may show higher frequency). CD10 shows negativity in clear cell carcinoma and microglandular hyperplasia and positivity in mesonephric hyperplasia.

Figure 12. Clear cell carcinoma versus Arias-Stella reaction. A, At low power, preexisting architecture is preserved in Arias-Stella reaction. The glands have intraglandular tufting and are lined by clear and hobnail cells alternating with preexisting cells. B, Characteristic vacuolated cytoplasm and nuclear atypia of degenerative type with smudged chromatin is seen at higher magnification. C, In contrast, clear cell carcinoma shows effacement of preexisting architecture, with complex glands associated with stromal response. D, At high-power magnification the cells display high-grade nuclear features (hematoxylin-eosin, original magnifications ×100 [A], ×400 [B and D], and ×200 [C]).
hyperplasia and, to the best of our knowledge, has not been tested in endocervical Arias Stella reaction. Monoclonal CEA is negative in most clear cell carcinomas and p16 has a wide spectrum of staining, ranging from negative to diffusely positive, which overlaps the staining pattern of microglandular hyperplasia, mesonephric hyperplasia, and Arias-Stella reaction, and thus it is not helpful.

All benign lesions, including microglandular hyperplasia, and most clear cell carcinomas are HPV unrelated. However, HPV may be detected in clear cell carcinomas, and thus a positive result would favor a diagnosis of malignancy.

Clear Cell Adenocarcinoma Versus Carcinomas Containing Clear Cells.—Squamous cell carcinomas may have clear cells due to abundant intracytoplasmic glycogen; however, typical areas of squamous cell carcinoma are often present and characteristic patterns of clear cell carcinoma are lacking. Rarely, clear cell carcinoma of the kidney may metastasize to the cervix. These tumors are usually characterized by a nested growth of tightly packed clear cells, separated by a sinusoidal network of capillaries and frequent hemorrhage. CD10 may be helpful in this setting as it shows negativity in endocervical clear cell carcinomas and positivity in 94% to 100% of renal clear cell carcinomas. CK7 was reported to show positivity in 1% and positivity in 94% to 100% of renal clear cell carcinomas. CK7 was reported to show positivity in 1% and positivity in 94% to 100% of renal clear cell carcinomas, while renal clear cell carcinoma is usually negative. The reduced number of endocervical tumors tested, and the fact that up to 37% of renal tumors may be CK7 positive, limits its usefulness. Recently studied immunomarkers in renal clear cell carcinoma, such as PAX-2, PAX-8, hKIM-1, and RCC, have not been tested in endocervical clear cell carcinomas and thus, they should be used with other markers in this differential diagnosis.

Serous Carcinoma.—These tumors are the rarest among endocervical adenocarcinomas and their primary origin in the cervix has been questioned by several investigators. A diagnosis of primary cervical serous carcinoma should not be rendered until a primary serous carcinoma elsewhere in the female genital tract or peritoneum has been excluded. It occurs in a wide age range (26–70 years), most being HPV related. Outcome of patients with stage I tumor, although based on a small number of patients, is similar to that of usual type and poorer in more advanced stages.

The microscopic appearance resembles its counterparts in the female genital tract and peritoneum except for a solid pattern, which is rare. Common features include: (1) complex papillary growth with epithelial stratification; (2) glandular growth with elongated and slitlike spaces; (3) marked nuclear pleomorphism and prominent nucleoli; (4) occasional cells with intracellular mucin; (5) high mitotic index; and (6) an intense inflammatory infiltrate typically present within the cores of the papillae and in areas of stromal invasion.

Serous Carcinoma Versus Other Cervical Adenocarcinomas With Papillary Pattern.—Unlike clear cell adenocarcinoma which may show prominent papillary growth of cells with cytologic atypia but its morphology should not be misconstrued as serous carcinoma. Clear cell carcinoma may also show a papillary growth but is typically associated with distinctive morphology.

Serous Endocervical Versus Other Female Genital Tract Serous Carcinomas.—Before establishing the diagnosis of primary serous carcinoma of the cervix, the possibility of metastasis from any other more common locations (above the cervix) in the female genital tract or peritoneum should be excluded. Immunohistochemistry is not helpful in this setting. If a low-grade serous neoplasm is encountered in the cervix, the origin should be sought in the ovary or peritoneum, as low-grade serous tumors have not been described in the cervix.

