Primary Peripheral Primitive Neuroectodermal Tumor of the Ovary With an Epithelial Cyst : A Case Report and Review of Literature

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Abstract : **Peripheral primitive neuroectodermal tumor (pPNET) has some histologic resemblance to a classic central primitive neuroectodermal tumor (cPNET), however it is distinctively different from cPNET by its CD99 immunoreactivity, characteristic chromosomal translocation, t(11;22)(q24;q12) and EWS/FLI-1 chimeric mRNA. Peripheral PNETs have a predilection for soft tissues rather than for viscera. Only 15 cases of primary ovarian PNET have been reported, and only one case was proven to be pPNET. Ovarian PNET is an aggressive tumor. We report a case of a 40-year-old Thai woman with a Stage IIIb right ovarian PNET. Despite debulking operation and vigorous adjuvant chemotherapy, the patient died of disease 6 months later. Grossly, the tumor was solid and cystic. Microscopically, the former displayed unique features mimicking cPNET, but the pPNET phenotype was validated by CD99 staining. The solid portion also contained mucin-producing gland-like structures, previously described as ependymal differentiation. In the cystic portion, the histology demonstrated epithelial lining tissue resembling cystadenoma of borderline malignancy of the ovary. It is generally accepted that both cPNETs and pPNETs can have polyphenotypic differentiation. PNETs can be originated from either totipotential germ cells, neural crest remnant or mullerian-derived cells.**

Key words : Peripheral primitive neuroectodermal tumor-PNET-Ovary-Ovarian PNET -CD99- Collision tumor.

เรื่องย่อ : **มะเร็งของรังไข่ชนิด Peripheral primitive neuroectodermal tumor ร่วมกับถุงน้ำของเนื้องอกของเซลล์เยื่อบุ : รายงานผู้ป่วยและทบทวนวารสาร**

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เนื้องอก primitive neuroectodermal tumor (PNET) จำแนกออกเป็น 2 ชนิดคือ Peripheral primitive neuroectodermal tumor (pPNET) และ Central primitive neuroectodermal tumor (cPNET) เนื้องอก pPNET มีข้อแตกต่างจาก cPNET คือ pPNET มีความผิดปกติของโครโมโซม t(11;22)(q24;q12), มี EWS/FLI-1 chimeric mRNA และย้อมติด CD99 เนื้องอกชนิดนี้โดยทั่วไปมักพบที่เนื้อเยื่อเกี่ยวพันต่าง ๆ กรณีที่พบที่อวัยวะภายในโดยเฉพาะรังไข่นั้นพบได้น้อย ปัจจุบันมีรายงานผู้ป่วยเนื้องอก PNET ของรังไข่แล้วทั้งสิ้น 15 ราย ซึ่งในจำนวนนี้มีเพียง 1 รายที่ได้รับการยืนยันว่าเป็น pPNET รายงานผู้ป่วยหญิงไทยอายุ 40 ปี ตรวจพบเนื้องอก pPNET ที่รังไข่ข้างขวาระยะ IIIb ผู้ป่วยเสียชีวิต 6 เดือนหลังจากรับการรักษาด้วยการผ่าตัดและเคมีบำบัด เนื้องอกประกอบด้วยส่วนที่เป็นเนื้อและถุงน้ำ ในส่วนที่เป็นเนื้อนั้นตรวจพบลักษณะทางจุลกายวิภาคของ PNET และย้อมติด CD99 บางส่วนของเนื้องอกย้อมติด neurofilaments, NSE และ S100 protein บางส่วนพบลักษณะของ ependymal/epithelial differentiation อีกด้วย สำหรับส่วนของถุงน้ำมีลักษณะของ cystadenoma of borderline malignancy อย่างไรก็ตาม เนื้องอกรายนี้ควรได้รับการตรวจทางอณูพันธุศาสตร์เพิ่มเติมต่อไป

