Gestational Trophoblastic Tumors

A Timely Review of Diagnostic Pathology

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• ***Context.***—**Gestational trophoblastic tumors include 3 distinct entities: gestational choriocarcinoma, placental site trophoblastic tumor, and epithelioid trophoblastic tumor. Accurate diagnosis is important for clinical management of the patient.**

Objective.—**To review clinical features and pathologic diagnosis of gestational trophoblastic tumors.**

Data Sources.—**Literature and personal experience are the sources for this study.**

Conclusions.—**Trophoblastic tumors are rare encounters in modern medicine, as a result of clinical practice of molar surveillance programs and early chemotherapeutic intervention for persistent gestational trophoblastic neoplasia. Diagnostic recognition of these tumors requires a high index of suspicion, awareness of their histologic characteristics, and appropriate application of immunohistochemical and molecular biomarkers. Recent attention has been given to a few precursor lesions of gestational trophoblastic tumors, including early/in situ choriocarcinoma and atypical placental site nodule.**

(*Arch Pathol Lab Med.* 2019;143:65–74; doi: 10.5858/arpa.2018-0234-RA)

Gestational trophoblastic diseases are proliferative disorders of the placental trophoblast, of either nonneoplastic (hydatidiform moles) or true neoplastic (gestational trophoblastic tumors) proliferation. Gestational trophoblastic tumors include 3 well-defined pathologic entities: gestational choriocarcinoma, placental site trophoblastic tumor (PSTT), and epithelioid trophoblastic tumor (ETT). These tumors arise from various subtypes of placental trophoblast, and each has a distinct pathobiology attributable to the proliferative ability of its constituent trophoblast.[1] Although they are encountered less often in modern medicine, gestational trophoblastic tumors continue to pose significant diagnostic challenges because of their infrequency, broad differential diagnoses, and the diagnostic uncertainty of their precursor lesions. This review intends to provide a refreshment and update on the diagnostic aspects of gestational trophoblastic tumors.

GESTATIONAL CHORIOCARCINOMA

Clinical Presentation

Gestational choriocarcinoma is the most common gestational trophoblastic tumor. There is a wide range in patient age at presentation, but it mainly occurs in the reproductive years, with a mean age of 30 years. The tumor may arise from any type of gestational event: 50% after term pregnancy, 25% after molar gestation, and 25% after other types of gestation.[2] The risk of developing choriocarcinoma following complete moles is approximately 2% to 3%. There is a rather low but finite risk (0.1%–0.5%) of developing choriocarcinoma after partial moles.[3] Uterine bleeding is the most common symptom, but extrauterine hemorrhagic events may be the first presentation in a patient with extrauterine spread: lung, liver, central nervous system, and gastrointestinal tract.[4,5] High levels of serum human chorionic gonadotropin (hCG) are invariably present in all patients. The diagnosis of postmolar choriocarcinoma is made in an average of 13 months (range, 1–48 months) after the evacuation of hydatidiform mole.[6] In most patients with choriocarcinoma following term delivery, the pathologic diagnosis is made 1 to 3 months after delivery.[6]

Diagnostic Histopathology

Gestational choriocarcinomas generally present with bulky, destructive uterine masses with extensive hemorrhage and necrosis.[6,7] Deep myometrial invasion is common and may lead to uterine perforation. Primary gestational choriocarcinoma may also arise from the cervix,[8] fallopian tube,[9] or sites possibly involved by ectopic pregnancy.[10–12]

Histologically, choriocarcinoma displays diffusely infiltrative or solid destructive growth involving endomyometrium.[13] The proliferating tumor cells recapitulate chorionic villous trophoblasts of various types and are organized in biphasic to triphasic growth patterns: sheets or cords of mononuclear tumor cells (large, intermediate trophoblasts with abundant amphophilic to eosinophilic cytoplasm and/or smaller cytotrophoblasts) rimmed by layers of multinuclear syncytiotrophoblastic cells (Figure 1). However, the focal haphazard arrangement of various tumor cells can be seen. Marked cytologic pleomorphism, nuclear enlargement, and brisk mitotic activity are always present.

Accepted for publication June 4, 2018.
Published online November 8, 2018.
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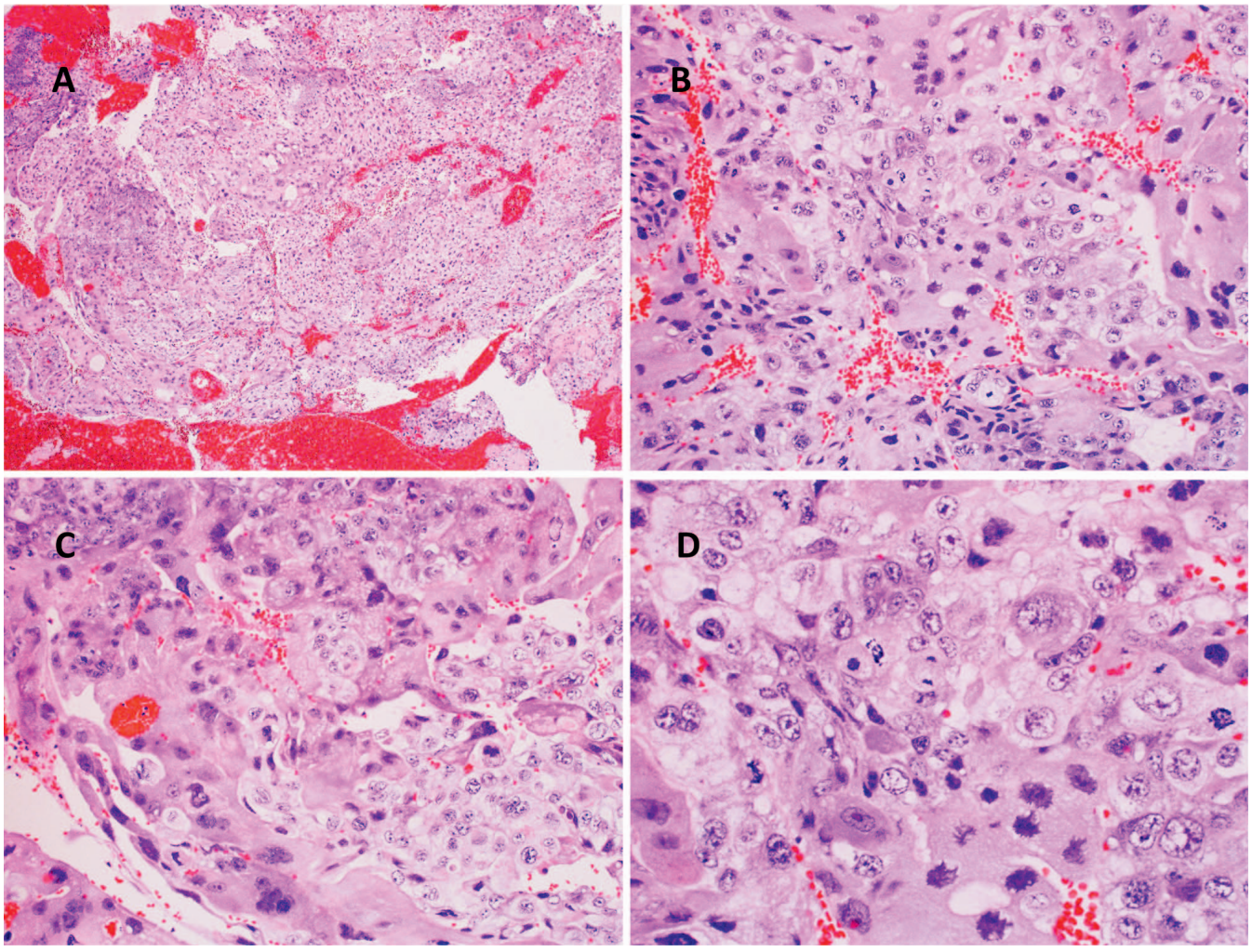

