Diversity among Teratomas, with a Historical Perspective

Thomas M. Ulbright, MD
Indiana University School of Medicine
Indianapolis, Indiana

Bookkeeping

- I have no conflicts of interests or financial disclosures to declare that are relevant to this talk. (More’s the pity.)

Teratoma

- **Etymology**: Greek τέρατα = monsters
- Teratoma, literally, “monster tumor;” same root for teratogenic, “monsters inducing”
- In antiquity, many “teratomas,” as originally defined, were likely malformed, non-separated monozygous twins (so-called “fetus in fetu”)
2 forms of teratoma:

- **External**: epignathic & coccygeal (explainable based on anomalies of the "organizers of Spemann;" likely what today we would consider inappropriately active signaling molecules stimulating stem cells)
- **Internal (gonadal)**: parthenogenesis of germ cells
Dr. James Ewing:
First Professor of Pathology at Cornell (1899). Appointed Pathologist at General Memorial Hospital in 1913. Published *Neoplastic Diseases: A Text-Book on Tumors*, in 1919, the first credible American pathology reference.

From: Ewing, Neoplastic Diseases, 1919
- 3 forms of “teratoma” (originating from “a nearly mature spermatoblast or its near antecedents”; also recognizes ovum as origin of ovarian teratomas)
  - Adult embryos or teratomas (i.e. – resembling fetal or adult tissues)
  - Embryoid, teratoid or mixed tumors (i.e. – as above but with a component of an “embryonal malignant tumor”)
  - Embryonal malignant tumors (what today we would consider seminoma, embryonal carcinoma, PNET, etc.)
- Similar to the BTP classification where embryonal carcinoma = “malignant teratoma, undifferentiated”
In this model there is no need for a distinction of teratomas based on site of origin. The difference between ovarian and testicular teratomas is attributed to the greater tendency for the latter to dedifferentiate. RA Willis, in the AFIP fascicle he authored in 1951, maintains this model. Accordingly benign teratomas are those that are "wholly mature."

**TUMORS OF THE TESTIS**

A REPORT ON 923 CASES

By MAJOR NATHAN R. FRIEDMAN, Medical Corps, Army of the United States, and ROBERT A. MOORE, M.D., Resident Consultant


<table>
<thead>
<tr>
<th>Type of Tumor</th>
<th>Tumor no.</th>
<th>No. of Deaths from Tumor</th>
<th>No. of Living Patients with Metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testicular</td>
<td>219</td>
<td>9 (4.1%)</td>
<td>16 (9.3%)</td>
</tr>
<tr>
<td>Teratomas</td>
<td>12</td>
<td>6 (50%)</td>
<td>6 (50%)</td>
</tr>
<tr>
<td>Teratomas</td>
<td>29</td>
<td>10 (35%)</td>
<td>10 (35%)</td>
</tr>
</tbody>
</table>

"If teratoma has no histologically recognizable malignant components, the qualified designation 'adult' is justified; the term 'benign' should never be used, because metastasis of testicular tumors which appeared to be only adult teratomas has occurred."

"The results of this study do not support the conventional theory that malignant tumors of the testis usually arise from teratomas."
It doesn't matter how beautiful your theory is; it doesn't matter how smart you are. If it doesn't agree with experiment, it's wrong.

Richard P. Feynman

From: Friedman & Moore, 1946

Additional support for the model

- Postpubertal testicular teratomas are aneuploid and associated with germ cell neoplasia in situ (GCNIS)
- In mixed GCTs the teratoma components have similar cytogenetic and molecular findings (LOH patterns) as the associated primitive germ cell tumors
- They have i(12p)
Meanwhile, pediatric testicular teratomas are proven entirely different from postpubertal ones

- Diploid DNA content
- Normal karyotype
- Negative for i(12p)
- Not associated with primitive germ cell tumors, except rarely YST & usually only focally
- Not associated with GCNIS
- Benign clinical course

Largely secondary to the work of Friedman and Moore, testicular teratomas are recognized as different from other teratomas.

Although no malignant areas may be identified, teratoma should not be designated as benign. – Mostofi and Price, 1973

Mature teratoma may be clinically benign in infants only – not in adults. - Garnick MB et al, in: Holland and Frei, 1982

In the majority of cases, teratomas are benign... The principal exception to this is in the testis, where the majority of teratomatous tumors have malignant potential. – Ashley, In: Evans’ Histological Appearance of Tumours, 1990

From: Friedman & Moore, 1946
Tetrahedron model of testicular germ cell tumor histogenesis.

Based on: Srigley et al. Ultrastruct Pathol, 1988
Oosterhuis et al, Lab Invest, 1989, and others

Meanwhile, ovarian teratomas are proven parthenogenetic

Dermoid cysts are homozygous for isozymes that are heterozygous in the non-teratomatous tissues of the patient
Linder, PNAS, 1969 (UCSF)
Dermoid cysts are homozygous for polymorphic genes in patients who are heterozygous for the same alleles.
Linder et al, NEJM, 1975 (Univ of Oregon Health Sciences Center)
The findings indicate origin from a germ cell between meiosis I and meiosis II.