INTRODUCTION

Primitive neuroectodermal tumors (PNETs) are well-known tumors since their first description in 1973 by Hart MN et al as densely cellular embryonal small-cell tumors of the cerebrum mimicking medulloblastoma[1]. In 1986, Dehner LP coined the term "peripheral primitive neuroectodermal tumors (pPNETs)" for all of the PNETs occurring anywhere outside the CNS[2]. The classic PNET of the CNS was referred to as cPNET. The latter has been named by the 2000 WHO classification of brain tumors as the supratentorial PNET (SPNET)[3]. Recent studies have suggested other unique features of pPNETs, including the positive CD99 (MIC2) staining, characteristic reciprocal chromosomal translocation, t(11;22) (q24;q12), and EWS/FLI-1 chimeric mRNA[4-6]. These three peculiarities are also found in its related tumors, Ewing's sarcoma and Askin's tumor. Peripheral PNET arises mostly in deep soft tissue, particularly extremities and paravertebral areas, while visceral pPNETs are extremely rare[6,7]. To our knowledge, only 15 cases of pure or almost pure primary ovarian PNETs have been reported in the English literature since they were first reported in 1982[8]. Ovarian PNET was seperate from the other peripheral-located PNETs because of its presumed emanation from germ cell (monodermal teratoma) rather than neural crest[9,10]. This implies that ovarian PNET can have either a cPNET or pPNET phenotype. Teratoma associated PNETs were the excellent instances[11,12]. Herein, we report a case of right ovarian pPNET with mucin-producing ependymal or epithelial differentiation in a 40-year-old Thai woman as a mixed solid and cystic tumor. The pertinent literature is reviewed with respect to the clinical and pathological parameters, including tumorigenesis.

CASE REPORT

A 40-year-old Thai woman was referred to Siriraj Hospital with complaints of a lower abdominal mass and a localized tenderness.

The patient had been well except for a problem of infertility until 4 months before admission, when she developed lower abdominal pain, constipation and a palpable rapidly growing mass. There was no familial history of malignant tumor of any type.

Physical examination disclosed a large, firm, tender lower abdominal mass of approximately 20 weeks' pregnancy in size. Pelvic examination demonstrated a 15-cm nodular, firm, tender mass, clearly separate from a normal-sized uterus. The tumor appeared to involve the right adnexum and the right ovary was difficult to identify. The rest of the internal genital organs were unremarkable. Serum AFP and βHCG were within normal limits. Only serum CA 125 was significantly elevated to

942.3 U/ml (normal range, up to 29.2 U/ml). The serum calcium level was not investigated.

The patient underwent a laparotomy revealing 200 ml of serosanguineous ascitic fluid and a right ovarian tumor, which was composed of solid and cystic components measuring 15 and 10 cm in maximal diameter, respectively. The latter ruptured accidentally disclosing a moderate amount of chocolate-like contents. The solid part adhered not only to the right swollen fallopian tube, but also to the rectosigmoid colon. Multiple enlarged paraaortic lymph nodes were identified. The pelvic cavity was totally impacted by this tumor. The omentum and peritoneum were unremarkable. Right salpingo-oophorectomy and partial omentectomy was performed with some difficulty, leaving a 10-cm residual tumor in the cul-de-sac. The postoperative course ran uneventfully except for recurrent ascites. Adjuvant chemotherapy (cisplatin, etoposide and bleomycin) was added to the treatment program. On follow-up, the serum CA 125 level was decreased to 52.3 U/ml.

Although the treatment seemed to be effective, the second laparotomy after 5 courses of chemotherapy still disclosed a 15-cm retroperitoneal tumor adhering to the rectosigmoid colon and also compressing the right ureter and causing hydronephrosis of the corresponding kidney. Only tumor biopsy and lysis of adhesions were performed. Postoperatively, acute postrenal renal failure and severe hyperkalemia developed. The patient deteriorated rapidly and died within 2 weeks after the second laparotomy or 6 months after recognition of the tumor. Permission for autopsy was not obtained.

MATERIALS AND METHODS

Tissues from both operations were fixed in 10% buffered formalin and processed. Paraffin-embedded tissue was stained with hematoxylin and eosin (H&E) and several histochemical stainings including periodic acid-Schiff with and without prior diastase digestion (PAS and PAS-D), mucicarmine, reticulin and also Masson-Fontana stains.

Immunohistochemical Staining

Immunohistochemistry was performed on 3-μm-thick deparaffinized tissue sections using the streptavidin-biotin peroxidase method. The primary antibodies and antigen retrieval techniques used are listed in Table 1.

RESULTS

Pathological Findings

The specimen from the first operation consisted of an irregular mass with attached right fallopian tube and a separate piece of omentum. The mass, measuring 10x6x5 cm, had a nodular surface, partly solid and cystic consistency and totally replaced the normal ovarian tissue (Figure 1). On sectioning, the solid part was composed of a yellow-brown solid area with extensive necrosis and hemorrhage extending close to the right fallopian tube which measured 10 cm. in length and 1 cm. in diameter. A separate mass of similar character, measuring 3 cm. in maximal diameter, was also noted attached to the fimbria. The remaining cystic portion appeared as a previously ruptured thin-walled cyst with few yellow-brown nodules and papillary excrescences on its inner surface. The 27x7-cm omentum was free of tumors.