Figure 1. *Gestational choriocarcinoma. Characteristically, the tumor forms a solid, destructive mass lesion (A), with tumor cells arranged in biphasic/triphasic proliferation of mononuclear intermediate/cytotrophoblastic cells rimmed by multinucleated syncytiotrophoblasts (B and C). Marked cytologic atypia is always present (D) (hematoxylin-eosin, original magnifications ×40 [A], ×200 [B and C], and ×400 [D]).*

Frequently, tumor nests display central areas of hemorrhage and necrosis, with only viable tumor cells at the periphery. Lymphovascular tumor thrombi are commonly found. Immunohistochemically, the neoplastic syncytiotrophoblastic cells show strong and diffuse positivity for hCG and HSD3B1. The intermediate trophoblasts express Mel-CAM, HLA-G, and MUC-4. Tumor cells also stain positive for cytokeratin (CK) AE1/AE3. A high Ki-67 labeling index of greater than 90% is typically observed.

Early Forms of Gestational Choriocarcinoma

In situ or intraplacental choriocarcinoma has been well documented to occur in full-term placentas.[14,15] In those who present initially with metastatic choriocarcinoma, revisiting the corresponding placentas may reveal intraplacental primary lesion, which may present as hemorrhagic infarcts or friable papillary to solid lesions upon gross inspection.[15] It can be speculated that in situ choriocarcinomas, particularly those of less than 1 cm, may be missed by a pathologist, yet the patient may present with uterine choriocarcinoma or even metastatic disease sometime after a seemingly "normal pregnancy."[16] Therefore, thorough examination of a term placenta with 5-mm interval sections of the entire organ has been recommended to capture such in situ choriocarcinoma.

Choriocarcinoma after molar gestation may present at its early stage. So-called intramolar choriocarcinoma may be encountered in a curettage specimen,[17] where villi of complete mole are surrounded by markedly atypical trophoblastic cells with focal biphasic to triphasic growth patterns, simulating choriocarcinoma. Rarely, in an evacuated complete mole (initial or follow-up curettage), aggregates of proliferating trophoblasts without the presence of molar villi may also show alarming cytologic and histologic abnormalities, simulating choriocarcinoma in isolation (Figure 2, A and B). Similarly, invasive complete moles generally have more atypical villous trophoblastic proliferation than initially evacuated complete moles do. The hysterectomy specimen may contain foci of myoinvasive trophoblastic proliferation with marked cytologic atypia, with or without associated molar villi. Such lesions likely represent an early form of gestational choriocarcinoma (Figure 2, C through F).[18] It must be pointed out that many such early forms of choriocarcinomas are currently treated without the requirement of tissue diagnosis as long as the patient has persistent abnormal serum hCG levels after the

