Case Presentation
Mr. M, a 57 year old male, presented to the ENT clinic with a 1-month history of a non-tender right-sided neck mass that was associated with a globus (globe, ball-like) sensation in his throat. Despite a negative history for significant dysphagia or odynophagia, he did note a 5-10 pound weight loss. There were no associated symptoms such as hoarseness, otalgia, fatigue, fevers, or night sweats. There was no history of cat-scratch disease or travel to an area endemic with tuberculosis. Three months prior to noting the neck mass, he was treated for a dental abscess with antibiotics. Mr. M has a significant history of alcohol and tobacco use.

His past medical history was remarkable for a history of previously excised non-melanoma skin lesions on his left scalp and shoulder. He had no history of heart, lung, liver, or kidney disease.

Mr. M underwent a fine needle aspiration biopsy of the neck mass by the referring otolaryngologist, the results of which suggested a malignancy of uncertain histology. He then underwent a panendoscopy (laryngoscopy, esophagoscopy, and bronchoscopy) under general anesthetic. The operative report of the panendoscopy described a non-pigmented mass in the right pyriform sinus involving the medial and lateral walls, with extension to the post-cricoid region. There was involvement of the supraglottic larynx with enlargement and thickening of the mucosa overlying the right arytenoid cartilage. The arytenoid cartilage appeared to be fixed. The biopsy of the hypopharyngeal mass showed a large cell malignancy.

Physical examination of his neck revealed a 5 cm right-sided neck mass situated in the level 2 distribution (extends from the skull base to the hyoid bone, posterior to the posterior belly of the digastic muscle and anterior to the back of the sternocleidomastoid muscle) that was tender on palpation. A smaller mass measuring approximately 1 cm in diameter was noted inferior to the larger neck mass. Examinations of his oral cavity and oropharynx were normal. Fiberoptic flexible endoscopic examination revealed a mass involving the right hypopharynx. The lesion appeared to be situated in the medial pyriform sinus with involvement of the lateral wall of the pyriform sinus and the lateral aspect of the right aryepiglottic fold. The overlying mucosa was ulcerated. There was no evidence of tongue-based or oropharyngeal extension. The right vocal cord appeared to be fixed. There were no lesions noted on examination of the skin of the head and neck.

Differential Diagnosis
While the differential diagnosis of a neck mass is rather extensive (Table 1 shows the KITTENS mnemonic), the differential diagnosis in a patient who also presents with an associated hypopharyngeal lesion is limited. The majority of hypopharyngeal lesions in adults are neoplastic, with malignancy being the most common. More than 95% of hypopharyngeal cancers are squamous cell carcinomas. Common presentations include ulcerative or infiltrative lesions; exophytic lesions are less common. The majority of the remaining 5% of hypopharyngeal malignancies are adenocarcinomas arising from glandular structures. Other rare malignancies of the hypopharynx include malignant fibrous histiocytoma, liposarcoma, and synovial sarcomas. These rare malignancies can have a similar appearance to squamous cell carcinoma and therefore diagnosis is dependent on biopsy. Malignancy should be suspected in any adult patient presenting with a hypopharyngeal mass, particularly those with an associated neck mass.

Benign tumors of the hypopharynx are very rare, the most common of which are fibrolipomas and leiomyomas. Other neoplasms include hemangiomas, angiofibromas, schwannomas, neuromas, and granular cell tumors. Benign neo-
Table 1
Differential Diagnosis of a Neck Mass¹,²

