Case Report
Overlap of microcystic stromal tumor and primary solid pseudopapillary neoplasm of the ovary

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Abstract: Ovarian microcystic stromal tumors (MCSTs) and ovarian primary solid pseudopapillary neoplasms (SPNs) are rare ovarian tumors, and recently classified as distinctive variant in the stromal category and miscellaneous tumors respectively in 2009 and 2010. Ever since, there were less then 10 MCSTs and ovarian primary SPNs reported in English literatures. Both of them had something in common, including microscopical morphology, immunohistochemical phenotype, even for the tumorigenesis pathway. Hence, is there any possible linkage between them? In addition to a thorough case description, the literature concerning this entity is reviewed and discussed.

Keywords: Ovarian microcystic stromal tumor, primary solid pseudopapillary neoplasm of the ovary, the morphologic and immunohistochemica display

Introduction
Microcystic stromal tumors (MCSTs) of ovary is a rare ovarian tumor, recently classified as a distinctive variant in the stromal category described by Irving and Young in 2009 [1]. They reviewed 16 ovarian neoplasms, and designate it microcystic stromal tumor for its most striking microcystic pattern. Ever since, there were less than 10 cases reported in English literatures.

Ovarian solid pseudopapillary neoplasms (SPNs) was first reported in 2010 [2], with the morphologic and immunohistochemical similarity to pancreatic counterpart. Hitherto, there are only 6 reported cases located in ovary. Both of them had something in common, including microscopical morphology, immunohistochemical appearance, even for the tumorigenesis pathway. For instance, they had the monotonous alike tumor cells, immunohistochemical positive for CD10, VIM and β-catenin, even for the point mutation in exon 3 of the β-catenin (CTNNB1) gene. Consequently, is there any possible link between them?

We recently encountered an unusual case of ovarian microcystic stromal tumor, which had distinct immunohistochemical appearance, different from before, while overlap with ovarian SPNs. Herein, we present the distinct histological and immunohistochemical display of MCSTs in detail, especially for differential diagnosis and review the literature.

Case report
Clinical information
A premenopausal 47-years-old woman, gravida 2, para 2 (G2P2), was found to have a large left-pelvic mass for more than 3 months and consulted to our hospital. Physical examination revealed a left pelvic mass of 6 cm. Ultrasound and computed tomography scan showed a mixed cystic and solid mass, 6 cm in greatest dimension, in the left-adnexa. During the operation, the mass was found to rupture, and the content flowed out. A small amount of ascites (less than 100 ml) was found. The uterus, right ovary and the other intra-abdominal organs were unremarkable. Levels of various tumor markers such as carcinoembryonic antigen (CEA), carbohydrate antigen (CA199), squamous cell carcinoma (SCC) and CA125 were all in the normal ranges. And the gonadal hormone was within normal limits. The patient underwent a left adnexectomy. The patient has not had recurrence of tumor over a follow-up of a year and a half.
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Pathology findings and Immunohistochemistry

Macroscopically, the left ovarian surface was smooth and nodular, measured 6.0 cm in the greatest dimension, with yellow-tan solid-spongy areas on the cutting surfaces. The contralateral ovary was grossly normal.

Microscopically, the mass was well demarcated contoured from the background ovarian parenchyma (Figure 1A). And a thin ovarian parenchyma was observed on the outer rim of the tumor with some follicles. The most striking appearance on the low-power field was the prominent solid cellular areas inserted by thick fibrous hyaline stroma (B). The micro and macro cysts filled with eosinophilic or myxoid content (C). Some of tumor cells had the eosinophilic cytoplasm mimicked luteinized cells (D). Intracytoplasmic vacuoles were observed, and the nucleus located by side (E). Bizarre and multiple nucleus tumor cells were also present focally (F). (A, B) H&E, 40 ×; (C) H&E, 100 ×; (D-F) H&E, 400 ×.

