

Case Report

Unclassified mixed germ cell-sex cord-stromal tumor with multiple malignant cellular elements in a young woman: a case report and review of the literature

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Abstract: Unclassified mixed germ cell-sex cord-stromal tumor composed of germ cells and sex cord derivatives is a rare neoplasm. Approximately 10% of such tumors have malignant germ cell components. We report the case of a 28 year-old female with a right adnexal mass measuring 8 cm in greatest dimension, containing areas with both germ cell and sex cord components. The germ cell portion contained multiple growth patterns with a malignant appearance, while the sex cord element consisted mainly of annular tubules. Within the malignant germ cell elements was a dysgerminoma that accounted for approximately 75% of the tumor volume. Other malignant germ cell elements included yolk sac tumor, embryonal carcinoma, and choriocarcinoma, which comprised about 15% of the tumor volume. The annular tubule structures comprised about 10% of the total tumor volume. To our knowledge, this is the first case reported in the literature of an unclassified mixed germ cell-sex cord-stromal tumor associated with embryonal carcinoma components. The patient had a 46XX karyotype, regular menstrual periods, and no evidence of gross abnormalities in the contralateral ovary. The patient remained clinically well and disease-free 2 years after surgery. In addition to a thorough case description, the literature concerning this entity is reviewed and discussed.

Keywords: Mixed germ cell-sex cord-stromal tumor, mixed malignant germ cell tumor, sex cord tumors with annular tubules, gonadoblastoma

Introduction

Although the majority of gonadal tumors composed of germ cell and sex cord stromal derivatives are classified as gonadoblastomas, another distinct and rare gonadal neoplasm composed of the same cellular elements designated as unclassified mixed germ cell-sex cord-stromal tumor (UMGSCT) [1] has been described. This type of malignancy differs from gonadoblastoma in its macroscopic appearance, histological pattern, absence of regressive changes, and occurrence in normal gonads of phenotypically and genetically normal females [2]. Furthermore, approximately 10% of UMGSCT and 60% of gonadoblastomas have malignant germ cell components [1, 3]. In the majority of cases, UMGSCTs are diagnosed in female infants and children in the first decade of life, and the prognosis is favorable even if the patient undergoes only conservative surgery.

We report a case of a 28 year-old female with a normal 46XX karyotype, presenting with a right adnexal mass measuring 8 cm in diameter, containing both germ cell and sex cord components. The germ cell portion contained multiple malignant elements, including dysgerminoma, yolk sac tumor, embryonal carcinoma, and choriocarcinoma, while the sex cord element consisted mainly of annular tubules. This is the first case reported in the literature describing a UMGSCT that has an embryonal carcinoma element. The patient underwent right salpingo-oophorectomy, lymphadenectomy, pelvic-peritoneal biopsy. She has been receiving Chinese herb therapy since surgery and been without recurrence or metastasis for 2 years.

Case history

A 28-year-old female presented with a lower abdominal mass that had persisted for 6 months and had amenorrhea for 2 months. She

Unclassified mixed germ cell-sex cord-stromal tumor with multiple cellular elements