Mesonephric Adenocarcinoma.—Mesonephric adenocarcinoma is an uncommon subtype of cervical adenocarcinoma, usually diagnosed in women of reproductive and postmenopausal age, and is typically HPV unrelated. Most patients present with abnormal vaginal bleeding or, rarely, with an abnormal Papanicolaou smear, but it may be an incidental finding. A cervical mass is often present on gross examination, although some tumors may be undetectable. Microscopically, a variety of morphologic growth patterns may be seen that vary from tumor to tumor and within the same tumor. These include: (1) tubular pattern with small, round, uniform, and back-to-back tubules, lined by cuboidal to flat cells; (2) ductal pattern typically composed of large glands with variable size, occasionally with intraglandular villous papillae and cellular budding; the glands being lined by 1 to several layers of columnar cells with endometrioid-like appearance; (3) retiform growth characterized by slitlike branching glands, some with intraglandular papillae lined by 1 to several layers of flat, cuboidal, or columnar cells; slit-like and cystic spaces may merge and impart a sievelike appearance; (4) solid pattern with nests and sheets of epithelial cells with scattered small glands; and (5) sex-cord-like growth. The last 3 patterns are usually seen as minor components of the tumor. Cells have variable amounts of cytoplasm without mucin, pleomorphic nuclei, and variable mitotic activity (more frequent in ductal and solid patterns).

Deep eosinophilic, hyaline, colloidlike secretion, PAS-positive, diastase-resistant material is often seen in the lumens of glands and tubules. Stromal response varies, being inconspicuous in some tumors and desmoplastic/myxoid in others (focal or diffuse). Tumors usually have an infiltrative border, although a pushing border has also been noted. Up to one-third of mesonephric neoplasms with a glandular component have an admixed sarcomatous component, usually resembling endometrial stroma sarcoma or nonspecific spindle cell sarcoma, but heterologous elements are exceedingly rare. The sarcomatous component places these neoplasms technically in the category of malignant mesonephric mixed tumor. A background of mesonephric hyperplasia, more commonly diffuse, often displaying focal cytologic atypia, is frequently seen in the vicinity of malignant mesonephric neoplasms. Lymphovascular and perineural invasion, as well as lymph node metastases, have been reported. Almost 40% of the patients with mesonephric carcinomas have an unfavorable outcome. Late recurrences (up to 9 years reported) may occur and extended follow-up is recommended.

Tumors with a sarcomatoid component may have worse prognosis.

Mesonephric Carcinoma Versus Mesonephric Hyperplasia.— Both mesonephric hyperplasia and mesonephric carcinoma are composed predominantly of tubules lined by cuboidal cells with frequent intraluminal deep eosinophilic, colloid-like, PAS-positive, diastase-resistant secretions, and thus it may be difficult to distinguish them from each other, especially if mesonephric hyperplasia also has: (1) associated symptoms and/or a visible gross abnormality...
(occasionally); (2) diffuse growth; (3) foci of glandular crowding; and (4) nuclear atypia. Moreover, mesonephric hyperplasia, as discussed earlier, may have unusual patterns such as slitlike anastomosing tubules resembling retiform or endometrioid-like growths seen in mesonephric adenocarcinoma. This differential diagnosis may be confounded by the fact that mesonephric adenocarcinoma is often seen arising in a background of diffuse mesonephric hyperplasia with or without atypia (Figure 13, A and B).\textsuperscript{95,97,98,281} However, in contrast to mesonephric hyperplasia, mesonephric carcinoma is typically associated with: (1) a grossly visible lesion; (2) admixture of morphologic patterns with complex growth (ductal, retiform, solid, or sex cord–like patterns); (3) diffuse back-to-back glands; (4) significant nuclear atypia; (5) increased mitotic activity; (6) associated desmoplastic stromal reaction (most cases); (7) presence of apoptotic bodies in gland lumens; and (8) occasional presence of a sarcomatoid component and/or lymphovascular invasion.\textsuperscript{95,100,296}

Mesonephric adenocarcinoma and mesonephric hyperplasia have an overlapping immunohistochemical profile\textsuperscript{100,295,297} except for MIB1 proliferation index, which increases from typical hyperplasia (1%–2%) to atypical mesonephric hyperplasia (2%–8%) (Figure 13, C) to carcinoma (5%–36%). Androgen receptor and inhibin may be potentially helpful in this differential diagnosis if they show negativity, as this points toward the diagnosis of mesonephric adenocarcinoma.\textsuperscript{100} Finally, PAX2 has been reported to be strongly and diffusely expressed in benign mesonephric lesions but negative in mesonephric adenocarcinoma, although only 1 case was tested,\textsuperscript{75} and at least mesonephric hyperplasia may show patchy p16 positivity (Figure 13, D).

