Ovarian Granulosa Cell Tumor Associated With Hyperparathyroidism-Jaw Tumor Syndrome

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*Potential conflict of interest may exist. Refer to the ENDO 2017 Meeting App.*

INTRODUCTION

Hyperparathyroidism-Jaw Tumor Syndrome (HPT-JT) is a rare autosomal dominant disorder characterized by primary hyperparathyroidism (PHPT), calcifying fibrous odontogenic tumor of the mandible or maxilla, kidney lesions and uterine tumors. This is caused by a heterozygous germline pathogenic mutation in CDC73. To our knowledge, this is the first reported case of an ovarian granulosa cell tumor (GCT) associated with HPT-JT.

CASE

A 31 year old woman with persistent abdominal pain was found to have a heterogenous 3 cm right ovarian cyst on pelvic ultrasound and MRI. A laparoscopic right ovarian cystectomy was performed which revealed an adult GCT. She was referred to gynecologic oncology. Surgical staging with possible bilateral salpingo-oophorectomy was planned.

She was also referred to endocrinology for low bone density although values were within the expected range for age.

Her history was significant for PHPT at age 23 with a calcium of 10.8 mg/dL, ionized calcium of 1.48 mmol/L, PTH of 170 pg/mL and 24 hour urinary calcium of 275 mg. She underwent subtotal parathyroidectomy. Of note, her father also had right nephrectomy with 12 cm renal mass as well as history of renal cysts. Her brother and 2 maternal aunts have reported normal calcium levels.

There was no history of fractures. Her examination was normal. Calcium, creatinine, phosphorus, PTH, 25-DH Vitamin D, and 24 hour urinary calcium were all normal. Her personal and familial history of PHPT, she underwent germline gene sequencing and exome/description analyses associated with HPT-JT involving CASR, CDC73, CDKNIB, MEN1 and RET. Result showed a CDC73 gene pathogenic mutation (c.687_688dupAG) which creates a premature translational stop signal causing loss-of-function. Due to the history of GCT, 52 other tumor predisposition genes, including STK11, were analyzed which did not show pathogenic mutations.

She underwent a right salpingo-oophorectomy with fertility sparing staging surgery. No residual disease was noted on final pathology (Stage IC). The uterus and left ovary were preserved.

Our patient was found to have a frameshift mutation at exon 7 of the CDC73 gene. HPT-JT is very likely in the setting of her personal and familial history of PHPT as well as renal cysts in her mother. She also has a rare granulosa cell tumor of her ovary.

Immunohistochemical analysis of paraffin was done in the ovarian tissue to see whether loss of expression is present as has been observed in cases of parathyroid carcinoma and HPT-JT. Paraffin staining was preserved in both the normal tissue and the malignant tumor. Although the presence of paraffin expression in the ovarian tumor is unrelated to the CDC73 mutation, we believe the chance occurrence of this rare ovarian tumor in a patient with HPT-JT is unlikely. Also, it is possible that it is the truncated, non-functional protein that may be deteched by the paraffin stain. Therefore, we believe we will not be able to include it in our analysis of the potential of other types of epithelia. Weak cytoplasmic immunostaining in the oesophagus as well the following findings of the adenomas were noted but staining was not preserved elsewhere in the female genital germ cell system including the uterus. A possible role of paraffin down regulation in promoting malignant transformation of ovarian epithelial cells has also been reported.

DISCUSSION

Hyperparathyroidism-Jaw Tumor Syndrome is one of the familial syndromes of primary hyperparathyroidism (PHPT), characterized by the presence of parathyroid adenomas and/or parathyroid hyperplasia inherited in an autosomal dominant fashion. About 80% of patients with HPT-JT syndrome develop PHPT from an underlying parathyroid adenoma, although 10-15% of these cases are caused by parathyroid carcinoma. AFFECTED individuals may also have benign neoplasia of the osseous tissues of the maxilla or mandible, as well as benign or malignant tumors involving the kidneys and the uterus. We found no reports of ovarian tumors with HPT-JT. However, there is a report of a bilateral ovarian granulosa cell tumor in a patient with MEN-1.24

Granulosa cell tumors are rare, accounting for less than 5% of all ovarian tumors. They usually occur in a younger age group who present with nonspecific symptoms such as abdominal pain or distention. Somatic mutation in the CDC73/Cdc73 homologous to yeast Cdc73p, which encodes for the parafibromin tumor suppressor gene. The parafibromin functions in promoting malignant transformation of ovarian epithelial cells has also been reported.

**Table 1: PHPT Labs**

<table>
<thead>
<tr>
<th>Calcium</th>
<th>Normal Values</th>
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<tbody>
<tr>
<td>Patient</td>
<td>10.8-10.2 mg/dL</td>
</tr>
<tr>
<td>Ionized Calcium</td>
<td>1.48</td>
</tr>
<tr>
<td>1-1.83 mmol/L</td>
<td></td>
</tr>
<tr>
<td>24hr Ur Calcium</td>
<td>275</td>
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<tr>
<td>100-321 mg/24h</td>
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**Table 2: Genetic Analysis**

<table>
<thead>
<tr>
<th>Mutation Present</th>
<th>Mutation Absent</th>
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<tr>
<td>CASR</td>
<td>CDKNIB, MEN1, RET, STK11</td>
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</table>

**Table 3: Paraffin staining of the granulosa cell tumor (A) and normal ovarian tissue (B)**

**REFERENCES**