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Case Report

When alpha-fetoprotein misleads: alpha-fetoprotein-producing Sertoli-Leydig cell tumor of the ovary mimicking a germ cell tumor

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ABSTRACT

Sertoli-Leydig cell tumor (SLCT) is an uncommon ovarian sex cord–stromal tumor, accounting for approximately 0.2% of primary ovarian tumors. Most SLCTs occur in young women and approximately half are hormonally active, producing androgenic manifestations; however, alpha-fetoprotein (AFP) production is distinctly unusual. We report a 25-year-old parous woman who presented with acute abdominal pain and a large solid-cystic ovarian mass. Serum AFP was elevated at 128 U/mL, while β-human chorionic gonadotropin was <2 IU/mL and CA-125 were 71.8 IU/mL. Because of the patient's age, serum AFP elevation, and the radiologic appearance of the mass, a germ cell tumor, particularly yolk sac tumor was clinically suspected. Histologically, the tumor was extensively necrotic and hemorrhagic, with viable areas showing variable-sized lobules, solid and tubular Sertoli-cell components, focal alveolar and annular tubule-like patterns, and interspersed clusters of Leydig cells. No germ-cell or heterologous component was identified despite extensive sampling. Tumor cells expressed WT1, inhibin, calretinin, and ER, with a Ki-67 index of 15-20%, while SALL4, EMA, cytokeratin, PAX8, and AFP was negative. The final diagnosis was moderately differentiated SLCT without heterologous elements or specific differentiation, FIGO stage IA (pT1b). Postoperatively, serum AFP and testosterone normalized, and imaging showed no residual or recurrent disease. This case highlights an important diagnostic paradox: an elevated serum AFP in a young woman with an ovarian mass strongly suggests a germ cell tumor, yet AFP is not pathognomonic for germ-cell neoplasia. Careful morphologic assessment, extensive tumor sampling, and a focused immunohistochemical panel are essential to avoid misclassification and inappropriate treatment.

Keywords: Sertoli-Leydig cell tumor, Sex cord-stromal tumor, Alpha-fetoprotein, Ovarian tumor, Leydig cells, Germ cell tumor, Young woman

INTRODUCTION

Sex cord-stromal tumors (SCSTs) are ovarian neoplasms composed of granulosa, theca, Sertoli, and Leydig cells, either singly or in varying combinations and degrees of differentiation. Sertoli-Leydig cell tumor (SLCT), also known as androblastoma, is a rare SCST characterized by testicular-type differentiation and accounts for approximately 0.2% of all primary ovarian tumors.[1] The diagnostic challenge is amplified when its clinical or biochemical profile overlaps with that of a more common ovarian neoplasm. AFP is a classic oncofetal protein produced during fetal life by the liver, yolk sac, and fetal gastrointestinal tract. Although adult serum levels are normally low, AFP may be re-expressed by several malignant neoplasms.[2] In ovarian tumors, marked AFP elevation is classically associated with non-seminomatous germ cell tumors, particularly yolk sac tumor, mixed germ cell tumors, embryonal carcinoma, and some teratomas.[3] Rarely, however, AFP may be associated with

dysgerminoma, epithelial ovarian malignancies, and SCSTs.[2,4]

Approximately half of SLCTs are hormonally active and may produce androgenic manifestations such as virilization or defeminization.[5] While cases of ovarian SLCT associated with increased levels of AFP are rare, they are reported to be the most common AFP-producing ovarian non-germ cell tumor and most have appeared as individual case reports or small series.[4,6]

Importantly, some AFP-producing SLCTs lack an identifiable heterologous component, raising the possibility that Sertoli or Leydig cells themselves may contribute to AFP production. We present an unusual case in which elevated AFP, rather than virilization, was the major biochemical clue as well as initially directed the clinical diagnosis toward the germ cell tumor.

CASE REPORT

A 25-year-old para 2 woman presented with acute abdominal pain of 2 days' duration with no history of amenorrhea, and no signs of hirsutism or other obvious signs of virilization. Her vital parameters were stable. Abdominal examination demonstrated a tender abdominopelvic mass corresponding approximately to a 24-week gestational size.

