Case Report

15-Year-Old Patient with an Unusual Alpha-Fetoprotein-Producing Sertoli-Leydig Cell Tumor of Ovary

Kaçar Serife,1 Stavros Karampelas,2 Nathalie Hottat,3 Christine Devalck,4 and Katherina Vanden Houte1

1Department of Pathology, Brugmann University Hospital Center, Université Libre de Bruxelles, Belgium
2Department of Gynecological Surgery, Brugmann University Hospital Center, Université Libre de Bruxelles, Belgium
3Department of Medical Imaging, Brugmann University Hospital Center, Université Libre de Bruxelles, Belgium
4Pediatric Oncology Reine Fabiola Children’s University Hospital, Université Libre de Bruxelles, Belgium

Correspondence should be addressed to Kaçar Serife; serifemedkacar@gmail.com

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Ovarian Sertoli-Leydig cell tumors (SLCTs) are extremely rare mixed-sex-cord stromal tumors of the ovary, concerning less than 0.5% of all primary ovarian neoplasms [1]. It affects all age groups of patients, with 75% detected in young women less than 30 years (mean age of 25 years) and less than 10% detected after menopause. Most of the cases (97%) are unilateral and confined to the ovary at the diagnosis (FIGO stage I) [2].

Due to testicular-like tumor cell types (Sertoli and Leydig cells) producing androgens, clinical signs and symptoms such as irregular menstruation and virilization are seen in 50% of cases with occasional patients presenting estrogenic manifestations [3, 4]. Usually, patients return to normal hormone levels after surgical excision.

Moderately and poorly differentiated forms are the most common types and may contain heterologous elements such as hepatocytes, intestinal type mucinous epithelium, cartilage, and skeletal muscle.

SLCTs are associated with somatic and germline mutations of DICER1 and FOXL2 [5].

The overall prognosis is favorable but is related to the degree of differentiation and stage of the tumor [2].

We report here a case of ovarian SLCT in a 15-year-old female with elevated testosterone and alpha-fetoprotein (AFP) without specific differentiation or heterologous elements and review SLCTs producing AFP reported in the literature.

1. Introduction

Ovarian Sertoli-Leydig cell tumors (SLCTs) are rare mixed-sex-cord stromal tumors of the ovary, concerning less than 0.5% of all primary ovarian neoplasms [1]. It affects all age groups of patients, with 75% detected in young women less than 30 years (mean age of 25 years) and less than 10% detected after menopause. Most of the cases (97%) are unilateral and confined to the ovary at the diagnosis (FIGO stage I) [2].

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2. Material and Methods

Tissue was obtained at the surgery time and fixed in buffered 10% formalin. All sections were stained with routine hematoxylin-eosin safron.
Immunostainings were performed using a Benchmark Ultra immunostainer (Roche). The panel of antibodies used was Calretinin (SP65 clone, dilution 1/25, Sanbio), Inhibin (Alpha R1 clone, ready to use, Roche), Wilms’ Tumor gene (WT1) (6F-H2 clone, ready to use, Roche), Pankeratins (CKAE1/AE3) (PCK26 clone, ready to use, Roche), CD10 (56C6 clone, ready to use, Agilent), EMA (E29 clone, dilution 1/300, VWR), Chromogranin A (LK2H10 clone, ready to use, Roche), Synaptophysin (SP11 clone, ready to use, Roche), Hepatocyte Paraﬃn 1 (HepPar1) (OCH1E5 clone, ready to use, Roche), alpha-1-antitrypsin (Rabbit Polyclonal clone, ready to use, Agilent), and alpha-fetoprotein (AFP) (Rabbit Polyclonal clone, ready to use, Agilent). All stainings were controlled with external positive control tissues.

Slides and blocks were sent at Institut Curie (Paris) for complementary studies such as NGS analysis for DICER1 mutation and OCT3/4, SALL4 immunostainings.