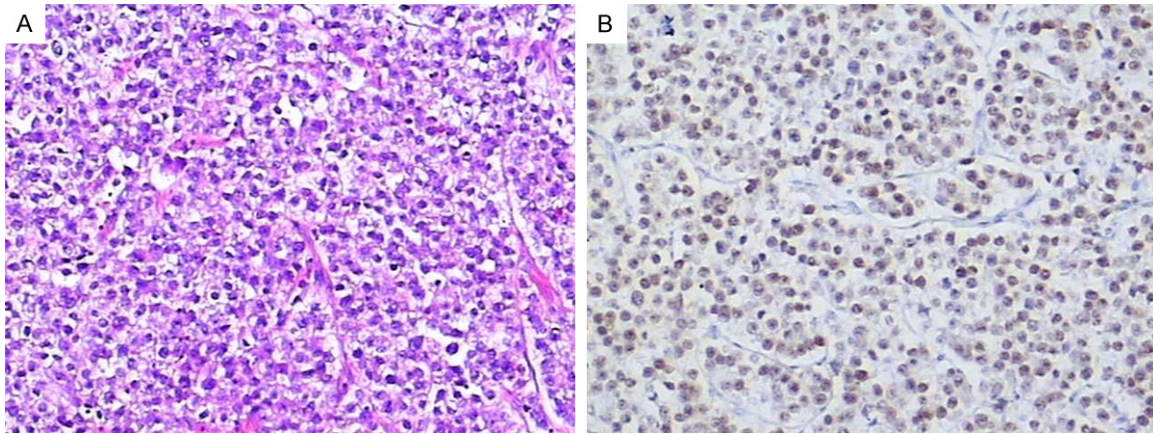


Figure 1. A. Dysgerminoma components consisted of large uniform cells with a central nucleus and pale, clear cytoplasm. B. Tumor cells stained diffusely positive for OCT4.

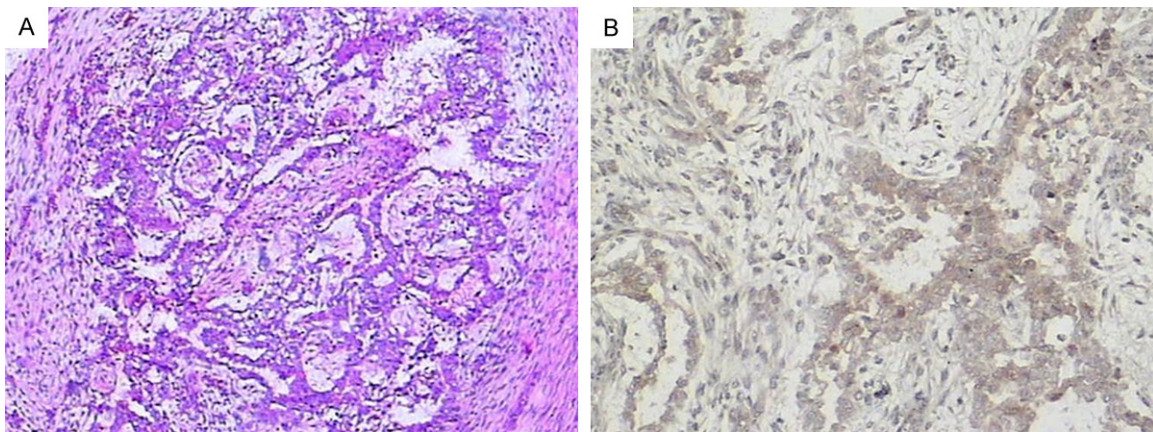


Figure 2. A. Yolk sac tumor components showed an alveolar-glandular pattern and reticular pattern within myxomatous matrix. B. Tumor cells stained positive for glypican-3 expression.

had regular menstrual periods prior to this time, and did not exhibit any abnormalities upon physical examination one year before. Ultrasound demonstrated a right pelvic mass measuring 118×47×60 mm with an anechoic area and a low-level echoic area noted. Serum HCG and AFP levels were elevated to 12,432 mIU/ml and 11.7 ng/ml respectively, which decreased to 121.8 mIU/ml and 7.28 ng/ml, respectively, 11 days postoperatively. Upon gynecological examination, the external genitalia and vagina were normally developed, and there was no evidence of virilization. At laparotomy, a solid cystic, irregular, dark red mass measuring 8×6×4 cm and a cyst measuring 5 cm in diameter were identified in the right ovary. Gross examination of the left ovary and bilateral fallopian tube was unremarkable. No ascites was noted, and abdominal exploration of liver, spleen, intes-

tine, omentum, and peritoneum showed no evidence of tumor. The patient underwent right salpingo-oophorectomy, lymphadenectomy, and pelvic-peritoneal biopsy. Post-operation examination showed that the patient's karyotype was 46XX.

Pathologic findings

Upon gross examination, an 8-cm solid mass with a lobulated surface was identified in the right ovary. The cut surface was solid with several cystic spaces less than 1 cm in diameter. The tumor was dark purple with a soft, fine texture, and gray-yellow nodules varying from 1 to 2 cm in diameter.

