An Aggressive Nasopharyngeal Tumor

Head & Neck/Endocrine Evening Specialty Conference
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Case History
- 52-year-old male, 6 month history of weight loss, hoarseness, dysphagia, double vision
- Multiple right cranial nerve palsies
- Mass in right nasopharynx ("fungating, vascular"), crossing midline
- Imaging: mass centered in right NP, extensive skull base involvement
- Osseous destruction, encasement of right internal carotid, “abutting” brainstem
- No regional adenopathy or distant disease
Differential diagnosis

- Salivary gland adenocarcinoma
  - Polymorphous low grade adenocarcinoma/crribiform adenocarcinoma of minor salivary glands
  - Others morphologically incompatible (e.g. MEC, AdCCa, AcCCa, EMCa, MASC, Ca ex PA)

- Nasopharyngeal adenocarcinoma, non-salivary type
  - Low grade nasopharyngeal papillary adenocarcinoma (surface derivation, complex papillae, TTF1 +, Tg -)

- Metastatic adenocarcinoma
  - From where? Thyroid, prostate, colon, lung, kidney...

<table>
<thead>
<tr>
<th>CK8/18</th>
<th>S100</th>
<th>Vimentin</th>
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5/22/2017
Conclusion

- Low grade salivary gland adenocarcinoma in the spectrum of polymorphous low grade adenocarcinoma/crribiform adenocarcinoma of minor salivary gland (CASMG)

Cribriform adenocarcinoma of minor salivary glands (CAMSG)

- Described by Michal et al, *Histopathology*, 1999 as “cribriform adenocarcinoma of the tongue”
- Authors acknowledged “...had usually diagnosed as PLGA”
- Clinically and morphologically distinctive:
  - All root/base of tongue
  - All had neck node mets at time of diagnosis; no distant mets
  - Solid and microcystic growth (cribriform and tubular)
  - Pale, vesicular, ground glass nuclei
  - “striking similarity to solid and follicular variants of papillary thyroid carcinoma” (TGD origin?)
- Treated successfully by surgery +/- radiation; no deaths

Cribriform adenocarcinoma of minor salivary glands (CAMSG)

- Next major paper Skalova et al, *AJSP*, 2011 (23 cases)
- Pointed to prior literature indicating propensity for lymph node metastases in PLGA:
  - Oropharynx or retromolar area
  - With “more than focal” papillary growth (LGPA)
- This study:
  - Included cases from elsewhere in OP, OC (new name applied)
  - Emphasized: nuclear features, “myoepithelial-secretory” hybrid cells, single cell type
  - 16/23 (69%) had LN mets at presentation
  - No deaths, but 9/23 (39%) lost to follow up

Cribriform adenocarcinoma of minor salivary glands (CAMSG) - summary

- BOT, but may arise elsewhere in oropharynx (soft palate, tonsils), oral cavity (retromolar BM), nasopharynx, nasal cavity (1/3 rd)
- Wide age range (3rd-9th decade), mean 50s, M=F
- Majority have neck LN metastases at presentation (~60%)
- Potential misdiagnosis of PTC on neck FNA?
- Good behavior, DM uncommon, very rare deaths
- Provisional entity in 2005 WHO classification, under PLGA
- Some are convinced of its distinct nature
Molecular

- PRKD1/2/3 gene rearrangements in 26 of 60 CAMSG/PLGA:
  - 16 of 21 (80%) typical CAMSG
  - 9 of 18 (45%) intermediate/overlap CAMSG/PLGA tumors
  - 1 of 21 (6%) typical PLGA
- PRKD1 commonest (incl. ARID1A-PRKD1, DDX3X-PRKD1)
- Other work: most PLGA contain somatic PRKD1 hotspot mutations

Back to this tumor...

- FISH studies showed PRKD2 gene rearrangement in this tumor
- Clinically, histopathologically and genetically c/w CAMSG (regardless of whether it is also PLGA)

CAMSG: typical features

- Architecture: solid mass, divided by fibrous septae
  - Solid nests, cribriform, glomeruloid (peripheral clefts), tubules, papillae, follicles
- Cytomorphology:
  - Pale, optically clear, ground glass nuclei
  - Overlapping (PTC-like)
  - Cytoplasm eosinophilic-clear
  - Mild atypia, rare mitoses, +/- psammoma bodies
- Stroma: mucinous matrix with myofibroblasts

CASMG: immunohistochemistry

- Positive: multiple keratins (AE1/3, Cam 5.2, CK7, CK8/18), S100, SOX10, vimentin, bcl2
- Typically/often positive, variable in extent: smooth muscle actin, calponin, p63, CK14, CK5/6, p16, c-kit
- Negative: CK20, TTF1, EMA, ER, PR, HER-2/neu