Urgent ultrasonography revealed a large solid-cystic left ovarian mass measuring 11×10.4×9.7 cm. Serum AFP was elevated at 128 U/mL. Other tumor markers included β-human chorionic gonadotropin (<2 IU/mL) and CA-125 (71.8 IU/mL), which were within the reported reference ranges. Peritoneal tap cytology was negative for malignant cells. In view of the patient's young age, large ovarian mass, and raised AFP, an ovarian germ cell tumor (GCT) was clinically suspected and exploratory laparotomy was planned.

At laparotomy, a large solid left ovarian mass with an intact capsule was identified. The uterus, both fallopian tubes, and the contralateral ovary were unremarkable. No intra-abdominal adhesions, peritoneal deposits, or free fluid were identified. Unilateral salpingo-oophorectomy with infracolic omentectomy was performed. The specimen comprised a left salpingo-oophorectomy measuring 12.5×12×5 cm, with a 3.5-cm-long fallopian tube. On cut section, the tumor was solid-cystic and markedly variegated, with extensive areas of hemorrhage and necrosis and a discrete solid yellow area measuring 3×2 cm. Variable-sized cystic spaces contained brownish, jelly-like material (Figure 1 A).

The combination of a large, variegated, hemorrhagic and necrotic ovarian mass and raised AFP prompted consideration of yolk sac tumor, teratoma/dermoid tumor, choriocarcinoma, and mixed GCT. Because a mixed GCT was a significant possibility, extensive sampling was performed, including sampling of both viable and necrotic areas. Sections showed extensive hemorrhage and necrosis with only focal preserved viable tumor. The viable tumor was arranged in variable-sized lobules with both solid and tubular components (Figure 1 B). Focal alveolar areas and solid tubules were present. The tubules were lined by cuboidal to columnar cells and contained basement membrane-like material within their lumina (Figure 1 C).

Focal antipodal cellular arrangement and annular tubule-like structures were also identified. The tumor cells were round to oval and largely monomorphic to mildly pleomorphic, with vesicular to hyperchromatic nuclei and abundant clear to vacuolated cytoplasm. Small clusters of Leydig cells were conspicuous between the tubular and solid areas (Figure 1 D-F).

Marked cytologic atypia and significant mitotic activity were not identified. No lymphovascular invasion or capsular invasion was seen. The fallopian tube and omentum were free of tumor. Based on the morphologic findings, the initial differential diagnosis included a sex cord–stromal tumor with annular tubules and Sertoli-Leydig cell tumor. The absence of an obvious germ-cell component despite extensive sampling was particularly noteworthy given the elevated serum AFP. Immunohistochemical evaluation showed tumor-cell positivity for WT1, inhibin, calretinin, and ER. The Ki-67 proliferation index was approximately 15-20%. SALL4, EMA, cytokeratin, PAX8, and AFP were negative. The negative SALL4 and AFP staining, together with the absence of morphologic germ-cell differentiation, argued strongly against yolk sac tumor and other germ cell tumors.

Negative EMA and cytokeratin expression also argued against epithelial ovarian malignancy. Inhibin expression may be encountered in both granulosa-cell tumors and other SCSTs; however, the overall morphology and calretinin expression supported Sertoli-Leydig cell differentiation rather than granulosa-cell tumor. Taken together, the morphologic and immunohistochemical findings established the diagnosis of moderately differentiated SLCT without heterologous elements or specific differentiation, FIGO stage IA (pT1b) (Figure 2).

The postoperative course was uneventful. At 4 weeks, serum AFP and testosterone had returned to normal, and contrast-enhanced CT of the abdomen showed no residual tumor or evidence of recurrence. Serum inhibin B was mildly elevated at 57.59 pg/mL (reported reference range 21-53 pg/mL). In view of the intermediate-grade tumor and the biochemical finding, completion staging surgery with hysterectomy and removal of the right adnexa was planned. At repeat exploratory laparotomy, no residual tumor was identified, and the patient was subsequently kept under follow-up.

