Association of Cystic Neck Metastases and Human Papillomavirus-Positive Oropharyngeal Squamous Cell Carcinoma

Jonathan B. McHugh, M.D., Assistant Professor of Pathology

Editor’s Note: This article is part of a Spectrum series demonstrating how MLabs Faculty are bringing state of the art surgical pathology, molecular diagnostic techniques and research to improve patient care.

HPV AND OROPHARYNGEAL SQUAMOUS CELL CARCINOMA

In recent years, it has become clear that the epidemiology and pathogenesis of head and neck squamous cell carcinoma is changing. Between 1973 and 2001 in the United States, the incidence of oral (mobile) tongue, base of tongue and palatine tonsil squamous cell carcinoma increased significantly in patients aged between 20 and 44 years. In contrast, the incidence of squamous cell carcinoma at other oral and head and neck sites, strongly associated with tobacco and/or alcohol use and with age older than 55 years, decreased or remained stable. Studies have indicated high-risk HPV, especially HPV16, accounts for 15-20% of new cases of head and neck squamous cell carcinoma and 68-72% of all oropharyngeal squamous cell carcinomas. This is especially true in this younger cohort of head and neck cancer patients.

The molecular data linking HPV to head and neck squamous cell carcinoma is most rigorous and reproducible for oropharyngeal tumors, specifically those occurring in the palatine tonsils and lingual tonsil (base of tongue); HPV DNA is present in high copy numbers, integrates into tumor cell DNA, is transcriptionally active, and can be localized to nuclei in both primary and metastatic tumor cells, confirming the vital role of the virus in carcinogenesis. Furthermore, HPV-positive squamous cell carcinomas have molecular alterations distinct from those present in HPV-negative tumors. Specifically, p16 tumor suppressor protein is over expressed in virtually all HPV-positive tumors as a result of HPV E7 viral oncoprotein inactivation of the hypophosphorylated (active) form of the retinoblastoma gene product (pRB), which in turn releases inhibition of p16 production. Similar to HPV-related uterine cervix cancers, p16 immunohistochemistry can be used as a surrogate marker for high-risk HPV in these tumors. In HPV-negative tumors, alterations of the pRB pathway typically result
from p16 mutations and alterations of cyclin D1, so p16 over expression on immunohistochemistry is not typically seen. In addition, whereas most tobacco and alcohol related head and neck squamous cell carcinomas manifest p53 mutations, HPV-positive carcinomas usually have wild-type p53; dysregulation of p53 occurs in HPV-related tumors but this is a result of HPV E6 viral oncoprotein mediating degradation rather than p53 mutation.

Chaturvedi et al. showed that the increase in HPV-related oral squamous cell carcinoma incidence rates was most prominent for younger individuals, and particularly men. Similar to risk factors for uterine cervix squamous cell carcinoma, epidemiologic studies reveal an increased risk for oropharyngeal squamous cell carcinoma associated with young age at first intercourse, increasing number of lifetime sexual partners and a history of genital warts. In women, increasing number of lifetime sexual partners is associated with oral cancer risk. In both sexes, practices involving oral-genital and oral-anal contact imparts an increased risk of HPV-related oral carcinoma.

A recent prospective study employed a standardized treatment protocol to evaluate the response and survival among patients with laryngeal and oropharyngeal squamous cell carcinomas. In this study, patients with HPV-positive tumors (all were oropharyngeal) had significantly higher response rates following induction chemotherapy as well as following chemoradiation treatment. In addition, they had significantly improved overall and progression free survival with a 61% lower risk of death and a 62% lower risk of progression compared to HPV-negative patients. The reasons for the improved therapy responses are uncertain but an intact apoptic response due to the presence of wild-type p53 is speculated.

From a clinical standpoint, HPV-positive oropharyngeal tumors have a characteristic manifestation with roughly 50% presenting with a cystic nodal metastasis, occasionally from occult primaries in the palatine or lingual tonsils. For example, among 20 patients with cystic metastases in Goldenberg et al., 17 had primary tumors located in the palatine/lingual tonsil and 3 had unknown primaries. Of these, 84% were found to have HPV-positive tumors in contrast to none of the 21 patients with solid metastases.

"BRANCHIOGENIC CARCINOMA" AND PATHOLOGIC CLUES TO THE PRIMARY SITE OF CARCINOMA

Approximately 11-21% of lateral neck cysts clinically suspected to be branchial cleft cysts turn out to be cystic squamous cell carcinoma. Because some of these patients do not have a known primary tumor at the time of excision, the possibility of a carcinoma arising from the lining of a branchial cleft cyst (so-called branchiogenic carcinoma) is often entertained. From literature reviews, it can now be concluded that if “branchiogenic carcinoma” exists at all, it is exceedingly rare; most cases historically described have been proven to be metastases from a primary squamous cell carcinoma arising in the palatine and lingual tonsils (Waldeyer’s ring).

