Korea-Taiwan-Japan Joint Meeting for Gynecological Pathology
Mini-lecture

Female Adnexal Tumor of Probable Wolffian Origin (FATWO) in Taiwan: A Small Case Series and Literature Review

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Outlines

• Introduction & Literature Review

• Case Series
  • Morphology
  • Immunohistochemical profiles
  • Genetic profiles

• Take Home Message
Introduction: Female Adnexal Tumor of Probable Wolffian Origin (FATWO)

- Rare extraovarian, extratubal tumors firstly reported by Kariminejad and Scully in a 9-case series in 1973.

- Currently “an epithelial tumor of Wolffian (mesonephric) origin.”

- Most of the cases are benign or indolent tumors confined within adnexa.

- Low grade malignant potential or aggressive behaviors in a minor (10%) cases
  - Recurrence / Metastasis
Location & Gross Features

- Often in broad ligament, mesosalpinx, ovarian hilus and pelvis.
Location & Gross Features

- Often in broad ligament, mesosalpinx, ovarian hilus and pelvis.

- **Encapsulated, solid** ovoid masses with **nodular, or lobulated** appearance.
Three Pattern in the Original Article

- Solid or diffuse arrangement
- Closely packed, winding, branching, and anastomosing tubules
- A sieve-like pattern with hollow tubules varying in size and shape with occasional cyst formation
Three Pattern in the Original Article
Case Series
Case Series in Taiwan

- An inter-institutional review
- Four cases (1 benign, 3 malignant) retrieved
- All arising from adnexa of middle to old age women (50~63 y/o)
- Size varies from <1 cm to 16 cm
- 3 malignant cases
  - Radical surgery and chemotherapy
  - One with local recurrence
  - Follow-up interval: 12~51 months
  - All alive with or without diseases
<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>primary site</th>
<th>Surgery</th>
<th>Chemo</th>
<th>Interval of F/U</th>
<th>Current status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>60</td>
<td>right fallopian tube</td>
<td>salpingo-oophorectomy</td>
<td>N</td>
<td>Loss of F/U</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>right adnexa</td>
<td>Staging surgery</td>
<td>Y</td>
<td>12 months</td>
<td>alive</td>
</tr>
<tr>
<td>3</td>
<td>61</td>
<td>left ovary</td>
<td>Staging surgery</td>
<td>Y</td>
<td>42 months</td>
<td>alive</td>
</tr>
<tr>
<td>4</td>
<td>63</td>
<td>left ovary</td>
<td>Staging surgery</td>
<td>Y</td>
<td>51 months</td>
<td>alive, recur once</td>
</tr>
</tbody>
</table>
Microscopic finding in four cases
Case 1
Sieve-like pattern
Case 2
Solid and sieve-like pattern
Case 3
Solid and tubular pattern
Case 4
Spindle cell morphology
Summary in morphology

- **Sieve-like** and **tubular** pattern are most characteristic.

- Solid or spindle cell morphology would cause difficulty in diagnosis
  - Try to find minor sieve-like or tubular components

- Malignant cases defined by **nuclear atypia, infiltrative growth pattern** and frequent mitoses
  - The nuclear grading is not so “high grade” to fit in typical high grade carcinoma or sarcoma
How to Make Differential Diagnosis?

• Gross examination
  • Primary site?
    • Ovary? Tube? Others?

• Microscopic examination
  • Diffuse pattern
  • Tubular pattern
  • Sieve-like pattern
  • Spindle cell morphology
How to Making Differential Diagnosis?

• **Diffuse pattern**
  • Un-/Poorly-differentiated carcinoma?
  • Neuroendocrine carcinoma?

• **Tubular pattern**
  • Endometrioid adenocarcinoma?
  • Granulosa cell tumor?
  • Sertoli (leydig) cell tumor?

• **Sieve-like pattern**
  • Endometrioid adenocarcinoma?
  • Granulosa cell tumor?
  • Adenomatoid tumor/Mesothelioma?

• **Spindle cell morphology**
  • Adenomatoid tumor/Mesothelioma?
  • Fibroma/Thecoma?
  • Sarcoma? (Leiomyosarcoma? Endometrial stromal sarcoma?)
Immunohistochemical profiles
## Table 1: Immunohistochemical Staining of Wolffian Adnexal Tumors and Controls

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Wolffian Adnexal Tumor</th>
<th>Rete Ovari</th>
<th>Mesonephric Remnants</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. Positive (%)</td>
<td>No. Positive (%)</td>
<td>No. Positive (%)</td>
</tr>
<tr>
<td>AE1/3, CK1</td>
<td>25 (100)</td>
<td>12 (100)</td>
<td>10 (100)</td>
</tr>
<tr>
<td>CAM 5.2</td>
<td>25 (100)</td>
<td>12 (100)</td>
<td>10 (100)</td>
</tr>
<tr>
<td>CK7</td>
<td>22 (88), focal</td>
<td>12 (100), focal</td>
<td>10 (100), diffuse</td>
</tr>
<tr>
<td>CK20</td>
<td>2 (8), focal</td>
<td>0 (0)</td>
<td>1 (10)</td>
</tr>
<tr>
<td>EMA</td>
<td>3 (12), focal</td>
<td>0 (0)</td>
<td>10 (100)</td>
</tr>
<tr>
<td>Keratin 903</td>
<td>4 (17)</td>
<td>7 (59), focal</td>
<td>9 (90)</td>
</tr>
<tr>
<td>Inhibin</td>
<td>17 (68)</td>
<td>7 (59)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>ER</td>
<td>7 (28)</td>
<td>1 (8)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>PR</td>
<td>6 (24)</td>
<td>1 (8)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>AR</td>
<td>11 (78)</td>
<td>5 (100)</td>
<td>5 (100)</td>
</tr>
<tr>
<td>Calretinin</td>
<td>20 (91)</td>
<td>3 (100)</td>
<td>5 (83)</td>
</tr>
<tr>
<td>Vimentin</td>
<td>25 (100)</td>
<td>9 (90)</td>
<td>5 (50)</td>
</tr>
<tr>
<td>mCEA</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>
Not performed
Inhibin
Not available, also positive
Are General Markers Helpful?