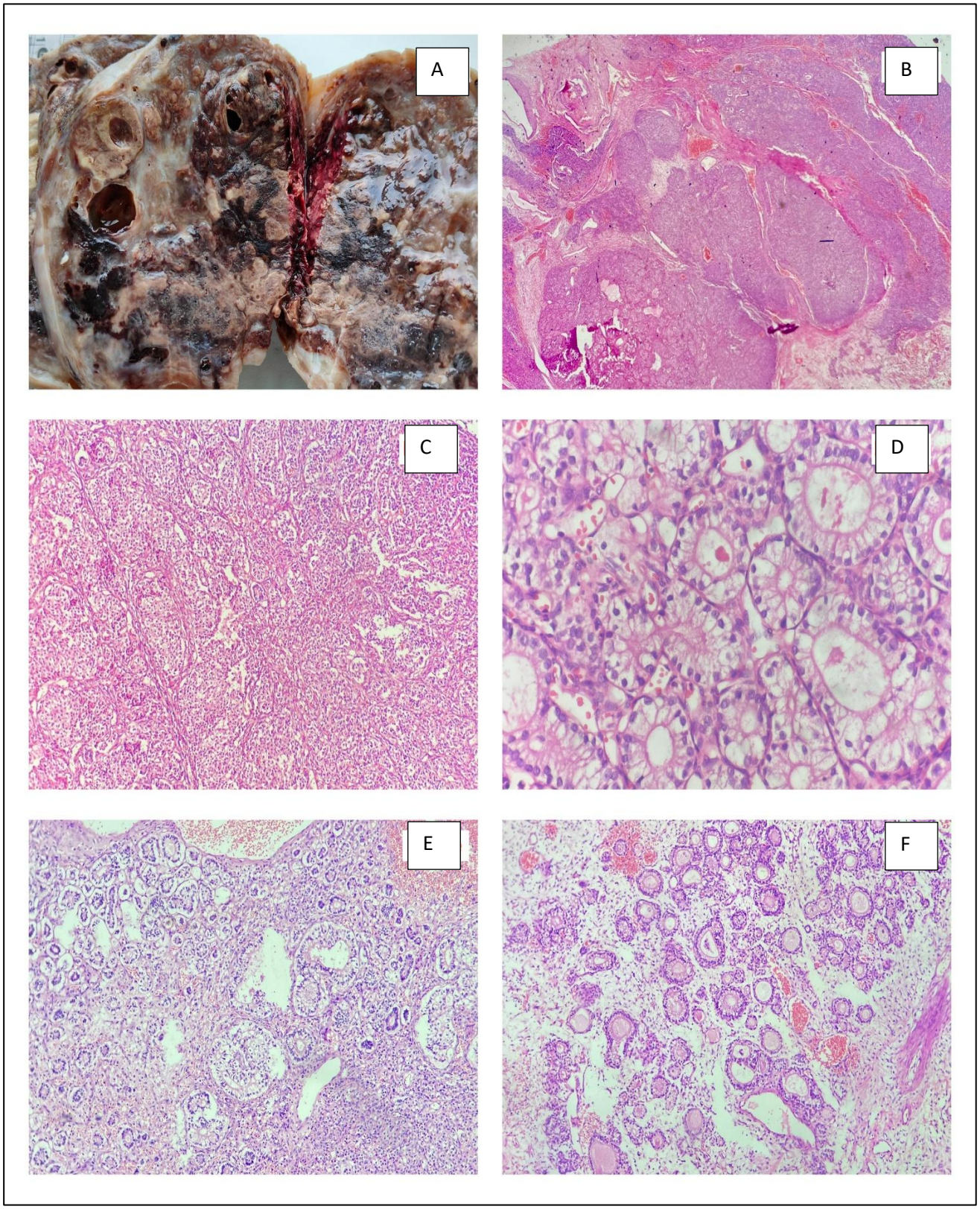


Figure 1: Gross and histomorphological features of the tumor; (A) Cut surface of the ovarian mass showing a markedly variegated solid-cystic appearance with hemorrhage and necrosis; (B) Variable-sized lobules of viable tumor (100×, hematoxylin and eosin); (C-F) Tumor cells arranged in solid and tubular patterns, with tubules lined by cuboidal to columnar cells containing basement membrane-like material in the lumina; tumor cells show round to oval, monomorphic to mildly pleomorphic nuclei and abundant clear to vacuolated cytoplasm, with interspersed Leydig-cell clusters (100×, hematoxylin and eosin).