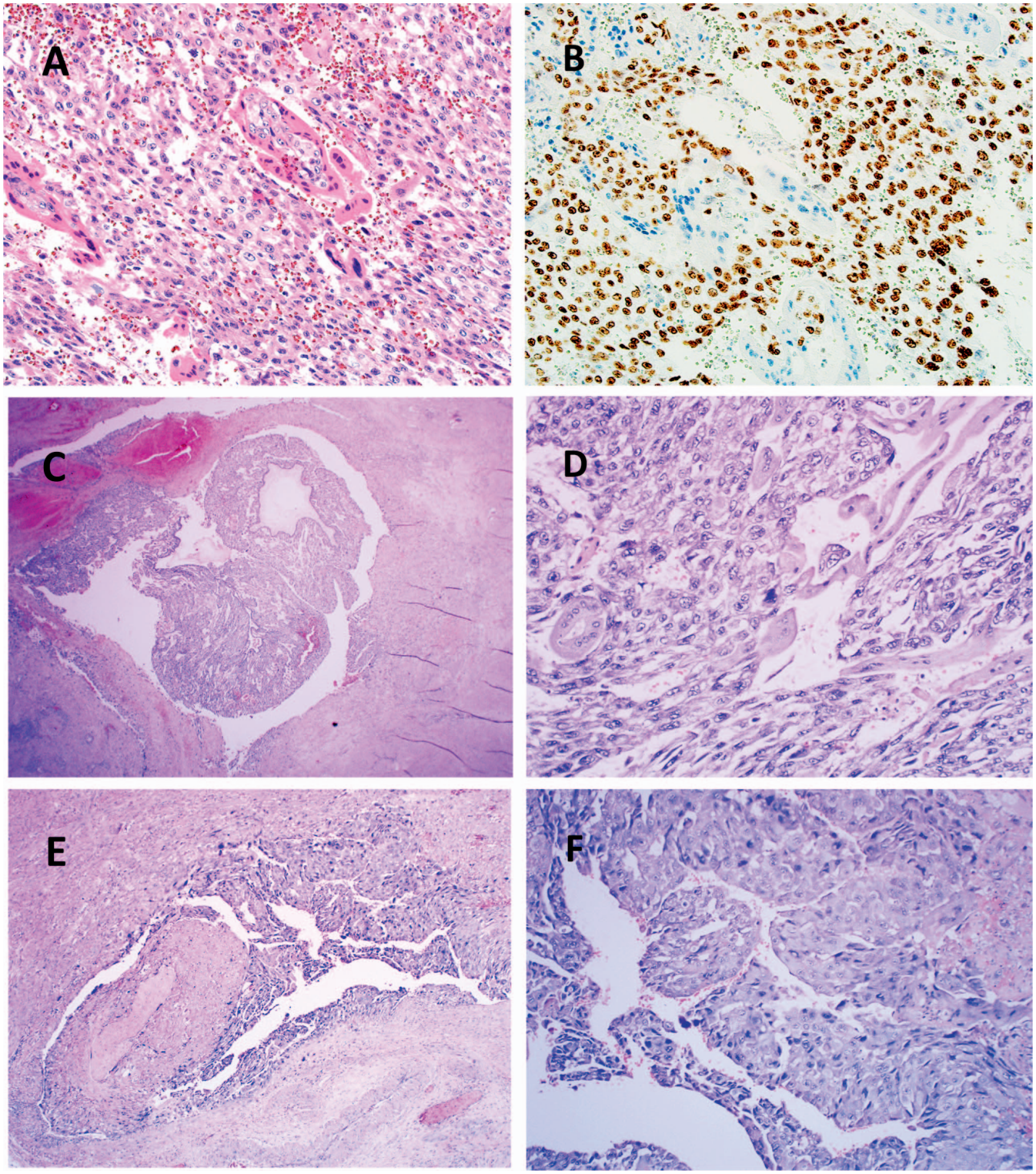

Figure 2. *Early forms of gestational choriocarcinoma. Markedly typical trophoblast in a curettage specimen without the presence of molar villi (A) and the presence of high Ki-67 labeling index (B). Invasive complete mole with morphologic evidence of transformation to early choriocarcinoma, including myometrial invasion and marked trophoblast proliferation in the presence of molar villi (C through F) (hematoxylin-eosin, original magnifications ×100 [A and E], ×20 [C], and ×200 [D and F]; Ki-67, original magnification ×100 [B]).*

initial evacuation of the mole. According to the current World Health Organization's "gestational trophoblastic neoplasia – gestational trophoblastic neoplasia (GTN)" classification, all such patients are considered to have persistent trophoblastic disease/neoplasia and will receive chemotherapy.[19] Therefore, when diagnostic separation of residual molar trophoblastic proliferation in a curettage specimen from an early choriocarcinoma cannot be reached histologically and additional tissue confirmation is not available, a diagnosis of "atypical trophoblastic proliferation

consistent with persistent trophoblastic disease or gestational trophoblastic neoplasia" is appropriate and sufficient for clinical patient management.

Differential Diagnosis

Gestational choriocarcinoma must be separated from its nongestational counterpart of germ cell or somatic origin. Nongestational choriocarcinomas commonly occur in children and young adults before they reach their forties and are unrelated to a prior gestation.[20–22] In fact, a choriocarcinoma in nulligravidae is nongestational by default. Patients often present with an adnexal mass, lower abdominal pain mimicking an ectopic pregnancy, and, rarely, hemoperitoneum. Elevated serum hCG may cause isosexual precocity in children. The tumor is frequently a component of mixed germ cell tumors, found in the ovary, extragonadal sites along the midline, and, rarely, the fallopian tube as a result of transformation of the migrating germ cells. In postmenopausal patients, nongestational choriocarcinoma is almost always a component of mixed carcinoma of the endometrium, with endometrioid carcinomatous component as the most frequent histologic type.[23,24] In general, the diagnosis of nongestational choriocarcinoma is not difficult because of the presence of nonchoriocarciomatous components (other germ cell tumor components or epithelial malignancy), absence of clinical history of pregnancy, or occurrence in a preadolescent child. However, the diagnosis of nongestational choriocarcinoma becomes very difficult when the tumor is pure in histology and presents at an unusual anatomic location or as a metastatic lesion. An extrauterine pure choriocarcinoma in a young woman should not be assumed to have a gestational origin in which the index pregnancy was unknown.[20] Extensive sampling of the lesion is important to identify nonchoriocarcinomatous components. Immunohistochemical studies are not helpful when dealing with a histologically pure choriocarcinoma. Because, as a result of pregnancy, gestational choriocarcinomas harbor a distinct paternal haploid genome that is not present in the patient's own tissue, DNA genotyping offers a definitive separation of gestational choriocarcinoma from nongestational choriocarcinoma of germ cell or somatic cell origin. Nongestational choriocarcinomas have a higher malignant potential of extensive local invasion than their gestational counterparts. They have a higher capacity to metastasize via lymphatics, whereas gestational choriocarcinomas mostly spread hematogenously.[25] Moreover, nongestational choriocarcinomas are more resistant to traditional chemotherapy for gestational trophoblastic disease. According to the International Federation of Gynecology and Obstetrics, patients with nongestational choriocarcinoma are treated with cisplatin-based multiagent chemotherapy regardless of the stage and risk factor scores, whereas patients with gestational choriocarcinoma are rigorously evaluated and separated into low- and high-risk groups for selection of methotrexate-based chemotherapy treatment (single agent versus multiagent, respectively).[26]

Curettage specimen of an early gestation may contain aggregates of highly proliferative mononuclear intermediate trophoblasts and syncytiotrophoblasts, without the presence of chorionic villi, thus simulating choriocarcinoma. However, trophoblastic tissue in an early gestation is limited in amount, and although a certain degree of cytologic atypia may exist, marked atypicality seen in choriocarcinoma should be not present. However, curettage specimens of a complete mole may show focal significant atypical trophoblastic proliferation, which, in isolation, is indistinguishable from choriocarcinoma and may represent ongoing transformation into an early choriocarcinoma (see the above section on early forms of choriocarcinoma).