Mesonephric Carcinoma Versus Other Cervical Adenocarcinomas.—Mesonephric adenocarcinoma with a predominant tubular or ductal pattern must be distinguished from clear cell carcinoma (Figure 14, A and C) and usual–type endocervical adenocarcinoma (mucin depleted) or endometrioid–type endocervical adenocarcinoma (including its minimal deviation variant), respectively (Figure 14, B). If a malignant spindle cell component is present, the differential diagnosis is with the rare malignant mullerian mixed tumor of the cervix. Key features to differentiate mesonephric adenocarcinoma from other endocervical adenocarcinomas...
include: (1) other characteristic morphologic patterns; (2) adjacent mesonephric hyperplasia/remnants; and (3) deep eosinophilic, hyaline, colloidlike secretion, PAS-positive, diastase-resistant material in the gland lumens.100,295,296 Moreover, specific features of the different subtypes of cervical adenocarcinoma in the differential diagnosis are also helpful, including: (1) cystic and papillary patterns and clear and hobnail cells in clear cell carcinoma296; (2) numerous mitoses, cells with mucinous differentiation, and occasionally associated AIS or squamous dysplasia in usual-type endocervical adenocarcinoma162,165,166; and (3) cells with cilia, mucinous differentiation, and associated tuboendometrioid metaplasia in endometrioid-type endocervical adenocarcinoma.204

Distinguishing mesonephric from müllerian endocervical adenocarcinomas may be difficult and in those cases, a panel of immunostains that includes CEA, vimentin, calretinin, CD10, and p16 can be useful (Table 2). Usual-type endocervical adenocarcinomas usually exhibit focal or diffuse CEA cytoplasmic and luminal reactivity58,62,155,183,184 and endometrioid-type endocervical adenocarcinoma shows cytoplasmic and luminal positivity in up to 67% of tumors,63,186,187,224 while mesonephric adenocarcinomas100,295,297,298 are typically negative with some exceptions.295,296,298 Most clear cell carcinomas are CEA negative, especially if a monoclonal antibody is used62,155 and thus, this marker is not useful to distinguish this subtype of müllerian carcinoma from mesonephric adenocarcinoma. Usual-type and endometrioid endocervical adenocarcinomas are usually vimentin negative (up to 13% of tumors show focal staining, usually with a lateral cell border or “perinuclear” pattern),183–187 and only 1 clear cell carcinoma has been studied, to the best of our knowledge, and was also negative,287 whereas mesonephric carcinomas are usually diffusely positive (>70%) with a characteristic cytoplasmic staining, most prominent in a basal location.100,295,296,298 Mesonephric adenocarcinomas typically exhibit focal CD10 positivity, usually showing a luminal distribution,93,101,295,298 while most müllerian endocervical adenocarcinomas, including usual, endometrioid, and clear cell types, are negative.93,101 However, this marker is neither specific nor sensitive for mesonephric lesions, as some authors93 have shown usual-type endocervical adenocarcinomas to be CD10 positive. Calretinin is reported to show focal to diffuse positivity in 57% to 88% of mesonephric carcinomas (focal or diffuse)93,100,295 but it usually shows

Figure 14. Mesonephric carcinoma. Tubular (A) and ductal (C) patterns may mimic clear cell carcinoma (B) and endometrioid-type endocervical or endometrial adenocarcinoma (D), respectively (hematoxylin-eosin, original magnifications ×100 [A and B] and ×40 [C and D]).
negativity in müllerian adenocarcinomas, although there is very limited experience. Although p16 often (but not always) shows strong and diffuse positivity in müllerian endocervical adenocarcinomas, especially usual and endometrioid types, only a few mesonephric adenocarcinomas have been studied, with inconsistent results, limiting the use of this marker. Moreover, most clear cell carcinomas are frequently p16 negative, with a few tumors reported to be focally or diffusely positive. Human papilloma virus detection may be a potential useful tool in this differential diagnosis as most, but not all, endocervical adenocarcinomas are HPV related, except for most clear cell carcinomas, and all reported mesonephric adenocarcinomas have been negative.