Microscopically, the tumor contained both germ cell and sex cord components. The germ cell portion comprised the majority of the tumor

Unclassified mixed germ cell-sex cord-stromal tumor with multiple cellular elements

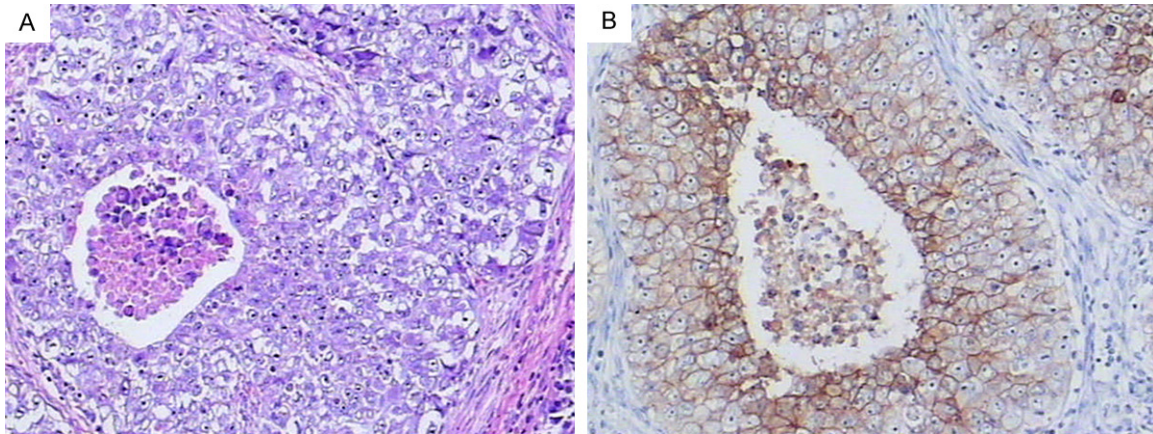


Figure 3. A. Embryonal carcinoma components consisted of aggregates of epithelial-like cells with a central vesicular nucleus and amphophilic cytoplasm. Necrosis was present in the center of the cell nests. B. Tumor cells showed diffuse membrane expression of CD30.

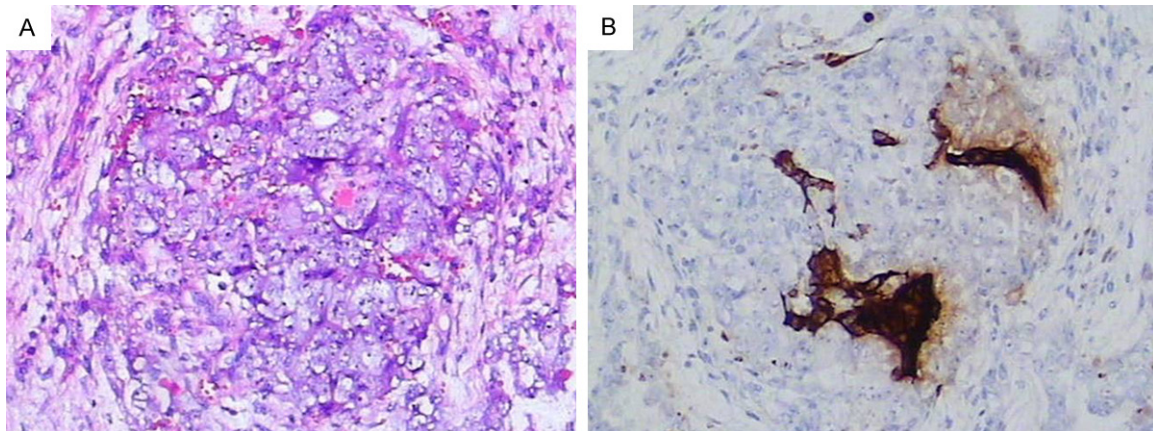


Figure 4. A. Choriocarcinoma components, note the multiple nuclei and eosinophilic cytoplasm. B. Tumor cells were positive for HCG expression.

and contained multiple growth patterns all with a malignant appearance, while the sex cord element consisted mainly of annular tubules.

