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Clinically aggressive primary solid pseudopapillary tumor of the ovary in a 45-year-old woman

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Abstract We report the first case of primary solid pseudopapillary tumor of the ovary with aggressive behavior and fatal outcome in a 45-year-old woman. The patient presented with weight loss, decrease of appetite, and abdominal bloating for the last several weeks. Computed tomography scan revealed an ovarian mass, omental caking, complex ascites, and 2 hepatic lesions. The pancreas was unremarkable. Grossly, the ovarian mass showed severe capsular adhesion, and the cut surface was cystic and solid. On histologic examination, the tumor was composed of diffuse solid pseudopapillary and pseudocystic patterns. The neoplastic cells were uniform and round with very dispersed chromatin. The cytoplasm was faintly pink. There was mild atypia, but the mitotic rate was as high as 62 per 50 high-power field, and the Ki-67 was elevated at 20%. The tumor exhibited severe necrosis. Numerous foci of lymphovascular invasion were also seen. The tumor cells were positive for cytokeratin (focal) and for β-catenin (cytoplasmic and nuclear patterns). They were negative for chromogranin, synaptophysin, thyroglobulin, calcitonin, hepatocyte-paraffin 1, epithelial membrane antigen, calretinin, and α-inhibin. Electron microscopic study revealed nests of tumor cells with oval nuclei. The cytoplasm contained numerous pleomorphic mitochondria interspersed among short strands of rough endoplasmic reticulum. The tumor involved the fallopian tube, omentum, cul-de-sac, and abdominal wall. The pelvic washing was also positive for tumor cells. Despite chemotherapy, the patient's condition had worsened, and she died of her disease 8 months after the initial diagnosis. We discuss the differential diagnosis of this tumor and the hypothesis of its origin.

Keywords: Solid pseudopapillary tumor; Ovary; Aggressive outcome

1. Case report

A 45-year-old woman was referred at Roswell Park Gynecologic Clinic by her treating physician for further evaluation of clinical suspicion of an ovarian mass. The patient reported weight loss, decreased appetite, and abdominal pain and bloating for several weeks. However, the patient had no medical care in the past 4 years. On physical examination, there was an upper abdominal firmness, adnexal mass, and discrete mass in the cul-de-sac. A computed tomographic scan of the abdomen and pelvis revealed complex ascites, omental caking, an 8 × 7 cm cystic mass of the right adnexa, and 2 masses in the medial right hepatic lobe. The pancreas was unremarkable. A serologic test showed an elevated CA-125 level of 372 U/mL (reference, 0-35.0 U/mL). Surgical history was significant for cholecystectomy in 1980, appendectomy in 1984, gastric bypass for obesity in 2004, and total abdominal hysterectomy with left salpingo-oophorectomy for cervical dysplasia in 2007. In her family history, the father died of bladder cancer, and the mother died of non–Hodgkin lymphoma.

The patient underwent an exploratory laparotomy, right salpingo-oophorectomy, omentectomy, complete staging, and tumor debulking. The right ovarian mass measured

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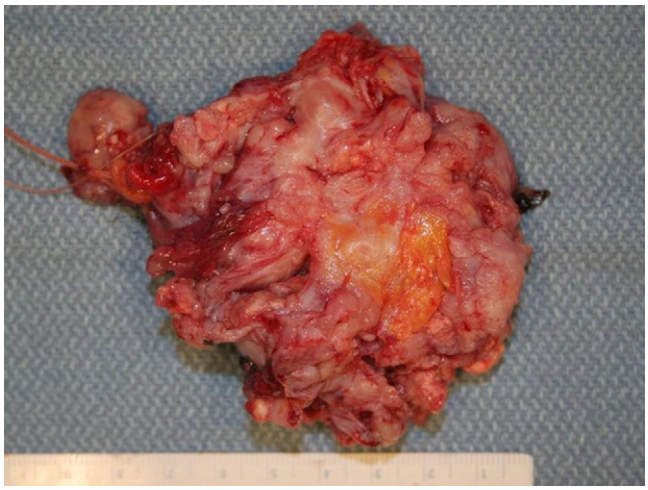


Fig. 1. The gross image of the ovarian mass showed an irregular, shaggy capsule with severe adhesions.