Ovarian teratomas with malignant transformation (usually SCC) have the same marker chromosomes in the benign and malignant components. Therefore the latter derives from the former.
My concept of gonadal GCT histogenesis, circa 2005

Some ovarian teratomas, however, are different

A 17-year-old boy presents with bilateral testicular masses that on U/S are heterogeneous and hypovascular. Serum marker studies are negative and radiographic studies show no evidence of metastatic disease. Biopsy of the left testis is performed.
Testis: “Dysgenesis”

GCNIS

12  i(12p)
Ancillary testing: No evidence of 12p amplification in teratomatous epithelium

Dx: Benign, postpubertal teratoma, non-dermoid type (WHO 2016: “Teratoma, prepubertal-type”)
Recent work re: benign testis teratoma in postpubertal patients (Zhang et al; AJSP, 2013)

- 25 cases of dermoid cyst (n=10) and non-dermoid teratoma with benign features (n=15) in postpubertal patients (12 – 59 years)
- No 12p amplification in 18 of 18 cases
- Rx - orchiectomy (n=17) or local excision (N=6) only (no information – n=2)
- F/U in 17 cases, 5–168 mos (median, 89). All alive with 11 NED & 6 disease status unknown; no patient known DOD

Proposed criteria for benign postpubertal teratoma

- No cytologic atypia
- No GCNIS
- Intact spermatogenesis w/o tubular sclerosis/atrophy, scars or microliths
- No 12p amplification
- (Often prominent ciliated epithelium, smooth muscle, squamous cysts and organoid features)

My concept of gonadal GCT histogenesis, circa 2016
Meanwhile, extragonadal teratomas of children are proven to be non-parthenogenetic

- Extragonadal teratomas (and YSTs) in children (predominantly SCTs) are proven to be heterozygous for polymorphic alleles in patients who are heterozygous for those same alleles.
  Linder et al, Nature, 1975
- Extragonadal teratomas have normal karyotypes.
  Bussey et al, Genes Chromosomes Cancer, 1999
- Sacrococcygeal teratomas lack i(12p).
  Gurda et al, Mod Pathol, 2014
They therefore arise from a benign, mitotic (?)somatic and not meiotic cell

Malignant change in SCTs (YST) probably represents progression from teratoma (the Ewing model)

Among 231 pure SCTs, 13 subsequently recurred as YST

There is a progression of cytogenetic changes in SCTs from teratoma to YST; teratoma is diploid; YST is aneuploid and exhibits variable chromosomal anomalies (gain of 1q, 12(p13) & 20q; loss of 1p, 4 & 6q)
In the mediastinum the whole spectrum of pathogeneses is present

- In children < 8 years old, mediastinal teratomas have normal CGH findings
- Malignant mediastinal GCTs (all=YSTs), show features similar to SCGCTs (gain of 1q, 3, and 20q; loss of 1p, 4q, and 6q; no 12p amplification)

Schneider et al: Genes Chromosomes Cancer, 2002
Probable Pathogenesis of Mediastinal Teratomas in Postpubertal Females

Benign Stem Cell → Germ Cell-like Stem Cell → Teratoma

Mediastinal Germ Cell Tumors in Postpubertal Female Patients (N=128)

- Teratoma: 93%
- Embryonal carcinoma: 2%
- Other: <1%
- Germinoma: 4%

Mediastinal Germ Cell Tumors in Postpubertal Male Patients (N=519)

- Teratoma: 35%
- Seminoma: 32%
- YST: 10%
- Mixed: 16%
- Embryonal carcinoma: 4%
- Choriocarcinoma: 3%
In males > 8 years old, malignant mediastinal GCTs are comparable to postpubertal testicular GCTs (12p amplification is present) but pure teratomas are benign.

Schneider et al: Genes Chromosomes Cancer, 2002

**Take home lessons**

- Teratomas are multiple diseases.
- Ovarian teratomas are parthenogenetic from a benign post-meiotic I germ cell. The malignant elements in ovarian teratomas with malignant transformation develop like cancers at somatic sites.
- Pediatric testicular teratomas develop from a benign germ cell but we don’t know at what stage.
- Most postpubertal testicular teratomas develop through differentiation of primitive malignant germ cell tumors.
- Uncommon postpubertal testicular teratomas develop from a benign germ cell, and may show either dermoid or non-dermoid morphologies.

**Take home lessons**

- Teratomatous elements in mixed GCTs of the ovary likely develop like postpubertal testicular teratomas (12p amplification is present).
- The pediatric extragonadal teratomas develop from an initially benign pluripotential cell, either a stem cell or a misplaced germ cell.
- The occurrence of YST in pediatric SCTs results from progression/dedifferentiation of immature elements (neuroectoderm). (Can also be seen in experimental stem cell transplants in animals.) (The early Ewing model may hold here.)
- There are likely 2 forms of mediastinal teratoma – one from a benign pluripotential cell (almost the exclusive type of mediastinal GCT seen in women) and the other from a malignant pluripotential cell (mostly postpubertal males who also have other GCT components).
- You need to know the gender, location and age of any patient with a teratoma before you can reach any reasonable conclusion regarding its future clinical course.