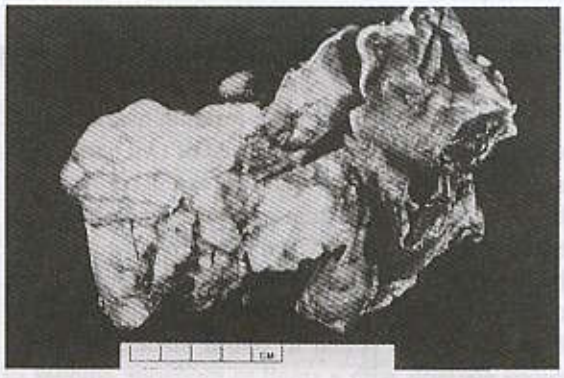


Figure 1. Showing two distinct components with the solid portion at the left side and ruptured cyst at the right.

Table 1. Antibodies used in the staining

Antibody	Source	Dilution	Clonality	Antigen retrieval
Cytokeratins-AE1/AE3	Zymed	1:2000	M(AE1/AE3)	MW,TR
Cytokeratin 7	Novocastra	1:2000	M(LP5K)	MW,TR
Cytokeratin 20	Novocastra	1:2000	M(Ks20.8)	MW,TR
CEA	Novocastra	1:500	M(CD66e)	MW,TR
CD45 (LCA)	Dako	1:3000	M(2B11,PD7/26)	MW
HMB-45	Dako	1:300	M(HMB45)	MW,TR
Vimentin	Novocastra	1:3000	M(V9)	MW
MSA	Dako	1:300	M(HHF35)	MW
Desmin	Dako	1:800	M(D33)	MW
S-100 protein	Dako	1:1500	P	TR
CD99 (MIC2)	Dako	1:1500	M(12E7)	MW
Neurofilaments	Dako	1:400	M(2F11)	MW
GFAP	Dako	1:2000	M(6F2)	MW
Neuron specific enolase	Dako	1:4000	M(BBS-NC,VI-H14)	MW
Chromogranin	Dako	1:800	M(DAK-A3)	MW
Synaptophysin	Dako	1:500	M(SY38)	MW
Alpha inhibin	Oxford Bio-Innovation	1:10	R1	MW,TR
ER	Novocastra	1:250	M(6F11)	MW
PR	Zymed	1:500	M(PR-2C5)	MW

M, monoclonal; P, polyclonal; MW, microwave retrieval technique; TR, trypsin digestion (0.1% trypsin/ 0.01 mol/ L phosphate buffer solution) at 37°C for 30 min; MSA, muscle specific actin; ER, estrogen receptor; PR, progesterone receptor.
*All dilutions are for overnignt treated in room temperature.

Microscopically, no residual ovarian tissue was present. The tumor consisted of two parts, solid and cystic. The former showed extensive necrosis; however, in the viable tumor areas, islands, nests and trabeculae of closely packed small round cells in the background of some myxoid substance were observed. These cells had small or medium-sized hyperchromatic round to ovoid nuclei, inconspicuous nucleoli with a small to moderate amount of pale acidophilic to clear cytoplasm. Mitotic figures ranged from 8 to 10 per 10 high-power fields in the most active area. Rare tumor cells with a rhabdoid feature (medium- to large-sized eccentric vesicular nuclei, prominent nucleoli with relatively abundant pale eosinophilic cytoplasm) were present. A few tumor cells were arranged in perivascular pseudorosettes, scarce Homer-Wright rosettes and gland-like structures lined focally by ciliated columnar epithelial cells (Figure 2 and 3). Angiolymphatic permeation was found. No teratomatous element was observed.

There was no fibrous capsule separating the solid portion from the cystic part. The latter was lined focally by ciliated, mucin-containing columnar cells forming true papillary excrescences resembling a mixed endometrioid, mucinous and serous tumor (Figure 4). The nuclei displayed moderate atypia. Stromal invasion was not present.

