Exploring the Role of DICER1 Mutations in Ovarian Sex Cord-Stromal Tumors: A Retrospective Analysis and Implications for Surveillance

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ABSTRACT

Objective: Ovarian sex cord-stromal tumors (OSCSTs) are a rare and heterogeneous group, accounting for less than 1% of all malignancies and about 10% of ovarian tumors in childhood and adolescence. Some OSCSTs have been associated with germline pathogenic DICER1 variations. This study aims to determine the incidence of DICER1 pathogenic variations in a small cohort of OSCSTs and evaluate the clinicopathological features and patient outcomes.

Material and Methods: We retrospectively reviewed the medical records of the patients diagnosed with OSCSTs between 2014-2021. Molecular genetic sequencing of the tumor samples to detect a RNase IIIb domain hot spot mutation in DICER1 was performed in five patients.

Results: Molecular genetic sequencing of the tumor samples revealed a DICER1 gene mutation in exon 27 c.5437G>C (p.E1813Q) in a patient with Sertoli-Leydig cell tumour.

Conclusions: Although our study included a small number of patients, our findings highlight the importance of knowing the possible association between OSCSTs and pathogenic germline DICER1 variants since detecting this mutation may provide the opportunity for surveillance of related conditions that could improve long-term outcomes and survival, and also enable screening of family members.

Keywords: Ovarian Sex Cord-Stromal Tumors, DICER1 Mutations, Clinicopathological Features, Patient Outcomes, Germline Variants, Surveillance and Screening

INTRODUCTION

Ovarian sex cord-stromal tumors (OSCSTs) represent a heterogeneous group of rare tumours, which account for less than one percent of all malignancies, and approximately 10% of all ovarian tumors during childhood and adolescence (1)

These tumors originate from the non-germ cell component of the ovary and can exhibit varying degrees of differentiation. Sex cord-stromal tumors (SCSTs) display diverse clinicopathological features and biological behavior, sometimes sharing histomorphological characteristics with non-SCSTs. The heterogeneity and rarity of these tumors can pose diagnostic challenges.

Recent advancements in molecular genetics have identified molecular changes that hold promise for improving the diagnosis, treatment, and prognosis of SCSTs. In particular, DICER1 mutations have been reported in some OSCSTs, especially Sertoli-Leydig cell tumors (SLCTs) (2).
Recognizing somatic and germline DICER1 pathogenic variants in SCSTS underscores the importance of clinical, histologic, and molecular correlation. Identifying germline DICER1 pathogenic variants can facilitate proband and familial testing and surveillance.

Initially associated with familial pleuropulmonary blastoma (PPB), DICER1 germline pathogenic variants are now known to be linked to an increased risk of other conditions, such as cystic nephroma, multinodular goiter, and ovarian SLCTs (3-5).

In this case series, we aimed to evaluate the demographic and clinical data, treatment approaches, outcomes of OSCSTs, and their association with DICER1 variants.

**MATERIAL and METHODS**

Medical files of five patients with OSCST who were diagnosed between 2014-2021 at XXX hospital were retrospectively evaluated. Tumors were staged according to the International Federation of Gynecological Oncology (FIGO) staging (6). Molecular genetic sequencing of the tumor samples was performed to detect a RNase IIIb domain hot spot mutation in DICER1 using polymerase chain reaction amplification of genomic DNA extracted from the formalin-fixed, paraffin-embedded tumors, followed by Sanger sequencing. This study was approved by the institutional review board (2020-731, 17.02.2020). All participants or guardians gave written informed consent for collecting genetic testing and medical records.

**RESULTS**

The demographic, clinical characteristics, treatment and outcome have been evaluated (Table I). The median age at diagnosis of the five female patients was 13.1 (10.5-15.3) years. Presenting symptoms were abdominal pain/mass in three menstrual irregularities in two patients, one of whom had signs of virilization. All patients had a unilateral tumor. FIGO stage was: Ia (n=4) and Ic (n=1). The histological subtypes of the tumors were granulosa cell tumor in two and Sertoli-Leydig cell tumor, steroid cell tumor, and sclerosing stromal tumor in one each.

All patients underwent resection by unilateral salpingo-oophorectomy (n=3), unilateral oophorectomy (n=1) or with tumor enucleation (n=1). None of the patients received additional treatment. They are under follow-up with no evidence of disease for a median of 13 (8-98) months. Molecular genetic sequencing of the patient’s tumour sample with SLCT revealed a DICER1 gene mutation in exon 27 c.5437G>C (p.E1813Q).

**DISCUSSION**

Ovarian SCSTS constitute approximately 10% of all ovarian tumors in childhood.1 These tumors, which are ovarian tumors that can produce hormones such as androgens and estrogen, should be considered especially in the presence of rapidly developing clinical hyperandrogenism and virilization findings in children and adolescents. They may also present with prepubertal vaginal bleeding, peripheral precocious puberty, unexplained menstrual changes and abnormal uterine bleeding. In addition, as with other ovarian tumors, symptoms such as abdominal pain and bloating may be the first sign or they can be detected incidentally on examination or imaging.

Ovarian SCSTS originate from the non-germ cell component of the ovary and are classified by the World Health Organization into three major groups: pure stromal tumors, pure sex cord tumors, and mixed sex-cord-stromal tumors. Pure stromal tumors originate from mesenchymal cells of the ovarian stroma and include fibromas, thecomas, sclerosing stromal tumors, microcystic stromal tumors. Leydig cell tumors, and steroid cell tumors. Pure sex cord tumors, such as granulosa cell tumors, Sertoli cell tumors, and sex cord tumors with annular tubules, originate from primitive sex cord cells. Mixed sex cord-stromal tumors include Sertoli–Leydig cell tumors and sex cord-stromal tumors not otherwise specified (7). SLCTs are histologically classified as well differentiated, moderately differentiated and poorly differentiated depending on the extent of tubular differentiation and quantity of primitive stroma.

