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Primitive Neuroectodermal Tumors of the Female Genital Tract: A Morphologic, Immunohistochemical and Molecular Study of 19 Cases

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Abstract

Primary primitive neuroectodermal tumor (PNET) of the female genital tract is rare, and its proper classification remains unclear. The clinical, histologic, and immunophenotypic features as well as *EWSR1* rearrangement status of 19 gynecologic PNETs, including 10 ovarian, 8 uterine, and 1 vulvar tumors, are herein reported. Patient age ranged from 12 to 68 years, with a median age of 20 and 51 years among those with ovarian and uterine PNETs, respectively. Morphologic features of central nervous system (CNS) tumors were seen in 15 PNETs, including 9 medulloblastomas, 3 ependymomas, 2 medulloepitheliomas, and 1 glioblastoma, consistent with central PNET. The remaining 4 PNETs were composed entirely of undifferentiated small round blue cells and were classified as Ewing sarcoma/peripheral PNET. Eight PNETs were associated with another tumor

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type, including 5 ovarian mature cystic teratomas, 2 endometrial low-grade endometrioid carcinomas and a uterine carcinosarcoma. By immunohistochemistry, 17 PNETs expressed at least 1 marker of neuronal differentiation, including synaptophysin, NSE, CD56, S100, and chromogranin in 10, 8, 14, 8, and 1 tumors, respectively. GFAP was positive in 4 PNETs, all of which were of central type. Membranous CD99 and nuclear Fli-1 staining was seen in 10 and 16 tumors, respectively, and concurrent expression of both markers was seen in both central and Ewing sarcoma/peripheral PNETs. All tumors expressed vimentin; while keratin cocktail (CAM5.2, AE1/AE3) staining was only focally present in 4 PNETs. Fluorescence *in situ* hybridization was successful in all cases and confirmed *EWSR1* rearrangement in 2 of 4 tumors demonstrating morphologic features of Ewing sarcoma/peripheral PNET and concurrent CD99 and Fli-1 expression. In conclusion, central and Ewing sarcoma/peripheral PNETs may be encountered in the female genital tract with central PNETs being more common. Central PNETs show a spectrum of morphologic features that overlaps with CNS tumors but lack *EWSR1* rearrangements. GFAP expression supports a morphologic impression of central PNET and is absent in Ewing sarcoma/peripheral PNET. Ewing sarcoma/peripheral PNETs lack morphologic features of CNS tumors.

INTRODUCTION

Primitive neuroectodermal tumor (PNET) is a term devised to represent a biologically aggressive, poorly differentiated malignant neoplasm that demonstrates cellular differentiation that recapitulates cell types of the central nervous system (CNS). The entity has been grouped into 2 major categories, namely, those that mimic neoplasms of the CNS, i.e. central PNET, and those composed of small round cells with or without rosettes known as extraosseous Ewing sarcoma or peripheral PNET. PNET may arise in many anatomic regions of the body, including the gynecological tract. Gynecologic PNETs have been reported in the ovary (1–7), broad ligament (1, 8), uterine corpus (1, 9–18), uterine cervix (1, 19–25), vagina (26–32), and vulva (1, 26, 31, 33–39); to date, none have been reported to have arisen in the fallopian tube. PNETs of the ovary and uterus are frequently associated with another tumor type (2, 4–6, 10, 11, 18), although many, including those arising elsewhere, occur in pure form (1, 3, 4, 7, 9, 10, 13–17, 19–37, 39–41). Together, they represent a peculiar group of rare neoplasms that show varying degrees of neuroectodermal differentiation and remain poorly understood when compared to their bone and soft tissue counterparts (42) and tumors that until recently were classified as PNETs of the CNS (43).

Some gynecologic PNETs harbor *EWSR1* rearrangements and thus are considered of the peripheral type or Ewing sarcoma, a neoplasm with a wide morphologic spectrum that is defined by translocations producing fusion of *EWSR1* to various members of the *ETS* family of transcription factors (42). PNETs arising in the female genital tract that lack *EWSR1* rearrangements and show readily recognizable neuroectodermal differentiation morphologically reminiscent of CNS tumors are likely histogenetically separate from Ewing sarcoma/peripheral PNETs (4, 10, 13). However, distinction of central PNETs from Ewing sarcoma/peripheral PNETs remains a significant challenge due to overlapping histologic and immunophenotypic features seen in both types and because the literature contains the term Ewing sarcoma/peripheral PNET that has been used loosely and is largely limited to

descriptive case reports and small case series in which the status of *EWSR1* rearrangement is not known.

A comprehensive classification of gynecologic PNETs incorporating morphologic, immunohistochemical, and molecular genetic features is critical to ensure accurate diagnosis, prognosis, and treatment for patients with these rare tumors. In this study, we evaluated clinical, histologic, and immunohistochemical features as well as the *EWSR1* rearrangement status of 19 gynecologic PNETs arising in various sites to determine whether these neoplasms are of the central type or belong to the Ewing family of tumors in order to provide refined criteria for accurate diagnosis.

MATERIALS AND METHODS

Case selection and classification

Nineteen gynecologic PNETs diagnosed between 1989 and 2007 were collected from the surgical pathology files of 6 institutions (Massachusetts General Hospital, McMaster Hospital, Saitama International Medical Center, University of Sassari, Prefectural Miyazaki Hospital, and Leipzig University) and the consultation files of E.O. and the late Dr. Robert E. Scully. Six cases were previously reported (4, 9). Pathology reports and hematoxylin-and-eosin (H&E) stained slides were reviewed by 4 pathologists (S.K., M.S., A.E.R, and E.O.) to confirm the diagnosis of PNET and further categorize the tumors as either central or Ewing sarcoma/peripheral PNET based on morphologic features of neuroectodermal differentiation. A tumor was designated as central PNET if it exhibited sheets of poorly differentiated small round blue cells and one of the following features: 1) neuronal differentiation with pale islands of neuropil, 2) glial features with astrocytic or ependymal differentiation with true ependymal rosettes or vascular pseudorosettes, and 3) architectural features of a primitive neural tube characterized by pseudostratified neuroepithelium with tubular spaces, neuroblastic rosettes, or tubular multilayered rosettes. Tumors classified as central PNET were further subcategorized by the type of divergent differentiation along neuronal, astrocytic, and ependymal lines. The presence of microvascular proliferation and pseudopalisading necrosis was also recorded. Tumors were classified as Ewing sarcoma/peripheral PNET if composed of sheets of undifferentiated small round blue cells with no morphologic features suggestive of central PNET. In all cases, the association with another tumor type was noted. Available clinical information, including presentation, stage, therapy, and follow-up, were obtained.