While squamous cell carcinomas arising in the esophagus, hypopharynx, nasopharynx, and larynx can produce cystic metastases in the neck, they do not share the characteristic morphology of oropharyngeal metastases. Tonsillar squamous cell carcinoma metastases recapitulate the crypt epithelium from which these lesions arise. They are typically composed of a uniform ribbon-like proliferation of predominantly non-keratinizing, squamous epithelium with a “transitional” or “basaloid” appearance. They frequently form unilocular cysts or multiple, variably-sized cysts with exophytic/papillary and endophytic components of varying quantities. The cells have high nuclear-cytoplasmic ratios with little appreciable surface maturation and little cytologic anaplasia. Whereas most are non-keratinizing, foci of abrupt keratinization of varying amounts can be identified in many tumors.

MAKING THE CLINICAL CONNECTION

In summary, HPV-related oropharyngeal squamous cell carcinomas are a unique subgroup of head and neck carcinoma that can be considered a distinctive clinicopathologic entity. They differ from HPV-negative squamous cell carcinoma in regards to patient demographics, risk factors, molecular alterations, tumor histopathology and behavior (Table 1). For these reasons, patients who initially present with cystic squamous cell carcinoma involving cervical lymph node(s) should undergo imaging studies as well as endoscopy to search for a primary. If the metastasis has the morphology described above, the primary tumor will almost always be located in the palatine or lingual tonsil region. If no obvious primary is identified, biopsies of the base of tongue,
nasopharynx and pyriform sinus (hypopharynx) should be taken. In addition, diagnostic tonsillectomy on the ipsilateral side should be performed.

**Table 1: Clinicopathologic differences of HPV-positive and negative oral/oropharyngeal squamous cell carcinomas**

<table>
<thead>
<tr>
<th>HPV-Positive</th>
<th>HPV-Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Younger</td>
<td>Older</td>
</tr>
<tr>
<td>Non-smoker/drinker</td>
<td>Tobacco/alcohol history</td>
</tr>
<tr>
<td>Sex risk factors +</td>
<td>Sex risk factors +/-</td>
</tr>
<tr>
<td>Non-keratinizing or “basaloid” morphology</td>
<td>Conventional SCC morphology</td>
</tr>
<tr>
<td>Moderately-poorly differentiated</td>
<td>Well-moderately differentiated</td>
</tr>
<tr>
<td>Cystic metastases</td>
<td>Solid metastases</td>
</tr>
<tr>
<td>Improved outcome</td>
<td>Worse outcome</td>
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</tbody>
</table>

Recognition of this unique subset of head and neck cancer by clinicians and pathologists will allow for the proper and most efficacious therapy to be delivered. Besides the characteristic morphology, studies to detect HPV DNA using in-situ hybridization or polymerase chain reaction methodologies may help in identifying this subset of head and neck squamous cell carcinoma. In addition, p16 immunohistochemistry can be applied as a surrogate marker for the presence of high-risk HPV. As HPV-related tumors have improved responses to therapy and improved prognosis, these patients are increasingly being offered organ preserving therapeutic regimens as first-line therapy at the University of Michigan. The impact of HPV vaccination on this subset of head and neck cancer is expected to be elucidated in future investigations.

**REFERENCES**


Spotlight on Jonathan McHugh, M.D.

Assistant Professor of Pathology

Dr. McHugh received his B.S. in biological sciences and M.A. in cellular biology from the University of Missouri-Columbia. He received his M.D. from the University of Nebraska Medical Center in 2002 and completed residency training in Anatomic and Clinical Pathology at the University of Michigan, earning honors as Assistant Chief Resident and Chief Resident. Following residency training, he completed a fellowship in Head and Neck Pathology with the world famous Dr. E. Leon Barnes at the University of Pittsburgh Medical Center.

Dr. McHugh is a member of the North American Society of Head and Neck Pathology and the United States and Canadian Academy of Pathology and is a Fellow of the American Society for Clinical Pathology. His research interests include salivary gland tumors and neoplasms of the upper aerodigestive tract. Dr. McHugh is recently published in the Archives of Otolaryngology - Head and Neck Surgery, the American Journal of Otolaryngology - Head and Neck Medicine, Diagnostic Cytopathology, and the Journal of Cutaneous Pathology. He is a popular speaker and teacher and has recently assumed a key role in the ASCP's recurring course on head and neck pathology.

