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Malignant bilateral ovarian steroid cell tumor without androgenic manifestation: an unusual finding

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ABSTRACT

Steroid cell tumor is a rarest ovarian neoplasm, classified as a pure stromal tumor and mostly is unilateral. Even though this tumor can exhibit malignant behavior but the morphology of cells showed benign characteristics which can become a diagnosis pitfall especially in the frozen section. Moreover patient without any hormonal imbalance or virilizing signs could make the diagnosis process more difficult. Here we reported a case bilateral steroid cell tumor of the ovary in a 42 y.o. unmarried woman without any virilization or hirsutism symptoms. Abdominal ultrasonography and computed tomography (CT) scan revealed a right ovarian solid tumor accompanied by ascites and right pleural effusion. There was significantly increased of Ca 125 level (1138 U/mL) and normal level of testosterone (0.10 ng/mL). Frozen section was done from the right ovarium mass and ascites fluid, the result was benign. From the total abdominal hysterectomy and bilateral salpingo-oophorectomy tissues, histological picture showed diffuse and nests tumor separated by thin fibrous connective tissue with small round centered nuclei, mild atypia, and abundant pale cytoplasm. Large area of necrosis was found especially in the right ovarian tumor, tumor implant to the right fallopian tube and in the uterine serous layer. Periodic acid-Schiff (PAS) stain was negative in more than half tumor cells population. Immunostaining for Melan-A and Calretinin were focally positive, with Ki-67 labeling index ± 5%, and negative for cytokeratin 7 (CK7), cytokeratin 20 (CK20) and smooth muscle actin (SMA). Based on the tumor size, necrosis area, tumor implantation, and immunohistochemistry profiles, we conclude that were malignant steroid cell tumor. Currently, the patient is undergoing postoperative recovery and planned for platinum-based chemotherapy. A careful correlation between clinical and radiological findings, as well as histopathological results, is always essential, as is amply demonstrated by this particular case.

ABSTRAK

Tumor sel steroid adalah sebuah neoplasma ovarium yang paling jarang yang diklasifikasikan sebagai tumor stroma murni dan sebagian besar bersifat unilateral. Meskipun tumor ini dapat menunjukkan sifat ganas tetapi morfologi sel menunjukkan sifat jinak sehingga dapat terjadi kesalahan diagnosis terutama dari potongan beku. Selain itu pada pasien tanpa gangguan ketidakseimbangan hormon atau tanda-tanda virilizing membuat diagnosis lebih sulit. Di sini dilaporkan kasus tumor sel steroid bilateral ovarium pada wanita belum menikah berusia 42 tahun tanpa gejala virilisasi atau hirsutisme. Ultrasonografi abdomen dan *computed tomography scan* (CT scan) mengungkapkan tumor padat ovarium kanan disertai asites dan efusi pleura kanan. Ada peningkatan nyata kadar Ca125 (1138 U/mL) dan kadar testosteron normal (0,10 ng/mL). Pemeriksaan terhadap pemotongan bekuan massa ovarium kanan dengan cairan asites menunjukkan tumor jinak. Dari histerektomi total abdomen dan jaringan salpingo-ooforektomi bilateral, gambaran histologis menunjukkan tumor difus dan bersarang dipisahkan oleh jaringan ikat fibrosa tipis dengan inti bulat kecil di tengah, atypia ringan, dan sitoplasma pucat berlimpah. Area nekrosis yang luas ditemukan terutama pada tumor ovarium kanan, tumor yang berimplantasi pada tuba falopi kanan

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dan pada lapisan serosa uteri. Pewarnaan periodik asam-Schiff (PAS) negatif pada lebih dari setengah populasi sel tumor. Imunostaining untuk melan-A dan calretinin secara fokal positif, dengan indeks pelabelan Ki-67 ± 5%, dan negatif untuk sitokeratin 7 (CK7), sitokeratin 20 (CK20) dan aktin otot polos (SMA). Berdasarkan ukuran tumor, area nekrosis, implantasi tumor, dan profil imunohistokimia dapat disimpulkan bahwa tumor sel steroid tersebut ganas. Saat ini, pasien sedang menjalani pemulihan pasca operasi dan direncanakan untuk kemoterapi berbasis platinum. Korelasi yang cermat antara temuan klinis dan radiologis, serta hasil histopatologis, selalu penting, seperti yang banyak ditunjukkan oleh kasus khusus ini.