Immunohistochemistry

Immunohistochemistry was performed on 5-μm formalin-fixed paraffin-embedded (FFPE) tumoral tissue sections mounted on charged glass slides in 18 cases for which sufficient tumoral tissue was available. Antibodies to Fli-1 (1:160 dilution, Santa Cruz Biotechnology, CA), CD99 (1:100 dilution; Novocastra, CA), synaptophysin (predilute, Ventana Medical Systems, Inc., AZ) , chromogranin A (predilute, Ventana Medical Systems, AZ), CD10 (predilute, Ventana Medical Systems, AZ), CD56 (predilute, Cell Marque, CA), glial fibrillary acidic protein (GFAP) (predilute, Ventana Medical Systems, AZ), neuron specific enolase (NSE) (1:150 dilution, Dako, CA; antigen retrieval not applied), S100 (predilute,

Ventana Medical Systems, AZ), vimentin (predilute, Ventana Medical Systems, AZ), and cytokeratins CAM5.2 (1:80 dilution, Becton & Dickinson, CA) and AE1/AE3, (1:160, Signet Laboratories, MA; Protease1 was used for antigen retrieval), were used for immunohistochemical staining with appropriate controls. Staining was done on a BenchMark XT automated tissue staining system (Ventana Medical Systems, AZ) using validated protocols as described previously (44). Endogenous peroxidase activity was blocked by H_2O_2 before antibody incubation. A combination of ethylenediaminetetraacetic acid and boric acid in Tris buffer (Mild to Standard CC1 reagent; Ventana Medical Systems, AZ) was applied to the tissue sections for antigen retrieval prior to primary antibody incubation. Tissue sections were washed and incubated with primary antibodies, followed by incubation with *UltraView* HRP-conjugated multimer antibody reagent (Igs; Ventana Medical Systems, AZ). Antigen detection was performed using *UltraView* diaminobenzidine chromogen (Ventana Medical Systems, AZ). Tissue sections were counterstained with hematoxylin.

Fluorescence *in situ* hybridization (FISH)

Dual color FISH was performed to identify the presence of an *EWSR1* rearrangement using an *EWSR1* break-apart probe (Vysis LSI® EWS (9q22) Dual Color, Break Apart Rearrangement Probe). Briefly, 5-μm sections of FFPE tumoral tissue from all 19 cases were mounted on charged slides. A serial H&E-stained slide was used to identify tumoral tissue. Unstained slides were deparaffinized, subjected to 2 25-minute rounds of pepsin digestion at 37 °C, dehydrated in 70%, 95%, and 100% ethanol for 2 minutes each, and air dried. Probe (3 μL) was applied to each slide, followed by denaturation of the probe and target at 80 °C for 5 minutes and overnight hybridization at 37 °C. Slides were washed in 2× standard sodium citrate for 2 minutes twice at 37 °C. Nuclei were counterstained with DAPI. Images were acquired with an Olympus BX61 fluorescent microscope equipped with a charge-coupled device camera and analyzed with Cytovision software (Genetix, San Jose, CA). For each slide, 50 cells were scored. *EWSR1* rearrangement was reported as present if >15% of the tumor cells showed split signals defined as separation of signals by more than 2 signal diameters.

RESULTS

Clinical features

Our cohort consisted of 10 ovarian, 8 uterine, and 1 vulvar PNET (Table 1). Patient age ranged from 12 to 68 (median, 34) years. The median age of patients with ovarian and uterine tumors was 20 and 51 years, respectively, while the vulvar PNET occurred in a 65 year old. Central PNET was found in patients with age ranging from 12 to 68 (median, 34) years. Patient age was known in only 2 patients with Ewing sarcoma/peripheral PNET being 26 and 65 years, respectively. Additional clinical history was available in 13 patients in whom vaginal bleeding and pelvic mass detected on physical examination or imaging were the most common presentations in 5 and 6 patients, respectively. Disseminated intraabdominal disease, ascites, and back pain were less common presentations of patients with ovarian PNET, while the patient with vulvar PNET complained of a rapidly growing

mass. Clinical data was limited in a subset of patients due to individual contributions from different institutions.

Tumor stage was highly variable among patients with ovarian and uterine PNETs (Table 1). Among 9 patients with ovarian PNET and available tumor staging data, 4 had stage I disease; however, 3 and 1 patients had stage III and IV disease, respectively. The majority of patients with uterine PNET had high-stage disease, including 5 stage III and 1 stage IV tumors; only 1 patient had a uterus-confined PNET. The single patient with a vulvar PNET had a stage I tumor. Among patients with central PNET, 4 had stage I or II disease (all ovarian), while 8 and 2 had stage III (3 ovarian, 5 uterine) and stage IV (1 ovarian, 1 uterine) tumors. Three of 4 patients with Ewing sarcoma/peripheral PNET had stage I disease (1 ovarian, 1 uterine, 1 vulvar). Staging information was not available for 1 patient with Ewing sarcoma/peripheral PNET.

Treatment among patients also varied widely (Table 1). Among 8 patients with ovarian PNETs and available treatment history, 6 underwent unilateral salpingo-oophorectomy, 1 of whom also had a contralateral salpingectomy and another had lymph node dissection and staging omental and peritoneal biopsies; and yet another had adjuvant radiation therapy. Among the 2 other patients, 1 underwent bilateral salpingo-oophorectomy and omentectomy followed by chemotherapy, while another had hysterectomy and bilateral salpingo-oophorectomy, lymph node dissection, and omental biopsies. Eight patients with uterine PNETs underwent hysterectomy with bilateral salpingo-oophorectomy, 2 of them with lymph node dissection. Two patients received adjuvant chemotherapy. The patient with a vulvar PNET underwent a wide local excision.

Outcome data was limited to 10 patients (Table 1). Among the 6 patients with ovarian PNETs, 5, including those with stage III and IV tumors, were alive with no evidence of disease at last followup (range, 12–36 months); however, 1 patient with a stage III tumor died of disease 3 months after her initial presentation. Clinical follow-up data was available in 4 patients with uterine PNET. Two patients with stage III tumors were alive without evidence of disease, while 2 patients with stage III and stage IV tumors died of disease 6 and 12 months after initial presentation, respectively.

Pathologic Features

Gross Findings—Gross features were available in 8 ovarian, 4 uterine, and vulvar PNETs. The ovarian tumors were all unilateral, except 1. Tumor size ranged from 5.5 to 55.0 (median, 18.0) cm. One tumor was entirely solid, and 7 were solid and cystic (6 multilocular and 1 unilocular). Teratomatous elements, including waxy sebaceous or gelatinous material, hair, bone, or teeth, were evident in 4 of the cystic tumors; fatty nodularity was seen in 2. The solid component had a white, tan, or pink, sometimes hemorrhagic cut surface, and appeared nodular in 2 neoplasms. The uterine tumors ranged in size from 5.3 to 20.0 (median, 5.7) cm and were pedunculated to polypoid, fleshy and at least focally hemorrhagic masses protruding into the endometrial cavity; 1 was transmurally invasive to involve the serosa and had a pale, lobulated, and gelatinous cut surface. The vulvar tumor measured 1.5 cm in greatest dimension and was well-circumscribed.