To send a pathology consult to Dr. McHugh, request him as a speaker at your next meeting, or request his assistance or collaboration with a research investigation, contact MLabs at 800-862-7284.

Test Updates

New Tests

OTC GENE SEQUENCING

Effective February 2, 2009, the MLabs MMGL Molecular Genetics Laboratory began offering Ornithine Transcarbamylase Deficiency (OTC) Gene Sequencing.

This test is used to detect the presence of OTC mutations in patients with Ornithine Transcarbamylase Deficiency or for carrier testing in families with a known OTC mutation. This assay will not detect large deletions in the OTC gene or intronic mutations outside the region sequenced in the OTC gene.

Collection Instructions: Collect specimen in a lavender top tube. Send intact specimen within 24 hours if stored at room temperature or within 5 days if stored refrigerated. Include the patient’s family history, pedigree, and ethnicity on the test requisition. Obtaining informed consent from the patient prior to genetic testing is strongly recommended. If desired, a “UMHS Request and Consent for Genetic Testing form” can be obtained from the MMGL Molecular Genetics Laboratory by contacting the MLabs Client Services Center at 800-862-7284.

PROTEIN S ACTIVITY

Effective February 16, 2009, the MLabs Coagulation Laboratory began performing the Protein S Activity assay in-house.

Collection Instructions: Samples from patients being treated with warfarin cannot be tested using this assay; the patient must be free of warfarin for two weeks prior to testing. Collect specimen in a blue top (citrate 3.2%) tube. Mix by inversion. Specimen should arrive at lab within 2 hours of collection; transport at room temperature. Alternatively, centrifuge, aliquot plasma into a polypropylene plastic vial, and freeze the specimen within 2 hours of collection. Transport frozen specimen on dry ice. If specimen is drawn through an indwelling catheter, the line should be flushed with 5 mL of saline and the first 5 mL of blood or six times the deadspace volume of the catheter being used discarded. Specimens will be rejected if not properly filled, clotted, grossly hemolyzed, or contaminated with heparin.
Reference Range: Male: 75 - 140%; Female: 55 - 125%

Note that this test is not available to University of Michigan hospital patients. UMHS orders will be changed to Protein S Antigen, Free.

**PTEN GENE SEQUENCING**

Effective February 2, 2009, the MLabs MMGL Molecular Genetics Laboratory began offering PTEN Hamartoma Tumor Syndrome (PTEN) Gene Sequencing.

This test is used to detect the presence of PTEN mutations in patients with PTEN Hamartoma Tumor Syndrome (PHTS); the PHTS diagnosis includes Cowden Disease/Cowden Syndrome, Bannayan-Riley-Ruvalcaba Syndrome, Proteus Syndrome, and Proteus-like syndromes. This test is also appropriate for patients exhibiting Macrocephaly/Autism Syndrome or VACTERL association with hydrocephalus, and for carrier testing in families with a known PTEN mutation. This assay will not detect large deletions in the PTEN gene or intronic mutations outside the region sequenced in the PTEN gene. Mutations in other genes associated with the aforementioned syndromes will not be detected.

Collection Instructions: Collect specimen in a lavender top tube. Send intact specimen within 24 hours if stored at room temperature or within 5 days if stored refrigerated. Include the patient’s family history, pedigree, and ethnicity on the test requisition. Obtaining informed consent from the patient prior to genetic testing is strongly recommended. If desired, a “UMHS Request and Consent for Genetic Testing form” can be obtained from the MMGL Molecular Genetics Laboratory by contacting the MLabs Client Services Center at 800-862-7284.

**UROVYSON(TM) FISH FOR BLADDER CANCER**

The MLabs Molecular Diagnostics Laboratory began performing UroVysion(TM) FISH for Bladder Cancer in-house effective February 16, 2009.

The UroVysion(TM) Bladder Cancer Kit (Abbott Molecular Inc.) is designed to detect aneuploidy for chromosomes 3, 7, 17, and loss of the 9p21 locus via fluorescence in situ hybridization (FISH) in urine specimens from persons with hematuria suspected of having bladder cancer. Results from the UroVysion(TM) kit are intended for use, in conjunction with and not in lieu of current standard diagnostic procedures, as an aid for initial diagnosis of bladder carcinoma in patients with hematuria and subsequent monitoring for tumor recurrence in patients previously diagnosed with bladder cancer.