INTRODUCTION

Steroid cell tumor is one of the pure stromal tumors of the ovary. The incidence rate is only 0.1% from all ovarian neoplasm which makes it very rare. This tumor is usually benign, unilateral and more than half cases have androgenic symptoms. Only one-third of cases that have malignant behavior and about 10-15% the cases without clinical signs or symptoms of increased hormone levels or asymptomatic.[1] It is widely known that even though the tumor histopathologically was benign. It can not exclude the possibility of malignancy which can be a pitfall especially in frozen section examination.[2]

The following report focuses on a case of malignant bilateral steroid cell tumor of the ovaries diagnosed in a 42 y.o. unmarried woman without any overt androgenic manifestations. There were discrepancies between clinicopathological findings and histomorphological features in the frozen section examination. This was a very rare case, also a diagnostic challenge for pathologists and as far as we know, the first case report from Indonesia.

CASE

Clinical history

A 42 y.o. unmarried woman referred to the Obstetrics and Gynecology Department of Dr. Sardjito General Hospital with chief complaints of abdominal enlargement for 2 mo with abdominal distention. There were no virilization nor hirsutism symptoms. Also no history of vaginal bleeding nor vaginal discharge. In physical examination, there was an abdominal distention due to a fixed huge solid abdominal mass. The upper margin of abdominal mass was 3 fingers above the umbilical, right margin was anterior axillary line, and left margin was midclavicular line. The lower margin of the mass was palpated in rectal examination while uterine was difficult to access. There was also a decreased vesicular sound in the right lung, a sign of pleural effusion. Transabdominal ultrasound examination and abdominal CT scan revealed a right ovarian solid tumor sized 20,1x11.7x16.8 cm^3 accompanied with ascites (FIGURE 1). Laboratory test showed significantly increased of Ca 125 level (1138 U/mL) and normal level of testosterone (0.10 ng/mL). The patient then underewent an exploratory laparotomy with frozen section for the right ovarian mass and ascites fluid, followed by total abdominal hysterectomy, bilateral salpingo-oophorectomy, and sampling of pelvic lymph nodes. Currently the patient is undergoing postoperative recovery and planned for platinum-based chemotherapy.