Microscopic Findings—All 19 PNETs were composed of sheets or nodules of densely packed primitive cells with small- to medium-sized, round to ovoid nuclei, 1 to multiple small nucleoli, and scant cytoplasm; mitoses were always numerous (>10/10 high power fields). Fifteen (77.8%) tumors, including 8 arising in the ovary and 7 arising in the uterus, demonstrated histologic evidence of CNS differentiation in addition to a predominant small round blue cell component and were classified as central PNET (Table 2). Neuroblastic differentiation was seen in 11, including 9 tumors composed of nodules and round pale islands of neuropil with low cellularity displaying cells with larger nuclei and occasional nucleoli, consistent with medulloblastoma (Figure 1A–D); more differentiated areas with finely granular eosinophilic neuropil (Figure 1A–C) were often found adjacent to the undifferentiated areas (Figure 1B, D). The other 2 tumors demonstrating neuroblastic differentiation had morphologic features of medulloepithelioma defined by primitive small round blue cells arranged in multilayered tubules and rosettes with mitoses present near the lumen (Figure 2A, B). Four tumors showed distinct glial differentiation with foci of dense eosinophilic fibrillarity often neighboring primitive undifferentiated small round blue cell areas. Ependymal differentiation including vascular pseudorosettes were seen in 3 of these tumors, but true ependymal rosettes were exceedingly rare. One tumor showed predominantly astrocytic differentiation and was composed of large cells with abundant pink cytoplasm, large nuclei, and prominent nucleoli accompanied by pseudopalisading necrosis (Figure 2C) and microvascular proliferation (Figure 2D), consistent with glioblastoma. Necrosis was present in 11 neoplasms classified as central PNET; however, only tumors demonstrating glial differentiation showed serpentine foci of pseudopalisading necrosis. Tumors with features of neuronal differentiation, including medulloblastoma and medulloepithelioma, showed large geographic areas of necrosis with an abrupt border adjacent to viable tumor and without pseudopalisading of nuclei. Central PNETs with glial differentiation showed glomeruloid microvascular proliferation which was most prominent in the case demonstrating features of glioblastoma. Eight of the 15 central PNETs were associated with another tumor, including 5 mature cystic teratomas of the ovary, 2 endometrial low-grade endometrioid carcinomas, and a uterine carcinosarcoma.

Four (22.2%) tumors in our cohort showed no morphologic evidence of CNS differentiation and were classified as Ewing sarcoma/peripheral PNET (Figure 3A). These included 2 tumors arising in the ovary, 1 in the uterus, and 1 in the vulva. The single uterine Ewing sarcoma/peripheral PNET demonstrated permeative/destructive invasion into the myometrium, while the vulvar Ewing sarcoma/peripheral PNET was well-circumscribed. Microvascular proliferation was absent. Necrosis was seen in only 1 Ewing sarcoma/peripheral PNET arising in the ovary and was extensive. None of the Ewing sarcoma/peripheral PNETs were found associated with another tumor type.

Immunohistochemical features—Immunohistochemical findings are summarized in Table 2. All tumors tested were strongly positive for vimentin. Both central and Ewing sarcoma/peripheral PNETs showed strong diffuse expression of various neuronal markers. Synaptophysin, chromogranin, CD56, NSE, and S100 were expressed in 64.3%, 7.1%, 85.7%, 42.9%, and 42.9% of CNS-like PNETs, compared to 50.0%, 0%, 75.0%, 50.0%, and 75.0% of Ewing sarcoma/peripheral PNETs, respectively. Synaptophysin highlighted pale

islands of neuropil in central PNETs (Figure 4A); however in some tumors, only scattered cells expressed this marker strongly. GFAP was strongly expressed in 3 central PNETs, including 2 with ependymal differentiation and 1 showing features of glioblastoma. In addition to these 3 cases, 1 central PNET with medulloblastoma showed scattered GFAP-positive cells demonstrating astrocytic features (Figure 4B). GFAP expression was absent in all Ewing sarcoma/peripheral PNETs. Neurofilament was negative in both central and Ewing sarcoma/peripheral PNETs. Membranous CD99 staining was seen in half of central PNETs, of which 5 showed diffuse and 2 focal positivity, and all 4 PNETs, of which half displayed diffuse and half focal staining. Nuclear Fli-1 positivity was observed 85.7% of central PNETs and was diffuse in half and focal in the remainder, while it was diffusely expressed in all 4 Ewing sarcoma/peripheral PNETs. Two central PNETs showed concurrent CD99 and Fli-1 expression, but only 1 had concurrent strong and diffuse staining of both markers (Figure 4C, D). In contrast, concurrent CD99 and Fli-1 expression was seen in all 4 Ewing sarcoma/peripheral PNETs (Figure 3B, C). CD10 was not expressed in any central PNETs with glial differentiation, but was noted in 4 central PNETs with neuronal differentiation (3 medulloblastomas and 1 medulloepithelioma) as well as 2 Ewing sarcoma/peripheral PNETs. Cytokeratin cocktail (CAM5.2 and AE1/AE3) was only focally positive in 1 Ewing sarcoma/peripheral and 3 central PNETs.

FISH

FISH analysis was successful in all 19 tumors and detected *EWSR1* rearrangement in only 2 (11.1%) cases in the vulva and uterus which both showed morphologic features consistent with Ewing sarcoma/peripheral PNET (Figure 3D). The other 2 ovarian tumors classified as Ewing sarcoma/peripheral PNET based on diffuse and strong membranous CD99 and nuclear Fli-1 expression did not show evidence of *EWSR1* rearrangement by FISH. All central PNETs were negative for *EWSR1* rearrangement.

DISCUSSION

Based on the findings from our study, the vast majority of gynecologic PNETs was of the central type and lacked *EWSR1* rearrangement, while a minority represented Ewing sarcoma/peripheral type PNET in which *EWSR1* rearrangement could be confirmed in two tumors. All central PNETs displayed at least focally morphologic features akin to those seen in CNS tumors and could be further classified into those exhibiting neuroblastic (i.e. medulloblastoma and medulloepithelioma) or glial differentiation (i.e. ependymoma and glioblastoma) by architectural growth patterns. Tumors that were composed entirely of sheets of primitive small round blue cells and showed both membranous CD99 and nuclear Fli-1 expression, but absence of GFAP staining by immunohistochemistry were more likely to harbor an *EWSR1* rearrangement detectable by FISH, consistent with Ewing sarcoma/peripheral PNET. The association with another tumor type was seen in approximately 50% of central PNETs, but not in Ewing sarcoma/peripheral PNETs. A combination of detailed morphologic assessment, panel of immunohistochemical stains, and *EWSR1* FISH were essential in distinguishing central and Ewing sarcoma/peripheral types of gynecologic PNET.