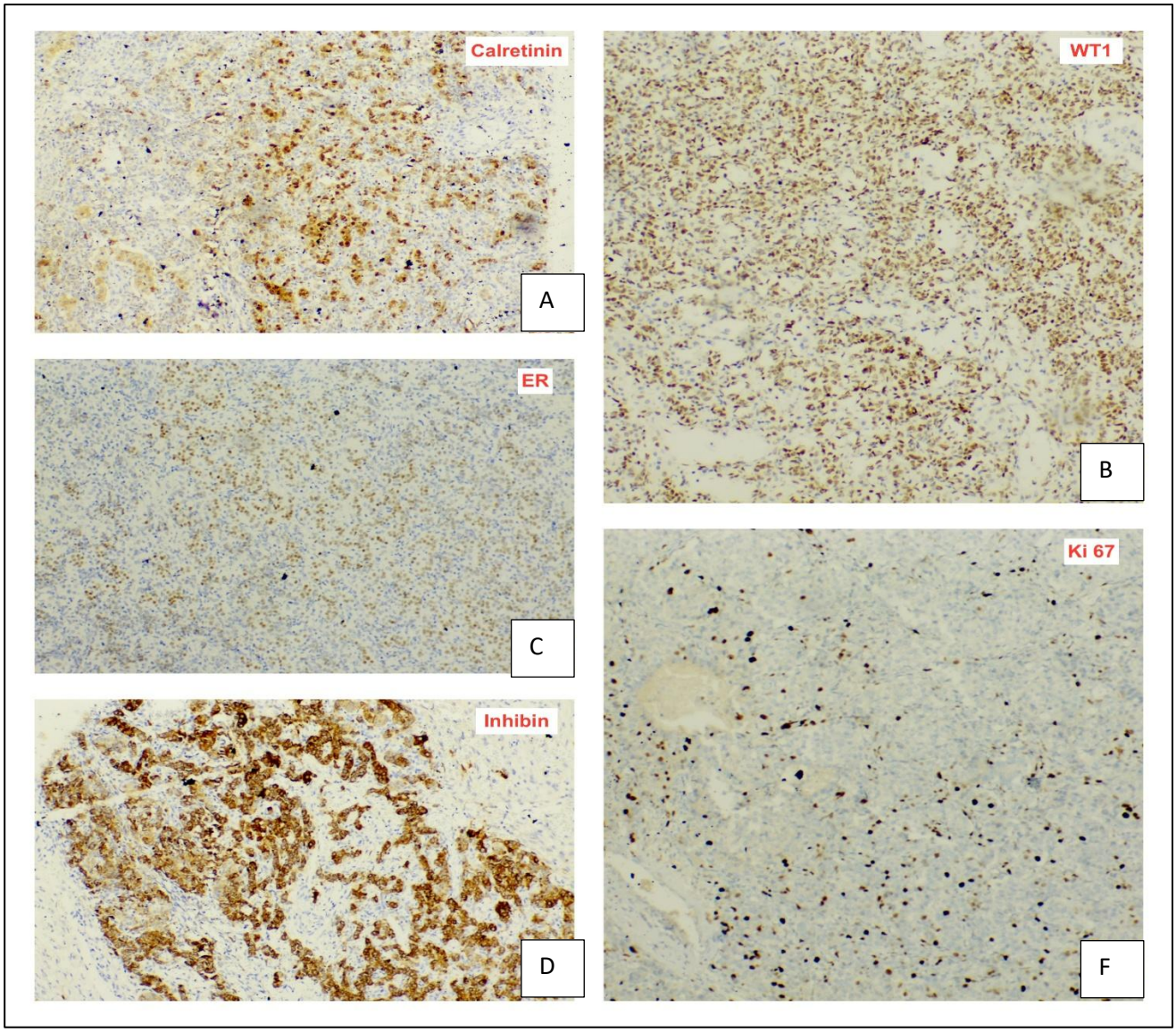


Figure 2 (A-F): Immunohistochemical profile supporting Sertoli-Leydig cell differentiation. Tumor cells show positivity for calretinin, inhibin, WT1 and ER, with a Ki-67 proliferation index of approximately 15-20% (10×).

DISCUSSION

The diagnostic identity of an ovarian mass is often shaped by the clinical setting and serum tumor markers before tissue is examined. This case illustrates how that sequence can become misleading. In a 25-year-old woman with a large ovarian mass and elevated AFP, a germ cell tumor is an entirely reasonable initial consideration. The diagnostic challenge arises when the histology does not confirm the presumed tumor lineage. In adults, serum AFP is generally low, and its postoperative kinetics are clinically useful because the reported half-life is approximately 4-5 days.[7,8] AFP, together with β-hCG, is routinely used in the evaluation and staging of ovarian germ cell tumors. Yolk sac tumors characteristically elevate AFP, whereas β-hCG is associated particularly with choriocarcinoma; both markers may be elevated in embryonal carcinoma.[9] Consequently, a raised AFP in a young woman with an ovarian mass can exert a powerful diagnostic influence.[17] SLCTs, occur predominantly in young women, with an average age of approximately 25 years, although they can occur across a broad age range.[10] Approximately 75% of reported AFP-producing SLCTs have occurred in patients younger than 30 years, while only a small number have been reported in postmenopausal women.[6,11] Most SLCTs are unilateral and stage I at diagnosis. Clinically, approximately half are hormonally active and may produce androgenic symptoms ranging from subtle virilization to marked defeminization. The present patient was unusual in having no clinically apparent hirsutism or virilization. Acute abdominal pain is also an uncommon presentation of SLCT. Approximately 5-10% of patients may present with acute pain related to torsion or rupture.