A literature review was made on Pubmed using the keywords: “Sertoli tumor,” “Sertoli-leydig tumor,” and “alpha-foetoprotein.” We searched for cases of SLCTs with elevated

Figure 1: PRISMA 2020 flow diagram for updated systematic reviews [7].

Figure 2: MRI findings. Right adnexal mass with a solid and cystic appearance.
AFP levels and associated with specific differentiation and/or heterologous elements or not; in order to understand the origin of AFP production. Only English articles were included. We treated especially the recent largest literature review published by AL-Hussaini et al. made an update with new case reports found on Pubmed using the PRISMA flow diagram for updated systematic reviews [6, 7] (Figure 1).

3. Case Presentation

A 15-year-old female presenting complaints of abdominal pain, constipation, and spaniomenorrhea for three months was referred to the department of gynecology. The patient reported menarche at the age of 11 with regular menstrual cycles. No familial history of malignancy was reported. At the physical examination, no abnormalities were noted.

Axial T2-weighted magnetic resonance imaging (MRI) showed a right adnexal mass measuring 7.8 × 6.4 × 7 cm. Left ovary and uterus were unremarkable. There were not any ascites (Figure 2).

Elevated testosterone (66, 5 pmol/L; normal range 3.0-37, 0) and AFP (117 ng/mL; normal range at 14) were noted. Other ovarian tumor markers including beta-human chorionic gonadotropin (β-HCG), CA 125, CA 19-9, and carcino-embryonic antigen (CEA) remained negative.

A germ cell tumor (dysgerminoma and yolk sac tumor) or a pure sex cord tumor (juvenile granulosa cell tumor) was clinically suspected.

Laparoscopic right salpingo-oophorectomy was carried out after a multidisciplinary oncological concertation. No adverse event was encountered after surgery.

Macroscopic examination revealed a right ovary totally replaced by a tumor measuring 8, 5 × 5 × 4, 5 cm with an intact capsule (Figure 3). Gross sections demonstrated a brownish solid aspect with fibrous areas and partially cystic zones filled with clear yellow fluid.

Microscopic examination showed a tumor displaying a multinodular pattern with heterogenous cellularity and an intact capsule.

Cellular zones were composed of Sertoli-like spindle cells having scant-to-moderate amount of cytoplasm with round

Figure 3: Macroscopic aspect of the tumor. Enlarged ovary replaced by a solid and partially cystic tumor. Solid areas appear yellow-brownish in color with multiple foci of fibrous tissue. Cystic part filled with clear yellow fluid.

Figure 4: H&E staining at low power view. Cellular lobules are separated by zones of loose fibrous and fibromyxoid mesenchymal stroma (a). Sertoli-like spindle cells with the clusters of Leydig-like cells at the periphery (b).

Figure 5: H&E staining at high power view. Area of retiform pattern.
to oval nuclei and 0 to 1 little nucleoli. At the periphery of these areas, there were clusters of larger cells with a pale foamy cytoplasm and oval nuclei. There were also rare isolated cells with abundant clear cytoplasm.

Tumoral cells showed moderate atypia with a mitotic rate less than 2 mitoses per 10 high-power fields.

The stroma containing the tumor was characterized by edema, vascularization, and fibro-sclerotic changes (Figure 4).

There was one focal zone of retiform pattern less than 1 mm composed of larger cells (Figure 5).

On immunohistochemical studies, Sertoli-like cells showed nuclear staining for WT1, moderately positive cytoplasmic staining for inhibin and weakly positive nuclear and cytoplasmic staining for calretinin.

The Leydig-like cells demonstrated a strong positivity for inhibin and a moderate positivity for cytoplasmic calretinin staining.

Rare isolated cells with abundant clear cytoplasm were positive for cytokeratins (AE1AE3), AFP, and alpha-1-antitrypsin suggesting a hepatocytic differentiation but they did not display any staining for Cytokeratin7 and HepPar1 excluding a complete mature hepatocytic differentiation (Figure 6).