7.5 × 5.5 cm and weighed 74 g. The capsule showed severe fibrous adhesions (Fig. 1). The ovary was serially sectioned, and the cut surface revealed an ill-circumscribed mass that was partially solid (80%) and partially cystic (20%). The solid areas were white tan and friable. The cystic areas were filled with hemorrhage and necrosis. The attached fallopian tube showed small serosal tumoral nodules. Also received was an omental caking measuring 4.5 × 3.5 cm, and on cut sectioning, it was totally occupied by a homogenous, white tan, friable tumor.

Histologic examination of the ovarian mass showed a tumor with heterogenous growth pattern with combination of solid, pseudopapillary, and pseudocystic structures. The solid area was composed of solid sheets and nests of neoplastic cells that were separated by small vessels (Fig. 2A and B). In few areas, the nests of neoplastic cells were surrounded by fibrous septa and sometimes by broad fibrous bands (Fig. 2C). The tumor cells were uniform, round, and exhibited no to mild pleomorphism and mild atypia. They had very inconspicuous nucleoli and a dispersed chromatin. The cytoplasm was faintly eosinophilic (Fig. 2D). The pseudopapillary structures were formed by papillae with central fibrovascular core that were covered by 1 or multiple layers of neoplastic cells (Fig. 3A and B). The mitotic rate was as high as 62 per