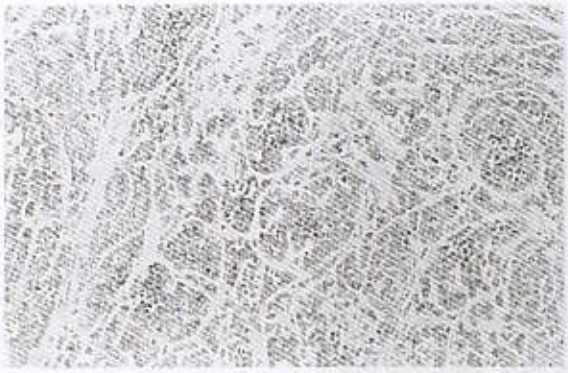


Figure 2A

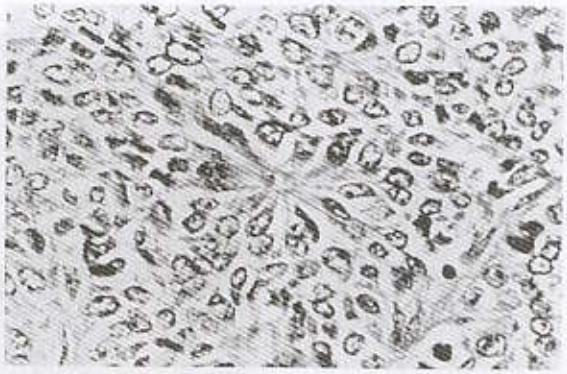


Figure 2B

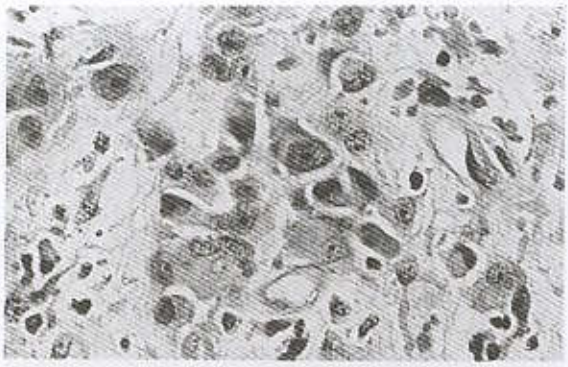


Figure 2C

Figure 2D

Figure 2A. Small round cell tumor arranged in either islands, nests or trabeculae (H&E, x100).
B. Homer Wright's rosette is evident at the central area (H&E, x400).
C. Rare tumor cells depicting a rhabdoid feature (H&E, x400).
D. Membranous staining with CD99 antibody (CD99, x200).

Focal squamous metaplasia was found. Entrapped papillae within islands of small undifferentiated cells were present. The omentum was unremarkable except for focal mesothelial hyperplasia.

Histochemically, PAS and PAS-D stains revealed glycogen in both small cells and epithelial cells. The small cells were devoid of mucin while the gland-like structures contained both intracellular and intraluminal mucin. Abortive intercellular reticulin fibers were also identified by the reticulin stain. Masson-Fontana stain showed no positive staining.

Immunohistochemical Staining

The tumor cells, both small and medium sized cells, displayed intense vimentin, focal immunostaining for CD99 (Figure 2D), NSE, S-100 protein, and neurofilaments. The gland-like structures focally expressed not only NSE, S-100 protein and vimentin, but also the epithelial markers, AEI/AE3 and CK7 (Table 2) (Figure 3B, 3C). GFAP did not mark any structures. The other antibodies used showed no positivity in these cells.