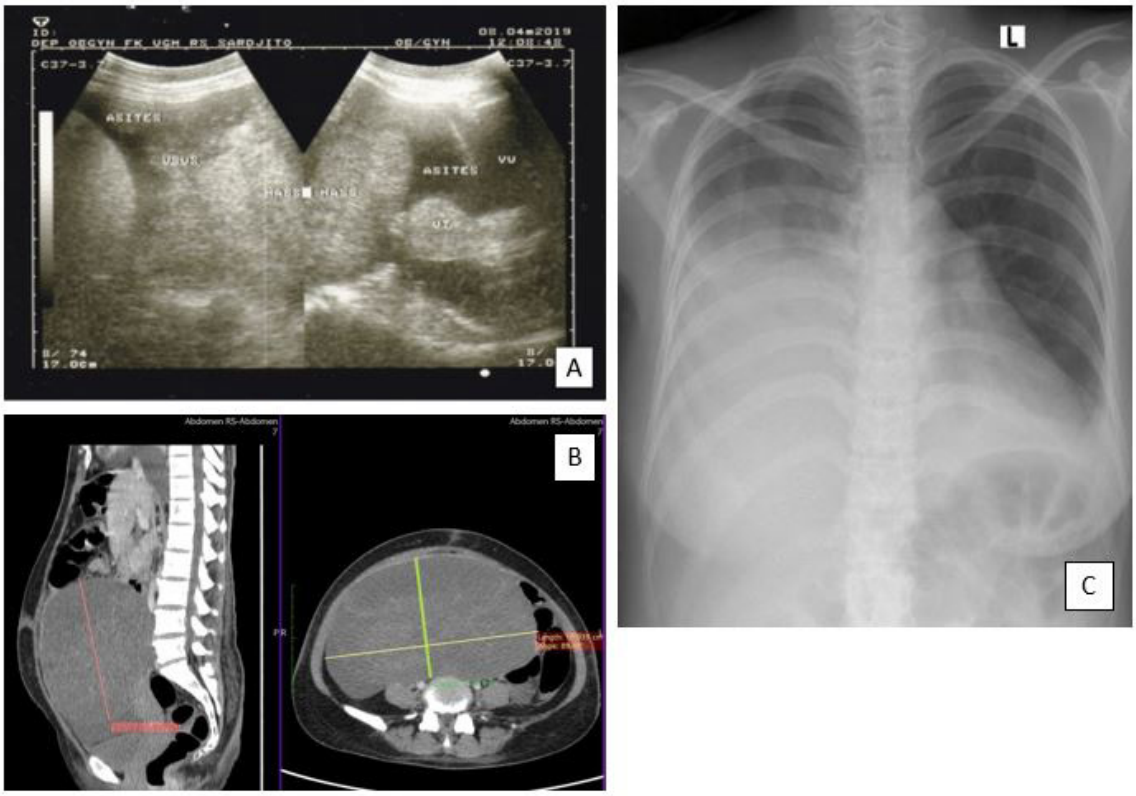

FIGURE 1. Radiological examination (A). Transabdominal ultrasound and, (B). Abdominal CT scan examination revealed a right ovarian solid tumor sized 20x11x15 cm^3 accompanied with ascites. (C). Chest X-ray showed a right pleural effusion.

Pathological findings

Frozen section of the right ovarian solid tumor showed a mass sized 22 x 17 x 8 cm^3, with firm solid cut surface and tan yellowish colored, some with black colored parts (FIGURE 2). The microscopic pictures showed tumor cells arranged in diffuse nests separated by thin fibrous connective tissue with a large area of necrosis. Cells were polygonal-shaped with abundant pale or clear cytoplasm. Small round centered nuclei, some are eccentric, with mild atypia (FIGURE 3). From the ascites fluid sample, microscopically showed hypocellular with 2 – 3 clusters of relatively monomorphic cells with pale cytoplasm and bland round to oval shaped nuclei with mild atypia degree (FIGURE 4). We concluded that the tumor and the ascites fluid were benign. But because of the clinical and laboratory findings led to malignancy, the patient underwent a total abdominal hysterectomy, bilateral salpingo-oophorectomy, and sampling of pelvic lymph nodes for prevention and clinical staging.

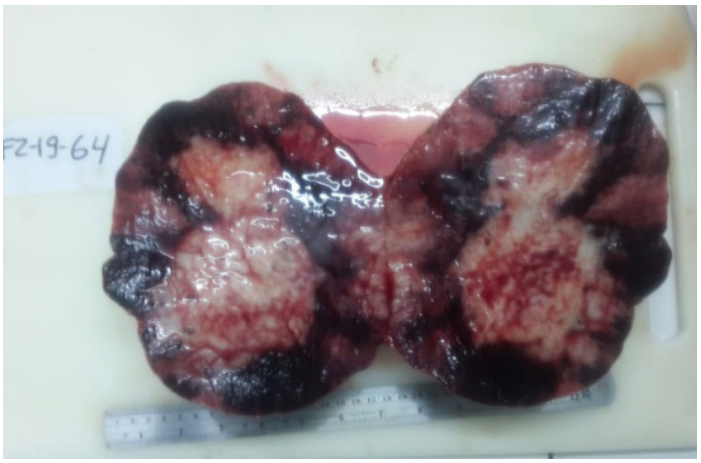

FIGURE 2. Gross appearance of the right ovarian solid tumor in frozen section examination showed solid tumor with tan yellow colored with some black patch