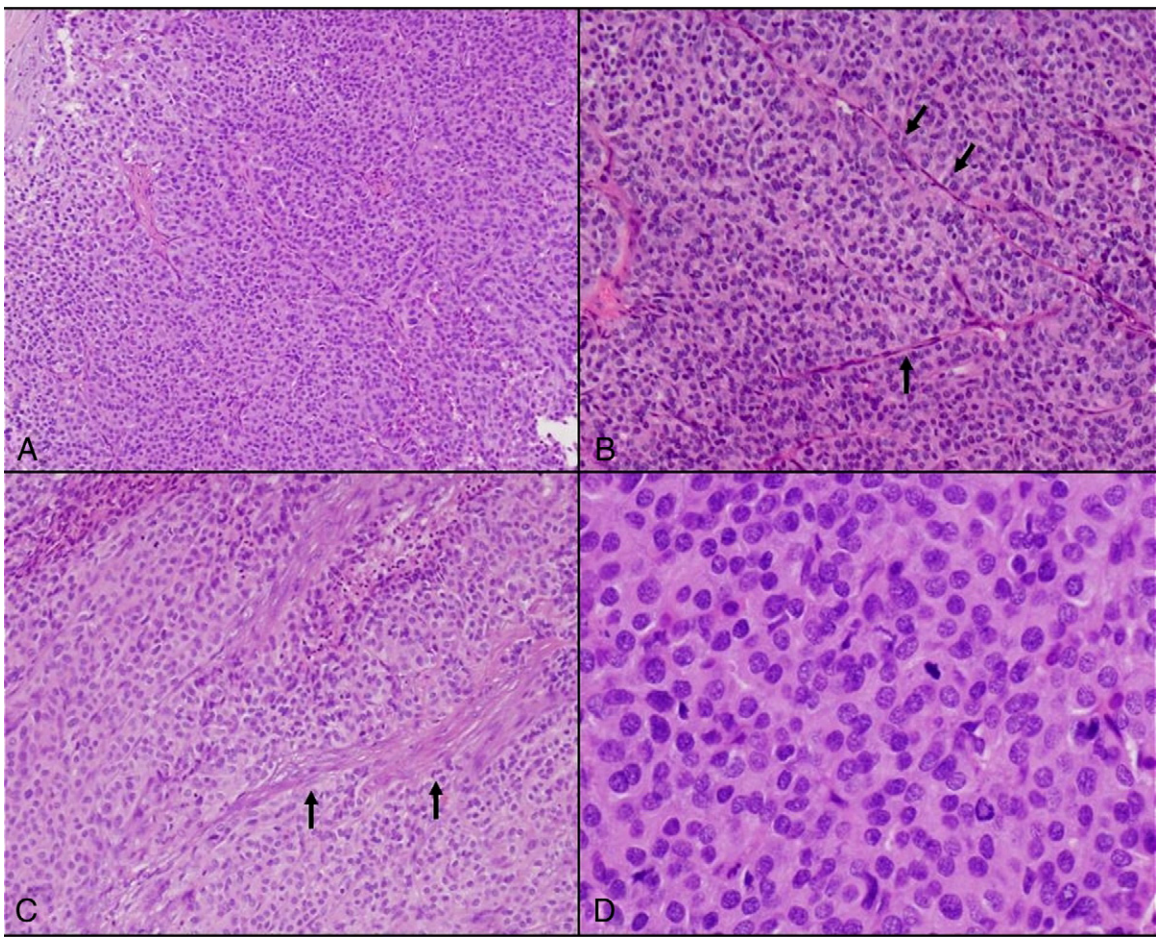
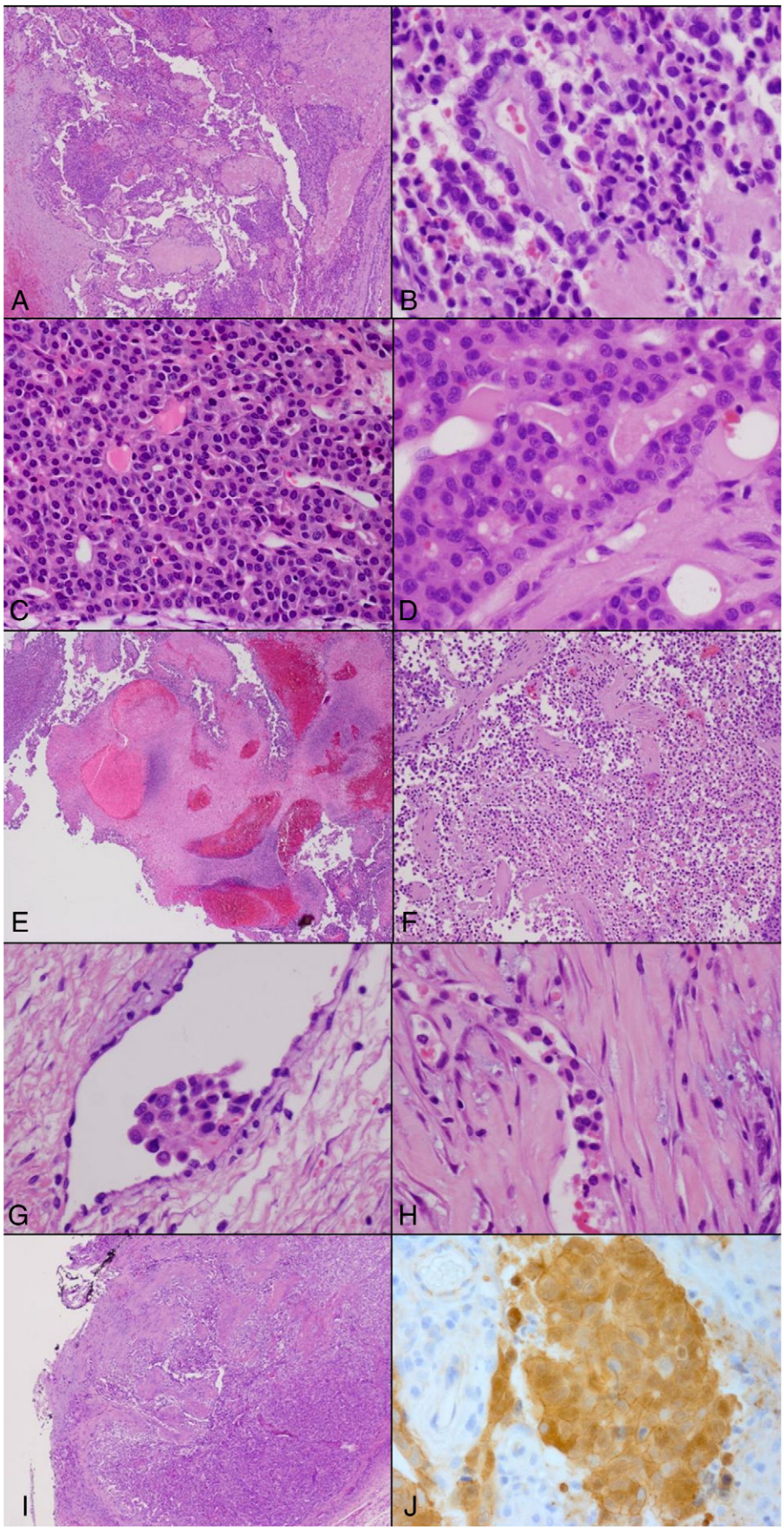