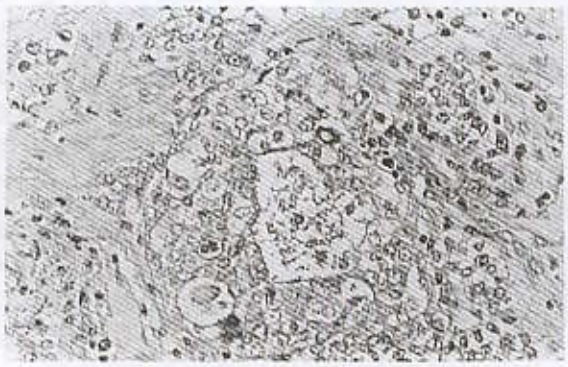


Figure 3A

Figure 3B

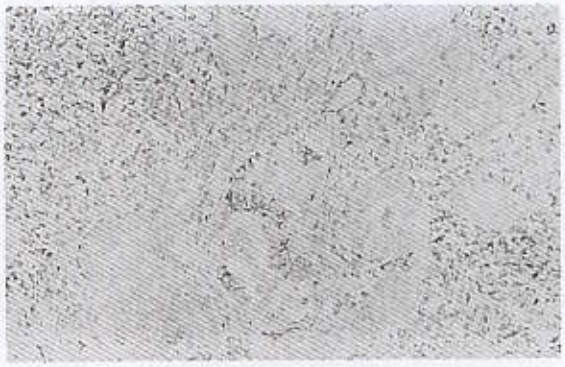
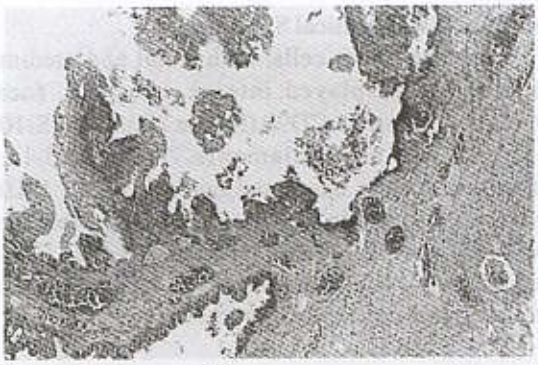


Figure 3C

Figure 3. Gland-like structure formed by tumor cells in solid area (A, Mucicarmine, x200) with cytokeratin (AE1 / AE3) expression (B, x200) and vimentin reactivity (C, x200).



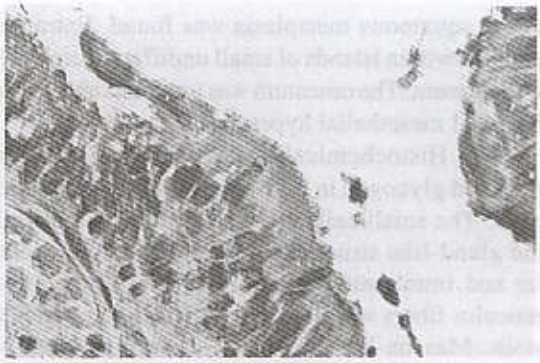


Figure 4. True papillary excrescences of the cystic portion lined by some ciliated columnar epithelial cells (H&E; A) x40, B) x400).

Table 2. Results of immunohistochemical staining of various histological patterns*

Antigen	Small cells in solid part	Gland-like structures	Cyst lining cells
AE1 / AE3	-	+(F)	+
CK7	-	+(F)	+
CK20	-	-	-
CEA	-	-	+
Vimentin	+	+(F)	-
S-100 protein	+(F)	+(F)	-
CD99 (MIC-2)	+	-	-
Neurofilaments	+(F)	-	-
NSE	+(F)	+(F)	+(R)
Chromogranin	-	-	+(R)

No expression in CD45 (LCA), HMB-45, MSA, desmin, GFAP, synaptophysin, alpha inhibin, ERand PR stains.
*Frequency of expression: -, negative; +(R), rarely positive; +(F), focally positive and +, strongly positive.

Unlike the solid part, the epithelial lining of the cystic portion reacted strongly with AE1/ AE3, CK7 and CEA while CK20, vimentin, S-100 protein, neurofilaments and CD99 were negative in these cells. NSE and chromogranin also marked the cyst lining, but rarely and with less intensity. The rest of antibodies used were also non-reactive.

DISCUSSION

Due to the rarity of the primary ovarian PNET, only 15 cases of pure or almost pure cases (not specified as cPNET or pPNET) had been reported in the English literature after two decades of description[5,8,13-15]. Table 3 summarizes their clinical and pathological features. The vast majority of tumors occurred in young patients (mean age 26); the ages ranged from 13 to 69 years. Four cases explicitly divulged small concomitant dermoid cysts. All but one arose in young patients. In general, tumors involved one ovary. Patients' symptoms were akin to presentation of other ovarian tumors.

The tumors varied from 4 to 26 cm (mean, 14.74 cm) in greatest dimension and were usually solid on cut surface. About 20% of the tumors were purely cystic while mixed features were encountered in only one case. Only a case reported by Kawauchi S et al. was proven to be pPNET by means of all three aforementioned features[5]. Other reports did not describe these approving methods, so their nature, cPNET versus pPNET, remains unknown. Immunohistochemistry for GFAP was positive in one of four cases performed. Patients usually presented with advanced stage (stage III, 66.66 %) at the initial diagnosis. Although nearly all received adjuvant therapy in addition to surgical interven-tion, most died of disease within one year after presentation. This suggests aggressive behavior. The one-year survival rate is approximately 38.46%, regardless of staging, compared with the 50% three-year survival rate of other pPNETs[6] and the 73% three-year survival rate of cPNET[16] (Table 4).

