An update on Oropharyngeal Carcinoma

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Objectives

- Overview of oropharyngeal carcinoma
- Discussion of demographic and reporting considerations
- Outcome and management differences based on histology and special studies
- Differential diagnoses for oropharyngeal carcinoma

Definition

Oropharyngeal squamous cell carcinoma (OPSCC) is a malignant epithelial neoplasm involving:
Oropharynx, including soft palate, tonsils, uvula, base of tongue, and oropharyngeal wall comprising Waldeyer ring
**Etiology/Pathogenesis**

- Environmental Exposure
  - Marijuana use is greater HPV positive OPSCC
  - Tobacco smoking and alcohol use greater in HPV negative OPSCC
- Infectious Agents
  - High-risk HPV associated with >70% of cases OPSCC
    - HPV 16 predominant type
    - Other HPV high-risk types are reported

**Epidemiology**

- OPSCC increased 1-2% annually in USA males in past 20 years
- Rates of oral cavity carcinoma have decreased
- Gender: Male > Female (3:1)
- Ethnicity: HPV-positive OPSCC more common in whites

**Presentation**

- Site:
  - Anterior tonsillar pillar and fossa most common sites
  - Tongue base
- Presentation
  - Early lesions generally asymptomatic
  - Tonsillar asymmetry
  - Dysphagia
  - Otolgia
  - Trismus
  - Enlarging cervical lymph node
    - Often presenting symptom
- >70% of patients present with stage III or IV disease
Radiographic Findings

- Computed tomography (CT) &/or magnetic resonance imaging (MR) for preoperative tumor staging and treatment planning
- Chest CT or plain film to rule out lung metastases
- Positron emission tomography (PET) useful particularly when dealing with unknown primary or in evaluating distant metastases
  - Distant metastases uncommon in oral cavity cancer at presentation
Microscopic Features

- HPV positive types
- HPV negative types
Microscopic Features

**HPV-positive OPSCC**

- Nonkeratinizing OPSCC
  - Tumor often seen arising from epithelium of tonsillar crypts rather than overlying epithelium
  - Basaloid oval to spindle-shaped cells with hyperchromatic nuclei and minimal cytoplasm forming trabeculae, sheets, or nests with sharply defined borders
  - Corneodecrosis frequently present
  - Brisk mitotic rate and numerous scattered apoptotic cells
  - Permeated by lymphocytes
  - Squamous maturation and focal areas of keratinization can be seen but should comprise <10%
**Microscopic Features**

**HPV-positive OPSCC**

- Hybrid-type OPSCC
  - Has features of both nonkeratinizing OPSCC and keratinizing SCC
  - Amount of squamous maturation is > 10%
  - Not all cases show p16 or HPV positivity
Microscopic Features

HPV-positive OPSCC

- Lymphoepithelial-like OPSCC
  - Similar in histology to EBV-related nasopharyngeal carcinoma
  - Syncytial-appearing large tumor cells with indistinct cell borders and vesicular nuclei intermingled with lymphocytes and plasma cells
  - Tumor cells immunoreactive for cytokeratin
  - Positive for p16 (IHC)
  - Negative for EBER (ISH)

Microscopic Features

HPV-negative OPSCC

- Papillary OPSCC
  - Exceedingly uncommon morphologic variant of SCC that can occur in oropharynx
  - Finger-like projections of cytologically malignant epithelial cells with fibrovascular cores
  - Surface keratinization absent or limited
  - Definitive invasive SCC may be difficult to see, particularly on biopsy specimens
  - Up to 2/3 of cases reported to be p16 positive but < 50% positive for high-risk HPV

- Keratinizing SCC
  - Exhibits features of conventional-type SCC, including nests of epithelial cells with abundant eosinophilic cytoplasm and well-defined cell borders
  - Frank keratinization present
  - Basaloid morphology not seen
  - Tumors divided into well, moderately, and poorly differentiated
Cytology