Fig. 2. (A) The tumor had a solid and diffuse pattern. (B) Tumor cells were arranged in nests and separated by small blood vessels (arrows). (C) In some areas, they were separated by thick fibrous bundles (arrows). (D) The neoplastic cells had a very round nucleus with dispersed chromatin and eosinophilic cytoplasm. Mild atypia and mitosis were also present.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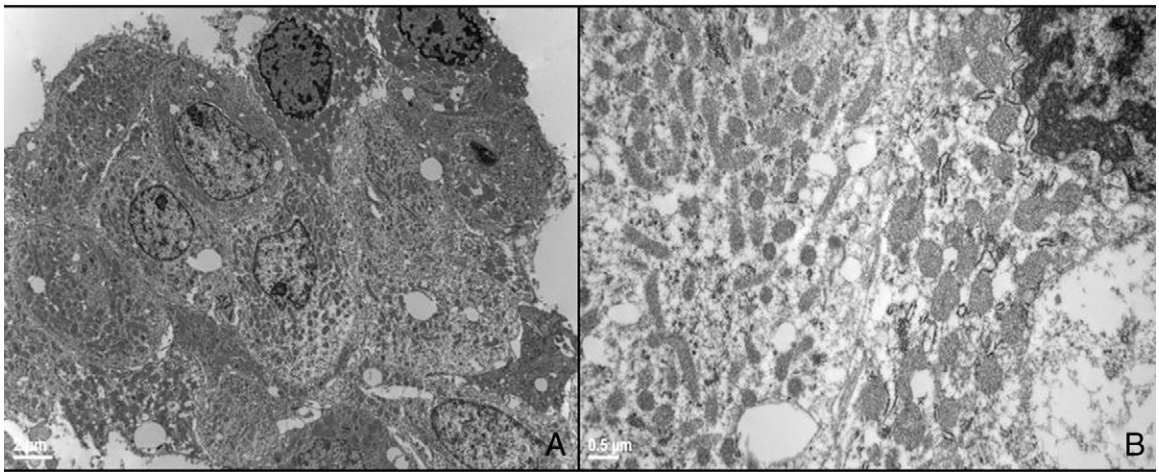

Fig. 4. (A) At low magnification, there were nests of tumor cells. The nuclei were mostly oval. (B) Higher magnifications of various cell cytoplasm demonstrated the presence of numerous pleomorphic mitochondria interspersed among short strands of RER.