The current tumor was composed of 2 distinct portions, solid and cystic. Microscopically, the former mainly showed closely packed small round cell tumors arranged in either islands, nests or trabeculae. This feature could mimic a variety of primary and metastatic ovarian tumors of small round cell types. The tumor was considered a primary lesion of the ovary, because of the absence of demonstrable tumor elsewhere. With regard to primary small round cell tumors of ovary besides PNET, differential diagnosis includes the following tumors. Small cell carcinoma of hypercalcemic type

Table 3. A summary of reported cases of PNETs of the ovary.

Reference	Age (yr)	Symptom	Size (cm) and Side	Gross Findings and Diagnosis	Stage	Primary surgery	Adjuvant therapy	Recurrence*	Therapy of recurrence	F/U
Burke M et al.,1984	53	Abdominal swelling for 8 months	15, right	Solid with partly cystic lesion, PNET with ectodermal and mesenchymal diff.	III	Tumor Removal	RT	Yes (7mo)	-	DOD 9mo
Shuangshoti et al.,1986	48	Acute onset of RLQ abdominal pain and past history of LSO for an ovarian cyst	8, right	Solid, PNET with ependymal, astrocytic and oligodendroglial diff.	III	RSO and subtotal hysterectomy	-	Yes (10mo)	Surgery, RT and CT	DOD 16mo
Kleinman et al.,1993	24	Abdominal mass	17, NA	Cyst, medulloblastoma, associated with dermoid	IA	USO	-	NA	NA	NA
Kleinman et al.,1993	20	Abdominal mass and ascites	12, left	Solid, medulloepithelioma	IA	LSO	CT	No	-	NED 9 yr
Kleinman et al.,1993	32	NA	13.5 left	Solid, medulloepithelioma associated with dermoid	IA	LSO	CT	No	-	NED 3 yr
Kleinman et al.,1993	16	Abdominal mass and pain	4, right	Solid, neuroblastoma, associated with dermoid	IC	RSO	CT	No	-	NED 7 mo
Kleinman et al.,1993	13	Abdominal pain	17, right	Cyst, medulloepithelioma	III	RSO	-	Yes (18 mo)	-	DOD 20 mo
Kleinman et al.,1993	18	Abdominal mass, irregular menstruation	20, right	Solid, ependymoblastoma	III	RSO	RT	-	-	DOD 3 mo
Kleinman et al.,1993	18	Abdominal distension	19, right	Solid, neuroblastoma	III	RSO	RT	-	-	DOD 7 mo
Kleinman et al.,1993	18	Abdominal mass and virilism	1955 grams, right	Solid, ependymoblastoma	III	RSO	CT	-	-	DOD 6 mo
Kleinman et al.,1993	26	NA	Diffuse pelvic and abdominal spread	Solid, ependymoblastoma	III	BSO	CT	-	-	AWD 1 yr
Kleinman et al.,1993	69	Abdominal mass and ascites	11, left	Solid, medulloblastoma with dermoid cyst of right ovary	III	LSO	RT and CT	-	-	DOD 6 mo
Kleinman et al.,1993	23	Ascites	Large pelvic mass	Solid, medulloepithelioma	III	TAH and BSO	RT and CT	-	-	DOD 2 mo
Kleinman et al.,1993	16	NA	26, Centrally located cyst	Cyst, neuroblastoma	NA	NA	NA	NA	NA	NA

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Reference	Age (yr)	Symptom	Size (cm) and Side	Gross Findings and Diagnosis	Stage	Primary surgery	Adjuvant therapy	Recurrence*	Therapy of recurrence	F/U
Kawauchi et al.,1998	29	Lower abdominal mass	22, left and 7, right	Solid, PNET	III	TAH, BSO POM and NR	CT	-	-	DOD 11 mo
Present case	40	Lower abdominal mass, pain and ascites, CA125= 942.3 U/ml	25, right	Solid, and cyst PNET with mucin secreting ependymal or epithelial diff.	III	Debulking surgery	CT	-	-	DOD 6 mo

RLQ, right lower quadrant; GBM, glioblastoma multiforme; diff., differentiation; USO, unilateral salpingo-oophorectomy; BSO, bilateral salpingo-oophorectomy; RSO, right salpingo- oophorectomy; LSO, left salpingo-oophorectomy; LS left salpingectomy; WLO, wedge left oophorectomy; TAH, total abdominal hysterectomy; NR, nodal removal; POM, partial omentectomy; APP, appendectomy; RT, radiotherapy; CT, chemotherapy; F/U, follow-up; DOD, dead of disease; NED, no evidence of disease; AWD, alive with disease; NA, not available
*-, Patient died during the first presentation.