Our series joins 2 others as the largest studies of gynecologic PNETs arising in the ovary and uterus to date (4, 10). Based on our study and several others with well-annotated microscopic descriptions of tumor morphology and documentation of *EWSR1* rearrangement status, central PNETs appear to arise only in the ovary and uterine corpus (3, 4, 7, 10, 13, 18). Ewing sarcoma/peripheral PNETs may also be encountered at these 2 sites (3, 7); however, findings from our study and few others (4, 10, 13) suggest that central PNETs predominate in the ovary and uterine corpus either alone or association with another tumor type, particularly an ovarian teratoma or a uterine carcinoma, carcinosarcoma, or sarcoma (2, 4–6, 9–12, 18). Interestingly, regardless of whether the tumor is central or peripheral type, patients with ovarian PNETs tend to be of reproductive age (median, 23 years) (1, 3–7, 45) compared to those with uterine PNETs who are typically postmenopausal (median, 57 years) (1, 9–18, 40, 41). Among the 14 PNETs with known *EWSR1* rearrangement status reported in the cervix, vagina, and vulva (26, 30, 31, 34, 36–38), approximately 87%, including our single vulvar tumor, are Ewing sarcoma/peripheral PNETs confirmed by FISH or RT-PCR. None of the PNETs occurring at these sites, including the present case, were found associated with another neoplasm (1, 26–39). While our patient with a vulvar Ewing sarcoma/peripheral PNET was postmenopausal, patients with Ewing sarcoma/peripheral PNETs arising in the cervix, vagina, and vulva tend to be of reproductive age (median, 35, 34, and 21 years, respectively) (26, 30, 31, 34, 36–38).

Despite the awareness that central and Ewing sarcoma/peripheral PNETs exist in the female genital tract, their distinction is only infrequently discussed in the published literature (5, 11, 13–15, 20, 24, 35). In many studies without molecular genetic analysis, the diagnosis of PNET particularly of the peripheral type was rendered based on the presence of CD99 positivity in the setting of a predominately small round blue cell tumor with or without rosettes. The extent and location of CD99 staining was variably described, and tumors with only focal membranous or even cytoplasmic CD99 staining was considered supportive evidence of central type PNET in some studies (10, 15), while absence of CD99 staining was considered diagnostic of central PNET in others (2). It has also been suggested that PNETs without morphologic evidence of CNS differentiation and no detectable *EWSR1* rearrangement be classified as central PNETs (10). Whether some reports lacking confirmation of *EWSR1* rearrangement truly represent Ewing sarcoma/peripheral PNET is subject to debate. Rare tumors that have morphologic and immunophenotypic features of Ewing sarcoma/peripheral PNET, but lack *EWSR1* rearrangement may harbor less common alterations affecting *FUS*, *BCOR*, *CCNB3*, *CIC*, or *DUX4* reported in the Ewing family of tumors involving the soft tissues and skeleton (46–49). A small portion of published gynecologic PNETs without molecular genetic analysis may in fact represent other more common entities in the differential diagnosis, including FIGO grade 3 endometrioid adenocarcinoma and undifferentiated or de-differentiated carcinoma based on the reported morphologic features and immunophenotype. Absence of *EWSR1* rearrangement in our 2 tumors initially classified as Ewing sarcoma/peripheral PNET prompted re-review of the morphologic and immunohistochemical findings. However, this diagnosis remained unchanged based on concurrent strong and diffuse membranous CD99 and nuclear Fli-1 expression along with the extent of neuroendocrine marker staining (>10% of the overall tumor) exceeding what is typically seen in undifferentiated and de-differentiated carcinomas

(50). It is possible that these 2 tumors harbor genetic abnormalities other than rearrangement of *EWSR1.*

The distinction between central and peripheral types of gynecologic PNET likely has important clinical implications. Presence of an *EWSR1* rearrangement in gynecologic PNETs may allow patients with Ewing sarcoma/peripheral PNET to be treated with therapeutic regimens used for the Ewing family of tumors in which a combination of surgery and/or radiation and multiagent systemic chemotherapy result in a 70% 5-year survival rate for localized disease (51, 52). Identification of central PNET and subclassification by neuronal, astrocytic, and ependymal lines of differentiation may also be helpful in identifying possible treatment modalities typically used for primary CNS tumors that may offer similar clinical benefit to patients with gynecologic central PNETs (53–55). A large number of CNS tumors classified as PNETs based solely on morphology and immunohistochemistry were recently found to display genome-wide DNA methylation profiles identical to other well-defined CNS tumor entities (43). True CNS PNETs were re-classified according to underlying genetic aberrations into 4 new molecular entities including CNS neuroblastoma with *FOXR2* activation, CNS Ewing sarcoma family tumor with *CIC* alteration, CNS high-grade neuroepithelial tumor with *MN1* alteration, and CNS high-grade neuroepithelial tumor with *BCOR* alteration (43). Epigenetic profiling of central PNETs arising in the female genital tract, particularly in the ovary and uterus where central PNETs tend to be encountered, is a worthwhile endeavor and may enable more accurate diagnosis and therapeutic strategies for patients affected by this rare tumor type. Clinical data is limited in our cohort as well as in published studies, and differences in tumor behavior between central and Ewing sarcoma/peripheral PNETs arising in the female genital tract remains unknown.

The pathogenesis of gynecologic PNETs is unclear, and mechanisms of tumor development are likely dependent on primary site and association with another tumor type. The identification of teratoma in a significant minority of ovarian PNETs based on our study and others (2, 4–6) suggests germ cell derivation in at least a subset of tumors arising at this site. There have been rare reports of teratomas (45, 56–60) arising in the uterus, and while it is conceivable that teratoma may be a source of uterine PNETs as it is in the ovary, teratoma has not been found in association with PNET in the uterus (1, 9–25, 40, 41). The identification of benign glial tissue (61–63) in the uterus which may result from implantation of aborted fetal tissue (63), represents another possible source of both uterine gliomas (64, 65) and PNETs. However, evolution from a Müllerian primary serves as a more likely explanation in the development of some uterine PNETs based on the not infrequent association with an endometrial carcinoma, carcinosarcoma, adenosarcoma, or pure sarcoma seen among mainly postmenopausal women in our study and in others (9–12, 18). Ectopic migration of neuroblasts from the neural crest during fetal development (9, 64) may be yet another hypothesis in the development of gynecologic PNETs in general, but does not explain the particular propensity for PNETs to develop in the female reproductive tract compared to the urinary or male genital tracts. The predominance of *EWSR1*-rearranged Ewing sarcoma/peripheral PNETs found in the cervix (19, 21, 22), vagina (26, 30, 31), and vulva (26, 31, 34, 36–38) suggests a developmental pathway at these sites similar to those arising in the soft tissues.