<table>
<thead>
<tr>
<th>Case</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>CK</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>EMA</td>
<td>-</td>
<td>-</td>
<td>Focal +</td>
<td>/</td>
</tr>
<tr>
<td>Inhibin</td>
<td>-</td>
<td>-</td>
<td>Weak +</td>
<td>-</td>
</tr>
<tr>
<td>Calretinin</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CD10</td>
<td>Focal +</td>
<td>Focal +</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>
Value of PAX-8 and SF-1 Immunohistochemistry in the Distinction Between Female Adnexal Tumor of Probable Wolffian Origin and its Mimics

Abha Goyal, M.D., Ramya P. Masand, M.D., and Andres A. Roma, M.D.
Summary in IHC profiles

- **Markers with diffuse expression**
  - Pan-CK / Calretinin / Vimentin

- **Markers with variable expression**
  - Inhibin / Hormonal marker (ER/PR) / CD10

- **Marker for differential diagnosis**
  - Inhibin / Pax-8 / CD10

A Possible Panel

- Pan-CK / Calretinin / Inhibin / CD10 / Pax-8
Case Report

Female adnexal tumor of probable wolffian origin: Morphological, immunohistochemical, and ultrastructural study with c-kit gene analysis

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Pathology International 2006; 56:95-100
Genetic Profiles

- CD117 (c-kit) expression: not necessarily relating to genetic mutation on c-kit and PDGFR gene (Harada, et al. Pathology International 2006; 56: 95-100)

- NGS analysis revealing FATWO a genetically heterogeneous tumor (Cossu, et al. Int J Gynecol Pathol 2017 (Epub ahead))

  - Three cases, three pathways: CTNNB1 + MET / PIK3CA / BRAF + CDKN2A

<table>
<thead>
<tr>
<th>Case</th>
<th>Gene</th>
<th>Protein</th>
<th>Coding</th>
<th>Function</th>
<th>Type</th>
<th>Coverage</th>
<th>Allele Coverage</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>CTNNB1</td>
<td>p.Ser33Cys</td>
<td>c.98C&gt;G</td>
<td>Missense</td>
<td>SNV</td>
<td>1768</td>
<td>C = 1090, G = 678</td>
</tr>
<tr>
<td>1</td>
<td>MET</td>
<td>p.Glu168Asp</td>
<td>c.504G&gt;T</td>
<td>Missense</td>
<td>SNV</td>
<td>1986</td>
<td>G = 1020, T = 966</td>
</tr>
<tr>
<td>1</td>
<td>KDR</td>
<td>p.Gln472His</td>
<td>c.1416A&gt;T</td>
<td>Missense</td>
<td>SNV</td>
<td>1994</td>
<td>A = 1036, T = 958</td>
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<tr>
<td>2</td>
<td>BRAF</td>
<td>p.Val600Glu</td>
<td>c.1799T&gt;A</td>
<td>Missense</td>
<td>SNV</td>
<td>1495</td>
<td>T = 1324, A = 171</td>
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<tr>
<td>2</td>
<td>CDKN2A</td>
<td>p.Tyr129Ter</td>
<td>c.387C&gt;A</td>
<td>Nonsense</td>
<td>SNV</td>
<td>1999</td>
<td>C = 1241, A = 758</td>
</tr>
<tr>
<td>2</td>
<td>TP53</td>
<td>p.Pro72Arg</td>
<td>c.215C&gt;G</td>
<td>Missense</td>
<td>SNV</td>
<td>1361</td>
<td>C = 74, G = 1287</td>
</tr>
<tr>
<td>2</td>
<td>KDR</td>
<td>p.Gln472His</td>
<td>c.1416A&gt;T</td>
<td>Missense</td>
<td>SNV</td>
<td>1055</td>
<td>A = 991, T = 64</td>
</tr>
<tr>
<td>3</td>
<td>PIK3CA</td>
<td>p.Ile391Met</td>
<td>c.1173A&gt;G</td>
<td>Missense</td>
<td>SNV</td>
<td>1726</td>
<td>A = 723, G = 1003</td>
</tr>
<tr>
<td>3</td>
<td>KDR</td>
<td>p.Gln472His</td>
<td>c.1416A&gt;T</td>
<td>Missense</td>
<td>SNV</td>
<td>1994</td>
<td>A = 971, T = 1023</td>
</tr>
</tbody>
</table>

Functionally unknown sequence variants are italicized.
NGS indicates next-generation sequencing; SNV, single-nucleotide variations.
Take Home Message

• FATWOs are rare and possibly misdiagnosed.
  • Identification of characteristic **Sieve-like** and **tubular** pattern would be helpful in diagnosis

• Using an IHC panel would be also helpful
  • Pan-CK / Calretinin / Inhibin / CD10 / Pax-8

• Heterogeneity in genetics

• No histological criterion predicting clinical behavior, and no standard treatment medication
Acknowledgement

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Thank you for your attention