Distinguishing choriocarcinoma from intermediate trophoblastic tumors (PSTT and ETT) is clinically relevant because of their different clinical managements. Unlike choriocarcinoma, PSTT and ETT are not chemosensitive and require hysterectomy.[27,28] Recent history of molar gestation, high-level serum β-hCG, histologic characteristics, and diffuse hCG immunostaining are features of choriocarcinoma.[27] Nevertheless, an otherwise typical choriocarcinoma may contain minor foci of PSTT or ETT differentiation, and a diagnosis of mixed gestational trophoblastic tumor may be considered.

PLACENTAL SITE TROPHOBLASTIC TUMOR

Clinical Presentation

Placental site trophoblastic tumor is a malignant proliferation of intermediate trophoblasts at placental implantation site. Patient age at presentation ranges from 20 to 63 years, with a mean age of 31 years.[29–31] The interval between antecedent pregnancy and clinical manifestation of the tumor is variable, ranging from a few months to 20 years, with a median latency of 12 to 18 months after a term delivery.[30–32] Antecedent complete mole and missed abortion were seen in 16% and 13% of the cases, respectively. Vaginal bleeding with uterine enlargement is the most common presentation, followed by amenorrhea and abdominal pain.[28,32,33] Mild to moderate elevation of serum hCG was seen in nearly 80% of the cases, with values ranging from 5 to 26 000 mIU/mL (average, 680 mIU/mL; median, 74.5 mIU/mL).[30,31] Recurrence or metastasis occurs in 25% to 30% of the patients postoperatively.[32,33]

Diagnostic Histopathology

Placental site trophoblastic tumor generally involves the endomyometrium as nodular, round, solid masses of 1 to 10 cm in size. Deep myometrial invasion is seen in 50% of the cases. The cut surface of the tumor is usually solid and fleshy, with a white-tan to light yellow color. Focal hemorrhage and necrosis are seen in nearly half of the cases.[29,30] Transmural myometrial invasion is seen in about 10% of the reported cases. Perforation may occur, with extension into the broad ligament and adnexa in rare cases.[34]

Histologically, the tumor has an infiltrative growth of large, polyhedral to round, predominately mononuclear intermediate trophoblasts (Figure 3, A through D). The tumor cells form cords, nests, and sheets. At the periphery, the tumor cells typically infiltrate and separate myometrial smooth muscle fibers. Cytologically, the tumor cells have abundant amphophilic, eosinophilic, or clear cytoplasm. The nuclei vary considerably in size, shape, and staining patterns. Large, convoluted nuclei with marked hyperchromasia, nuclear grooves, and nuclear pseudoinclusions are present in most cases. But round, small nuclei with a pale chromatin pattern can be seen in some. Scattered multinucleated cells resembling syncytiotrophoblasts are common. Nucleoli are generally present and may be prominent. Mitotic count is usually between 2 and 4 per 10 high-power fields in most cases.[29,30,35] Microscopic to large areas of hemorrhage are common, and coagulative tumor cell necrosis may be focal or even extensive. The pattern of vascular invasion of PSTT recapitulates that of normal implantation trophoblast: tumor cells replacing the vascular

