INTESTINAL-TYPE SINONASAL ADENOCARCINOMA

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ITAC – EARLY TERMINOLOGY

- Mucinous adenocarcinoma
- Colonic-type adenocarcinoma
- Heterotopic tumor with intestinal mucous membrane
- Enteric-type adenocarcinoma
- Papillary adenocarcinoma
- Simple adenocarcinoma

- Barnes, 1986 => Intestinal-type adenocarcinoma

ITAC – TERMINOLOGICAL MOTIVATIONS

- Intestinal morphology
  - intestinal adenocarcinomas
  - intestinal adenomas
  - normal intestinal mucosa (rarely)

- Intestinal ultrastructure
  - glycoalyx bodies
  - features of Paneth cells, endocrine cells

- Gastrointestinal hormones
  - gastrin, glucagon, serotonin, cholecystokinin, somatostatin

WHO Classification 2017

SINONASAL ADENOCARCINOMAS

- Intestinal-type
- Non-intestinal-type
**Histological patterns of ITAC**

Barnes, ASP 1986

- Papillary
- SOLID
- COLUMN

**Table 1: Classification of intestinal-type adenocarcinoma**

<table>
<thead>
<tr>
<th>Type</th>
<th>Barnes</th>
<th>Ohnohara and Sch موا</th>
<th>ITAC, intestinal-type adenocarcinoma; PTGC, papillary tubular column cell.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well differentiated</td>
<td>Papillary-type</td>
<td>PTGC-I</td>
<td></td>
</tr>
<tr>
<td>Moderately differentiated</td>
<td>Columnar-type</td>
<td>PTGC-II</td>
<td></td>
</tr>
<tr>
<td>Poorly differentiated</td>
<td>Subtype</td>
<td>PTGC-III</td>
<td></td>
</tr>
<tr>
<td>Macular-type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtyping: pseudoglandular or amorphous carcinoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>Mixed</td>
<td>Transitional</td>
<td></td>
</tr>
</tbody>
</table>

**INTESTINAL-TYPE ADENOCARCINOMA**

- M-F ratio: 4:1
- Locations:
  - Ethmoid sinus (40%)
  - Nasal cavity (28%)
  - Maxillary antrum (23%)
- Local spread:
  - Orbit
  - Pterygopalatine & infratemporal fossae
  - Cranial cavity

**Early descriptions**

- Citelli & Calamida, 1903
- Masson & Martin, 1928
- Ringertz, 1938
- Järvi, 1945

**NASAL CANCER IN WOODWORKERS**

- Connection with exposure to hardwood dusts
  - Maddeth, J Laryngol (1966)
  - Acheson et al., Cancer (1967)
  - Ironside & Matthews, Cancer (1975)
ITAC - OCCUPATIONAL EXPOSURE

- Hardwood dusts (beech, oak)
- Leather dusts
- Softwood dusts (pine, fir)
- Others: Textile dusts

- Risk for ITAC in occupational dust exposure up to 500-1000 times that of general population
- 20% of all ITACs are connected to occupational dust exposure
- Average occupational exposure time 40-43 is years (Barnes, 1986)

ITAC - Histological types

- Colonic type
  - 40% of all cases (Barnes, 1986)
  - tubuloglandular architecture, few papillae

- Papillary type
  - 27% of all cases (Barnes, 1986)
  - predominantly papillary with some tubuli
ITAC - Histological types

- Solid type
  - 13% of cases
  - predominantly solid growth patterns
ITAC - Histological types

- Mucinous type
  - 8% of cases

1) Mucin-filled glands, cells in mucin pools, signet-ring cells

2) Solid cell clusters, papillae, predominantly intracellular mucin

ITAC - IMMUNOPHENOTYPE
Immunophenotypic Differences Between Intestinal-type and Low-grade Papillary Sinonasal Adenocarcinomas
An Immunohistochemical Study of 22 Cases Utilizing CDX2 and MUC2
Helen E. Codner, RNCS, and Josey E. Hui, MD

Abstract: Sinonasal adenocarcinomas can be divided into mucous glandular adenocarcinomas, squamous cell carcinoma, and other non-mucous glandular adenocarcinomas. The most common type of sinonasal adenocarcinoma is the mucous glandular adenocarcinoma (MGA). MGA is characterized by the presence of glandular structures and is further divided into high-grade and low-grade subtypes. The least common type of sinonasal adenocarcinoma is squamous cell carcinoma. This case study describes a case of sinonasal adenocarcinoma with a high-grade and low-grade component. The case study includes a detailed histologic examination and immunohistochemical analysis. The immunohistochemical analysis was performed using antibodies to CDX2 and MUC2. The results showed that the high-grade component was positive for CDX2 and MUC2, while the low-grade component was negative for both antibodies. The case study highlights the importance of immunohistochemical analysis in the diagnosis and management of sinonasal adenocarcinomas.

Figure a: CK20
Figure b: CDX-2
Figure c: CDX-2
## The Role of SATB2 as a Diagnostic Marker of Sinonasal Intestinal-type Adenocarcinoma

**Authors:** Skalova et al., 2016

**Background:**

Intestinal-type adenocarcinoma (ITAC) is a rare entity and can be found in sinonasal tumors. ITACs are associated with a poor prognosis due to a typical lack of adenocarcinoma differentiation, mucus production, and markers of colorectal differentiation.