Collection Instructions: Collect random urine specimen (minimum 33 mL) directly into ThinPrep UroCyte collection kit available from MLabs. Alternatively, mix fresh urine 2:1 (v:v) with Carbowax (2% polyethylene glycol in 50% ethanol) or PreservCyt® preservative. Refrigerate and send within 48 hours of collection.

**WARFARIN SENSITIVITY ANALYSIS**

Effective January 31, 2009, the MLabs Molecular Diagnostics Laboratory began performing Warfarin Sensitivity Analysis by Polymerase Chain Reaction (PCR) with enzyme digestion followed by electrochemical detection. This test is an in vitro diagnostic for the detection and genotyping of the *2 and *3 alleles of the cytochrome P450 (CYP450) 2C9 gene locus and the Vitamin K epoxide reductase C1 (VKORC1) gene promoter polymorphism (-1639G>A) as an aid in the identification of patients at risk for increased Warfarin sensitivity.

Collection Instructions: Collect specimen in a lavender top (EDTA) tube. Send intact specimen at room temperature within 24 hours of collection.

**Test Methodology, Reference Range, and Specimen Handling Changes**

**BLOOD AND BONE MARROW AFB CULTURES**

Effective January 28, 2009, the MLabs Microbiology Laboratory implemented partial automation of culture incubation and reporting using the BacT Alert system for AFB cultures. This requires a change in the specimen container, collection and handling of Bone Marrow and Blood AFB Cultures. The MB BacT/Alert bottle (black top) replaces the Isolator tube (yellow top) for these specimen types. For all other specimen types, specimen collection and handling remains unchanged.

Blood Collection Instructions: Swab skin over the site of venipuncture with iodoform solution for 1 minute in a 2 inch circular area around vein to be used, using vigorous strokes and working from the center to the periphery. Allow to dry 2 minutes before performing venipuncture. If use of a 2% iodine preparation is
contraindicated in patients sensitive to iodine, alcohol alone may be used. DO NOT palpitate venipuncture site after preparation. Draw 5 mL (minimum 3 mL) of blood into a syringe, and transfer to MB BacT/Alert bottle available from MLabs. Do not refrigerate or incubate. For optimum recovery, send directly to the laboratory STAT. Label bottle with patient’s name, medical record number, and culture number or anatomic site if more than one culture is drawn at one time. Indicate on the requisition if mycobacteria are suspected. Indicate specimen source, collection date/time, current antibiotic therapy, and clinical diagnosis. If unacceptable specimen is received, the client will be called and another specimen will be requested before disposal of the bottle.

Bone Marrow Collection Instructions: Collect 3 mL (minimum 0.5 mL) of bone marrow in an MB BacT/Alert bottle available from MLabs. Do not refrigerate or incubate; store at room temperature. For optimum recovery, send directly to the laboratory BacT/Alert bottle may be stored up to 16 hours. Label bottle with patient’s name, medical record number, and culture number or anatomic site if more than one culture is drawn at one time. Indicate specimen source, collection date/time, current antibiotic or antifungal therapy, and clinical diagnosis. If unacceptable specimen is received, the client will be called and another specimen will be requested before disposal of the bottle.

C-REACTIVE PROTEIN, HIGH SENSITIVITY

Beginning March 16, 2009, High Sensitivity CRP testing has moved from the MLabs Immunology Laboratory to the Automated Chemistry Laboratory, where it is performed on the Advia 2400 using a Latex Enhanced Immunoturbidimetric method. This change will reduce the volume of blood required for testing and improve turnaround time. Testing is available 24 hrs per day/7 days per week.

Collection Instructions: Collect specimen in an SST tube. Centrifuge, aliquot 1 mL (minimum 0.5 mL) of serum into a plastic vial within 30 minutes of collection, and freeze.

Reference Range: \( \leq 3.6 \) pg/mL.

OSTEOCALCIN

Effective February 3, 2009, Mayo Medical Laboratories began performing Osteocalcin, Serum by Electrochemiluminescence Immunoassay.

Collection Instructions: Collect specimen in a red top or SST tube. Centrifuge, aliquot 0.5 mL of serum into a plastic vial and freeze.