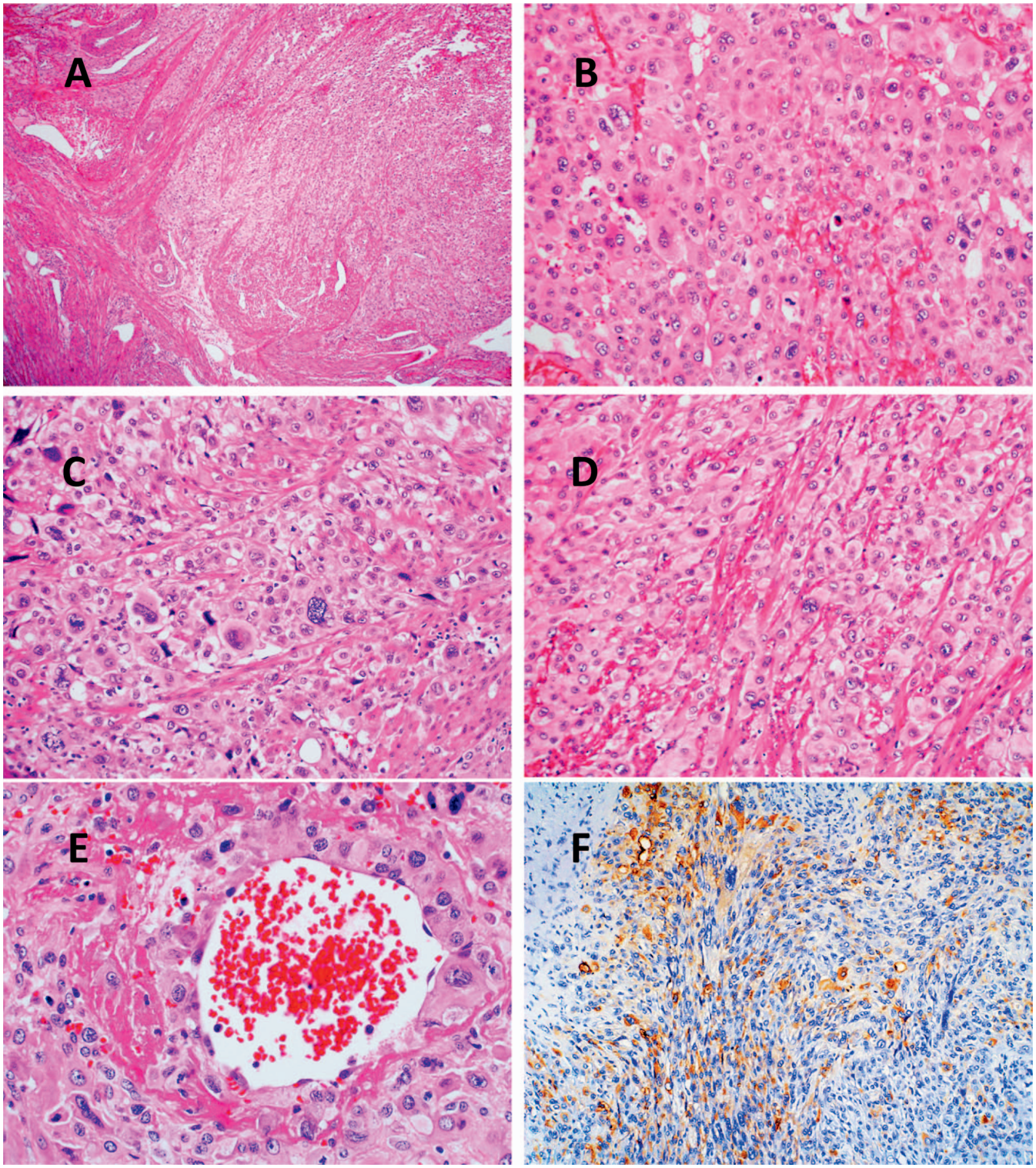

Figure 3. *Placental site trophoblastic tumor (PSTT). Mass proliferation of atypical implantation intermediate trophoblasts involving myometrium (A). Tumor cells are large epithelioid and show moderate to marked cytologic atypia (B and C). The tumor characteristically infiltrates among uterine smooth muscle cells at the tumor-myometrial interface (D). Complete replacement of existing veins by tumor cells leaves only the original endothelial cells in place (E). Diffuse expression of human placental lactogen (hPL) is seen in PSTT (F) (hematoxylin-eosin, original magnifications ×20 [A], ×100 [B through D], and ×200 [E]; hPL, original magnification ×40 [F]).*

wall (mainly venous structures) while maintaining the overall vascular architecture. Frequently, the replacement is close to completeness, leaving only the existing endothelial cells (Figure 3, E).

Tumor cells generally show immunostain positivity similar to that of implantation site intermediate trophoblasts, that is, human placental lactogen (hPL), hCG, MUC-4, HSD3B1, CD10, HLA-G, and Mel-CAM (CD146). The staining of hPL

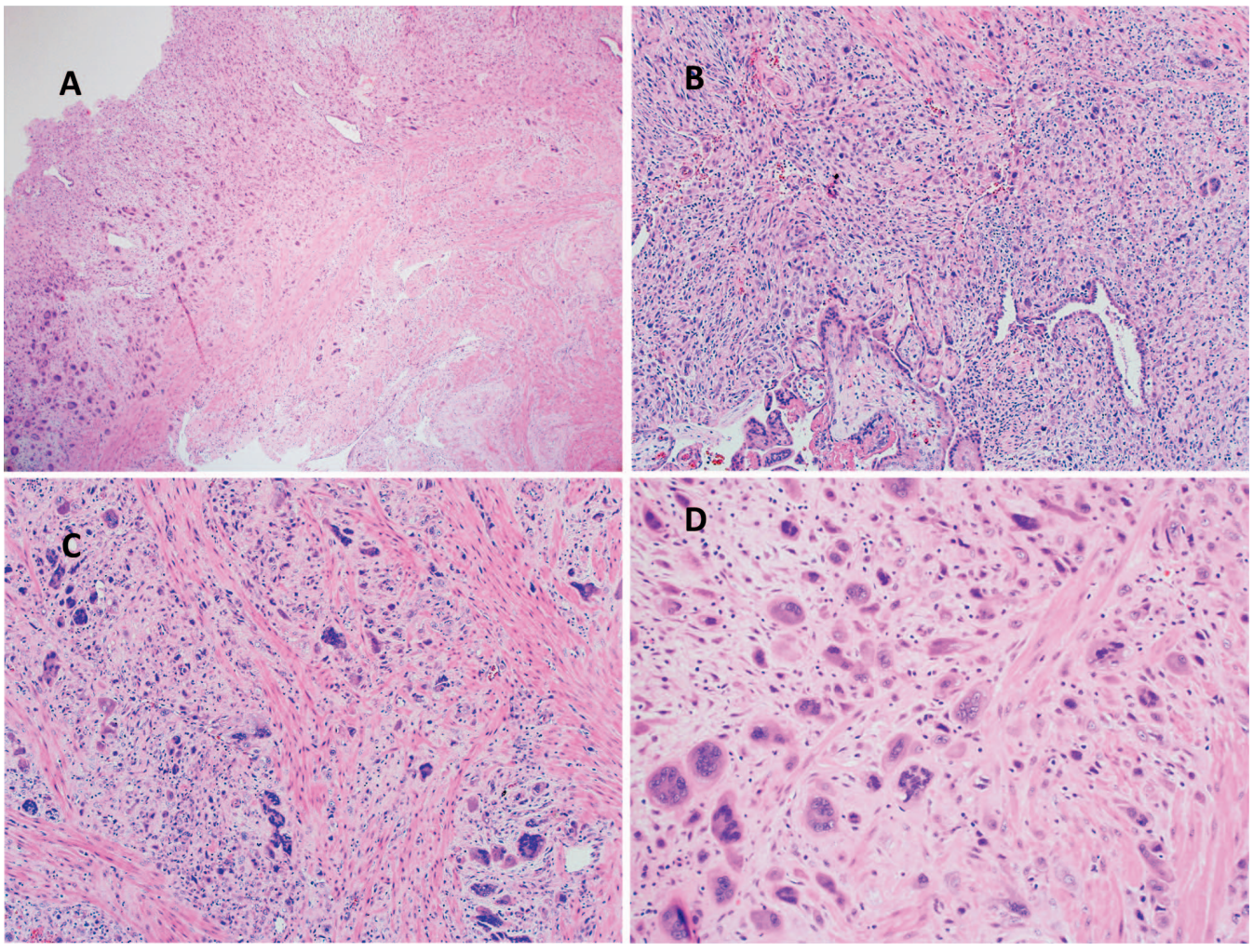

Figure 4. *Exaggerated placental site reaction. Exuberant proliferation of implantation site intermediate trophoblasts involving the superficial myometrium (A), with the presence of concurrent gestational chorionic villi (B). Presence of relatively evenly distributed multinucleated intermediate trophoblasts (C and D) (hematoxylin-eosin, original magnifications ×40 [A], ×100 [B], ×200 [C], and ×400 [D]).*

is generally strong and diffuse in more than two-thirds of the cases (Figure 3, F). In contrast, hCG and inhibin are positive only in scattered multinucleated tumor cells. Epithelial markers, including CK AE1/AE3 and CK18, are strongly expressed. Ki-67 is expressed in the range of 10% to 30% of the tumor cells.[36]