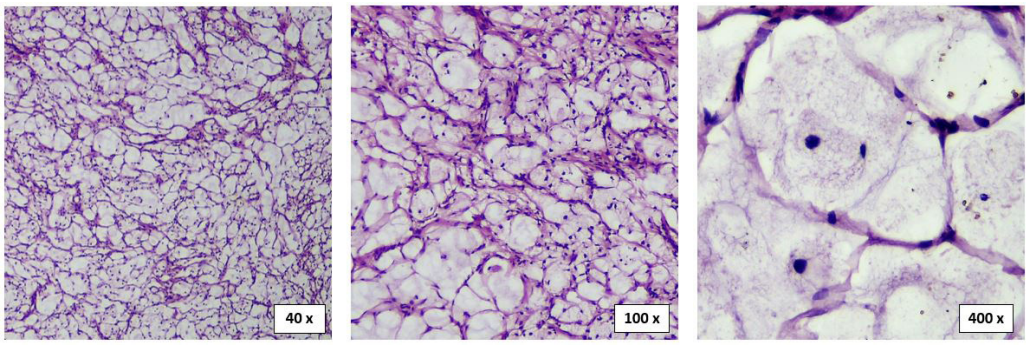

FIGURE 3. Microscopic appearance of the right ovarian solid tumor in frozen section examination: tumor cells arranged in diffuse pattern also in nests with scant fibrous stroma. Cells were polygonal shaped with abundant pale clear cytoplasm. Round small nuclei with mild atypia.

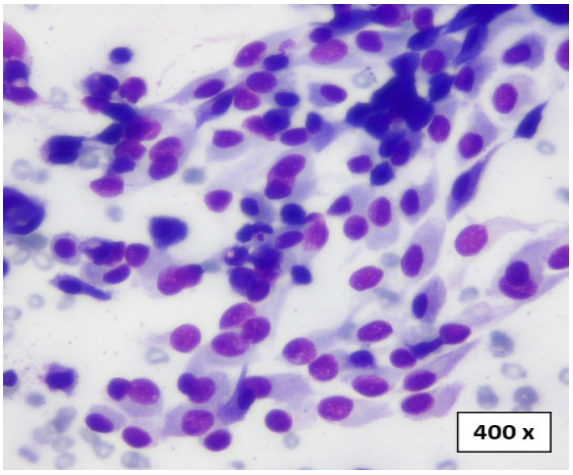

FIGURE 4. Microscopic appearance of the ascites fluid, hypocellular smear with few cluster of mildly atypia cells with pale cytoplasm and bland nuclei.

In specimens of total abdominal hysterectomy, bilateral salpingo-oophorectomy, and sampling of pelvic lymph nodes there were similar right ovarian tumor in the right fallopian tube (FIGURE. 6A), left ovary (FIGURE. 6B). Tumor also implanted in uterine serous layer (FIGURE. 6C). Based on the tumor behavior , we suspected a malignant tendency. Our differential diagnosis was malignant steroid cell tumor (lipid cell tumor), malignant signet ring stromal tumor, and metastasis of signet ring cell adenocarcinoma from gastrointestinal site (Krukenberg tumor). To established the main diagnosis and excluded the differential diagnosis, histochemical staining of PAS and immunostaining of CK7, CK20, Calretinin, Melan-A, SMA and Ki-67 were performed. The results showed that PAS staining was negative in more than half tumor cells population. Immunostaining for Melan-A and Calretinin were focally positive, with Ki-67 labelling index ± 5%, and negative for CK7, CK20 and SMA (FIGURE 7). Clinical, histopathological, histochemical and immunohistochemical findings confirmed the diagnosis of malignant bilateral ovarian steroid cell tumor.

The pleural effusion fluid was a highly turbid fluid approximately 42 mL, also submitted for cytological evaluation. The result showed hypocellular smear with evenly distributed amorphic mass. There were no malignant cells.

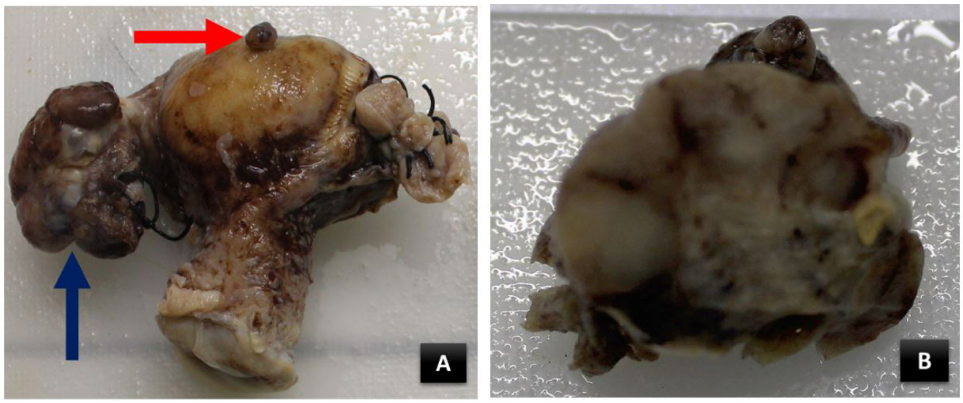

FIGURE 5. Gross appearance of the total abdominal hysterectomy and bilateral salpingo-oophorectomy: (A) Left ovarian mass (blue arrow) and implantation in the uterine serosal layer (red arrow), (B). Cut surface of the left ovarian mass.