50 high-power field, and the Ki-67 was as high as 20% to 30%. Areas of pseudocystic spaces filled with colloid-like material were focally noted (Fig. 3C and D). Extensive areas of necrosis were also present (Fig. 3E and F). Lymphovascular invasion was seen throughout the tumor (Fig. 3G and H). The tumor reached the inked ovarian capsule (Fig. 3I). Immunohistochemistry was performed on 3 tumor blocks. The neoplastic cells were positive for AE1/3 (very focal) and β-catenin (cytoplasmic and nuclear) in 80% of tumor cells (Fig. 3J). They were negative for endoplasmic reticulum (ER), progesterone receptor (PR), synaptophysin, chromogranin A, calcitonin, thyroid transcription factor-1 (TTF1), thyroglobulin, calretinin, hepatocyte paraffin 1 (Hep-par-1), HMB-45, α-inhibin, PAX2, α-fetoprotein (AFP), placental alkaline phosphatase (PLAP), S-100, CD10, BRST-2 (also known as gross cystic disease fluid protein-15 [GCFPD-15]), CD30, OCT3/4, Wilm's tumor-1 (WT1), and CD56 (for antibody conditions, please refer to supplemental Table 1).

Electron microscopy was performed on the paraffin block representing the tumor. Despite that the tumor was extracted from paraffin, the morphological structures were well preserved. At low magnification, there were nests of tumor cells (Fig. 4A). The nuclei were mostly oval, and some had indented nucleoli. Higher magnifications of various cell cytoplasm showed numerous pleomorphic mitochondria interspersed among short strands of rough ER (RER) (Fig. 4B). Cell junctions were rarely seen, and microvilli were lacking. No other distinctive subcellular organelles were observed. The pelvic washing was positive for the tumor similar to those seen in the ovary (Fig. 5A and B). Finally, biopsies from different sites including the cul-de-sac, small bowel, upper and lower anterior abdominal wall nodules, perirectal tumor, and left periureteric tumor were also submitted, and they were all positive for tumor.

The diagnosis was that of primary solid pseudopapillary tumor (SPT) of the ovary, with metastasis to the omentum, other organs, and the liver.

The patient started carboplatin and paclitaxel. After 3 cycles of chemotherapy, a firm mass at the vaginal apex was noted, indicating disease progression. The chemotherapy was switched to carboplatin and Gemzar for 3 cycles. The CA-125 dropped to 38.5 U/ mL, but after the third cycle, the patient had a stroke. The patient died of her disease 8 months after the initial diagnosis.

2. Discussion

Solid pseudopapillary tumors are rare tumors of the pancreas that usually occur in young women [1,2]. They exhibit unique clinical and pathologic features, and they are readily diagnosed based on their characteristic histologic and cytologic appearances [3]. Histologically, the tumor is composed of mixture of solid, cystic, and pseudopapillary patterns. Tumor cells are round and uniform, and they have abundant cytoplasm. However, they lack cytologic atypia, and mitoses are very rare [4]. β-Catenin mutation and cytoplasmic/nuclear accumulation were seen in almost all SPTs of the pancreas, suggesting a significant role of Wnt (wingless type) signaling in the tumorigenesis of SPTs [5]. Electron microscopic findings are not very specific, such as tumor cells are round with indented nuclei containing single small nucleoli. The cytoplasm is abundant and rich in

Fig. 3. (A) In some areas, the tumor cells were arranged in pseudopapillary pattern. (B) The papillae were lined by 1 layer of neoplastic cells. (C) In other areas, tumor cells were arranged as pseudocystic pattern. (D) The spaces are filled with colloid-like material. (E and F) Areas of tumoral necrosis and hemorrhage are present. (G and H) Numerous lymphovascular invasion. (I) Tumor cells seemed to involve the inked capsular margin of the ovary. (J) β-Catenin was positive in a cytoplasmic and nuclear pattern.