Differential Diagnosis

Exaggerated placental site reaction is a benign reactive condition of intermediate trophoblasts at the implantation site associated with a gestational event of either molar or nonmolar pregnancy. In curettage specimen, exaggerated placental site reaction may pose a diagnostic challenge because of shared histologic features with PSTT, including infiltrative pattern, alarming cytologic atypia, and vascular invasion by implantation site intermediate trophoblasts (Figure 4). Exaggerated placental site reaction is generally not visible on gross examination. Histologically, the lesion is poorly defined with an infiltrative border. The lesional trophoblastic cells are mononuclear, large, and pleomorphic, with abundant eosinophilic cytoplasm. The cells are arranged in single cells, cords, and nests to small, confluent sheets. Multinucleated trophoblasts are characteristically present and distributed evenly within the lesion. Significant nuclear enlargement with marked hyperchromasia may be seen in some cases. However, despite the exuberant infiltration, the normal architecture of the endomyometrium is not altered. The histologic features in favor of exaggerated placental site reaction include absence of mass lesion, presence of chorionic villi, and mononuclear trophoblastic cells admixed with evenly distributed multinucleated forms. Mitotic activity is very low or absent in EPS, in contrast to the presence of frequent mitoses in PSTT. Exaggerated placental site reaction has a low level of Ki-67 labeling index (<1%). Placental site trophoblastic tumor is a space-occupying lesion involving endomyometrium, and patients usually present with vaginal bleeding or amenorrhea with mild elevation of serum hCG months or years after full-term pregnancy or abortion. Ki-67 immunostaining typically demonstrates a higher labeling index (>5%).[37]

Histologic features in favor of PSTT over ETT include infiltrative tumor border, uterine corpus location, and tumor cells resembling implantation site trophoblastic cells. Placental site trophoblastic tumor is diffusely positive for hPL and Mel-CAM (CD146), whereas ETT is negative or only focally positive for these markers.[23,35,38] On the other

hand, p63 is strongly positive in ETT and consistently negative in PSTT.[39] Nevertheless, mixed trophoblastic tumors with both PSTT and ETT differentiation do occur.

Separation of PSTT from poorly differentiated endometrial carcinomas with trophoblastic differentiation should not be difficult once the presence of other carcinoma components is recognized. Trophoblastic markers, such as hPL, HLA-G, and hCG, should confirm the trophoblastic nature of PSTT, although focal hCG-positive syncytiotrophoblastic differentiation may be present in a poorly differentiated carcinoma.

Epithelioid leiomyoma or leiomyosarcoma may simulate PSTT because of their shared epithelioid cytology. Expression of CK and hPL should confirm a trophoblastic tumor, whereas positivity of muscle markers (desmin and caldesmon) ensures a diagnosis of smooth muscle tumor.

EPITHELIOID TROPHOBLASTIC TUMOR

Clinical Presentation

Epithelioid trophoblastic tumor, or ETT, is the rarest form of gestational trophoblastic tumor as a result of malignant transformation of intermediate trophoblasts at chorionic laeve. The tumor occurs in women of 15 to 48 years of age (mean, 36.1 years).[38,40] However, a significant percentage of ETT has been observed in premenopausal and postmenopausal patients.[41] Antecedent gestations include term pregnancy in 67%, spontaneous abortion in 16%, and hydatidiform moles in 16% of the reported cases.[38,42,43] The latency ranges from 1 to 15 years, with an average of 6.2 years.[40,41] Mild to moderate elevation of serum hCG of less than 2500 mIU/mL is detectable in 80% of the cases.[40,44] Vaginal bleeding or menometrorrhagia is the most common symptom, but amenorrhea can also occur.[40] Compared with gestational choriocarcinoma and PSTT, 50% of ETTs arise from the uterine cervix or lower uterine segment.[38,40] Epithelioid trophoblastic tumor may occur at extrauterine locations, including fallopian tube,[45] ovary,[46] and pelvic peritoneum.[47] Metastasis occurs in 25% of patients postoperatively to involve vagina, lungs, liver, gallbladder, kidney, pancreas, and spine.[48–50]

Diagnostic Histopathology

Nearly half of the cases arise in the cervix or lower uterine segment. The tumor generally forms discrete nodules or cystic hemorrhagic masses, deeply invading the surrounding structures.[38,40,51] The tumor size ranges from 0.5 to 5 cm.[38,52] The cut surface of the tumor is white-tan to brown, with varying amounts of hemorrhage and necrosis. Ulceration and fistula formation are common.

Characteristically, ETT shows nodular, expansile growth of relatively uniform, medium-sized tumor cells arranged in nests, cords, or large sheets. Well-circumscribed tumor border is characteristic (Figure 5, A through D).[52] The tumor cells have a moderate amount of finely granular, eosinophilic to clear cytoplasm with distinct cell membrane and round nuclei with small nucleoli. Moderate nuclear atypia is seen in most of the tumors, and the mitotic count ranges from 0 to 9 per 10 high-power fields, but as high as 48 per 10 high-power fields has been observed.[40] Eosinophilic hyaline-like material is characteristically present in the center of some tumor nests, simulating keratin formation. Extensive or "geographic" necrosis is often present (Figure 5, E).

There are a few highly unique pathologic features of ETT.[40] Scattered decidualized benign stromal cells may be present at the tumor periphery. When involving the cervix, ETT tumor cells frequently colonize the mucosal surface or glandular epithelium, simulating high-grade squamous intraepithelial lesion (Figure 5, F). Immunohistochemically, the tumor cells diffusely express H3D3B1, HLA-G, p63, cyclin E, CD10, inhibin-α, EMA, and CK (CK18, CAM5.2, AE1/AE3). Mel-CAM and hPL are expressed only in individual cells, and the Ki-67 labeling index is greater than 10%.[36]

Differential Diagnosis

More than 50% of ETTs arise in the cervix or low uterine segment, and the tumor can occur many years after a remote gestation, and it can even occur in perimenopausal[41] and postmenopausal[53] women. The single most important differential diagnosis of ETT is cervical squamous cell carcinoma.[40,54] Absence of definitive squamous intraepithelial neoplasia, lack of true squamous differentiation (true keratin formation or cell bridges), presence of decidualized stromal cells at the tumor periphery, and immunohistochemical evidence of trophoblastic differentiation (H3D3B1, HLA-G, inhibin-α, Mel-CAM, and hPL) are diagnostic features of ETT.[40] Clinically, elevated serum hCG is also supportive of the diagnosis of ETT. In difficult cases, tissue DNA genotyping can be used to confirm a gestational trophoblastic tumor by detection of unique paternal genetic complement in the tumor tissue.