- Fine needle aspiration of cervical lymph node may be initial biopsy
- Nonkeratinizing OPSCC show cohesive groups of cells with distinct cell borders and hyperchromatic nuclei
- Keratinization absent or minimal
- Cellular debris and inflammatory cells
- May be hypocellular because of cyst formation
- Serous fluid in cystic lymph node metastasis
- Distinct from metastatic lymph node with central necrosis
**Immunohistochemistry**

- p16 strongly positive in HPV-associated OPSCC
  - Both nuclear and cytoplasmic staining of tumor cells
  - Normal epithelium is negative or shows minimal patchy staining
  - p16 considered reliable surrogate marker for high risk
- p16 useful on FNA cell block from occult neck mass to help localize tumor origin to oropharynx
  - Strongly positive with cytookeratin(s)
  - Usually not required for diagnosis except in lymphoepithelial-like variant

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**In Situ Hybridization**

- HPV 16 correlates with p16 immunohistochemistry
  - Positive test shows nuclear dots, which can range from strongly and diffusely positive to only a rare positive cell
  - May see single punctate nuclear dot or multiple nuclear dots in tumor cell
  - Not detected in normal tonsillar epithelium
  - May see hybridization signals in dysplastic epithelium
- Other HPV types have been detected, including HPV 6, 18, 33, 35, 45, and 52/58
- HPV ISH can be used on FNA cell block from metastatic lymph node
Treatment & Prognosis

- Approaches depend on clinical stage
  - Tonsillectomy for small T1 tumors confined to tonsil
  - Radiation therapy, specifically intensity-modulated radiation therapy (IMRT) (including brachytherapy)
  - Concurrent radiotherapy with multiagent chemotherapy
  - Targeted agents such as cetuximab

- Prognosis
  - HPV-positive OPSCC associated with improved survival outcomes
  - Tumor size and presence of metastases influence prognosis

Differential Diagnosis

Basaloid Squamous Cell Carcinoma

- Highly aggressive tumor
- Lobules and trabeculae that form "jigsaw" configuration
- Pleomorphic basaloid cells with peripheral nuclear palisading
- Hyaline or mucoid hyaline material
- Prominent comedo-type necrosis
- Numerous mitoses
- Squamous component is minor
- Dysplasia, CIS, or invasive SCC
- HPV-negative
- Detection of HPV in BSCC from oropharynx is associated with better prognosis
- Best to classify these tumors as nonkeratinizing SCC
- Poor prognosis
**Differential Diagnosis**

* Nasopharyngeal Carcinoma
  - Share similar clinical presentation of enlarged cervical lymph node as initial manifestation of disease
  - Lymphoepithelial carcinoma pattern
  - Strong association with EBV
    - EBER in situ hybridization may be helpful in separating occult metastasis from either nasopharynx or oropharynx
Metastatic Cystic Squamous Cell Carcinoma

- Nearly all arise from Waldeyer’s ring
- Large, unilocular cystic node
- Lymph node architecture
- Ribbon arrangement
- Limited to profound pleomorphism
- Mitoses may be present
- Keratinaceous debris in center
- p16 strongly positive
AJCC Staging

CLINICALLY SIGNIFICANT:
- Human papillomavirus associated carcinoma (p16 immunoreactivity: in situ hybridization, others)
  - Present
  - Negative
- Epstein-Barr virus (EBER): other
  - Present
  - Negative
- Other (specify):
  - Not specified

*Clinical History (select all that apply):
- Necrosis/ulceration
- *Yes (specify type):
  - **
  - **
  - **
  - **
  - **
- *Other (specify):

Pathology Diagnosis Pearls

- OPSCC should be evaluated for p16/HPV as it may direct treatment planning and prognosis
  - Radiation therapy will be different
  - Outcome will be improved
- When evaluating cystic neck mass in older individual, first diagnostic consideration should be cystic metastasis from oropharyngeal primary
- Branchial cleft cysts are p16 negative

References