Therapy-associated polyposis in survivors of childhood and young adulthood cancers – a multi-institutional analysis

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Survivors of childhood/young adulthood cancers (CYAC) are at increased risk of developing colorectal cancer (CRC)

- Abdominopelvic radiotherapy (RT): Odds ratio (OR) >8
- Alkylating chemotherapy: OR >8

Children’s Oncology Group (COG) guidelines

- For CYAC survivors treated with ≥30 Gy abdominopelvic RT, begin colonoscopic screening at age 30 or 5 years after RT, whichever occurs LATER

We previously described a phenomenon of therapy-associated polyposis (TAP) in a small series of 5 CYAC survivors (4 Hodgkin lymphoma, 1 neuroblastoma)

- All received alkylating chemotherapy and abdominopelvic RT
- GI polyposis developed median of 24 years after initial cancer treatment
- Negative germline APC and MUTYH testing; no family history of polyposis

https://childrensoncologygroup.org/index.php/survivorshipguidelines
Aim: Further describe the phenotypic spectrum of TAP in a multi-institutional analysis

Descriptive case series – ascertainment through cancer genetics/high-risk clinics at 7 different institutions
- Dana-Farber Cancer Institute
- Columbia University Medical Center
- Memorial Sloan Kettering Cancer Center
- University of Wisconsin
- Cleveland Clinic
- Fox Chase Cancer Center
- University of Southern California

Data extracted from chart review

TAP case definition:
- Survivor of childhood/young adulthood cancer
  - Age ≤30 at initial cancer diagnosis OR Age ≤45 if polyps developed >10 years after initial cancer treatment
- Lifetime aggregate of ≥10 upper and/or lower GI polyps
- No known pathogenic/likely pathogenic germline variant in a hereditary cancer predisposition gene

Study Aim & Methodology
### Study Cohort – Initial CYAC Diagnosis

<table>
<thead>
<tr>
<th>Type of Cancer</th>
<th>N=33 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hodgkin lymphoma</td>
<td>27 (82)</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Acute myeloid leukemia</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Wilms’ tumor (nephroblastoma)</td>
<td>1 (3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sex</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>21 (64)</td>
</tr>
<tr>
<td>Female</td>
<td>12 (36)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Median Age at CYAC Diagnosis (range)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>18 years (0.7-44)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment for CYAC</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy</td>
<td>25 (76)</td>
</tr>
<tr>
<td>RT (any)</td>
<td>27 (82)</td>
</tr>
<tr>
<td>Abdominopelvic RT</td>
<td>20 (61)</td>
</tr>
<tr>
<td>Unknown</td>
<td>3 (9)</td>
</tr>
</tbody>
</table>

| Any 1\textsuperscript{st}/2\textsuperscript{nd} degree relative with CRC age <50 years | 1 (3) |
| Any family history of colorectal polyposis (≥20 polyps) | 0 (0) |
## Study Cohort – TAP Manifestations

<table>
<thead>
<tr>
<th>Median Duration from CYAC Treatment Until 1st Polyp (range)</th>
<th>N=33 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAP developed before COG-recommended screening start</td>
<td>27 years (10-43)</td>
</tr>
<tr>
<td></td>
<td>7 (21)</td>
</tr>
</tbody>
</table>

### Aggregate # Colorectal Polyps

<table>
<thead>
<tr>
<th>Median # (IQR)</th>
<th>Aggregate # Colorectal Polyps</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>31 polyps (14-50)</td>
</tr>
<tr>
<td>&gt;50</td>
<td>10 (30)</td>
</tr>
<tr>
<td>21-50</td>
<td>14 (42)</td>
</tr>
<tr>
<td>10-20</td>
<td>8 (24)</td>
</tr>
</tbody>
</table>

### Any Upper GI Polyps

<table>
<thead>
<tr>
<th>Aggregate # Upper GI Polyps</th>
</tr>
</thead>
<tbody>
<tr>
<td>21 (64)</td>
</tr>
</tbody>
</table>

### Colorectal cancer (CRC)*

<table>
<thead>
<tr>
<th>CRC developed before COG-recommended screening start*</th>
</tr>
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<tbody>
<tr>
<td>3 of 7 (43)</td>
</tr>
</tbody>
</table>