Within the malignant germ cell elements, the dysgerminoma comprised approximately 75% of the tumor volume, which was characterized by aggregates, islands, or strands of large uniform cells surrounded by varying amounts of connective tissue stroma containing lymphocytes. The tumor cells were oval to polygonal with a central vesicular nuclei and clear or eosinophilic cytoplasm full of glycogen (**Figure 1A**). In some regions, the stroma was infiltrated by lymphocytes that formed focal lymphoid follicles. The tumor cells showed diffuse immunohistochemical expression of OCT4 (**Figure 1B**), placental alkaline phosphatase (PLAP), CD117,

and D2-40. Other malignant germ cell elements included yolk sac tumor, embryonal carcinoma, and choriocarcinoma, which comprised about 15% of the tumor volume. Yolk sac tumor components (**Figure 2A**) exhibited an alveolar-glandular pattern, reticular structure, and vague Schiller-Duval body-like structure within a fine, loose, myxomatous matrix. Eosinophilic hyaline droplets were observed in the cytoplasm of tumor cells and in the myxomatous matrix. Tumor cells were positive by immunohistochemistry for Alpha Feto-Protein (AFP), Alpha-1 Anti-Trypsin (AAT) and Glypican-3 (**Figure 2B**) expression. Embryonal carcinoma components (**Figure 3A**) consisted of solid aggregates of epithelial-like large polygonal cells with necrosis present in the center of the aggregating cell nests in some areas. The tumor cells had a

Unclassified mixed germ cell-sex cord-stromal tumor with multiple cellular elements