Recent studies on SCSTS have revealed molecular alterations with significant diagnostic, prognostic and therapeutic implications. The association between DICER1 variants and SLCTs is one of these alterations (8, 9).

**Table I.** Clinicopathological Characteristics, Treatment Modalities Used, Outcomes of the Patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age at diagnosis (years)</th>
<th>Histologic type</th>
<th>Signs and symptoms at presentation</th>
<th>DICER1 mutation status</th>
<th>Stage, FIGO</th>
<th>Treatment</th>
<th>Type of surgery</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12.2</td>
<td>SLCT</td>
<td>Groin pain</td>
<td>+</td>
<td>IC</td>
<td>Surgery</td>
<td>Left salpingo-oophorectomy</td>
<td>NED</td>
</tr>
<tr>
<td>2</td>
<td>10.5</td>
<td>JGCT</td>
<td>Abdominal pain</td>
<td>-</td>
<td>IA</td>
<td>Surgery</td>
<td>Left salpingo-oophorectomy</td>
<td>NED</td>
</tr>
<tr>
<td>3</td>
<td>13.1</td>
<td>SST</td>
<td>Menstrual irregularity</td>
<td>-</td>
<td>IA</td>
<td>Surgery</td>
<td>Left salpingo-oophorectomy</td>
<td>NED</td>
</tr>
<tr>
<td>4</td>
<td>15</td>
<td>aGCT</td>
<td>Abdominal distension</td>
<td>-</td>
<td>IA</td>
<td>Surgery</td>
<td>Right salpingo-oophorectomy</td>
<td>NED</td>
</tr>
<tr>
<td>5</td>
<td>15.3</td>
<td>Ovarian steroid cell tumor</td>
<td>Menstrual irregularity, virilisation</td>
<td>-</td>
<td>IA</td>
<td>Surgery</td>
<td>Tumor enucleation</td>
<td>NED</td>
</tr>
</tbody>
</table>

©SLCT: Sertoli-Leydig cell tumours; JGCT: juvenile granulosa cell tumor; SST: sclerosing stromal tumor; aGCT: adult-type granulosa cell tumor; NED: no evidence of disease.
DICER1 gene is located on chromosome 14q32.13 and encodes protein DICER1, whose endoribonuclease domains RNAse IIIa and IIIb play a critical role in the maturation of microRNAs, which are non-coding small RNA fragments that regulate post-transcriptional gene expression. Oncogenic and tumor suppressor effects of miRNAs have been demonstrated in several studies. When mutations occur in any component of the miRNA functional pathway, miRNA expression is affected, resulting in dysregulation of target mRNA expression (10).

Prior studies have shown that DICER1 somatic mutations are seen at a frequency of 30-70% in SLCTs; it has been reported that this frequency may be up to 100% in moderately and poorly differentiated tumors. Germline pathogenic variants may be seen in up to 60% (3, 11-14). DICER1 somatic mutations in SLCTs are missense 'hotspots' mutations that affect codons encoding metal-binding sites in RNAse IIIb catalytic centers that are obligatory for the interaction and splitting of microRNAs (11, 15).

Germline pathogenic variants were first reported in familial pleuropulmonary blastoma and are now known to be associated with the development of other rare neoplasms such as cervical and uterine embryonal rhabdomyosarcoma, pituitary blastoma, medulloblastoma, pineoblastoma, and Wilms tumour (16-20). Although many individuals with germline pathogenic DICER1 variants are healthy, neoplastic conditions develop in approximately 19% by the age of 50. (21) Germline variants are often truncating mutations such as nonsense, frameshift or splice site variants resulting in loss-of-function (22).

DICER1 mutations are present in the vast majority of moderately and poorly differentiated subtypes (3, 11). SLCTs with DICER1 mutations are typically diagnosed at a younger age (median 24.5 years) compared to those with sporadic tumors. (9, 12)

DICER1 variants may also be found in other sex cord-stromal tumors. Both somatic and germline mutations of DICER1 have been reported with a frequency of 19-80% in gynandroblastomas, tumors that contain both juvenile granulosa cell tumor and SLCT components (4). In the literature, DICER1 somatic mutations in JGCTs have been reported with a frequency of 5% and the presence of germline variants in two cases (23). In a previous study, the frequency of DICER1 mutations in ovarian Sertoli cell tumors was reported to be around 60% which is almost similar to that in SLCTs. (24)

Demonstrating the relationship between DICER1 mutation and SCSTs, especially SLCT, has shed light on the clinicopathological features that may predict the molecular status.

**CONCLUSION**

In summary, our study aims to describe the spectrum of OSCST seen in children and adolescents in a single center in Turkey and highlights the importance of clinical correlation and consideration of DICER1 testing to facilitate early diagnosis of other DICER1-related. In addition, detection of a germline pathogenic variant in a proband and genetic counselling may provide the opportunity for surveillance of related conditions in family members and improve long-term outcomes and survival.

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**Author Contributions:** UMY, DD, OD, IY, NK, EE, SO, KAPS, RK; contributed to the conception of the work, execution of the study, revision of the draft, RK; approval of the final manuscript version, and concur with all aspects of the work. All authors have reviewed the manuscript, and affirm that they fulfill the ICMJE criteria for authorship.

**Ethical approval:** The present study was conducted in strict accordance with the principles outlined in the Declaration of Helsinki. Ethical approval for the study was obtained from the appropriate ethics committee, and all participants provided informed consent before participating in the study.

**REFERENCES**