Mesonephric Endocervical Versus Endometrioid Endometrial Adenocarcinoma.—Mesonephric adenocarcinoma with a predominant ductal pattern comprises glands lined by 1 to 2 layers of columnar cells with endometrioid-like appearance, which may be misconstrued as endometrioid endometrial adenocarcinoma involving the cervix (Figure 14, D). Features favoring mesonephric adenocarcinoma include: (1) presence of other characteristic morphologic patterns; (2) adjacent mesonephric hyperplasia/remnants; and (3) deep eosinophilic, hyaline, colloidlike secretion, PAS-negative, diastase resistant material in the lumens of glands (although the latter can be seen in endometrioid carcinoma). Specific features of endometrioid endometrial adenocarcinoma are also helpful: (1) tumor centered in the uterine corpus; (2) coexisting atypical endometrial hyperplasia; (3) occasional ciliated cells; (4) benign squamous elements; and (5) stromal foamy histiocytes. Although this differential diagnosis is seldom a problem in routine practice, in difficult cases a panel of antibodies, including vimentin, ER, PR, and CD10, may be used. Vimentin is strongly and diffusely expressed in most (>85%) endometrioid endometrial adenocarcinomas, with a characteristic lateral cell border pattern, although in some, especially those with mucinous differentiation, it may show focal positivity or no positivity. Although mesonephric carcinomas are also usually positive (>70%), the pattern of staining is different, with cytoplasmic staining being most prominent in the basal than apical regions. Estrogen receptor and PR typically show strong and diffuse positivity in endometrioid endometrial adenocarcinomas, with PR more frequently showing strong and diffuse positivity than ER, while mesonephric carcinomas are negative in all reported tumors. CD10 typically shows focal positivity with an apical-luminal pattern (diffuse cytoplasmatic staining is reported) in most mesonephric carcinomas; however, endometrioid endometrial adenocarcinomas as well as squamous morules may express this marker, thus limiting its use in this context. Calretinin also has limitations in this differential diagnosis, as although this marker shows focal to diffuse positivity in a large percentage of mesonephric adenocarcinomas (57%–68%), endometrioid endometrial adenocarcinomas also have been reported to be positive in up to 33% of cases, although staining is always focal. CEA and p16 are not useful markers in this differential diagnosis as both tumors exhibit the same patterns of staining, being typically CEA negative and p16 negative to focally positive.

Endocervical Carcinomas with Glandular and Nonglandular Components.—Endocervical carcinomas with glandular and nonglandular components are briefly discussed in this review for completeness, emphasizing morphologic key features helpful in their differential diagnoses.

Adenosquamous Carcinoma.—Adenosquamous carcinoma is composed of a mixture of malignant glandular and squamous elements, both recognizable without the use of special stains. This entity should be distinguished from (1) a collision tumor with squamous cell carcinoma and adenocarcinoma (both components not admixed); (2) secondary involvement by endometrioid endometrial adenocarcinoma with squamous differentiation (see “Endocervical Versus Endometrial Adenocarcinoma’’); (3) clear cell carcinoma if glycogen-rich (other characteristic patterns); and (4) adenoid-basal cell carcinoma (see below). Glassy cell carcinoma is a poorly differentiated variant of adenosquamous carcinoma, characterized by solid sheets of large cells with distinct cell borders, a ground-glass cytoplasm, and large nuclei with macronucleoli. The presence of abundant inflammatory cells, predominantly eosinophils and plasma cells, helps to differentiate it from nonkeratinizing squamous cell carcinoma. Adenoid Basal Carcinoma.—Adenoid basal carcinoma is a low-grade carcinoma consisting of rounded, well-differentiated nests of basoid cells with focal gland formation or sometimes, central squamous differentiation associated with an overlying component of squamous dysplasia. The differential diagnosis includes: (1) ectopic prostate (double cell layer in glandular component, benign central squamous component, no stromal response, positive for prostatic markers); (2) adenoid cystic carcinoma (see below); (3) basaloal squamous cell carcinoma (high-grade nuclear features and frequent mitoses); and (4) adenosquamous carcinoma.

Adenoid Cystic Carcinoma.—Although adenoid cystic carcinoma resembles to some degree its counterpart in the salivary glands, this tumor does not have the same cell composition as the salivary tumors, lacking a component of myoepithelial cells. The most relevant differential diagnosis of adenoid cystic carcinoma is with adenoid basal carcinoma as the former may have: (1) basoid nests of cells at the periphery of the tumor; and (2) associated squamous carcinoma in situ or squamous differentiation. However, in contrast to adenoid basal cell carcinoma, adenoid cystic carcinoma is characterized by: (1) conspicuous cribriform growth; (2) intraluminal hyaline or mucinous material; (3) higher-grade nuclear atypia; (4) brisk mitotic activity; (5) necrosis; (6) stromal response; and (7) may also have solid areas. References


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