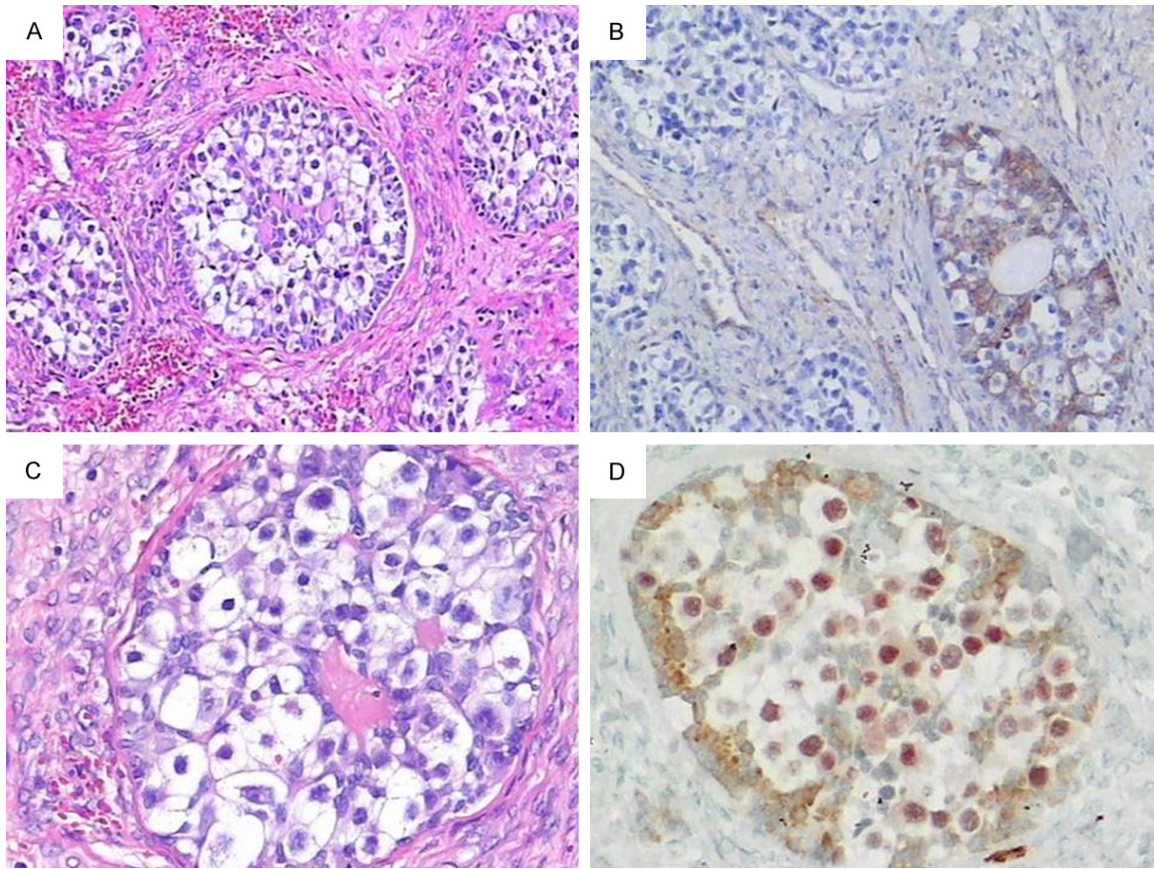


Figure 5. A. Tumor cells arranged in rounded lobules, which were composed of larger germ cells with round nuclei and pale, clear cytoplasm along with smaller sex cord cells with scant cytoplasm. The nuclei of the sex cord cells form a rosette-like arrangement around the hyaline nodules and are distributed around the periphery of the lobules. B. Germ cells generally outnumbered sex cord cells in the lobules. Several germ cells were located in the periphery of the lobules and appeared to grow outside the lobule borders. C. Sex cord cells stained positively for inhibin expression. D. Oct4 staining was localized to the nuclei of germ cells (red-brown staining), while the cytoplasm of sex cord cells stained positively for inhibin (yellow-brown).

large prominent vesicular nucleus and an ample amount of amphophilic cytoplasm with poorly defined cytoplasmic borders. Mitoses were easy to find. Immunohistochemical staining revealed that tumor cells had diffuse membrane expression of CD30 (Figure 3B), and also stained for PLAP. A few choriocarcinoma components (Figure 4A) were present in the embryonal carcinoma cell aggregates; these were characterized by multinuclear trophoblastic giant cells with an eosinophilic cytoplasm. Tumor cells stained positive for human chorionic gonadotropin (HCG) (Figure 4B) expression. The germ cell elements described above were intermixed or formed separate areas adjacent to each other and separated by fibrous septa.

Areas of intermixed germ cells and sex cord derivatives comprised 10% of the tumor vol-

ume. Two primary growth patterns composed of both germ cells and sex cord components were observed. In most areas, tumor cells formed rounded nests or lobules (Figure 5A). The larger germ cells characterized by large centrally located nuclei, with pale, clear cytoplasm were identical to cells of the dysgerminoma that were scattered throughout the lobules. The sex cord derivatives were small, hyperchromatic, oval or spindle-shaped cells with scant cytoplasm and elongated nuclei with inconspicuous nucleoli. Within the lobules, the sex cord cells mainly palisaded in the periphery around the lobules and some formed microfollicles filled with collagen. The features described above had an appearance resembling sex cord tumors with annular tubules (STCAT), but differed from the latter due to the presence of germ cells. However, the germ cells in general outnumbered sex cord cells and several large

Unclassified mixed germ cell-sex cord-stromal tumor with multiple cellular elements

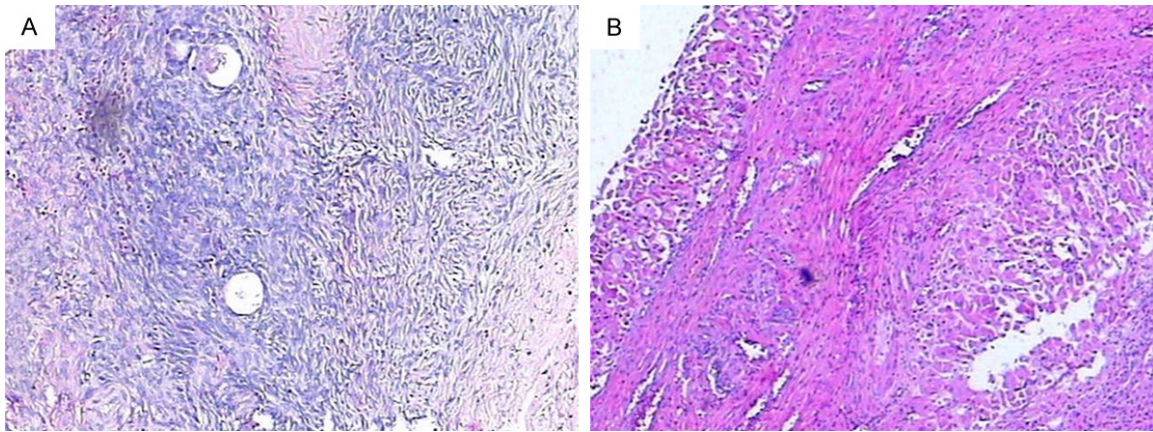


Figure 6. A. Residual normal ovarian tissue containing primordial follicles present in the middle of the figure. B. Corpus luteum cyst present in the ovary.

