

# Poorly differentiated ovarian Sertoli-Leydig cell tumor with heterologous rhabdomyosarcomatous elements associated with elevated serum alpha-fetoprotein level: a case report and review of the literature

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## Summary

Ovarian Sertoli-Leydig cell tumors (SLCTs) are uncommon sex cord-stromal tumors. Moreover, SLCTs with heterologous mesenchymal elements are extremely rare and usually associated with poor differentiation and prognosis. Herein, the authors describe a case of SLCT involving the right ovary in a 16-year-old girl who presented with acute lower abdominal pain and fever. Serum investigation demonstrated abnormally elevated level of alpha-fetoprotein (AFP), slightly elevation of testosterone, and CA125 concentration. Right salpingo-oophorectomy was performed due to ovarian tumor torsion and then histopathological analysis revealed a poorly differentiated Sertoli-Leydig cell tumor with heterologous rhabdomyosarcomatous elements. A brief review of the literature was conducted to explore the management options for patients with SLCTs and the prognosis.

**Key words:** Ovary; Sertoli-Leydig cell tumors; Sex cord-stromal tumors; Rhabdomyosarcoma; Alpha fetoprotein.

## Introduction

Sertoli-Leydig cell tumors (SLCTs) are a rare subgroup of sex cord-stromal tumors, which represent less than 0.5% of primary ovarian neoplasms [1]. They tend to occur frequently in the second and third decades, and the average patient age is 23–25 years [2]. The tumor is usually unilateral with size ranging from 0.8 to 30 cm. Some patients present with abdominal distension or acute pain due to tumor torsion or rupture requiring emergently surgical intervention. Most of patients with SLCTs complain of hyperandrogen-related symptoms like virilization, lower tone of voice, oligo- or amenorrhea and in the most severe cases with clitoromegaly and reduction in breast volume. Occasionally patients have excessively estrogenic manifestations. In 50% of the cases they are asymptomatic. The diagnosis is sometimes delayed for lack of typical gynecological symptoms. Currently, alpha-fetoprotein (AFP) is established as an important marker of germ cell tumors, meanwhile, it has been identified in SLCTs with special histologic pattern [3].

SLCTs usually have a good long term prognosis and the overall five-year survival can reach as high as 70–90%. However, higher stage or poorly differentiated tumors are

associated with a worse prognosis [4]. Variants of SLCTs with heterologous elements account for approximately 40% and most of them contain benign gastrointestinal epithelium, but in approximately 25% of these variants, heterologous mesenchymal elements, such as rhabdomyosarcoma (RMS) are encountered [2], which is related to low-grade differentiation and a poor prognosis. Issues and dilemmas in the management of adnexal mass in juvenile are numerous, from diagnosis to surgical therapeutic procedures along with adjuvant therapy [5]. Therefore, any medical case related to juvenile SLCT is meaningful. Herein, the authors report an extremely rare case of poorly differentiated SLCT exhibiting extensive overgrowth of heterologous rhabdomyosarcomatous (RMS) component and abnormally elevated concentration of serum AFP in a 16-year-old girl. A brief review was conducted to explore the clinicopathological features and management options for patients with SLCTs.

## Case Report

A 16-year-old girl was admitted to the gynecologic emergency department with complaint of severe right-sided lower abdominal pain and fever of two days. Her temperature was 38.7°C. She

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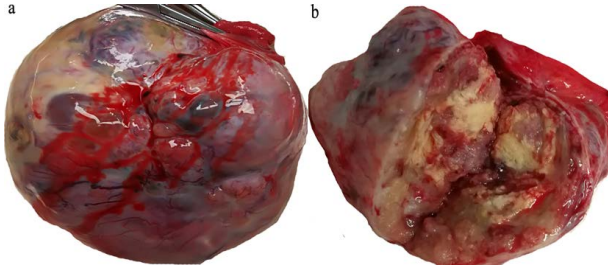


Figure 1. — A) Abdominal exploration reveals a large ovarian mass measuring 14×12×10 cm with attached tube. B) Cross-section showing yellow-white gelatinous areas.