Tumoral cells demonstrated no staining for CD10, EMA, OCT3/4, SALL4, Chromogranin, and Synaptophysin. These stainings excluding the diagnosis of endometrioid carcinoma (CD10 and EMA), embryonal carcinoma (OCT3/4), yolk sac tumor (SALL4), and neuroectodermal-type tumors (ChromograninA and Synaptophysin).

Next-generation sequencing (NGS) revealed somatic DICER1 (c.5113G > A/p. (Glu1705Lys)) and (c.3007C > T/p.(Arg1003 *)) mutations.

Based on the above findings, we concluded to moderately differentiated SLCT with alpha-fetoprotein-producing cells without heterologous elements or specific differentiation (FIGO stage IA). No adjuvant therapy was given.

The patient reported spontaneous menstruation a few days after surgery with improvement of clinical symptoms.

AFP returns to normal range two months after tumor resection. A regular follow-up was planned, and no complaints or clinically relevant abnormalities were noted six months after surgery.

4. Discussion

We, hereby, report a rare case of SLCT of moderate differentiation with an unusual AFP-producing cell component and a clinical suspicion of germ cell tumor. In their large literature review, Al-Hussaini et al. reported approximately 50 cases of SLCTs with alpha-fetoprotein-producing component in the last 50 years [6].

We compare our case to these cases and to new case reports since this publication to understand the origin of AFP-producing cells (Table 1) [6, 8–11].

SLCTs present, in 40–60% of the cases, with signs and symptoms of hormone production related to the androgenic activity such as virilization, hirsutism, voice hoarseness, abnormal hair distribution, clitoromegaly, menstrual abnormalities, anovulation, and infertility. These elements are helpful to clinicians to make the differential diagnosis between epithelial and germ cell tumors [4]. SLCTs represent 20% of ovarian sex cord-stromal tumors in children [12].
Table 1: Cases of SLCT with elevated serum AFP: literature review [6, 8–11].