Table 4. A summary of significant features in subtypes of PNETs

Parameters	cPNET	pPNET	Ovarian PNET
Age (yr)	< 10	10 - 30	13 - 69
Location	CNS	Extremities, paravertebral tissue and viscera	Ovary; unilateral
CD99 expression	-	+	+
t (11;22) (q24;q12)	-	+	+
EWS/FLI-1 mRNA	-	+	+
Differentiating potential	Common	Rare	Common
Survival rate (%)	3 yr = 73	3 yr = 50	1 yr = 37

and granulosa cell tumor of the ovary are considered, unless it exhibits rosette formation that hints the neural nature. Interestingly, both were recently proven to have a competency of CD99 expression[17], but granulosa cell tumors usually exhibit alpha inhibin reactivity. According to a preponderance of neuroectodermal tissues, it has to be differentiated from immature teratoma, which often contains differentiating tissues of normal development or tissues of different germ layers[10, 13].

Immunohistochemical studies indicate the propensity of neural nature by means of immunoreactivity of neurofilaments, NSE and S-100 protein. Neuroblastoma also is one of the differential diagnoses because it may display not only rosette formation but also the expression of these markers. However, it usually presents mats of neuropil and ganglionic differentiation, a feature rarely found in PNET[6]. In addition, vimentin is rarely positive in neuroblastoma, but almost always present in PNET[18]. Expression of CD99 also clearly refutes the diagnosis of neuroblastoma, and in combination with the histologic appearance validate the diagnosis of PNET. Even though the closest relevant tumor, extraskeletal Ewing's sarcoma (ES), can stain with CD99 antibody, it never ever shows

well-defined rosettes of any type or marks with neuronal markers. Nevertheless, several recent studies expound the disease-continuum concept of PNET and ES[6,18,19]. Therefore, such discrimination may become obsolete[6]. The tumor may show rhabdoid feature which was previously observed in ovarian PNET by Shuangshoti S et al[14].

Developmentally, primitive neuroepithelial cells, neural tube lining, have three divergent differentiating pathways: neuron, glia and ependyma[20]. Consequently, PNETs also have a potential to differentiate along each lineage. In fact, each tumor might exhibit diverse areas with varying degrees of differentiation. It is not surprising that neural, glial or ependymal differentiations are occasionally found in PNETs and usually present in combination.

In our case, apart from clusters of small round cells with some degree of neuronal differentiation based on the positivity of neurofilament, NSE, S-100 protein and CD99. The solid part also disclosed occasional gland-like structures of enigmatic nature. Burke M et al first mentioned this similar feature as rare epithelial differentiation in ovarian PNET, but there was no immunohistochemical study[15]. Shuangshoti S et al subsequently described this feature again as the ependymal differentiation in the ovarian PNET based on its GFAP staining[14]. The biphasic nature, glia or epithelium, of ependyma and ependymomas has been discussed in the literature[21-26]. GFAP highlights normal immature ependyma, reactive and neoplastic ependyma[21]. In ependymoma, either cerebrospinal or ovarian origins, GFAP marks only focally rosette formations[21-26]. GFAP-negative cells are virtually always stained by epithelial markers[22-25,27-29]. It is not surprising that our case replicated the staining of epithelial markers, while GFAP was negative. Uematsu Y et al further demonstrated the absence of these markers in anaplastic ependymomas and ependymoblastomas and suggested that the epithelial markers were markers of good differentiation[27]. Moreover, these gland-like structures in the current case demonstrated mucin. The latter can be found in ependyma under both normal and pathologic conditions including myxopapillary and non myxopapillary ependymomas[14,21,30]. Thus our findings of epithelial differentiation with mucin secretion and without positivity for GFAP are consistent with the ependymal differentiating nature of the tumor. Ultrastructural evaluation of GFAP-negative ependymoma was worthless in the case of distinctive epithelial differentiation[21].

