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CASE REPORT

Case of Gynandroblastoma of the Ovary with Raised AFP and Associated *DICER 1* Mutation

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Abstract
The case report depicts a 16-year-old female, who presented with complaints of an abdominal mass extending up to the xiphisternum. A CECT of the abdomen and pelvis showed a large right ovarian mass, solid cystic in consistency with raised *alfa-fetoprotein*. The patient underwent a right salpingo-oophorectomy. The frozen section histopathology showed a Sex cord-stromal tumor. The fertility-sparing staging surgery was performed, considering the young age of the patient. The final histopathology with immunohistochemistry revealed it to be a case of Gynandroblastoma [Sertoli Leydig cell component is intermediate to poorly differentiated (80%) + Juvenile Granulosa Cell Tumour (20%)]. The final FIGO stage was stage IA, grade 3. The patient was given adjuvant chemotherapy (4 cycles of BEP). NGS analysis showed a mutation in *the DICER1* gene. The follow-up at 12 months post-treatment of the patient is recurrence-free with serum tumor marker AFP within the normal range.

Keywords Gynandroblastoma · Sertoli–Leydig cell tumor · Alpha-fetoprotein (AFP) · *DICER1* gene

Abbreviations

SLCT	Sertoli–Leydig cell tumour
CECT	Contrast enhanced computed tomography
SCST	Sex cord stromal tumour
HPE	Histopathological examination
IHC	Immunohistochemistry
BEP	Bleomycin, etoposide, platinum
NGS	Next generation sequencing

Introduction

Gynandroblastoma, a rare sex cord-stromal tumour of the ovary usually exhibits an amalgam of two different histological elements, Granulosa cell tumour and Sertoli–Leydig cell tumour (SLCTs) differentiation. Conventionally, Gynandroblastoma mostly has adult-type granulosa cells, but Gynandroblastoma with a juvenile granulosa cell tumour component is extremely uncommon [1]. The alpha-fetoprotein (AFP) is a well-recognized tumour marker of germ cell tumours of the ovary. It has also been linked in SLCTs with some special histologic criteria. Sertoli Leydig cell tumour and Gynandroblastoma were commonly observed to be associated with *DICER1* mutation. *DICER1* mutation is a rare genetic mutation that predisposes individuals to numerous other benign and malignant tumours. We thus present our experience regarding the management of this rare case scenario of Gynandroblastoma with raised AFP and the presence of DICER1 mutation, as there are no standardized treatment protocol guidelines for this rare entity.

Case Summary

A 16-years female presented in the clinic with chief complaints of gradual abdominal distention along with complaints of irregular cycles for the last 6 months. The physical examination revealed a mass in the abdomen extending cranially almost up to the xiphisternum. A CECT of the abdomen and pelvis showed a large right ovarian mass, solid-cystic in appearance. The patient had operative tumour markers CA-125, B-HCG, and LDH within normal limits, except for the increased AFP level which was 263 ng/ml

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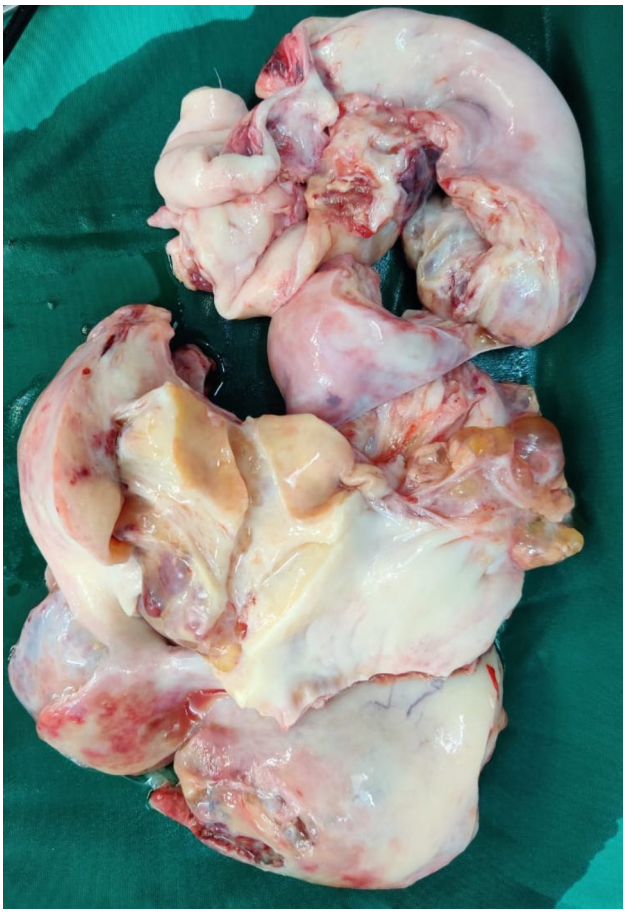