| References       | Year of publication | No. of cases | Age year | Diagnosis                   | Heterologous elements                                      | Serum AFP levels before the surgery (ng/mL) (normal range: 10-20) or (IU/mL) 0.0-5.8 IU/ml | Localization of AFP in tumor |
|------------------|---------------------|--------------|----------|-----------------------------|-------------------------------------------------------------|------------------------------------------------------------------------------------------------|-------------------------------|
| Benfield et al.  | 1982                | 1            | 16       | Androblastoma               | Intestinal-type mucinous epithelium                         | 400                                                                                 | Not performed                 |
| Chumas et al.    | 1984                | 1            | 16       | Moderately differentiated SLCT | Absent                                                       | 4 IU/mL                                                                           | Leydig cells                  |
| Young et al.     | 1984                | 1            | 13       | Retiform SLCT               | Intestinal-type mucinous epithelium and hepatocytes        | 14 000                                                                             | Hepatocytes                   |
| Sekiya et al.    | 1985                | 1            | 21       | SLCT                         | Absent                                                       | 109                                                                                 | Unidentified cells            |
| Mann et al.      | 1986                | 2            | 16/16    | SLCT                         | Absent                                                       | 40/62                                                                              | Leydig cells/not interpretable |
| Tetu et al.      | 1986                | 1            | 17       | Retiform SLCT               | Absent                                                       | 256                                                                                 | Leydig cells                  |
| Tiltman et al.   | 1986                | 1            | 27       | SLCT                         | Absent                                                       | 153                                                                                 | Leydig cells in the recurrence |
| Chadha et al.    | 1987                | 2            | 16/11 months | SLCT/retiform SLCT          | Intestinal-type mucinous epithelium and hepatocytes        | 4500/1500                                                                         | Sertoli cells/ hepatocytes    |
| Talerman.        | 1987                | 2            | Not available | Retiform SLCT               | Absent                                                       | 380-900/7000-1170                                                              | Sertoli and Leydig cells      |
| Gagnon et al.    | 1989                | 4            | 17/16/62/18 | Retiform SLCT/ moderately differentiated SLCT | Absent                                                   | 256/elevated/not available                                                   | Leydig cells                  |
| Motoyama et al.  | 1989                | 1            | 18       | Retiform SLCT               | Intestinal-type mucinous epithelium                         | 1443                                                                               | Sertoli cells                 |
| Taniyama et al.  | 1989                | 1            | 55       | SLCT                         | Absent                                                       | 105,7                                                                              | Leydig cells                  |
| Larsen et al.    | 1992                | 1            | 55       | Bilateral SLCT              | Absent                                                       | 200                                                                                | Not performed                 |
| Farley et al.    | 1995                | 1            | 18       | Poorly differentiated SLCT  | Absent                                                       | 850                                                                                 | Not available                 |
| Hammad et al.    | 1995                | 1            | 17       | Moderately differentiated SLCT | Hepatocytes and carcinoid tumor                            | 194                                                                                 | Hepatocytes                   |
| Singh et al.     | 1996                | 1            | 17       | SLCT                         | Intestinal-type mucinous epithelium                         | 40                                                                                  | Leydig cells                  |
| Gard et al.      | 1998                | 1            | 17       | Moderately differentiated SLCT | Absent                                                       | 2682                                                                                | Leydig cells                  |
| Mooney et al.    | 1999                | 5            | 44/74/18/23/15 | Moderately or poorly differentiated SLCT with retiform pattern | Hepatocytes                                              | Not available but elevated                                                   | Leydig cells/ hepatocytes     |
| Jang et al.      | 2002                | 1            | 26       | Moderately differentiated SLCT | Intestinal-type mucinous epithelium                         | 56,6                                                                                | Leydig cells                  |
| Gheorghisan-Galatenu et al. | 2003 | 1          | 69       | Well-differentiated SLCT     | Absent                                                       | Not available but elevated                                                   | Sertoli cells                 |
| Watanabe et al.  | 2008                | 1            | 20       | SLCT                         | Intestinal-type mucinous epithelium                         | 306                                                                                 | Intestinal-type mucinous epithelium |
| Poli et al.      | 2009                | 1            | 25       | Bilateral SLCT              | Absent                                                       | 101 U/mL                                                                            | Intestinal-type mucinous epithelium |
Laboratory tests are disturbed with elevated plasma testosterone at least 2.5 times its normal value. Elevated serum AFP levels are uncommon in SLCTs, and the significance of this production remains to be elucidated [12]. Tumors that are classically characterized by elevated AFP serum levels include yolk sac tumor, hepatocellular carcinoma, hepatoblastoma, and adenocarcinoma with hepatoid differentiation. Rare reports of female genital tract tumors with serum AFP elevation that concern ovarian neoplasms other than yolk sac tumor are immature teratoma, serous carcinoma, clear cell carcinoma, hepatoid carcinoma, mucinous carcinoma, and carcinosarcoma [6].

In normal situation, AFP is a major fetal plasma component produced in early fetal period by yolk sac, liver, and upper gastrointestinal tract. Its production declines rapidly in a few months after birth and reaches nearly undetectable levels for less than 10 ng/mL [12, 13]. Serum AFP is generally used as tumor marker of hepatocellular carcinomas in
adults and germ cell tumors in young patients. Elevated AFP is less frequently identified in lung, oesophagus, stomach, and pancreas carcinomas [14].

The origin of AFP-producing cells in SLCTs remains to elucidate. Several hypotheses have been reported defining AFP-producing cells to be Sertoli-Leydig-like cells, or endodermal derived cells such as hepatocytes or gastrointestinal type mucinous epithelia [15]. Based on the literature review of Al-Hussaini et al., we treated the 29 articles with a total of 46 reported cases.

26 cases presented heterologous elements with AFP production linked to the presence of intestinal-type mucinous epithelium or hepatocytes [15–17]. In their case report, Mooney et al. explained that hepatocytes and Leydig cells have morphological similarity and are closely located to each one [18].