PNET should be considered in the differential diagnosis of any small round blue cell tumor involving the female genital tract and confirmed as central or peripheral type by a combination of morphologic assessment, immunohistochemical analysis. PNETs may be encountered in pure form in most gynecologic sites, but may be associated with another histologic subtype in the ovary and uterus. A fibrillary background and/or rosette-like structures should raise suspicion for PNET and prompt the use of a panel of immunohistochemical stains, including cytokeratin, GFAP, neuronal markers, CD99, and Fli-1. These morphologic features alone are not diagnostic of central PNET and may also be seen in Ewing sarcoma/peripheral PNET, unless histologic evidence of neuronal or glial differentiation or architectural features of primitive neural tube is present. While neuronal markers are expressed in both central and Ewing sarcoma/peripheral PNETs, GFAP highlights glial differentiation that is seen only in the former. Cytokeratin expression is usually negative, but may be weak and focal in rare PNETs of both types; strong and more than focal cytokeratin staining should prompt reconsideration of other entities in the differential diagnosis. CD99 is highly sensitive in recognizing Ewing sarcoma/peripheral PNET, but is non-specific and should not be used alone. Strong and diffuse concurrent expression of CD99 and Fli-1 is characteristic of Ewing sarcoma/peripheral PNET in our study and should prompt confirmatory molecular genetic studies. Based on our study and one other (10), CD99 staining may be absent in central PNETs. However, all published gynecologic Ewing sarcoma/peripheral PNETs and our 2 tumors that harbor *EWSR1* rearrangement were CD99-positive (3, 7, 18, 19, 21, 22, 26, 31, 34, 36–38); thus, absent CD99 staining should prompt reconsideration of the diagnosis of Ewing sarcoma/peripheral PNET in the setting of a small round blue cell tumor.

Two entities should be considered in the differential diagnosis of PNET particularly when involving the ovary in women of reproductive age. The more common consideration is a grade 2 or 3 immature teratoma given the significant extent of neuroepithelial differentiation in both tumor types and the frequent association of PNET with teratoma. High grade immature teratomas often show a wider spectrum of neuroepithelial differentiation compared to PNETs which typically differentiate along only 1 or 2 cell lines (4). Immature teratomas also exhibit an admixture of endodermal, mesodermal, and ectodermal tissues which in PNETs, are overgrown by a confluent mass of neuroectodermal elements (4). Albeit rare, small cell carcinoma of hypercalcemic type should also be considered in the differential diagnosis of an ovarian small round blue cell tumor in a young patient. While small cell carcinoma of hypercalcemic type consists of sheets of small round blue cells that may stain for neuroendocrine markers similar to PNET, there are usually at least focal follicle formation and less frequently minor foci of mucinous epithelium; variable nuclear WT1, EMA and cytokeratin expression; and loss of BRG1 and BRM expression that are distinctive from PNET (66–68).

The differential diagnosis broadens in the setting of a uterine or ovarian tumor in the peri- and postmenopausal age groups. Undifferentiated carcinoma shares considerable morphologic and immunohistochemical overlap with PNET as both are often composed of sheets of monotonous, often dyshesive cells and show little if any immunoexpression of epithelial markers and may exhibit staining of various neuroendocrine markers. However, the extent of staining for neuroendocrine markers is more extensive in PNET than that

acceptable for undifferentiated carcinoma (50). Focal gland formation in grade 3 endometrioid adenocarcinoma may mimic rosettes and tubules of a PNET; however, there is extensive keratin expression in high grade endometrioid adenocarcinoma compared to little if any staining in PNET. GFAP expression confirms central PNET, but may also rarely be seen in Müllerian carcinomas (69). Concurrent diffuse and strong membranous CD99 and nuclear Fli-1 expression, immunoreactivity with at least one neuroendocrine marker and no or limited keratin staining are also features helpful in distinguishing Ewing sarcoma/peripheral PNET from undifferentiated and high-grade endometrioid carcinoma. Additionally, DNA mismatch repair protein deficiency may favor high-grade endometrioid and undifferentiated carcinoma, the latter also sometimes demonstrating loss of BRG1, BRM, and INI1 expression (70, 71). Metastatic tumors, such as malignant melanoma, lymphoma, small cell carcinoma of pulmonary origin, and round cell sarcomas, may be mistaken as PNET; however, clinical history, bilateral adnexal involvement in the setting of an ovarian tumor, thorough sampling of the tumor tissue, and immunohistochemistry should facilitate the correct diagnosis.

In summary, the vast majority of PNETs arising in the ovary and uterus are of the central type, display morphologic features reminiscent of CNS tumors, and lack *EWSR1* rearrangement. Central PNETs may be further subtyped along neuronal, glial, or ependymal lines of differentiation. Ewing sarcoma/peripheral PNETs may also be found in the ovary and uterus, but tend to predominate in the cervix, vagina, and vulva. Tumors that consist of small round blue cells with concurrent strong and diffuse membranous CD99 and nuclear Fli-1 staining likely harbor *EWSR1* rearrangement. Tumors with the morphology of Ewing sarcoma/peripheral PNET morphology, but without *EWSR1* rearrangement should remain classified as such unless morphologic or immunohistochemical (i.e. GFAP) evidence of CNS differentiation is seen. Distinction between central and peripheral types of PNET in the female genital tract may be useful in developing treatment strategies for patients with this rare tumor type.