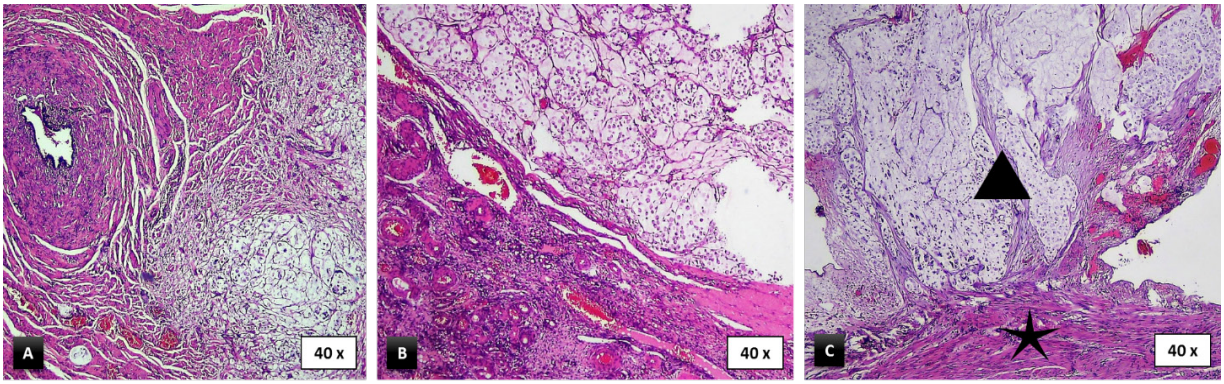

FIGURE 6. Microscopic apperance: (A). Tumor spread to the right fallopian tube, (B). Similar tumor in the left ovary, (C). Implantation of the tumor to the uterine serous layer (★: uterine serous layer; ▲: tumor's implantation).