**Findings:**

SATB2 immunohistochemistry of ITACs

- **Markers**
  - AT-rich sequence-binding protein 2 (SATB2)
  - Nuclear matrix-associated transcription factor
  - Marker of osteoblastic differentiation
  - Positive in colorectal carcinomas
  - Positive in ITACs (7/7)

**ITAC Immunophenotype**

- **CK20:** 70-100% of tumor cells
- **CDX2:** 80-100% of tumor cells
- **MUC2:** 50-100% of tumor cells
- **SATB2:** 100% of tumor cells
- **Villin:**
- **MUC5AC, MUC5B:**
- **CK7:** variable, 30-95% of tumor cells
- **Chromogranin A:** variable

**Distinct glandular differentiation and CK20 positivity are more reliable than CDX-2 alone.**

**CDX-2 expression in sinonasal carcinomas**

<table>
<thead>
<tr>
<th>Carcinoma Type</th>
<th>CDX-2 Expression</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITAC</td>
<td>100% (64)</td>
</tr>
<tr>
<td>Non-intestinal</td>
<td>15% (4/26)</td>
</tr>
<tr>
<td>SCC</td>
<td>10% (2/20)</td>
</tr>
<tr>
<td>Late SCC</td>
<td>10% (2/20)</td>
</tr>
<tr>
<td>Small cell</td>
<td>10% (2/20)</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>50% (10/20)</td>
</tr>
</tbody>
</table>

**CDX-2 expression in colorectal carcinomas**

<table>
<thead>
<tr>
<th>Carcinoma Type</th>
<th>CDX-2 Expression</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITAC</td>
<td>100% (64)</td>
</tr>
<tr>
<td>Non-intestinal</td>
<td>0.5% (1/197)</td>
</tr>
<tr>
<td>NK-SCC</td>
<td>2.5% (5/199)</td>
</tr>
</tbody>
</table>
**ITAC – MOLECULAR FEATURES**

- **K-RAS mutations**: in 10-15% of ITACs, significantly less frequent than in colorectal carcinomas.
- **B-Raf mutations**: in less than 10% of ITACs.
- **Activating mutations in KRAS and B-Raf are rare in ITACs**. 15% of colorectal carcinomas carry activating B-Raf mutations.
- **EGFR protein overexpression**: frequent in woodworkers.
- **EGFR gene copy number gains**: in 38-55% of ITACs.
- **EGFR mutations and amplifications**: uncommon.
- **No relation between gene copy number, protein expression and clinico-pathological parameters**.
- **p53 overexpressed in normal mouse after wood dust exposure**.
- **p53 overexpressed in normal mouse after wood dust exposure**.
- **p53 overexpressed more frequently in occupational than in sporadic tumors**.
- **MET protein overexpressed in 2/3 of ITACs**.
- **MET gene is not amplified**.
- **Chromosome 7 polysomy in 52% of ITACs**.
- **Aberrations in MET signaling may be significant in pathogenesis**.
Expression of mismatch repair protein, β-catenin, and E-cadherin in intestinal-type sinonasal adenocarcinoma

- ITACs are microsatellite-stable
- ITACs do not lose expression of mismatch repair proteins
- E-cadherin and β-catenin expressions are normal
- P16/CDKN2A is frequently altered
  - promoter methylation
  - LOH in 9p21

ITAC – DIFFERENTIAL DIAGNOSIS

**ITAC – DIFFERENTIAL DIAGNOSIS (Barnes, 1986)**

- Papillary sinusitis/hyperplasia
  - Bilateral, non-invasive, ciliated
  - No nuclear pleomorphism, low mitotic count
- Oncocytic Schneiderian papilloma
  - Broccoli-like patterns, diffusely oncocytic, bland epithelial cells
- Low-grade sinonasal adenocarcinoma
  - Single layer of uniform epithelial cells, minimal mitotic activity

**Features of ITAC**

*BTACs in other locations?*

- Palate: Spiro, 1973
- Floor of the mouth: Spiro, 1973
- Cheek-lip area: Spiro, 1973
- Base of the tongue: Bell et al., 2009
- Base of the tongue: Slova et al., 2012
- Major salivary glands: Gillenwater et al., 2013

**ITAC – DIFFERENTIAL DIAGNOSIS (Barnes, 1986)**

- Metastatic adenocarcinoma of G-I tract (and breast, if mucinous ITAC)
  - Colonoscopy (and breast imaging)
    - Maxillary sinuses >> Ethmoid sinuses >> Frontal sinuses >> Nasal cavity
  - Respiratory epithelial adenomatous hamartoma (REAH)

**Outcomes**

<table>
<thead>
<tr>
<th>Site</th>
<th>Histological pattern</th>
<th>Behavior</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystic treated</td>
<td>Squamous</td>
<td>Benign</td>
<td>No</td>
</tr>
<tr>
<td>Sinonasal</td>
<td>Adenocarcinomatous</td>
<td>Malignant</td>
<td>Yes</td>
</tr>
<tr>
<td>Cystic sinus</td>
<td>Adenocarcinomatous</td>
<td>Malignant</td>
<td>Yes</td>
</tr>
<tr>
<td>Oral mucosa</td>
<td>Adenocarcinomatous</td>
<td>Malignant</td>
<td>Yes</td>
</tr>
<tr>
<td>GIT</td>
<td>Adenocarcinomatous</td>
<td>Malignant</td>
<td>Yes</td>
</tr>
</tbody>
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Intestinal-type Adenocarcinoma WHO 2017

ITAC - SURVIVAL

- Low-grade papillary tumors: 3 year survival > 80%, 5 year DFS > 80%
- Grade 2 papillary tumors: 3 year survival 54%
- Mucinous tumors, alveolar pattern: 3 year survival as above
- Mixed tumors: 3 year survival as above
- Grade 3 papillary tumors: 3 year survival 36%
- Mucinous tumors, signet ring cells: 3 year survival worse

Thank you!