Fig. 1 Gross finding of a 25 × 20 cm ovarian mass with smooth outer surface. Cut surface shows solid and cystic area. Cystic area contains pale yellow non-sticky material, while solid area is yellowish in colour and soft to firm in consistency

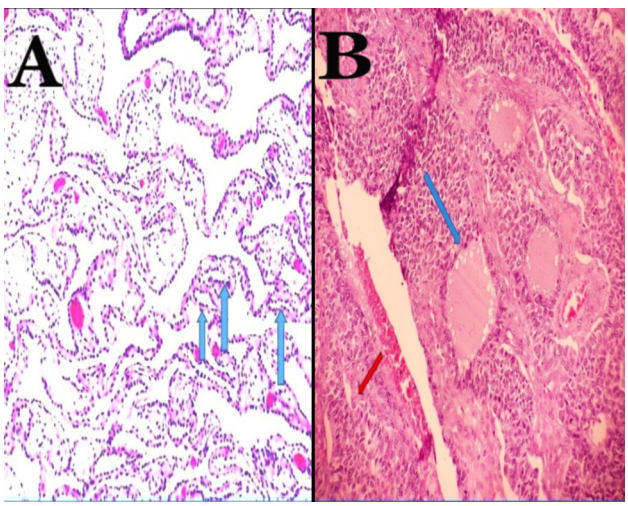

Fig. 2 **A** Microscopic finding slide showing Sertoli–Leydig cell tumour with poorly differentiated component and reticular pattern. **B** Microscopic finding slide showing Gynandroblastoma with mixed Sertoli Leydig cells tumour and Juvenile Granulosa cell tumour

(Normal 0–40 ng/ml). The patient underwent the operative procedure of right salpingo-oophorectomy. The frozen section histopathology (HPE) report revealed a sex cord-stromal tumour (SCST). Further, a fertility-sparing complete staging surgery was performed, considering the young age of the patient. The final FIGO stage for the case was stage IA, grade 3. The gross examination revealed a 25 × 20 cm ovarian mass with a smooth outer surface. The Cut surface showed a solid and cystic area (Fig. 1). The final HPE revealed it to be a very rare case scenario of Mixed sex cord-stromal tumour (Gynandroblastoma) [SLCT (80%) + Juvenile Granulosa Cell Tumour (20%)]. Sertoli Leydig cell component was intermediate to poorly differentiated with few scattered Leydig cell components, along with a focal retiform pattern. Diffuse mitosis was evident (15–20 mitosis/HPF). The juvenile component shows multiple solid nodules with secretions (resembling graffian follicles) (Fig. 2). The immunohistochemistry (IHC) markers inhibin, calretinin, vimentin, cytokeratin, and Melan A./Mart 1 were positive, while IHC markers EMA, CK7, and SALL4 were negative. The patient on genetic evaluation next-generation sequencing (NGS) technology was discovered to have a pathogenic *DICER1* mutation. She was advised to further familial genetic screening and counselling related to *DICER 1* syndrome. The onco-physician suggested adjuvant chemotherapy (4 cycles of BEP) based on poor prognostic factors as intermediate to poor differentiation of Sertoli Leydig cell component, tumour size > 30 cm, and 15–20/10 HPF mitosis. The patient is recurrence-free with serum tumour marker AFP within the normal range on 12 months post-treatment follow-up.