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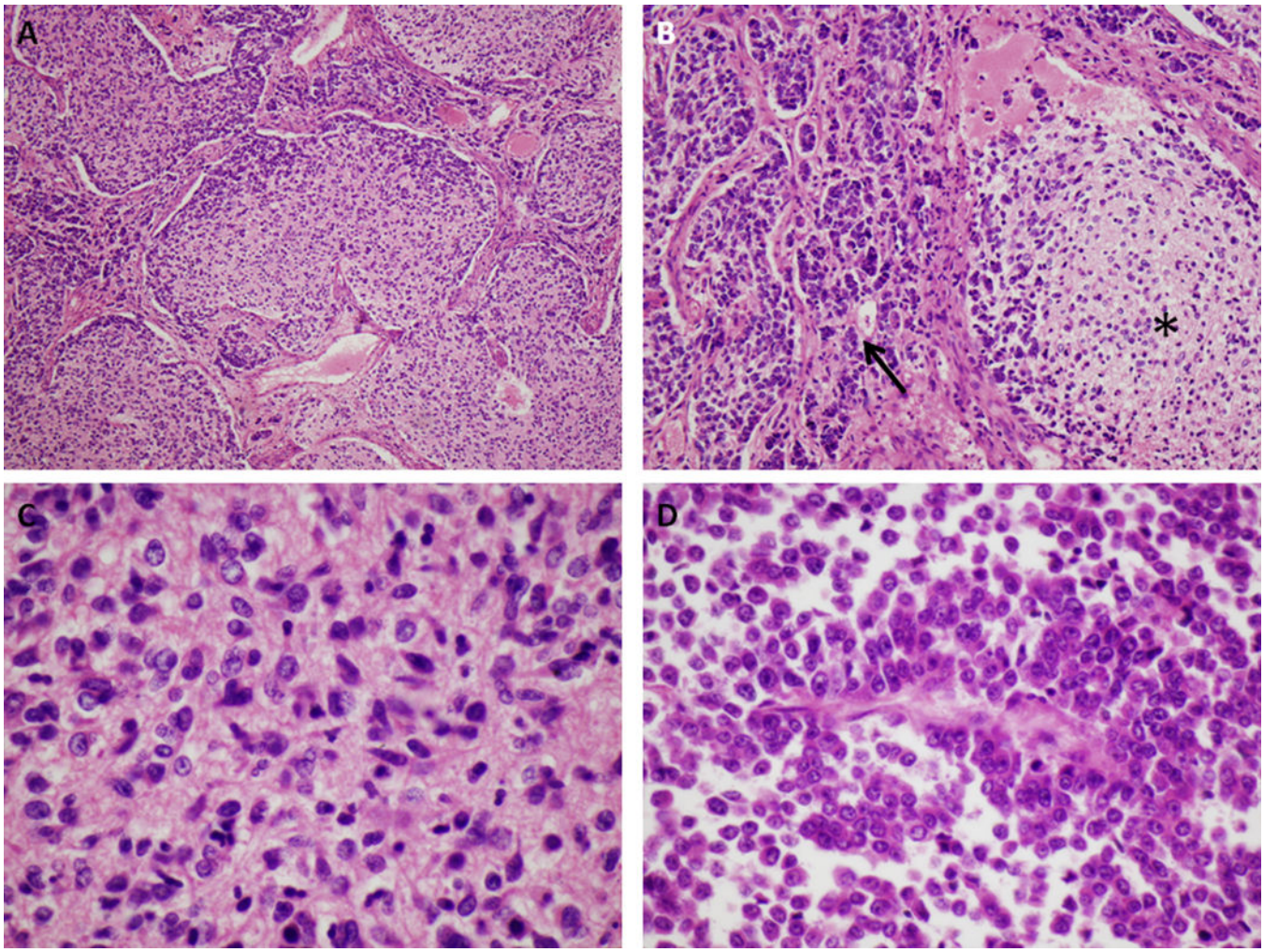

Figure 1.

Morphology of central PNET with features of medulloblastoma. A–D, Medulloblastoma demonstrating nodular growth (A) with pale islands of neuronal differentiation (B, star and C) neighboring primitive undifferentiated areas (B, arrow and D).

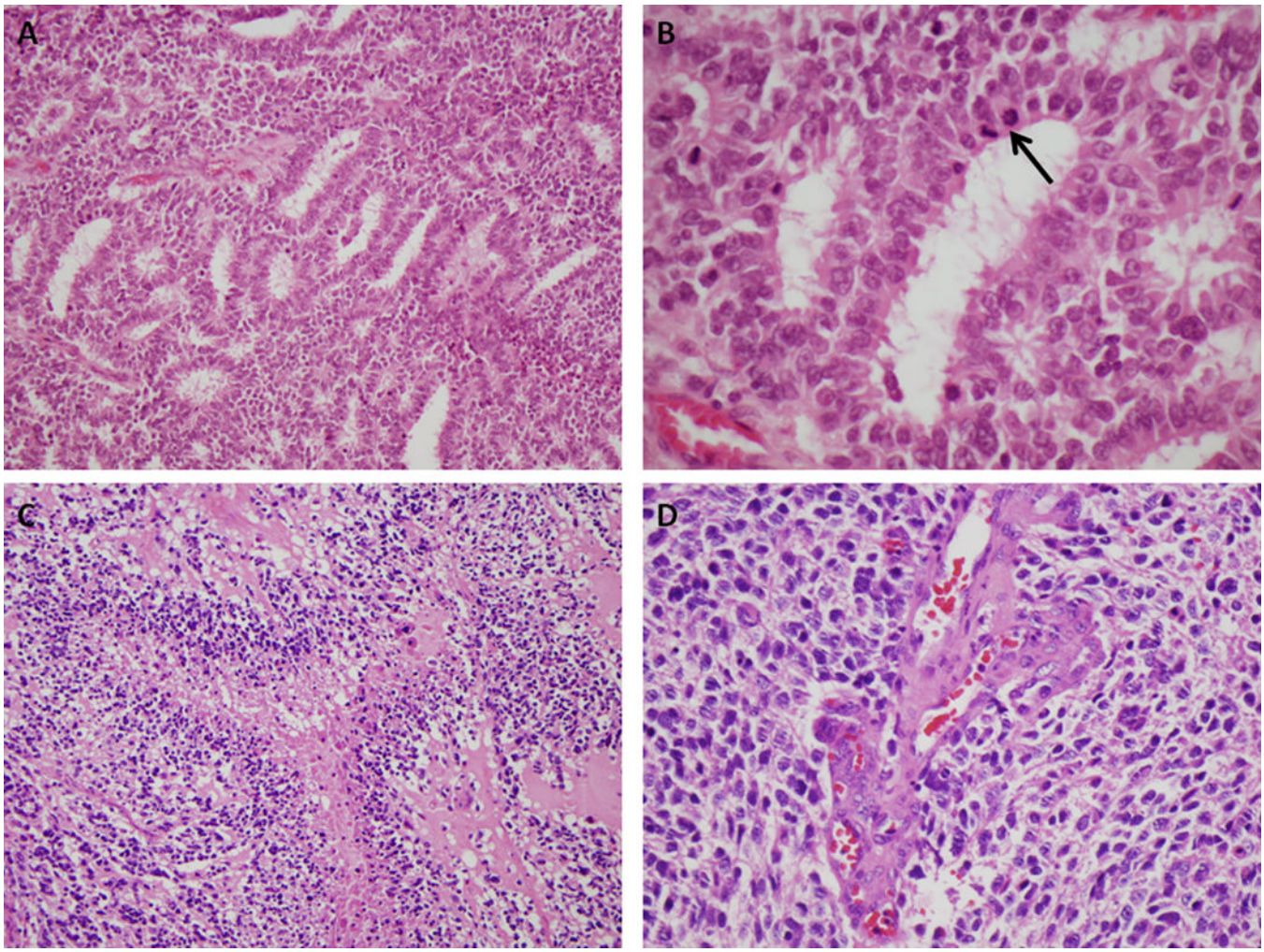

Figure 2.