Figure 1. Well demarcated contoured mass with the background ovarian parenchyma (A). The prominent solid cellular areas inserted by thick fibrous hyaline stroma (B). The micro and macro cysts filled with eosinophilic or myxoid content (C). Some of tumor cells had the eosinophilic cytoplasm mimicked luteinized cells (D). Intracytoplasmic vacuoles were observed, and the nucleus located by side (E). Bizarre and multiple nucleus tumor cells were also present focally (F). (A, B) H&E, 40 ×; (C) H&E, 100 ×; (D-F) H&E, 400 ×.
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fibrous stroma, sometimes with conspicuous hyaline (Figure 1B). In most solid areas, there was myxoid changed stroma, and variable-sized cystic patterns were also outstanding. The micro and macro cysts filled with eosinophilic or myxoid content (Figure 1C). The individual tumor cells had round-to-ovoid and sometimes short-spindled nuclei with very fine chromatin. Most of tumor cells had moderate amount of cytoplasm and inconspicuous nucleoli, some of which had the eosinophilic cytoplasm mimicked luteinized cells (Figure 1D). Intracytoplasmic vacuoles were observed, and the nucleus located by side (Figure 1E). Bizarre and multiple nucleus tumor cells were also present focally (< 1%) (Figure 1F). Mitoses were

Figure 2. CD10 (A) and CD56 (F) displayed strong cytomembrane positive, diffuse and focally respectively, while diffuse and strong nuclear positive for β-catenin, WT-1 and PR (B-D). There was patchy cytoplasm positive for cytokeratin (AE1/AE3) (E). (A, E, F) IHC, 400 ×; (B-D) IHC, 40 ×.
hardly detected and necrosis was not prominent in all sections.

Immunohistochemical staining was also performed, displaying diffuse and strong positive in cytoplasm for vimentin and cytomembrane for CD10 respectively (Figure 2A), while diffuse and strong nuclear positive for β-catenin, WT-1 and PR (Figure 2B-D). There was patchy cytoplasm positive for cytokeratin (AE1/AE3) (Figure 2E). Neuroendocrine markers (synaptophysin and chromogranin A) were negative, except for CD56 patchy cytomembrane positive (Figure 2F). The tumor cells were completely negative for sex cord markers (α-inhibin and calretinin), and other negative markers included SMA, DES, CD99, SALL4, TTF-1, EMA, P53, CK7 and CK20. Ki67 index was approximately 5%.

Discussion

Microcystic stromal tumor (MCSTs) of ovary is a rare subtype of ovarian tumor recently denominated and classified as a stromal tumor by Irving and Young in 2009 [1]. As for nomenclature and classification, although the lack of hormone production and negative staining for α-inhibin and calretinin argue against the stromal origin, the tumor mostly resembled the solid regions of thecoma and the stromal catalog was recommended the most rationally. After well sampled, the tumor should exhibit the following features: solid and microcystic pattern with intervening or hyalinized fibrous stroma; absent any of morphologic features enabling other specific diagnosis in the sex cord-stromal category; absent of epithelial elements; absent of teratomatous or other germ cell elements [1]. Our case exhibited features similar to those reported. The unique and impressive histology and immunophenotype in this case prompt us to figure out its pathogenesis.

In this case, the variable solid areas separated by the fibrous stroma with mucinous degeneration were the prominent growth pattern, some of which confluence with each other. Then, some of areas displayed varied-sized cysts, containing mucous-like or eosinophil substance. On the basis of these observations, we prefer to the cysts coming from the tumor cells degenerated.

In general, the nuclear of MCSTs are round to ovoid. Nucleoli are not prominent, and nuclear polymorphism is minimal. Some tumor cells nucleus located by side for the intracellular mucous-like substance. Degenerated multinucleus cells dispersed in mucinous stroma and the mitosis was not found. Although foci of bizarre nuclei were reported in more than half of the English literature, there was rare mitosis and necrosis [1].