Placental site nodule (PSN) is a nonneoplastic proliferation of chorionic laeve intermediate trophoblast and has been proposed to be the benign counterpart of ETT. Typically an incidental finding in a curettage specimen, PSN consists of single to multiple, well-circumscribed, oval nodules or plaques of less than 5 mm in size. Variable numbers of intermediate trophoblasts are haphazardly arranged in single cells or cords embedded in an abundant hyalinized matrix. The nodule is usually less cellular in the center. Mitotic activity is very low. Immunohistochemically, the lesional cells express hPL, inhibin-α, p63, CD10, CKs (CAM5.2, AE1/AE3), and epithelial membrane antigen, similar to ETT. Vimentin is also strongly positive in most cases. However, Ki-67 proliferative index is less than 8%.[36] Atypical PSN (APSN) is a recently proposed trophoblastic lesion with morphologic features intermediate between typical PSN and ETT. Histologic features of APSN include larger size of the nodule (>5 to 10 mm), increased cellularity, marked nuclear atypia, increased mitotic activity, and Ki-67 proliferation index between 8% and 10% (Figure 6). A few cases of APSN have been reported to show cyclin E expression. However, definitive diagnostic criteria have not been established. Atypical PSN has been proposed as an immediate precursor lesion to gestational trophoblastic tumors (ETT and PSTT).[55] Transitional lesion has been described between PSN and its adjacent trophoblastic tumors, and APSN transformed into malignant ETT was recently documented in a 20-year-old patient who rapidly developed pulmonary metastatic lesions after the curettage diagnosis of APSN.[56] In the most recent series of 21 APSNs, 3 patients had concurrent or subsequent malignant trophoblastic tumors: 1 patient had concurrent APSN and PSTT, 1 patient developed PSTT after 16 months, and 1 patient received a diagnosis of ETT 6 months after the diagnosis of APSN.[57] Therefore, it is clinically relevant that patients with APSN should undergo imaging studies to rule out underlying mass lesion and require clinical follow-up, including serum hCG measurement.

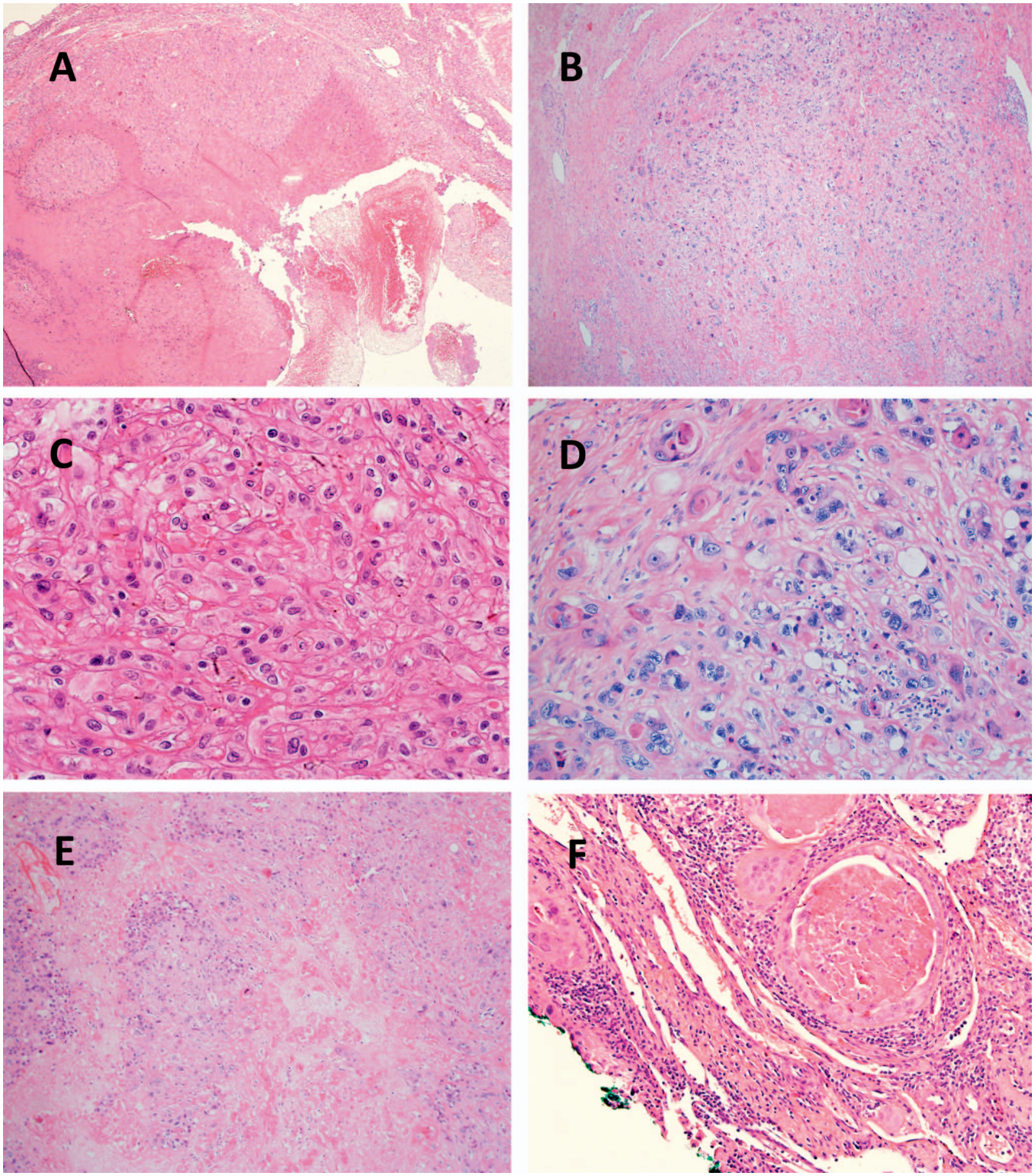

Figure 5. *Epithelioid trophoblastic tumor (ETT). Histologic features of ETT include expansile proliferation (A and B) of cohesive tumor nests of intermediate epithelioid tumor cells (C and D) admixed with degenerative hyalinized materials, simulating keratinizing squamous cell carcinoma (D and F). Geographic tumor necrosis is common (E). When involving the cervix, the tumor cells frequently colonize mucosal surfaces, simulating cervical intraepithelial neoplasia (F) (hematoxylin-eosin, original magnifications ×20 [A], ×40 [B, E, and F], and ×100 [C and D]).*