Reference Range: 9 – 42 ng/mL (age \( \geq 18 \) years)

TPMT ENZYME ACTIVITY, ERTHYROCYTES

Effective January 6, 2009, Mayo Medical Laboratories changed their reference values for the Thiopurine Methyltransferase (TPMT), RBC assay:
The MLabs Clinical Microbiology Laboratory has discontinued mecA testing as part of susceptibility testing procedure for staphylococci. In-house verification studies were performed to compare the performance of mecA PCR and Cefoxitin Screen on the new VITEK 2 susceptibility panels and found these methods to be equivalent in predicting Methicillin resistance in staphylococci. With the implementation of the Cefoxitin Screen, staphylococcal isolates that test Cefoxitin Screen Positive possess mecA-encoded Methicillin resistance, and all beta-lactam/cephalosporin/carbapenem antibiotics are therefore reported as Resistant. For staphylococcal isolates that test Cefoxitin Screen Negative, beta-lactam/cephalosporin/carbapenem antibiotics are reported as tested.

**Discontinued Tests**

**MECA SUSCEPTIBILITY BY PCR**

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**MUMPS VIRUS ANTIBODY, IGM**

Effective February 17, 2009, the MLabs Microbiology Laboratory has discontinued performing the following IgM antibody tests due to low volume. Requests for Herpes simplex, Rubeola, and Varicella zoster Virus IgM Antibodies will be forwarded to Mayo Medical Laboratories.

**Herpes simplex IgM**

Requests for Herpes simplex IgM or both IgG and IgM will be sent to Mayo test #84422 Herpes simplex Antibody, Types 1 and 2. This assay includes separate determinations for Herpes simplex type 1 IgG and Herpes simplex type 2 IgG and has found to be specific for differentiation of HSV1 and HSV2 IgG antibodies. This assay also includes Herpes simplex IgM by EIA; if this screen is positive, Herpes simplex IgM by IFA will be performed at an additional charge.

Collection Instructions: Collect specimen in a red top or SST tube. Centrifuge, aliquot 1 mL (minimum 0.6 mL) of serum into a plastic vial and refrigerate.

Reference Range: Negative

**Rubeola Virus Antibody, IgM**

Requests for Rubeola Virus IgM will be sent to Mayo test #80979 Rubeola (Measles) Antibodies, IgM, Serum.

Collection Instructions: Collect specimen in a red top or SST tube. Centrifuge, aliquot 0.5 mL (minimum 0.2 mL) of serum into a plastic vial and refrigerate.

Reference Range: Negative

**Varicella zoster Virus Antibody, IgM**

Requests for Varicella zoster IgM will be sent to Mayo test #80964 Varicella-Zoster Virus (VZV) Antibody, IgM, Serum.

Collection Instructions: Collect specimen in a red top or SST tube. Centrifuge, aliquot 0.5 mL (minimum 0.2 mL) of serum into a plastic vial and refrigerate.

Reference Range: Negative

**T3 (TRIIODOTHYRONINE), REVERSE**

Due to reagent issues and declining clinical utility of this test, Mayo Medical Laboratories (MML) has discontinued their T3 (Triiodothyronine), Reverse, assay effective December 19, 2008. There is no replacement assay offered by MML.
For additional clarification concerning any of the information contained in this Spectrum, please contact the MLabs Client Services Center at 734-936-2598 (local) or 800-862-7284.

Address correspondence to:
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Ann Arbor, MI 48106-0976

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MLabs News

U-M DEPARTMENT OF PATHOLOGY NEWS

Congratulations are extended to Steven L. Kunkel, Ph.D., Senior Associate Dean for Research and Endowed Professor of Research and Co-Director, Division of Sponsored Programs in the Department of Pathology. Dr. Kunkel is one of seven University of Michigan faculty elected as fellows of the American Association for the Advancement of Science.

Andrew P. Lieberman, M.D., Ph.D., Associate Professor has been selected for membership in the American Society for Clinical Investigation (ASCI). The ASCI is one of the nation’s oldest and most respected medical honor societies, comprising more than 2,800 physician-scientists from all medical specialties. The ASCI is dedicated to the advancement of research that extends our understanding and improves the treatment of human diseases. The Society elects up to 80 new members each year for their outstanding records of scholarly achievement in biomedical research. Members are selected from among several hundred physician-scientists from the United States and abroad.

Duane Newton, Ph.D., Assistant Professor and Director of the Microbiology/Virology Laboratory has been appointed to the editorial board of the Journal of Clinical Virology. This international journal publishes papers on any aspect of human virology that directly pertains to virus-induced clinical conditions and is the official journal of the Pan American Society for Clinical Virology and the European Society for Clinical Virology.

MLabs is delighted to announce that Raja Rabah, M.D., Associate Professor of Pathology at Wayne State University and Director of Pediatric Pathology at Children’s Hospital of Michigan, will join our faculty as Director of Pediatric Pathology effective July 15, 2009.

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