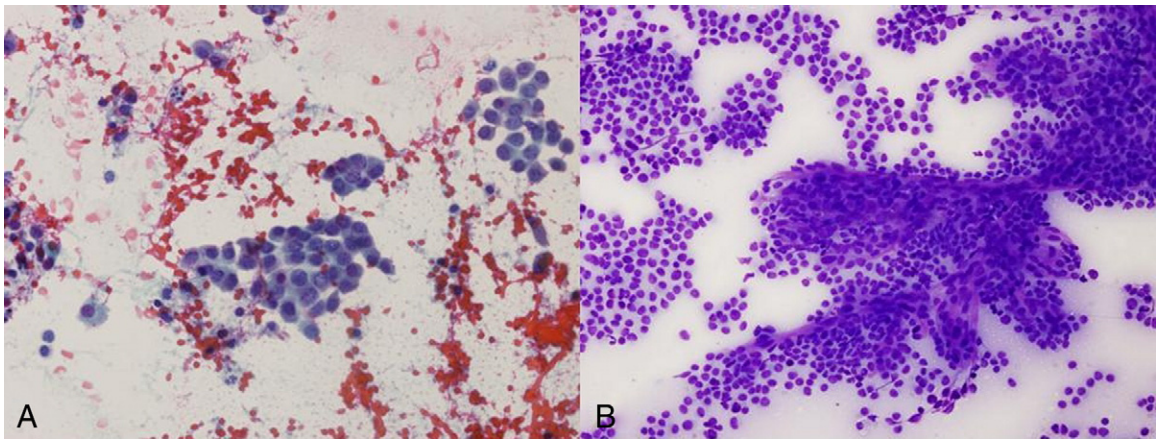

Fig. 5. (A) The Papaniculaou stain on the pelvic washing showed groups of neoplastic cells. These cells were very uniform, round, and had very dispersed chromatin and inconspicuous nucleoli. (B) Geimsa stain showed branching capillaries surrounded by numerous neoplastic cells.

mitochondria, and the RER is sparse to moderate. Tumor cells contain large, osmiophilic, zymogen-like granules of variable sizes. Finally, intermediate cell junctions are rarely seen, and microvilli are absent [1,6].

Solid pseudopapillary tumors are considered tumors of low-malignant potential, but 15% can develop metastasis mostly involving the liver and peritoneum. Even in the presence of disseminated disease, the clinical course is usually very slow, and long-term survival rate was observed in more than 95% of the cases [2,3,7]. However, recently, Tang et al [8] have reported 2 cases of clinically aggressive SPTs of the pancreas where the patients died within months after the initial diagnosis. Based on these 2 cases, the authors suggested that some histologic features might be associated with aggressive behavior including perineural and vascular invasion, invasion of surrounding organs, nuclear atypia, elevated mitotic rate, and necrosis.

On the other hand, Deshpande et al [9] reported 3 cases of SPT of the ovary resembling those of the pancreas. The patients were 17, 21, and 57 years old. The size of the ovarian masses ranged from 3 to 25.5 cm. CA-125 serum level was not mentioned in any of these 3 cases. All 3 patients had disease confined to 1 ovary. Grossly, the mass was well circumscribed. Histologically, all 3 cases had diffuse pseudopapillary growth and pseudocystic patterns. However, cellular atypia and mitosis were not seen. In this report, 1 patient was disease free at 6-year follow-up, and 2 patients did not have any follow-up.

Our case is unique because in addition to the presence of the classic histologic features of SPTs as seen in the pancreas and in the 3 ovarian cases [8], it also exhibits features suggestive of an aggressive behavior, including cytologic atypia, high mitotic rate, elevated Ki-67, necrosis, vascular invasion, invasion of the ovarian capsule and involvement of the omentum and adjacent organs, and liver metastasis. Once more and similar to the 2 recent cases reported by Tang et al [8], our patient had a rapidly fatal outcome where she died of her disease within 8 months after the initial diagnosis.