Discussion

The diagnosis of Gynandroblastoma tumour chiefly depends on the histologic features. The prerequisite diagnostic criteria for Gynandroblastoma requires that the minor tumour component (either Sertoli–Leydig cells in a GCT, or granulosa cells in an SLCT) should account for at least 10% of the entire tumour. Therefore, sufficient tumour sampling is essential for an accurate diagnosis. Although most reported GCT cases are of the adult type, a juvenile type has also been identified. The histology of adult-type and juvenile-type cells is the same for GCT; therefore, it is not difficult to diagnose these tumours. A study observed that despite several immunohistochemical markers that exist that aid differential diagnosis, these markers have a generalized application to diagnose every type of ovarian sex cord-stromal tumour and they are not specific to Gynandroblastoma. The representative sex cord-stromal cell markers include inhibin, calretinin, SF1, WT-1, CD99, cytokeratin, and vimentin [2]. MART-1/melan-A is a marker specific to SLT and

steroid cell tumours. In our case, both JGCT and SLT components were positive for inhibin, calretinin, cytokeratin, and vimentin.

The ovarian SLCTs can be classified into well-, moderately-, and poorly-differentiated, heterogeneous, and reticular tumours according to the degree and characteristics of differentiation as per the 2020 World Health Organization guideline. The prognosis of ovarian SLCTs is parallel to the clinical stage and pathological grade. The 5-year cancer-related survival was 100% for patients with (stages I–II) and 0% for an advanced tumour stage and 100%, 96%, and 33%, respectively, according to grade [2]. A study in the literature signifies the fact that SLCT relapses have a poorer prognosis and affect chiefly young patients, primarily after the initial diagnosis. It is difficult to characterize the biological behaviour of Gynandroblastoma due to its extremely low incidence. Based on the reported cases, it appears to have a benign course.

The proposed treatment recommendation for SLCTs depends on the fertility expectations as fertility-preserving procedures can be performed with complete surgical staging. Post-operative adjuvant chemotherapy is usually advisable in moderately or poorly differentiated cases, due to a higher risk of recurrence [2]. The commonly used chemotherapy regimen is bleomycin, etoposide, cisplatin, and paclitaxel combined with the platinum regimen. There is no clear consensus regarding the most effective chemotherapeutic regimen. The same treatment guideline was followed in our study.

The alpha-fetoprotein (AFP) is a distinguished tumour marker for germ cell tumours of the ovary, while it has also been identified in SLCTs with some special histologic patterns and with heterologous elements of gastrointestinal type [3]. Since, it is secreted in both primary and recurrent tumours, making it an important serological follow-up marker along with indicating the disease response to the treatment. In our study, the AFP level was found to be normalized after the surgery and was maintained within the normal range on follow-up.

Approximately 50–60% of SLCT occur in carriers of germline *DICER1* mutations. The study in medical literature concluded that moderately and poorly differentiated SLCT components often coexist with each other and are associated with *DICER1* mutations in almost all cases. In individuals with *DICER1* syndrome, SLCT is the most commonly observed sex cord–stromal ovarian tumour. SLCT patients with a family history often have thyroid abnormalities such as goitre and thyroid adenoma. These findings in amalgamation warrant a family heredity history for individuals affected with *DICER1* mutation. The vast majority of *DICER1* syndrome cancers have biallelic *DICER1* mutations limited to tumour tissue, which may represent mutations confined to the tumour. The studies in medical literature suggested that a mutation analysis study should combine germline mutation testing and tumour tissue testing for *DICER1*. This approach usually detects nearly all the SLCTs linked to *DICER1* mutation.

Hughes et al. [4], highlighted the fact that ovarian SCLTs are mostly unilateral, but bilateral neoplasms have also been reported, with different *DICER1* somatic hotspot mutations within the two ovarian tumours providing definitive proof that they represent independent neoplasms. These findings support the notion that bilateral ovarian SLCTs are indeed separate events and do not necessarily represent recurrent or metastatic disease. This led to a long-term follow-up of this case as the prognosis of metachronous SLCT is better compared to the recurrent tumour.

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Declarations

Conflict of interest The authors declare that they have no conflicts of interest and nothing to disclose.

Ethical Approval Research involving human participants and/or animals: Ethical committee approval not required, as it is a retrospective original case report.

Informed Consent Informed consent was obtained from the participant included in the study.

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