germ cells appeared on the periphery and tended to grow outside the borders of the lobules (**Figure 5B**). By immunohistochemistry, germ cells within the lobules stained positively for OCT4 expression, while the sex cord cells inside and surround the lobules were positive for inhibin and CD99 (**Figure 5C** and **5D**). The MIB1 antibody reacted with about 30%-50% of the germ cells and less than 2% of the sex cord cells. Another pattern showed occasional intermixing of cord or trabecular structures with germ cells and sex cord derivatives. Residual normal ovarian tissue, evidenced by the presence of ovarian cortex, primordial follicle, and a corpus luteal cyst was identified (**Figure 6A** and **6B**).

Discussion

UMGSCT composed of germ cells and sex cord derivatives is a rare neoplasm is a rare neoplasm. Only a few well-documented cases have been described in the literature over the past 30 years. This tumor containing a mixture of two distinct cell types that have completely different embryonic origins is much less common than gonadoblastoma, which also is composed of the many of the same cellular elements. Chromosomal abnormalities or gonadal dysgenesis generally were not present in the patients with UMGST except for a single patient reported to have monosomy 22 [4]. Most of the known cases in females are encountered in children within the first decade of life, and rarely are these tumors seen in post-menarchal girls and women of reproductive age. Only six cases have been detected in post-

pubertal females according to the literature [3, 5, 6]; three of the patients had normal pregnancies. Patients usually do not exhibit obvious clinical or endocrine symptoms, but isosexual precocious puberty may be observed in premenarchal girls [7-9]. The endocrine symptom encountered in our case was a short period of amenorrhoea. Most UMGST are unilateral except for two cases in which the tumors were bilateral [6, 10]. All reported cases with UMGST having malignant germ cell components have been unilateral.

Approximately 10% of UMGSTs have malignant germ cell components, a frequency that is much lower than that observed for gonadoblastoma, which is as high as 60% [1, 3]. Nine such cases have been well documented so far [3, 7]: in three cases, patients aged 26, 31, and 43 years old, respectively, progressed to dysgerminoma; in another case, a 26 year-old woman and five 4-to-16 year-old children were associated with other malignant germ cell components, including yolk sac tumor, choriocarcinoma, and immature teratoma. Seven cases, including our UMGST case, occurred in post-pubertal girls [7-9]; five of these cases were associated with other malignant germ cell components. Therefore, about 80% of mixed germ cell-sex cord stromal tumors that have been reported in postpubertal females have a concomitant malignant germ cell neoplasm. The unusual characteristic of our case is the mixture of multiple germ cell elements composed of dysgerminoma, yolk sac tumor, embryonal carcinoma, and choriocarcinoma. To our knowledge, no other case has been reported with an

Unclassified mixed germ cell-sex cord-stromal tumor with multiple cellular elements

embryonal element in UMGST. Some studies indicated that amplification of chromosome 12p may be crucial in the development of an invasive germ cell neoplasm [11, 12]; however, only one ovarian UMGST was reported to show amplification of 12p [13]. The relationship of this genetic event with UMGST that has an associated invasive germ cell component remains unclear.

Histologically, two cellular elements were present in the tumor. Germ cells and sex cord derivatives were intimately intermixed with each other and formed three basic histological patterns. The neoplasm formed 1) intersecting cords or trabeculae, 2) tubular structures devoid of a lumen, and 3) a solid, diffuse growth pattern. The fourth pattern consisted of an unusual structure similar to the sex cord tumor with annular tubules (SCTAT) that was first described in a 30 year-old woman with recurrent tumors in the uterine fundus [5]. The present case is the second report to describe a tumor that exhibits this unique structure that was similar to the previous report; however, our case differs from the former by the presence of germ cells that outnumbered sex cord cells in general. In addition, cells grew not only within the lobule but also outside the borders formed by sex cord cells. The mixture of the above described patterns was frequently seen within a single tumor. The sex cord element of UMGST can share unusual histological features such as a cystic or retiform pattern [14], which is a pattern formed by hollow tubules. Occasionally, heterologous elements also may be found in UMGST. Michal et al. [13] reported a case with heterologous elements showing columnar glandular epithelium with a ciliated brush border. Zuntova et al. [2] described a case in which a small focus of glands and cysts lined by mucinous columnar epithelium containing numerous goblet cells and occasional argyrophilic neuroendocrine cells was observed.