<table>
<thead>
<tr>
<th>Category</th>
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| K = Congenital | A. Cysts  
1. Sebaceous  
2. Branchial cleft  
3. Thyroglossal duct  
4. Dermoid  
5. Thymic (rare)  |
|             | B. Lymphangioma  
C. Hemangioma  
D. Teratoma (rare)  
E. Ectopic thyroid tissue  
F. Laryngocele  
G. Pharyngeal diverticulum  
H. Congenital torticolis (rare) |
| I = Infectious and Inflammatory | (includes iatrogenic and idiopathic)  
A. Bacterial lymphadenopathy  
1. Beta-hemolytic streptococci  
2. Staphylococcus aureus  
3. Cat-scratch disease (rare)  
4. Actinomycosis (rare)  
5. Tularemia (rare)  
6. Mycobacterial tuberculosis  
7. Atypical mycobacteria  
B. Viral lymphadenopathy  
1. Epstein-Barr virus  
2. HIV  
3. Herpes simplex virus  
4. Cytomegalovirus  
C. Parasitic  
D. Fungal  
E. Carotidynia  
F. Thyroiditis  
1. Acute  
2. Subacute  
3. Chronic  
G. Neck abscess  |
| T = Traumatic | A. Hematoma  
B. Foreign body  
C. Aneurysm  
D. Dissection  |
| E = Endocrine | A. Thyroid  
B. Parathyroid  
C. Carotid body  
D. Multiple endocrine neoplasia (MEN)  
1. MEN I  
2. MEN II  |
| N = Neoplastic | A. Benign  
1. Neuroma  
2. Lipoma  
3. Fibroma  
4. Hemangioma  
B. Malignant  
1. Thyroid  
2. Lymphoma  
3. Salivary  
4. Lipoma  
5. Angioma  
6. Carotid body tumor  
7. Rhabdomyosarcoma  
C. Metastatic  
1. Unknown primary  
2. Epidermoid carcinoma  
3. Melanoma  
4. Adenocarcinoma  
5. Adenoid cystic  
6. Mucoepidermoid  
7. Breast  
8. Lung  
9. Kidney  
10. Gastrointestinal tract  |
| S = Systemic | A. AIDS  
B. Kawasaki disease  
C. Storage disorders  
D. Malabsorption syndromes  
E. Drug effects  
F. Typhus antigen  
G. Kaposi sarcoma  
H. Psychiatric disorders can cause factious disease  |
Benign neoplasms do not metastasize to cervical nodes. Non-neoplastic lesions rarely present in the hypopharynx. Amyloidosi appears as a submucosal mass. Systemic inflammatory conditions, such as pemphigus, can affect the hypopharynx as well. However, these lesions are usually not confined to the hypopharynx and affect other mucosal sites of the upper aerodigestive tract, making differentiation from neoplasms relatively easy. Similar to benign lesions, these disorders tend not to involve lymph nodes of the head and neck.

Investigations
A CT scan was ordered to assess the extent of the hypopharyngeal mass and cervical adenopathy. The CT showed an ulcerated lesion involving the right pyriform sinus extending onto the right aryepiglottic fold and right false cord (Figure 1). There was no evidence of thyroid cartilage invasion or pre-vertebral involvement. There was a large necrotic nodal mass with extracapsular spread on the right side in level 2, measuring approximately 4.5 cm (Figure 2). The mass displaced the neurovascular bundle but did not encase the carotid. There were enlarged ipsilateral nodes in levels 2 and 3, the largest measuring 2 cm in diameter with central necrosis. There were a few small non-pathologic appearing nodes on the contralateral side.

CT scans of the pelvis and abdomen were clear. A CT scan of the chest revealed an 8 mm lesion in the endobronchial area on the right lower lobe, which was felt to be most likely consistent with mucus rather than a second primary or metastases.

The pathology specimen obtained on panendoscopy was reviewed by a head and neck pathologist at a tertiary care oncology center. The biopsy showed ulcerated squamous mucosa with a largely submucosal neoplasm composed of epithelioid cells arranged in nests and sheets (Figures 3 and 4). The tumor cells were strongly positive for Melan-A, with patchy expression of S-100 and HMB-45. Keratin staining was negative.

Pathological Diagnosis
Mr. M had a primary mucosal melanoma of the right hypopharynx with regional metastases to the ipsilateral cervical lymph nodes. He was clinically (and radiologically) staged as a T3N2bM0.
Mucosal Melanoma

Mucosal melanoma is a neural crest-derived malignancy arising from melanocytes that have migrated to the mucosa of the upper aerodigestive tract. Despite the relatively common occurrence of cutaneous melanoma (CM), mucosal melanoma (MM) is a very rare entity. MM accounts for less than 3% of all melanomas. This review will highlight the important features of mucosal melanoma.