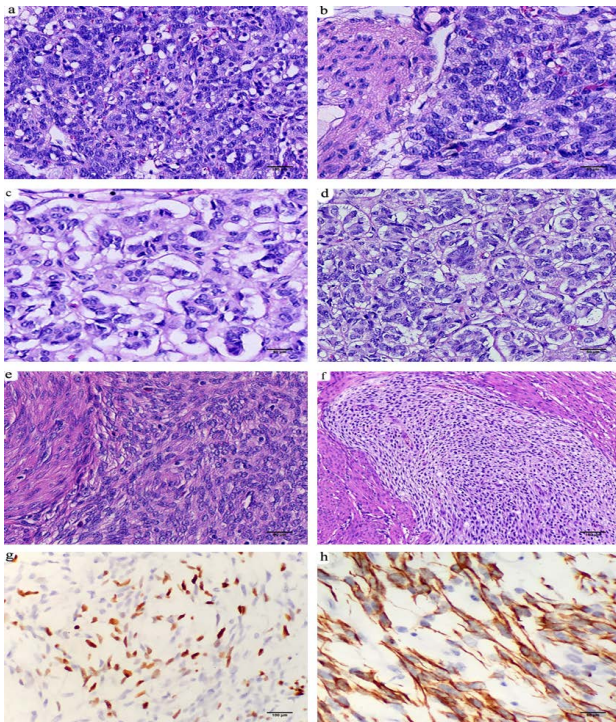


Figure 2. — Microscopically pathological findings. A) The tumor is composed of diffuse Sertoli cells forming cords and ill-defined tubules surrounded by sparse Leydig cells with more abundant eosinophilic cytoplasm (H&E staining, magnification power: ×20). B) Area of SLCT with diffuse Sertoli cells, sparse Leydig cells, and rhabdomyoblasts cells (H&E staining, magnification power: ×40). C) Focal myxoid area containing Sertoli cells with bizarre nuclei and mitotic activity was identified (H&E staining, magnification power: ×40). D) Fine trabecular area simulating patterns seen in granulosa cell tumor (H&E staining, magnification power: ×40). E) Pleomorphic rhabdomyosarcoma consisting of interlacing bundles of spindle-shaped mesenchymal cells, uniform and immature rhabdomyoblasts (H&E, staining, magnification power: ×40). F.) Small island of fetal hyaline cartilage with only mild cellular pleomorphism (H&E, staining, magnification power: ×20). G) IHC showing moderate positive staining for desmin (Envision: magnification power: ×20). H) IHC showing moderate cytoplasmic staining for MyoD1 in morphologically-appearing rhabdomyoblasts (Envision: magnification power: ×40).

was otherwise healthy, without any regular medical therapy. On abdominal examination, a large mass was palpated, extending from lower pelvis to umbilicus. Serum analysis indicated the following results: total testosterone 3.73 nmol/l (normal range 0.35-2.64 nmol/L), AFP 644.93 µg/L (normal range 0-20 µg/L), CA 125 103.8 IU/L (normal range 0-35 IU/L) and WBC 11×10<sup>9</sup>/L (normal level 4-10×10<sup>9</sup>/L). Serum levels of CEA, CA199, beta hCG, FSH, LH, and PRL were normal. Coagulation, renal, liver, and thyroid profile were within normal limits. Transabdominal ultrasound scan showed a well-defined solid heterogeneous mass. Ultrasound scan demonstrated a solid mass originating from right adnexa. Informed consent, after an explanation of the potential benefits and risks of surgical alterations, was obtained from the patient. The patient's written consent was also obtained for the use of the photographs. Abdominal exploration revealed a large ovarian mass measuring 14×12×10 cm with attached tube, a complete and smooth outer surface, twisted on its pedicle, with focal signs of ischemic ovarian surface (Figure 1a). Cross-section showed yellow-white gelatinous areas (Figure 1b). A small amount of yellow ascites was seen and then peritoneal washing was performed to explore exfoliative cancer cells. The uterus, left adnexa, intestine, and omentum showed normal appearance. No enlarged pelvic lymph nodes or peritoneal deposits were seen. Right salpingo-oophorectomy was performed and sent for frozen section analysis. Intraoperative pathological investigation indicated spindle-shaped cell tumor suspicious of sex cord stromal tumors or juvenile granulosa cell tumor. Peritoneal washing did not find any malignant cells.

On final histopathology, microscopy revealed a tumor consisting of solid areas with diffuse Sertoli cells forming cords and ill-defined tubules surrounded by sparse Leydig cells with more abundant eosinophilic cytoplasm (Figure 2a). Some areas showed coexistence of diffuse Sertoli cells, rhabdomyoblast cells, and sparse Leydig cells (Figure 2b). Fine trabecular area simulating patterns seen in granulosa cell tumor was found in focal area (Figure 2c). Focal myxoid area demonstrated Sertoli cells with bizarre nuclei and mitotic activity was identified (Figure 2d). Investigation of many sections revealed pleomorphic rhabdomyosarcoma consisting of interlacing bundles of spindle-shaped mesenchymal cells, uniform and immature rhabdomyoblasts. A few cells were spindle-shaped with an abundant eosinophilic cytoplasm with cross striation (Figure 2e). In a few sections, small foci of fetal, hyaline cartilaginous elements were seen (Figure 2f). Immuno-histochemical (IHC) analysis demonstrated moderately positive staining for desmin (Figure. 2g) and MyoD1 in morphologically appearing rhabdomyoblasts (Figure 2h). The heterologous elements constituted approximately 25% of the tumor, which did not contain any heterologous epithelial elements or retiform foci. Diagnosis of poorly differentiated SLCT with heterologous rhabdomyosarcoma elements was made.