The major differential diagnoses in this case are sex-cord stromal tumors such as granulosa, Sertoli-Leydig, and steroid cell tumors, not otherwise specified. Sex-cord stromal tumors are usually positive for α-inhibin and calretinin, which were negative in our case. Besides, the pseudopapillary pattern has never been described as a pattern in those tumors. Yet, another differential diagnosis will be neuroendocrine tumors of the ovary, but all neuroendocrine markers were negative in our case. Another differential diagnosis was poorly differentiated or high-grade surface epithelial tumor of the ovary. However, the lack of severe atypia and pleomorphism, the uniformity of the nuclei, and the negativity for epithelial membrane antigen (EMA) exclude the diagnosis of high-grade surface epithelial tumor. Very unlikely diagnosis was malignant struma ovarii, which is excluded based on the thyroglobulin immunostain by tumor cells. A metastatic tumor from the thyroid such as medullary carcinoma is a remote possibility, but the negativity of tumor cells for calcitonin made this diagnosis most unlikely. In addition, the thyroid gland was explored, and it was negative for malignancy. In summary, the diagnosis of primary SPTs of the ovary was made based on (*a*) the characteristic morphological features; (*b*) positivity for β-catenin; (*c*) negativity for α-inhibin, calretinin, thyroglobulin, calcitonin, EMA, synaptophysin, and chromogranin; (*d*) electron microscopy findings, although they are not specific; (*e*) complete computed tomography scans to explore a metastatic disease from pancreas, adrenal gland, and others were normal; and (*f*) exploration of the thyroid gland for malignancy was negative.

The origin of SPTs has not been clarified. Despite the discussion of its origin in numerous reports, the line of cellular differentiation still remains uncertain. Many investigators speculated that SPTs could originate from pleuripotent embryonic cells of the pancreas with

multipotential differentiation. However, others suggested an extrapancreatic origin, such as from the genital ridge–related cells, that were incorporated into the pancreas during organogenesis [10]. This last hypothesis was still controversial mainly because of lack of ovarian tumors with strong similarity to SPTs of the pancreas until now. The 3 cases of ovarian SPTs reported by Deshpande et al [9] as well as our case could be circumstantial, but it might as well be a validation to the hypothesis that SPTs might derive from genital ridge–related cells, which were attached to the pancreatic tissue during early embryogenesis.

Supplementary materials related to this article can be found online at http://dx.doi.org/10.1016/j.anndiagpath.2011.04.007.

References

[1] Klimstra DS, Wenig BM, Heffess CS. Solid-pseudopapillary tumor of the pancreas: a typically cystic carcinoma of low malignant potential. Semin Diagn Pathol 2000;17:66-80.

[2] Chakhachiro ZI, Zaatari G. Solid-pseudopapillary neoplasm. A pancreatic enigma. Arch Pathol Lab Med 2009;133:1989-93.

[3] Adamthwaite JA, Verbeke CS, Stringer MD, Guillou PJ, Menon KV. Solid pseudopapillary tumour of the pancreas: diverse presentation, outcome and histology. JOP 2006;7:635-42.

[4] Santini D, Poli F, Lega S. Solid-papillary tumors of the pancreas: histopathology. JOP 2006;7:131-6.

[5] Abraham SC, Klimstra DS, Wilentz RE, et al. Solid-pseudopapillary tumors of the pancreas are genetically distinct from pancreatic ductal adenocarcinomas and almost always harbor beta-catenin mutations. Am J Pathol 2002;160:1361-9.

[6] Miettinen M, Partanen S, Fraki O, Kivilaasko E. Papillary cystic tumor of the pancreas: an analysis of cellular differentiation by electron microscopy and immunohistochemistry. Am J Surg Pathol 1987;11:855-65.

[7] Kim CW, Han DJ, Kim J, Kim YH, Park JB, Kim SC. Solid pseudopapillary tumor of the pancreas: can malignancy be predicted? Surgery 2011;5 [Epud ahead of print].

[8] Tang LH, Aydin H, Brennan MF, Klimstra DS. Clinically aggressive solid pseudopapillary tumors of the pancreas: a report of two cases with components of undifferentiated carcinoma and a comparative clinicopathologic analysis of 34 conventional cases. Am J Surg Pathol 2005;29:512-9.

[9] Deshpande V, Oliva E, Young RH. Solid pseudopapillary neoplasm of the ovary: a report of 3 primary ovarian tumors resembling those of the pancreas. Am J Surg Pathol 2010;34:1514-20.

[10] Kosmahl M, Seada LS, Janig U, Harms D, Kloppel G. Solid-pseudopapillary tumor of the pancreas: its origin revisited. Virchows Arch 2000;436:473-80.