### Germline testing history

<table>
<thead>
<tr>
<th>Germline testing history</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative panel testing (including APC/MUTYH)</td>
</tr>
<tr>
<td>Negative APC and MUTYH testing only</td>
</tr>
<tr>
<td>No germline testing**</td>
</tr>
<tr>
<td>27 (82)</td>
</tr>
<tr>
<td>3 (9)</td>
</tr>
<tr>
<td>3 (9)</td>
</tr>
</tbody>
</table>

* All CRCs diagnosed on patients’ first ever colonoscopy
** Includes one patient who underwent blood-based germline testing after allogeneic stem cell transplant
Polyp Number and Histology by Patient

- **Tubular adenoma**
- **Serrated polyp**
- **Hyperplastic polyp**
- **Hamartomatous polyp**
- **Unknown histology**
Polyp Number and Histology by Patient

Attenuated FAP phenotype (≥10 tubular adenomas); N=17 (52%)

- Tubular adenoma
- Serrated polyp
- Hyperplastic polyp
- Hamartomatous polyp
- Unknown histology
Polyp Number and Histology by Patient

- **Attenuated FAP phenotype (≥10 tubular adenomas); N=17 (52%)**

- **Extracolonic FAP manifestations (desmoid, fundic gland polyps, duodenal adenomas); N=20 (61%)**

![Polyp Distribution Chart]

- Tubular adenoma
- Serrated polyp
- Hyperplastic polyp
- Hamartomatous polyp
- Unknown histology
Polyp Number and Histology by Patient

- Attenuated FAP phenotype (≥10 tubular adenomas); N=17 (52%)
- Extracolonic FAP manifestations (desmoid, fundic gland polyps, duodenal adenomas); N=20 (61%)
- Met WHO serrated polyposis syndrome criteria; N=9 (27%)
Polyp Number and Histology by Patient

- Attenuated FAP phenotype (≥10 tubular adenomas); N=17 (52%)
- Extracolonic FAP manifestations (desmoid, fundic gland polyps, duodenal adenomas); N=20 (61%)
- Met WHO serrated polyposis syndrome criteria; N=9 (27%)
- MMR-D Colon Cancer N=2 (6%)
Attenuated FAP phenotype (≥10 tubular adenomas); N=17 (52%)

Extracolonic FAP manifestations (desmoid, fundic gland polyps, duodenal adenomas); N=20 (61%)

Met WHO serrated polyposis syndrome criteria; N=9 (27%)

MMR-D Colon Cancer N=2 (6%)

Hamartomatous Polyposis (≥5 hamartomas) N=1 (3%)
Results Summary

• As an apparently acquired phenotype, TAP may mimic various hereditary CRC syndromes
  • 94% of cohort had phenotypic manifestations of at least one syndrome
  • 42% had manifestations of multiple syndromes
  • 94% of individuals had multiple polyp histologies

• Median duration of 27 years (range 10-43 years) from initial CYAC treatment until identification of polyposis

• TAP was not just limited to CYAC survivors treated with abdominopelvic RT
Limitations

- Descriptive case series
- Inherent ascertainment bias
- Incomplete records on some patients (some with missing polyp histology, details of prior chemo/RT)
- No molecular testing on polyp tissue to further assess pathophysiology/causation
Conclusions and Future Directions

• TAP should be considered in CYAC survivors who present with polyps/GI neoplasia

• Likely under-recognized phenomenon (nearly 1/3 developed polyposis or CRC prior to COG recommended initiation of colonoscopies)

• Hope to further assess the molecular biology of tissue from TAP patients to better understand pathophysiology
  • Heterogeneous phenotype suggests multiple neoplastic pathways
Acknowledgements – Collaborators

- Leah Biller
- Sapna Syngal
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- Ramona Lim
- Anu Chittenden
- Yana Chertok
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- Carol Burke
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- Erin Salo-Mullen
- Rania Sheikh
- Zsofia Stadler
- Gregory Idos
- Megan Lutz
- Jennifer Weiss
- Elana Levinson
- Fay Kastrinos
SAVE THE DATE
2019 CGA
ANNUAL MEETING

November 3-5, 2019
Salt Lake City, UT

Join us at the 23rd Annual Meeting of the Collaborative Group of the Americas on Inherited Gastrointestinal Cancer at the Hilton Salt Lake City Center in Salt Lake City, UT.