Morphology of central PNETs with features of medulloepithelioma and glioblastoma. A and B, Multilayered rosettes with apical mitoses (B, arrow) typical of medulloepithelioma. C and D, Glial differentiation with foci of pseudopalisading necrosis (C) and microvascular proliferation (D).

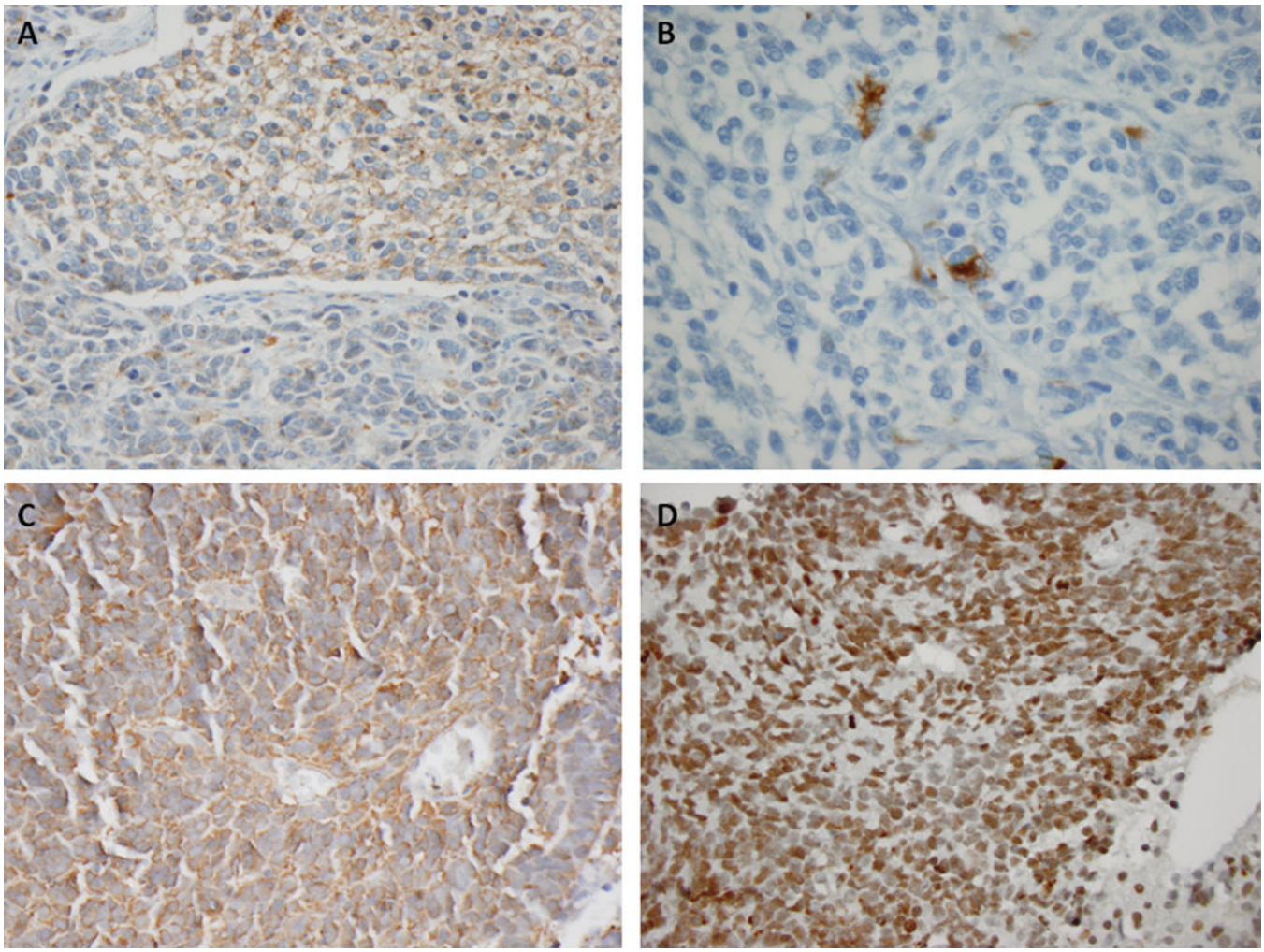

Figure 3.

Ewing sarcoma/peripheral PNET. A, Sheets of small round blue cells. B, Strong nuclear Fli-1 expression. C, Membranous CD99 staining. D, *EWSR1* rearrangement confirmed by separation of green and red FISH probe signals flanking the *EWSR1* gene.