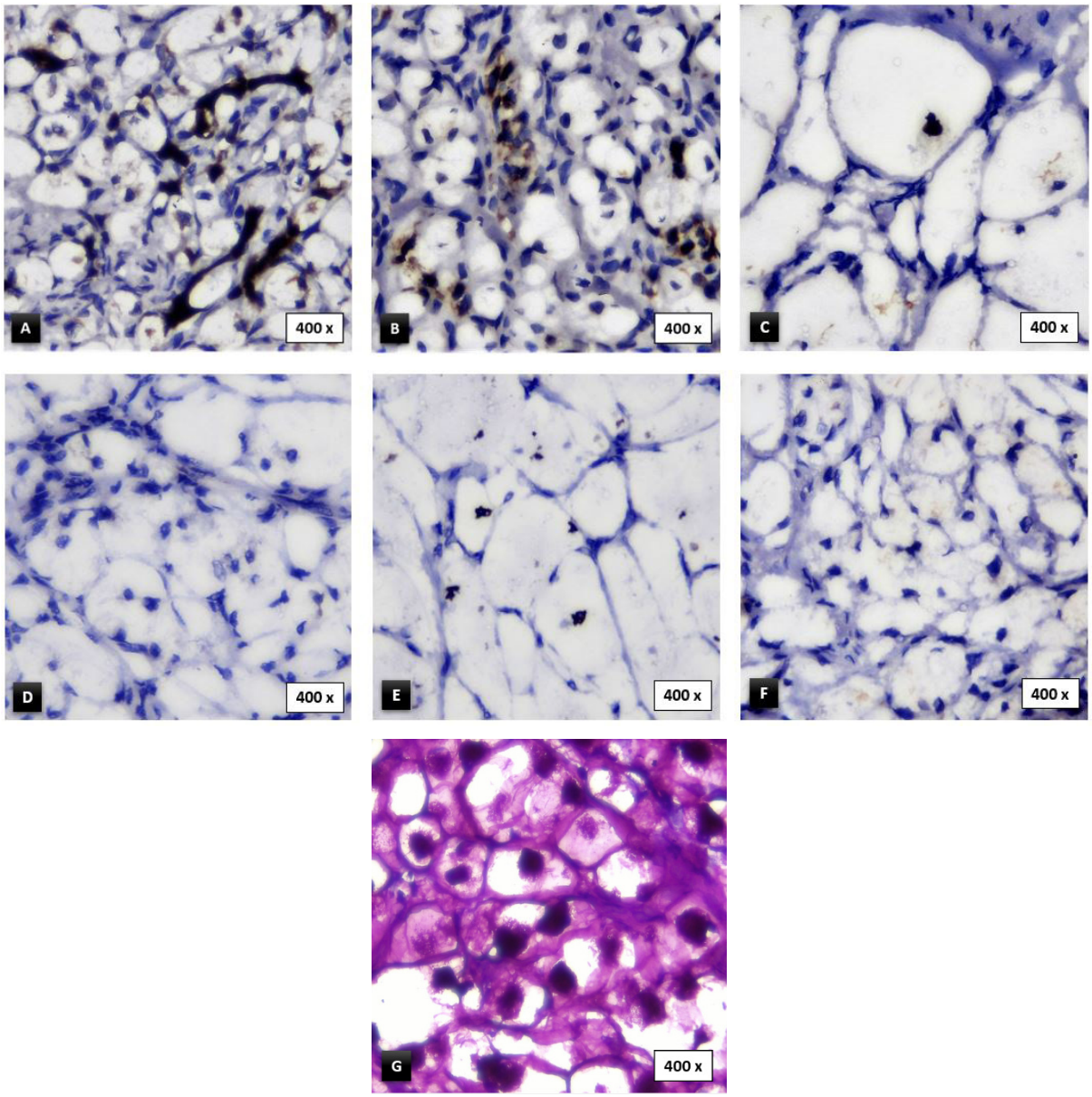

FIGURE 7. Immunostaining of (A) Calretinin, showed focal positivity in nuclei and cytoplasm; (B) Melan-A, showed focal positivity in cytoplasm; (C) Ki-67, low proliferation index; (D) Negative for CK7,(E) CK20 and (F) SMA. Histochemical staining of PAS (G) showed negativity in more than half tumor cells population

DISCUSSION

Ovarian steroid cell tumors composed of cells that resemble steroid hormone-secreting cells (Leydig/lutein/adrenal cortical rest cells) with lack of Reinke crystals, which was the origin of their entity. It was thought to arise from ovarian stromal cells. These tumors occur in a wide age range from premenarchial girls to postmenopausal women, with mean age of 43 years old. This mean age was very similar to our patients' age which was 42 years old. Steroid cell tumors are usually unilateral, with mean diameter is 8.4 cm. The cut surface usually solid, with yellow-orange, brown, red, or black colored, and accompanied by areas of hemorrhage.[1,3]

According to the literature, combined clinical symptoms, microscopic features, and immunohistochemical results

are important to diagnose a steroid cell tumor.[2,6] About one-third of cases were malignant and about 20% of them metastasis to other organs even when the histopathological findings were benign. Because of this reason, it is important to be able to recognize whether the tumor was malignant or not and performed careful follow-up. Hayes and Scully in 1987 identified 5 certain histopathological characteristics that could predict malignant behavior of ovarian steroid cell tumor which are: two or more mitotic figures per 10 high power fields (92% malignant), areas of necrosis (86% malignant), tumor's diameter 7 cm or greater (78% malignant), areas of hemorrhage (77% malignant) and grade 2-3 of nuclear atypia (64% malignant).[1,4-6]

It was difficult to determine the type and behavior of the tumor. Our case also showed benign morphology in the frozen section but evaluation of the total abdominal hysterectomy, bilateral salpingo-oophorectomy, and sampling of pelvic lymph nodes showed tumor implantation to the right fallopian tube and uterine serous layer. Tumor largest diameter was 22 cm with large areas of necrosis also highly indicate the malignant behavior of the tumor.