The distinction of ETT from epithelioid leiomyosarcoma and other smooth muscle neoplasms can easily be made immunohistochemically using combined smooth muscle and trophoblastic immunomarkers.[54] Other rare differential diagnoses include poorly differentiated endometrioid carcinoma with focal syncytiotrophoblastic cell differentiation. An appropriate panel of immunohistochemical markers should resolve the diagnostic issue.

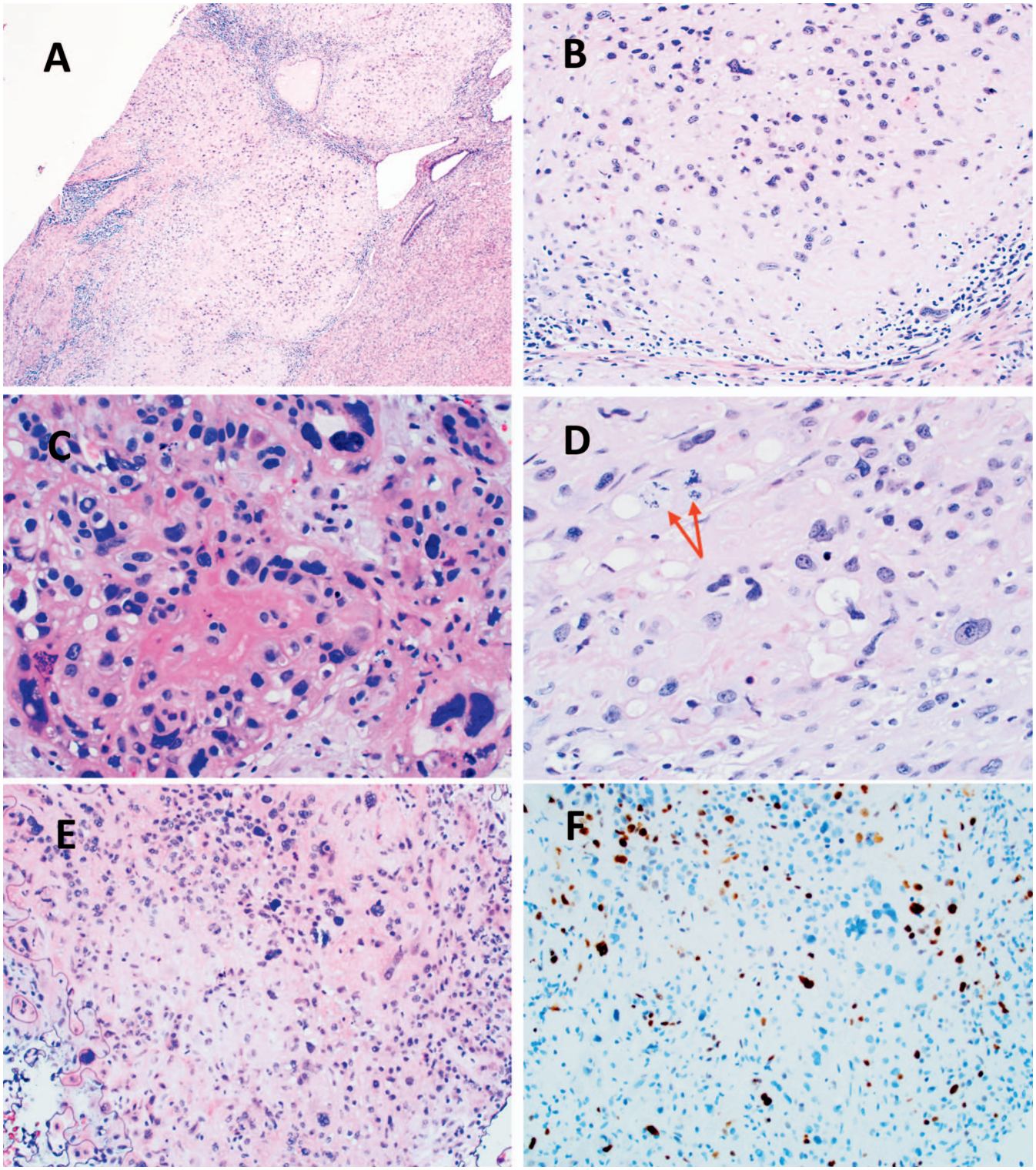

Figure 6. *Atypical placental site nodule (APSN). As a precursor lesion to epithelioid trophoblastic tumor, APSN has morphologic features, including larger size of greater than 5 mm (A), increased cellularity (B and C), marked nuclear atypia (C and D), increased mitotic activity (D, arrows), and increased Ki-67 proliferation index to 8% to 10% (E and F) (hematoxylin-eosin, original magnifications ×20 [A], ×100 [B and E], and ×400 [C and D]; Ki-67, original magnification ×100 [F]).*

CONCLUSIONS

Recognition of gestational trophoblastic tumors continues to be problematic, largely because of their relative rarity and significant histologic overlap with common gynecologic tumors. However, precise diagnosis of these tumors is crucial for patient management because of their overwhelmingly good response to chemotherapy (gestational choriocarcinoma) or excellent postsurgery outcome

(PSTT and ETT). Awareness of these rare tumors with a high index of suspicion is crucial for accurate diagnosis. Ancillary immunohistochemistry and tissue DNA genotyping may provide valuable and sometimes decisive diagnostic contribution. Further refinement of the histologic criteria of early gestational choriocarcinoma and atypical placental site node are needed for the ultimate integration of these precursor lesions into the diagnostic algorithm.

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