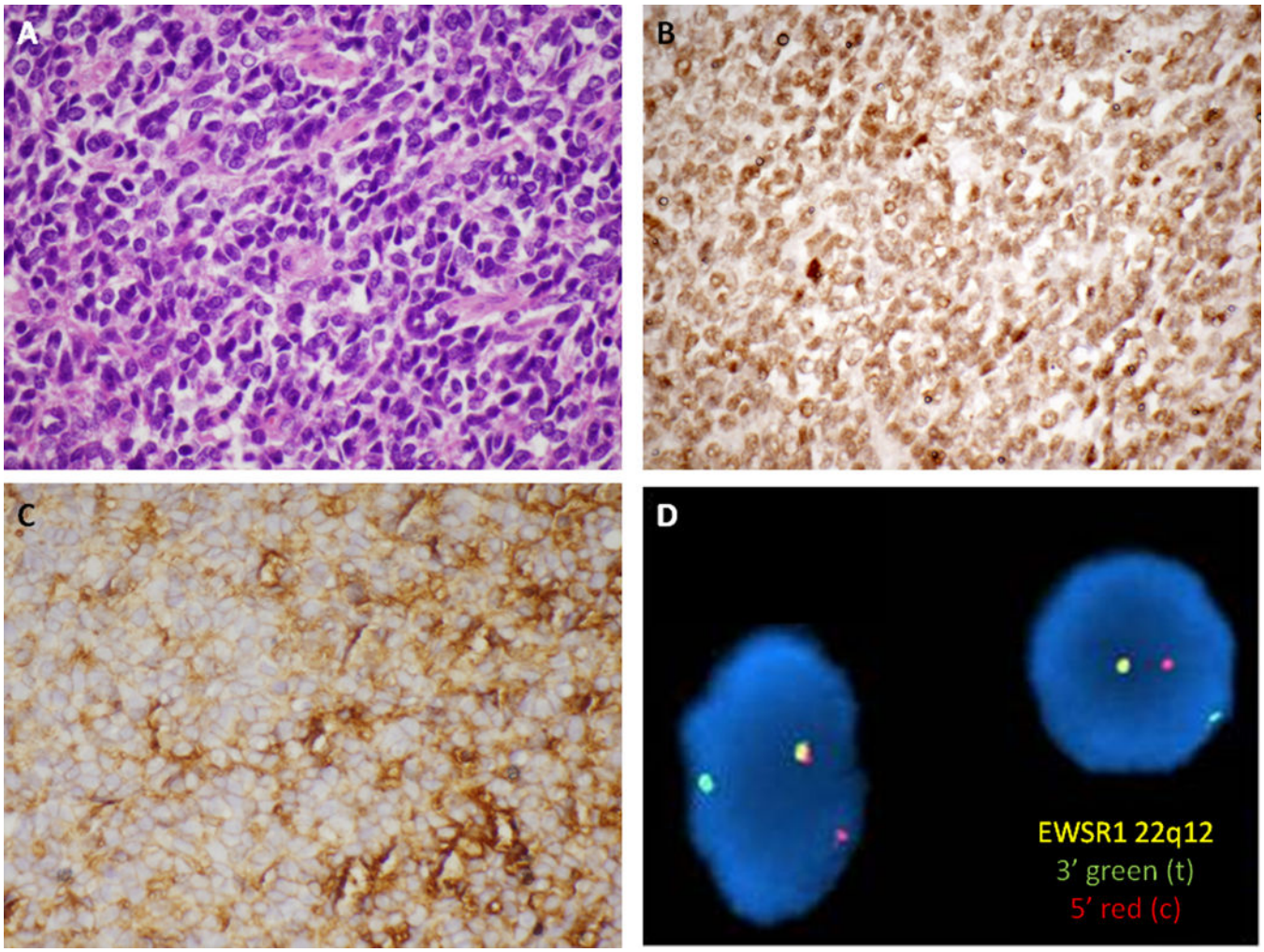

Figure 4.

Immunohistochemical features of central PNET. A, Diffuse, focal, and scattered synaptophysin positivity confirming neuronal differentiation in differentiated (top) and undifferentiated foci (bottom). B, GFAP expression of scattered glial cells in central PNET. C and D, Central PNET with features of ependymoma demonstrating concurrent strong and diffuse membranous CD99 (C) and nuclear Fli-1 (D) expression.

Table 1

Clinical features of primitive neuroectodermal tumors of the female genital tract.

Case	Site	Age	Presentation	FIGO Stage	Therapy	Outcome
1	Ovary	39	Disseminated intraabdominal disease	III	S, C	NED
2	Ovary	12	Pelvic mass	IA	S	NA
3	Ovary	15	Back pain	IV	S	NED, 12 mo
4	Ovary	24	Pelvic mass	III	S	NA
5	Ovary	36	Pelvic mass, ascites	II	S	NED, 36 mo
6	Ovary	14	Pelvic mass, vaginal bleeding	III	S, R	DOD, 3 mo
7	Ovary	28	NA	I	S	NA
8	Ovary	NA	NA	NA	NA	NA
9	Ovary	NA	NA	I	NA	NED, 12 mo
10	Ovary	16	Pelvic mass	I	S	NED, 36 mo
11	Uterus	66	Vaginal bleeding	III	S	DOD, 6 mo
12	Uterus	51	Vaginal bleeding	III	S, C	NED
13	Uterus	50	Vaginal bleeding	III	S	NA
14	Uterus	31	Vaginal bleeding	III	S	NA
15	Uterus	26	Vaginal bleeding	I	S	NA
16	Uterus	68	NA	IV	S	DOD, 12 mo
17	Uterus	64	NA	III	S, C	NED
18	Uterus	NA	NA	NA	NA	NA
19	Vulva	65	Vulvar mass	I	S	NA

C indicates chemotherapy; DOD, died of disease; mo, month; NA, not available; NED, no evidence of disease; R, radiation; S, surgery.

Table 2

Pathologic features and *EWSR1* rearrangement status of gynecologic primitive neuroectodermal tumors.

Case	Diagnosis	Other tumor	Immunohistochemistry												*EWSR1* FISH
			VIM	SYN	NSE	CD56	S100	CHR	NF	GFAP	CD99	Fli-1	CK	CD10	
1	cPNET Mb		+	−	−	+	−	−	−	−	+	+	F +	F +	−
2	cPNET Mb	MCT	+	+	−	+	−	−	−	−	−	F +	−	−	_
3	cPNET Mb	MCT	F +	F +	−	F +	+	−	−	F +	−	+	−	−	_
4	cPNET Mb	MCT	F +	−	−	−	F +	−	−	−	−	+	−	−	_
5	cPNET E		+	−	+	F +	−	−	−	+	−	F +	F +	−	_
6	cPNET E		+	F +	F +	F +	F +	−	−	F +	−	+	−	−	_
7	cPNET E	MCT	+	F +	F +	F +	−	−	−	−	+	+	−	−	_
8	pPNET		+	F +	−	+	F +	−	−	−	+	+	−	−	_
9	pPNET		F +	−	−	F +	−	−	−	−	F +	+	−	+	_
10	cPNET G	MCT	F +	+	−	+	+	+	−	+	−	+	−	−	_
11	cPNET Me		+	+	+	F +	−	−	−	−	+	−	−	−	_
12	cPNET Mb	EEC	F +	+	+	+	−	−	−	−	−	F +	−	−	_
13	cPNET Mb	EEC	F +	F +	−	−	F +	−	−	−	+	F +	F +	F +	_
14	cPNET Me	CS	+	−	−	+	−	−	−	−	F +	−	−	+	_
15	pPNET		+	−	−	−	−	−	−	−	+	+	−	−	+
16	cPNET Mb		+	+	+	+	F +	−	−	−	F +	F +	−	F +	_
17	cPNET Mb		+	−	−	+	−	−	−	−	+	F +	−	−	_
18	cPNET Mb		NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	−
19	pPNET		+	F +	F +	+	F +	−	−	−	F +	+	F +	F +	+

CHR indicates chromogranin; CK, cytokeratin; cPNET, central PNET; CS, carcinosarcoma; E, ependymoma; EEC, endometrioid endometrial carcinoma; F, focal; FISH, fluorescence in situ hybridization; G, glioblastoma; GFAP, glial fibrillary acidic protein; Mb, medulloblastoma; MCT, mature cystic teratoma; Me, medulloepithelioma; NP, not performed; NSE, neuron-specific enolase; pPNET, peripheral PNET; SYN, synaptophysin; VIM, vimentin