Because steroid cell tumor is considered as a pure stromal ovarian neoplasm, it will be positive for sex cord-stromal immunohistochemical markers such as calretinin, inhibin, and steroidogenic factor-1. In general, calretinin and inhibin were considered as a sensitive with a percentage of positivity of approximately 100% but less specific marker for ovarian sex-cord stromal tumors and useful to distinguish sex-cord stromal from non-sex-cord stromal tumors. Many studies also report that steroid cell tumor is positive for melan-A. The positivity rate of melan-A in a study by Jones et al. was 86%.[1,4,7] In our case, calretinin and melan-A were both focally positive.

Our case showed negative expression of CK7 and CK 20, these results excluded the diagnosis of metastasis of signet ring cell adenocarcinoma from gastrointestinal site (Krukenberg tumor). In a few literature, other epithelial markers such as AE1/AE3 and CAM 5.2 were reported positive in 30-40% steroid cell tumor. Nevertheless, the staining pattern was predominantly weak and focal.[7] Negative expression of SMA also excluded ovarian signet-ring stromal cell tumor. This result was in line with Jones *et al.*[7] study which stated that most of the steroid cell tumor was negative for muscle-specific actin and SMA. Our case showed low proliferation index (± 5%) but there was more than 2 mitoses per 10 high power fields. PAS staining in more than half tumor cells population was negative due to their lipid-rich cytoplasm.

Before diagnosing a steroid cell tumor, signs of metastasis or other primary mass in other organs need to be evaluated using radiographical imaging because a majority of steroid cell tumors have a more favorable prognosis than the metastatic or malignant primary tumors of the ovary with a similar histomorphology.[7] There were no signs of other primary tumor nor distant metastasis of steroid cell tumor in our case.

Until now, there are no specific tumor markers or imaging techniques for preoperative diagnosis of steroid cell tumors. Ovarian tumor markers such as Ca 125 and α-fetoprotein were generally normal. A significant elevation of these tumor markers also does not indicate malignant characteristics.[3] In our case, the level of Ca 125 level was 1138 U/mL but soon after the surgery it decreased to 90.38 U/mL.

Our case also without androgenic manifestations such as virilization and hirsutism, this was an unusual finding. The level of testosterone in our patient was normal (0.10 ng/mL). About 50% of patients have androgenic symptoms

because the tumor-secreted steroids, mostly testosterone, 10% have estrogenic symptoms, some can show Cushing syndrome or progestational changes, and a minority of 10-15% of patients have no symptoms of increased steroid hormone production.[3]

Because this tumor can be malignant and has aggressive behavior, it should be staged and aggressively cytoreduced. In patients who desire future fertility, conservative surgery with unilateral oophorectomy and proper staging should be performed. The management would be different for women who have completed childbearing, which are total abdominal hysterectomy with bilateral salpingo-oophorectomy with complete surgical staging. Adjuvant chemotherapy were given based on the tumor's histopathological appearance and on its surgical stage. Until now there are no well defined chemotherapy guidelines for steroid cell tumor. Steroid cell tumors with signs of malignancy histologically based on Hayes and Scully's criterias, or were at an advanced stage should be treated with additional postoperative platinum-based chemotherapy.[8,9] In our case, the patient was an unmarried woman but due to signs of malignant behaviour of the tumor and the tumor already affected both of the ovaries, total abdominal hysterectomy with bilateral salpingo-oophorectomy with complete surgical staging were performed with the consent of the patient. After the post-operative surgery, clinician planned to perform postoperative platinum-based chemotherapy.

CONCLUSION

Ovarian steroid cell tumor especially the malignant one is a rare case of all ovarian tumors. Not to mention that only 10-15% of these patients have no symptoms of increased steroid hormone production, making the preoperative definitive diagnosis for this tumor was difficult. The benign appearance of this tumor microscopically but with malignant behaviour are also challenging in this case. A careful correlation between clinical findings, radiological findings, and histopathology is always essential, as is amply demonstrated by this particular case. Moreover, the definitive diagnosis whether the tumor was steroid cell tumor, benign or malignant would very much affect the standar management for the patient. The necessity of a regular follow up must be stressed upon, with the aim of detecting a possible recurrence or evidence of distant metastasis.

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