[9] In the present case, the acute presentation, large tumor size, extensive hemorrhage and necrosis, and absence of androgenic symptoms created a clinical picture that did not immediately suggest SLCT.

Grossly, SLCTs are usually solid-cystic tumors with a characteristic yellow solid component reflecting steroid-producing cells; hemorrhage and necrosis may be present, and retiform tumors may show papillary areas.[2,10] Microscopically, they range from well differentiated to moderately and poorly differentiated forms. Moderately and poorly differentiated tumors constitute the majority and may show tubules, trabeculae, cords, and less well-formed Sertoli-cell structures, with Leydig cells present singly or in clusters.[2] The presence of a retiform component or mesenchymal heterologous elements may be associated with unfavourable prognosis.[12] Heterologous elements occur in a subset of moderately and poorly differentiated tumors, most commonly intestinal-type mucinous epithelium.[2,13]

The present tumor showed the expected spectrum of Sertoli–Leydig differentiation, including solid and tubular architecture, focal alveolar and annular tubule-like patterns, and recognizable Leydig-cell clusters. Most importantly, extensive sampling did not identify a germ-cell component or heterologous tissue that could explain the elevated serum AFP.

Serife et al noted that among 21 cases in their analysis, including their case, no specific differentiation or heterologous element was identified, and Leydig-like cells were proposed as a possible source of AFP.[6] AFP-producing SLCTs have consequently become an important, although uncommon, diagnostic consideration when elevated AFP is accompanied by ovarian sex cord–stromal morphology.