Thus, AFP immunostaining is mandatory to distinguish these cells; Leydig cell is showing a fine cytoplasmic granular positivity for AFP and true hepatocytes displaying a stronger positivity [18].

In the other 20 cases, like our current case with no specific differentiation or heterologous element, the most frequent hypothesis is that AFP-producing cells are Leydig-like cells. The hypothesis is that the presence of crystalloid present in the cytoplasm of Leydig-like cells at HE stain cannot be identified in immunohistochemical stainings because of technical dissolution of crystalloid [6]. Other authors suggest that AFP-producing cells are endodermal sinus differentiation tissue too early to be recognized histologically [12, 19, 20].

Some consider these cells as hepatoid whether or not a clear immunohistochemical staining for HepPar1 is seen [21, 22]. In our case, AFP positive cells displayed immunostaining for CKA1/CKAE3 and alpha-1-antitrypsin with no staining for Cytokeratin7 and HepPar1. Moreover, like the article of Ikota et al., the AFP-producing cells were negative for ovarian sex cord-stromal stainings (alpha-inhibin and calretinin). These results support that these cells are neither Sertoli nor Leydig-like cells. Thus, like Ikota et al., we suggest that AFP-producing cells can be derived from an abruptly differentiated tumor element into immature hepatocytes [23].

Talerman and Farley et al. suggest that AFP quantity would be associated to the importance of Leydig-like cell component and tumor size [24, 25]. According to Tiltman et al., retiform pattern that is defined as irregular glandular zone resembling to rete testis seems to be associated with AFP production too [21].

Most authors insist that if AFP staining does not identify any cells, additional tissue sampling is mandatory to identify them [26].

In our complementary literature review, we found four new additional articles reporting five new cases since the last biggest review of Al-Hussaini et al. These cases are associated to heterologous elements and/or hepatocytes and mucinous epithelium with elevated AFP. AFP production is associated to Leydig cells in the case report of Singh et al. or to glandular mucosa cells of the colon in the others [8–11].

According to a large cohort study of Ovarian Sertoli-Leydig cell tumors by Young et al. in 1985, adjuvant chemotherapy is recommended for patients presenting advanced stage, intermediate differentiation, poor differentiation, retiform pattern, and presence of heterologous elements [2]. The optimal treatment algorithm is unknown given the rarity of SCSTs and clinical implications of different AFP producing cell origin are not known.

Furthermore, retiform pattern appears to be a misinterpretation problem and leads to describe it such as endodermal sinus tumor or serous adenocarcinomas [27].

Testing for DICER1 mutations should be performed in all patients with SLCTs because of management and therapeutic consequences. DICER1 mutations can be of germline or somatic type. In the case of germline mutations, called DICER1 syndrome, significant clinical relapse and morbidity occur in patients at young age [28].

5. Conclusion

In summary, we reported the case of a 15-year-old female with an unusual type of SLCT and highly elevated serum alpha-fetoprotein levels. AFP and alpha-1-antitrypsin stainings identified isolated AFP-producing cells.

An adequate sampling and microscopic examination are mandatory to identify AFP-producing cells in the cases of SLCT with AFP serum level elevation because of adjuvant therapy management.

These cases are reported to be of several origins such as intestinal-type mucinous epithelium, hepatocytes, Sertoli-Leydig cells, undifferentiated endodermal sinus differentiation tissue, retiform pattern, or abruptly differentiated tumor element into immature hepatocytes. In our case, we consider the AFP-producing cells to be immature hepatocytes.

This case contributes to the available knowledge on the biological, clinical, and histological diversity of SLCTs and specifically at this exceptional form with AFP-producing cells.

Data Availability

The data that support the findings of this case report are available from the corresponding author, Kacar Serife.

Conflicts of Interest

The authors declare that they have no conflict of interest regarding the publication of this article.

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