Carcinoma of Unknown Primary (CUP)

Biopsy proven malignancy, within one or more lymph nodes of the head and neck region, where the primary site is unidentified after complete workup.

- Small lesion in hidden location
  - Deep in tonsillar crypts (palatine and lingual)
  - Fossa of Rosenmuller
  - Pyriform sinus
- Slow growth rate with faster proliferation rates in lymph nodes
- Spontaneous regression

CUP

- 3% (1-9%) of pts with H&N CA
  - Increasing due to HPV
- >50% clinically unknown primary revealed after imaging, endoscopy, biopsy
  - 2/3 are SCC
  - Lymphoma
  - Thyroid CA
  - Melanoma
  - Adenocarcinoma
- Nodes involved
  - Level II/III
  - Bilateral < 10%

Work-up

- History and Physical Exam
- Flexible fiberoptic laryngoscopy
- Fine needle aspiration (FNA) of node
- Imaging
  - CT/MRI
  - PET-CT if not detected on CT/MRI
- Panendoscopy
- Directed biopsy
- Random biopsy
- Tonsillectomy
- HPV/EBV test of node if primary not found

History

- Tobacco, alcohol
- Previous Malignancy
  - Skin cancer ("growth removed")
- Associated symptoms
  - Pain/numbness, otalgia
  - Dysphagia/odynophagia
  - Trismus
  - Hemoptysis
  - Hoarseness
  - Nasal congestion/epistaxis
Physical Examination

- Skin
  - Malignancy
  - Scar from prior surgery
- Visual inspection of oral cavity, pharynx and larynx
  - palpation of tonsils and tongue base for irregular firmness or ease of bleeding
  - Flexible fiberoptic laryngoscopy of upper aerodigestive tract

Imaging

- CT/MRI is first line
- PET / PET/CT if lesion not identified on CT/MRI
  - Optimal performed prior to endoscopy not only for guidance but to avoid false positives at biopsy sites
  - Increased detection from 25 to 55% (Rudmik)
  - Prospective, surgeon initially blinded to PET results
  - Traditional L/20, after PET/CT L/10
- What to look for
  - Subtle asymmetry, fullness, and/or enhancement of mucosa

Benefits of Locating Primary Lesion

- More information to weigh therapeutic options (surgery, radiation therapy, chemotherapy)
- Primary site may be more appropriately addressed
- Changes radiation therapy plan
  - Targeted to lesion as opposed to more extensive coverage (which may decrease side effects)
  - Primary site may be treated to higher dose
- More effective surveillance after therapy if primary site known

Primary Location

- 1940s – tonsils and nasopharynx
- 1960s – piriform sinus
- 1970s – supraglottic larynx and piriform sinus
- 1998 – Mendenhall, Mancuso, et al. – 130 pts – 83% tonsillar fossa or base of tongue – lower incidence in nasopharynx, hypopharynx and supraglottic larynx
  - better fiberoptic endoscopy
  - better imaging (CT and MRI)
- 2009 – Cianchetti, Mancuso, et al. - 236 pts – 90% in tonsil and BOT

HPV-Related SCC

- Galloway - 175 cases CUP from 1990-2013
  - Linear increase in CUP since 1990
  - 72% patients tested for HPV, 75% of those tested were HPV-related SCC
- Compton - 25 cases CUP from 2002-2009
  - 28% HPV-related
- Fakhry – 84 cases CUP from 2005-2014
  - 88% male, 64% tob, mean age 57
  - 14 cases 2005-2008, 39 cases 2012-2014
  - 75 pts tested, 91% HPV-positive

HPV-related OPSCC

- Lower T and Higher N Stage
  - ? Due to early invasion of tonsillar crypt
  - Porous nature of epithelial/lymphoid junction
  - Incomplete basal cell layer and disrupted, noncontiguous basement membrane

Galloway et al. IJROBP. 2014 Feb;88(2):494
**Imaging**

- Determine N/M

**Endoscopy**

- Panendoscopy under general anesthesia with directed/random biopsy
- Endoscopy of nasopharynx, oral cavity, oropharynx, hypopharynx, larynx, tracheobronchial tree and esophagus
- Biopsy of nasopharynx, base of tongue, pyriform sinus and tonsil (tonsillectomy)

**Cases**

- Operating Room
  - Panendoscopy
  - Biopsy
  - Tonsillectomy

**Lab Testing**

- HPV – primary likely located in oropharynx
- EBV – nasopharyngeal carcinoma (NPC more common in: China, Southeast Asia, Arctic, Middle East, North Africa)

**Tonsillectomy**

- McQuone (1998) - >25% primaries found in the tonsil
- Koch (2001) – 34% primary found in the tonsil (10% primary in the tonsil contralateral to the adenopathy)
- 10% tonsillar CA have bilateral adenopathy
- ? Lingual tonsillectomy

Summary of Diagnostic Approach

- History, physical exam, flexible fiberoptic laryngoscopy
- Fine needle aspiration biopsy (FNAB) of node
- CT/MRI (consider PET / PET/CT if primary not found)
- Panendoscopy under general anesthesia with directed/random biopsies and palatine tonsillectomy (lingual tonsillectomy)
- HPV/EBV of FNAB if primary not found (unless already known)