In the present case, the tumor itself was negative for AFP by immunohistochemistry, and no heterologous hepatic or gastrointestinal component was found, as in Žilinskienė et al study.[13] Therefore, the precise cellular mechanism underlying the raised serum AFP cannot be established from the present findings. One proposed explanation is that Leydig or luteinized cells may produce AFP, potentially facilitated by extensive hemorrhage and necrosis. Jashnani et al. similarly proposed that torsion-associated hemorrhagic necrosis could permit release of AFP from Leydig or luteinized cells.[14] This remains a biologically plausible explanation rather than a proven mechanism in the present case.

Immunohistochemistry is particularly valuable in this setting because AFP elevation alone cannot establish germ-cell lineage. In SLCTs, inhibin and calretinin are typically expressed in Sertoli and Leydig cells, often more strongly in Leydig cells. By contrast, SALL4 is a useful marker in the evaluation of germ-cell differentiation, while the absence of AFP staining and the absence of morphologic yolk sac tumor are important when excluding an AFP-producing germ cell tumor. The present immunophenotype-WT1, inhibin and calretinin positivity with negative SALL4, AFP, cytokeratin, EMA and PAX8-supported the final diagnosis.

The major practical lesson is that serum tumor markers should inform, but should not override, histomorphology. An ovarian neoplasm in a young woman with elevated AFP may be assumed to be a germ cell tumor; however, the differential diagnosis must remain open until adequate tissue sampling and appropriate immunohistochemistry have been completed. This distinction is clinically consequential because SCSTs and germ cell tumors differ in treatment strategies, chemotherapy indications, and prognosis.

SLCTs are strongly associated with DICER1 mutations and may occur as part of the clinical spectrum of DICER1 syndrome. Reported mutation frequencies vary widely, ranging from 15% to 97%. Importantly, DICER1 alterations are predominantly associated with moderately and poorly differentiated SLCTs, whereas well-differentiated tumors appear largely DICER1-independent. However, in the present scenario, the genetic testing was not performed.[15]

For stage I SLCT, unilateral salpingo-oophorectomy is the principal surgical treatment, particularly when fertility preservation is relevant. Chemotherapy is generally reserved for advanced disease and selected high-risk tumors, including those with rupture, malignant cells in ascites or washings, poor differentiation, frequent stromal mitoses, or significant heterologous elements, but it is still controversial.[16] Routine pelvic and abdominal lymph-node dissection is generally discouraged.[16] The prognosis is broadly favourable and is closely associated with tumor stage and grade. Reported recurrence rates for ovarian SLCTs range from 0% to 33.3%, usually within the first few years after treatment.[10,17] When it occurs, it is associated with an unfavourable outcome and low survival rates.[12,17] These observations underscore the need for vigilant, long-term follow-up, even in patients who present with apparently localised disease. Surveillance should include a detailed clinical history and physical examination, with particular attention to recurrent androgenic manifestations, together with serial laboratory assessment of serum testosterone and AFP levels and periodic ultrasonographic evaluation of the abdomen and pelvis.[12,17] Such structured follow-up may facilitate early detection of biochemical or radiologic recurrence and enable timely therapeutic intervention.

In the present case, completion staging surgery was undertaken because of the intermediate-grade morphology and mildly elevated postoperative inhibin B; nevertheless, no residual tumor was found. The absence of extraovarian disease, intact capsule, lack of lymphovascular invasion, and FIGO stage IA status with no heterologous component are all relevant features in the clinical assessment of this patient.

CONCLUSION

An elevated serum AFP should not be regarded as synonymous with an ovarian germ cell tumor. This case

represents a rare and diagnostically important presentation of AFP-associated SLCT in a young parous woman who presented with acute abdominal pain but lacked the typical clinical manifestations of androgen excess. The absence of heterologous elements and the lack of an identifiable germ-cell component make the case particularly instructive. When serum markers and morphology appear discordant, extensive sampling and a carefully selected immunohistochemical panel are essential. Recognizing this uncommon diagnostic pitfall can prevent misclassification of an AFP-producing non-germ-cell tumor and thereby avoid inappropriate germ-cell-directed treatment.

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