54-year-old woman, 2.7 cm, tonsil, no +ve nodes

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"Classical" PLGA

- Oral cavity predominance (esp. palate)
- 2:1 female:male
- Architectural diversity, but includes lobular, narrow tubules or fascicles, targetoid patterns
  - Glomeruloid, papillary less common (LGPA as 3rd group?)
- Nuclei: uniform, but vary from case to case (may be round/oval and not optically clear)
- Similar IHC to CAMSG
- Hotspot somatic mutations at g.Glu 710 Asp of PRKD1 in 73% (single study Nature Genetics, 2014)
- PRKD1 rearrangements are rare
- Regional LN metastases uncommon (15%, up to 29%)

Xu et al. AJSP Nov 2016: Predictors of outcome in the phenotypic spectrum of PLGA and CASG: a retrospective study of 69 patients

- Focus: considered classification issue unresolved, emphasized predictive features across the spectrum
- 23 classical PLGA, 21 classical CASG, 22 indeterminate PLGA/CASG, 3 TPPP (> 50% papillary, LGPA)
- 39 of 69 (57%) on palate, NOS
- 4 parotid tumors, 10 BOT, 6 sinonasal
- Only 5 (21%) CASG were BOT, 8 (35%) were palate, NOS
- FU on 60 patients (87%), median 46 months

- Documented multiple histological features, limited IHC
- 7 of 69 (10%) L-R recurrence or had distant metastases
  - 3 local (5%)
  - 2 nodal metastases (3%)
  - 2 distant metastases (3%)
- 5 of 7 recurrent cases were CASG
  - 27% of CASG recurred, 71% of all recurrences
- 1 death: 25 yo f, CASG of soft palate with bone, lung mets at presentation (9.3 years overall survival)
- Adverse outcome predictors (MVA): > 10% papillary, > 30% cribriform
- Tumor size, bone invasion, necrosis, LVI did not predict DFS
Xu et al. AJSP Nov 2016: Predictors of outcome in the phenotypic spectrum of PLGA and CASG: a retrospective study of 69 patients

- PLGA does not always behave as a low grade malignancy
- Small risk of death
- No conclusions re: necessity for subclassification (PLGA/LGPA/CASG), emphasizing patterns of growth
- Polymorphous adenocarcinoma preferred to PLGA
- Document extent of papillary and cribriform patterns

Clear as mud? A summary...

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<thead>
<tr>
<th></th>
<th>Classical PLGA</th>
<th>CASG</th>
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<tbody>
<tr>
<td>SITE</td>
<td>Oral cavity, esp palate; rare in pharynx</td>
<td>Oropharynx, esp RNT</td>
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<tr>
<td>NECK LYMPH NODES</td>
<td>Usually negative at presentation</td>
<td>Majority positive at presentation</td>
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<tr>
<td>ARCHITECTURE</td>
<td>Variable and broad; tubular, targetoid areas typical</td>
<td>Variable but limited; glomeruloid, papillae common</td>
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<tr>
<td>NUCLEI</td>
<td>Uniform; variable case-to-case</td>
<td>Uniform; PTC-like</td>
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<tr>
<td>OTHER MORPHOLOGY</td>
<td>Crystals, mucous cells</td>
<td>Occasional psammoma bodies</td>
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<tr>
<td>IHC</td>
<td>Similar</td>
<td>Similar</td>
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<tr>
<td>MOLECULAR</td>
<td>Hotspot PRKD1 mutation E710D</td>
<td>PRKD1/2/3 rearrangement</td>
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<td>OUTCOME</td>
<td>Largest AFIP study 125 cases; may undergo HGT; rare deaths</td>
<td>Similar; rare deaths, perhaps more prone to recurrence</td>
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WHO 2017 Classification

- Polymorphous adenocarcinoma (PAC) replaces PLGA
- Acknowledges aggressive behaviour of some tumors (7 deaths)
  - “Deaths have occurred after prolonged periods”
- Includes cribriform adenocarcinoma of tongue/minor salivary glands
- Controversy acknowledged; separate classification is pending further evidence
- Still an “emerging entity”

Follow-up on this patient

- Tumor deemed unresectable, no clear role for chemotherapy
- Treated with high dose stereotactic radiation with palliative intent
- Repeat MRI 4 months post-radiotherapy: “mild response”
- Decrease in size of tumor: 51.6 mm to 47.4 mm
- Some symptomatic improvement, persistent diplopia
- No evidence of metastatic disease
- Died fall 2016, 14/12 after presentation, 11/12 post-Rtx

Questions/Comments?