Immunophenotype results of this case were interesting. Consist with the previous reports, this case displayed diffuse and strong positive in cytoplasm for VIM and cytomembrane for CD10 respectively, and diffuse and strong nuclear positive for β-catenin and WT-1. And there was patchily cytoplasm positive (20%) for cytokeratin (AE1/AE3), in accordance with the previous literatures [1, 3]. Hence, the tumor cells were thought to be pluripotent. Although the tumor was cataloged to the stromal tumor in 2014 WHO [4], the lack of hormone production and negative staining for α-inhibin and calretinin (sex cord markers), and cytoplasm positive for cytokeratin (AE1/AE3) should not be neglected. Being placed in unclassifiable or uncertain origin category should be more advisable. As for the origin, the relation to hormone sensitive tissue was also suspected, or was there heterologously expression of being pluripotent?

Ovarian primary SPNs was really rare and there are only 6 reported cases. Wherever SPN origin from, they had the same morphology and immunophenotype. As is known to all, nearly all case (90-100)% of SPNs had the β-catenin nuclear positive and the point mutation in exon 3 of the β-catenin (CTNNB1) gene, involved codon 32, 33, 34, and 37 [5, 6]. According to the limited DNA sequencing analysis, the point mutation in exon 3 of β-catenin (CTNNB1) gene of MCSTs involved the codon 33 [3, 7, 8]. The mutation point of CTNNB1 differed between SPNs and MCSTs. In our case, the β-catenin nuclear positive verily verified the mutation of β-catenin (CTNNB1) gene, although gene sequencing and mutation analysis was not performed in this study. Therefore, both of them lost the phosphorylation site in the β-catenin protein and lead to the dyregulation of the Wnt/β-catenin pathway.

Although previous reports did not display PR and CD56 positive in MCSTs [3], our case displayed PR diffuse and strong nuclear positive and CD56 patchily moderate cytomembrane positive. It was well known that nearly all pan
creatic SPNs have been reported to be positive for PR and CD56 [9]. Dacha et al. observed a significant difference in the immunophenotypes of MCSTs and SPNs, with MCSTs displaying a WT1+/PR+/CD56+ pattern and SPNs a WT1+/PR+/CD56+ pattern [3]. However, from our results, whether PR and CD56 expressed or not could not be differentiated with each other.

It was well known there was no counterpart of SPN in normal pancreas tissue. According to literature, the ovary is the most common extra-pancreatic site for the occurrence of SPN in the absence of ectopia pancreatic tissue [10]. Therefore, as for the origin of pancreatic SPNs, one suspected explanation is via embryonic transfer during embryonic development. SPNs are postulated to arise from genital ridge/ovarian anlage-related cells, which were attached to the pancreatic tissue during early embryogenesis [9]. In other words, during 5 to 8 weeks of embryonic development, the right gonad is positioned dorsolaterally to the liver and the left gonad dorsolaterally to the pancreas and spleen, allowing for potential transfer of ovarian gonads cells to pancreas tissue and vice versa [11]. Hence, both of the two tumors had so many features in common, including resembling monomorphous tumor cell, immunohistochemical display, tumorigenesis molecular events, even the potential histological origin, which offered a possible linkage between them. Of course, there are some significant differences between MCSTs and SPNs. A pseudopapillary structure is characteristic of SPNs, whereas this structure is absent in MCSTs. Between them a further examines for similarities and differences need in the future on the basis of a larger number of cases.

According to the stated descriptions, MCSTs had unique histological and immunohistochemical features, and the differential diagnoses were not difficult. Of course, various ovarian tumors, such as thecoma, granulosa cell tumor (AGCT and JGCT), sclerosing stromal tumor, and yolk sac tumor and so on, need to be ruled out in some situations. However, different tumor had distinctive histological exhibition, even immunohistochemical features. The differential diagnoses were not in trouble.

Our case has not recurrence of tumor over a follow-up of a year and a half and the overall clinical course of MCSTs appears to be not aggressive, although the number of reported cases is limited so far.

Disclosure of conflict of interest

None.

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References

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