The presence of multiple cell types in UMGST has generated controversy regarding its true nature. Some have proposed that it is the germ cells that account for the heterogeneity of UMGST. Proliferation is mainly demonstrated in germ cells, which is supported by the finding that the MIB1 antibody reacted with about 30%-50% the germ cells in our case and 20%-30% in another four cases without malignant

germ cell tumors. In contrast, less than 2% of the sex cord cells were MIB1-positive in all cases examined. The presence of proliferation mainly by germ cells and the development of invasive malignant germ cell components in the tumor probably represent the main malignant potential of this tumor. It also has been suggested that the heterologous elements described above perhaps represent somatic differentiation of the germ cell element forming a focus of a monodermal teratoma. Germ cells demonstrated remarkable ability to stimulate the simultaneous proliferation not only of sex cord stromal cells but likely also of coelomic epithelium. However, the mixture of germ cells and sex cord stromal elements in two cases that had recurrence and metastases [5, 8] indicate that the malignant features are not necessarily limited to one cell type.

In a differential diagnosis, UMGST with malignant germ cell components should be distinguished from gonadoblastomas that have germ cell tumor overgrowth. Our case occurred in a young adult woman with a normal karyotype. There was no evidence of familial inheritance. The gonad of origin was normal ovary, in which a corpus luteum cyst was present indicating that the patient has had normal endocrine function and regular ovulation in the past. There was no evidence of gonadal dysgenesis or any somatosexual abnormalities in the contralateral ovary. Upon microscopic examination, the tumor lacked calcification, hyalinization, and Leydig or lutein-like cells. UMGST cases in which the germ cells predominate can be confused with a germ cell tumor, and the sex cord component can be overlooked when there is a concomitant germ cell tumor component. Identification of aggregates of intermixed germ cells and sex cord elements and immunohistochemical staining for inhibin, CD99, and calretinin may facilitate the diagnosis.

The behavior of this neoplasm is obviously different from gonadoblastoma. The prognosis of patients with a pure form tumor that is not associated with other neoplastic malignant germ cell elements is favorable. In the majority of cases, the tumor was confined to the ovary, and there was no recurrence or metastases after excision of the affected adnexa [3, 10, 13]. The disease-free periods varied from 1 to 15 years, and only two cases reported recur-

rence or metastases [5, 8]. The primary treatment in patients with mixed germ cell-sex cord-stromal tumor is excision of the gonad containing the tumor, and conservation of the contralateral gonad that is normal. This is in contradistinction to the treatment of patients with gonadoblastoma where radical surgery is the treatment of choice because in most cases the gonads are non-functional; the tumor is often bilateral and typically associated with dysgerminoma or another malignant germ cell tumor. Thus, treatment of patients with mixed germ cell-sex cord-stromal tumor is completely different from the treatment of patients with gonadoblastoma. Moreover, differentiation between these two entities and the correct diagnosis are not only of academic, but of clinical importance. Patients with UMGST associated with malignant germ cell elements have a favorable prognosis in line with that of primary malignant germ cell tumors if treated with appropriate chemotherapy and radiation therapy. In nine cases associated with other malignant germ cell elements, three patients were clinically well and disease-free from 2-7 years after unilateral adnexectomy and radiation therapy; one patient treated with cisplatin-based chemotherapy was alive and well 5 years later, and the patient whose case is reported herein has no evidence of recurrence or metastases after 2 years. However, if the associated components were malignant germ cell other than dysgerminoma, the prognosis is relatively poor, where metastases and death occurred in three out of five cases.

In summary, we present a case of a rare type of malignancy, an unclassified mixed germ cell-sex cord-stromal tumor with multiple cellular elements and compare its clinico-histopathological characteristics to other similar tumor types. Importantly, the correct differentiation and diagnosis are critical because the prognosis for these tumors is generally good with simple surgery.

Disclosure of conflict of interest

None.

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Unclassified mixed germ cell-sex cord-stromal tumor with multiple cellular elements

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