From the review of reported ovarian PNETs and the current case, 80% of the cases demonstrated at least one lineage of differentiation. Neural and glial lineages are occasionally found, while ependyma, the most common lineage, occurred in approximately one third of the cases. Kleinman GM et al reported 6 cases of ovarian ependymoma showing that these tumors either with or without metastasis had better prognosis than ovarian PNETs[13]. This might indicate that ependymal differentiation alone is not associated with better prognosis, but the ratio of ependymal differentiation and the primitive cells could play a role.

The cystic portion of the current tumor is of particular interest. It could represent a portion of coexistent PNET and mixed epithelial ovarian tumor or PNET with epithelial differentiation or PNET with ependymal cyst. Based on microscopic examination alone, the cyst showed a close resemblance to ovarian mixed epithelial tumor of borderline malignancy. Immunohistochemistry of neural markers (chromogranin) stained some lining cells. It is not surprising to see chromogranin staining in this structure, as rare staining can be found in normal endocervical epithelium as well as in ovarian mucinous tumor[31]. An example of a similar collision tumor in the uterus has been recently reported by Sinkre P et al[32]. On the other hand, the cystic portion might purport epithelial differentiation of ovarian PNETs. Molecular clonal analysis might help sort out this issue. Burke M et al described an ovarian PNET made up of equally prominent cystic and solid portions[15]. The cyst lining was too degenerated to give microscopic information, with only occasional epithelial tissue of both glandular and stratified types. In non-ovarian PNETs, epithelial differentiation, gland-like structures and epithelial-like cell clusters have been mentioned in two cases of pure soft tissue PNETs with immunohistochemical evidence[33,34]. Gu M et al and

O'Sullivan MJ et al[35,36] have demonstrated cytokeratin expression in PNETs and have suggested this as an evidence of epithelial differentiation. CEA expression of ependymomas, either mucin producing or not, remains debatable. Positive CEA staining in ependymomas is exceedingly unusual[37]. Cases with indirect evidence of CEA-production in cerebrospinal ependymomas by the diminution of serum CEA level after treatment have been reported[38,39]. Therefore, though negative for GFAP and positive for CEA expression, the ependymal nature of the current tumor cannot be entirely excluded. In addition, the latest study of cerebrospinal ependymomas demonstrated CD99 staining in all 25 cases[40]. However, the comparison of CD99 and GFAP expression has not been established. Our case was the first to demonstrate the presence of an elevated serum CA125 level in PNET, it seems to emanate from the cystic portion rather than primitive cells by dint of the decreased serum CA 125 level after resection of the entire cystic portion, while leaving some solid portion behind. It is generally reported that more than 80% of patients with ovarian cancer, particularly nonmucinous epithelial tumors, show this elevation[41]. This underscores epithelial nature of the cystic portion, either a collision tumor or an epithelial component of PNET, rather than ovarian ependymoma.

The histogenesis of ovarian PNETs is somewhat uncertain. Three distinct cells of origin have been proposed: totipotential germ cells, neural crest remnant and mullerian derivative. Indeed, some ovarian PNETs have existed with either ipsilateral or contralateral concomitant teratomas. Thus, it is conceivable that the tumor might originate either as a de novo monophyletic germ cell tumor composed solely of primitive neuroepithelial cells or as a neoplastic transformation of ovarian teratomas in which other elements have regressed or minimally represented[2,9,10]. Neural crest remnant occasionally observed in normal ovary could differentiate into neuroectodermal tissue[14]. This hypothesis was corroborated with aberrant differentiation of PNETs including epithelial and mesenchymal lineages[2,14]. Furthermore, PNETs may derive from metaplasia of mullerian origin. The presence of neuroectodermal tumors in carcinosarcoma[42], and GFAP expression in epithelial cells of endometrial and ovarian carcinomas[43], although rare, verify this mechanism. The collision tumor of endometrial endometrioid adenocarcinoma and pPNET also supports this possibility[32].

In summary, we report a case of primary pPNET of the ovary with mucin-producing ependymal or nonependymal epithelial differentiation. Ovarian PNET should be included in the differential diagnoses of small round cell neoplasms involving the ovary, especially in those with a combined epithelial lining cyst and small round cell tumor with rosette formation. Clinical and prognostic comparison of cPNETs and pPNETs of the ovary should be considered in the future.

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