Postoperative course was uneventful with serum AFP and testosterone reducing to 104.15 ug/l and 1.25 nmol/l, respectively. The patient was recommended four courses of combined chemotherapy with cisplatin, etoposide, and bleomycin (PEB). Follow-up result within one year after operation did not show any evidence of recurrence.

## Discussion

As an uncommon group of primary ovarian tumors, SLCTs consist of variable combinations of Sertoli cells and Leydig cells and sometimes with heterologous elements. According to the WHO classification [6], SLCTs are categorized as well, intermediate, and poorly differentiated tu-

mors based on the degree of tubular differentiation of Sertoli cell component. The most common heterologous pattern is mucinous epithelium of enteric type, while only 5% of SLCTs contain mesenchymal elements [7]. In the present report, IHC analysis revealed positive staining of desmin and MyoD1, consistent with one previous study that rhabdomyosarcoma cells could express desmin, as well as myogenic transcription factors MyoD<sub>1</sub> or myogenin, or both [8]. Due to the high sensitivity and specificity of MyoD1 in the diagnosis of RMS, it is a very useful tumor marker to identify RMS from other non-RMS [9]. Meanwhile, the tumor showed poorly differentiated ovarian SLCT, according with the statement that heterologous rhabdomyosarcoma was usually associated with moderately and poorly differentiated neoplasms [10].

As an important tumor marker, AFP has been identified highly in ovarian germ cell tumors [11] such as ovarian yolk sac tumor (OYST) and also an early AFP decline during chemotherapy was an independent prognostic factor for patients with OYST [12]. AFP was detected in cells with the histologic appearance of Sertoli cells, and testosterone was detected in the Leydig cells [13]. The major component in the present patient was contained in Sertoli cells, explaining why the patient had an extremely higher level of AFP and slightly raised testosterone concentration. Although elevated levels of AFP in SLCTs with heterologous elements of gastrointestinal type have been reported in several cases [3, 14, 15], the present report represents the first attempt to describe abnormally raised serum level of AFP in SLCTs with differentiation of rhabdomyosarcoma, laying a foundation for follow-up strategy.

Due to their rarity, there is no standardized protocol guideline for SLCTs. It is generally believed that conservative surgery could be sufficient in younger patients, and especially for those patients who desire to retain their fertility, unilateral salpingo-oophorectomy, and close follow-up could be beneficial. Nevertheless, most of moderately and poorly differentiated tumors or those with heterologous elements had a potential for recurrence. Trisha and Plastini reported three cases of SLCT with RMS elements and then reviewed previous studies, with a total of 14 patients in Stage IA, of whom 11 patients were found to show evidence of recurrence around one year after initial operation [16]. Particularly, Zaloudek and Norris described a 16-year-old patient with Stage IA poorly differentiated SLCT with RMS elements who was treated with USO and later thiotepa and 5-fluorouracil after recurrence at 1.4 years. She was found to have peritoneal metastases on autopsy after her death four months later [17]. Controversial statements exist concerning the relationship between the presence of heterologous RMS and outcome of SLCTs. Two cases where the RMS component almost overgrew the SLCTs, had a malignant disease course with recurrence at seven and ten months postoperatively [18, 19]. In contrast, two of the previously described cases of moderately dif-

ferentiated SLCTs with RMS elements occupying only small parts of the tumor had a favorable outcome [20, 21]. Therefore, the management for SLCTs with RMS differentiation poses a great challenge for gynecologists.

Due to limited information about effectiveness of post-operative therapy, adjuvant therapy remains controversial and requires further investigation. Adjuvant therapy is not recommended for patients with Stage I and G1 SLCTs, but postoperative chemotherapy and long-term follow up is indicated for patients with high-risk factors including beyond Stage I, intermediate or poor differentiation, high mitotic profile, existence of heterogonous elements, and tumor rupture [20, 22, 23]. The present authors recommended chemotherapy to their patient due to poorly differentiated SLCTs with heterologous elements. At present, the most frequently used chemotherapeutical regimen is PEB [24]. However, Gershenson *et al.* considered that the PEB regimen apparently lacks durable activity and more effective drugs and modalities should be attempted [25]. More studies are needed to evaluate the effectiveness and toxicity of PEB in patients with SLCTs.

## Conclusion

The authors report the first example of poorly differentiated ovarian Sertoli-Leydig cell tumor with heterologous rhabdomyosarcomatous elements, associated with elevated serum AFP level. SLCTs are sometimes delayed for diagnosis due to lack of typical gynecological symptoms. Their rarity, especially those with heterologous elements, poses a great challenge for gynecologists. For younger patients, fertility-sparing surgical procedure should be considered. Adjuvant chemotherapy may be effective in improving survival in SLCTs with malignant heterologous elements. Further studies with a larger number of cases and a longer follow-up are needed to determine the role of chemotherapy and to better predict the prognosis in such cases.

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