Epidemiology

Mucosal melanoma has been reported to affect the mucosa of the upper aerodigestive tract, GI tract and genitalia. Primary MM in the head and neck make up 55% of all MM and include the oral cavity and respiratory tract melanomas. The nasal cavity and paranasal sinuses are the most common head and neck sites for mucosal melanoma, with the lateral nasal wall and septum being the most common sub-sites. The oral cavity is the second most common site for MM involvement, with the palate and alveolus being the most frequent sub-sites involved. Other sites, including laryngeal involvement, are relatively rare. Compared to Caucasians, there is an increased proportion of malignant melanomas of the oral cavity in the Japanese and of the oral cavity in African populations. There is a slight male preponderance in MM of the head and neck although gender does not appear to affect mortality. MM tends to occur most frequently between the sixth and eighth decade of life.

Etiology

Unlike cutaneous melanoma where there are well recognized risk factors such as UV radiation, genetics, family history, and pre-malignant skin nevi, there are no known risk factors for malignant melanoma. Although MM is not caused by UV exposure, the pathogenesis of malignancy may be similar in both CM and MM. Normally, cells that undergo DNA mutations undergo apoptosis if repair is not possible. Melanocytes, in contrast, contain several anti-apoptotic proteins, which allow them to survive the UV insult and the resulting DNA mutations. Transformation to a melanoma state involves the activation of proto-oncogenes, such as Braf and ras, and the inactivation of tumor suppressor genes. Activated Braf and ras impact the MAP kinase and ERK pathways that are involved in the regulation of growth control mechanisms. Disruption of these pathways results in increased cell survival, uncontrolled rates of growth, and the ability to invade surrounding tissues and organs. Stimulation by growth factors at this point will also promote cell proliferation.

Clinical Features

MM may present as a visible lesion, evidence of mass effects or metastatic disease. Melanomas of the oral and nasal cavities often present as pigmented lesions. Early lesions may be noted incidentally by the patient, a dentist, or family practitioner. As these lesions are often asymptomatic, patients may not seek treatment until the lesions become advanced and complications arise. Complications of an oral cavity melanoma include dysphagia, ill-fitting dentures, ulceration, or bleeding. Patients with a nasal cavity melanoma can present with epistaxis, pain, facial deformity, nasal obstructive symptoms, or visual disturbances. Nasopharyngeal and sinus melanomas are not detectable upon simple inspection; these lesions can be associated with hemoptysis and local pain, respectively. Lesions of the oral and nasal cavity may be visualized by nasopharyngoscopy. Metastases to cervical nodes or distant sites, such as the lungs and bone, may be the presenting sign or symptom. Patel et al reported incidences of 25% for nodal metastases at the time of initial presentation for oral cavity MM and 6% for sinonasal MM.

Diagnosis

Lesions located in the oral and nasal cavities are further assessed by biopsy. Very small lesions in an accessible location can be removed with wide margins (>1cm) in a full thickness excisional biopsy. It is important to note that patients who undergo biopsies involving wide local excision (WLE) have better survival rates but the procedure may alter lymphatic drainage patterns and decrease the efficacy of sentinel node investigations. Larger lesions should be examined by an incisional or punch biopsy through the thickest or most pigmented part of the lesion. The latter can be done safely in a clinic setting; however, the procedure can be complicated by bleeding from the biopsy site as a MM can be quite vascular. Needle or shave biopsies are not recommended for lesion biopsies as these techniques do not adequately assess lesion thickness. Needle biopsies can be useful for lymph node or distant metastases. Systemic metastases are investigated with chest x-rays, full body CT scans, and PET scanning where available.

Pathology

Diagnosis of melanoma is frequently made on conventional histological inspection alone. This process is more difficult when melanomas are poorly differentiated and mimic the morphological and architectural patterns of other neoplasms. On gross examination, MM may vary in its appearance and extent of pigmentation. Mucosal tumors may appear polypoid or sessile with or without ulceration. Some tumors exhibit marked pigmentation, appearing black, while others may be amelanotic with no pigmentation and appear white.

Histologic examination reveals a diffuse cellular infiltrate, often with focal mucosal ulceration. Tumour cells may appear as epithelioid cells or spindle cells. The epithelioid cell variant consists of round to oval markedly pleomorphic cells that can
have different growth patterns (i.e. solid, nested). Cells tend to have an increased nuclear to cytoplasmic ratio, prominent eosinophilic nucleoli, nuclear grooving, and pseudoinclusions. The spindle cell variant features oblong, pleomorphic cells with large vesicular to hyperchromatic nuclei and scarcely eosinophilic cytoplasm. Growth patterns include storiform or fascicular patterns with an associated myxoid stroma. A desmoplastic variant exists, which is characterized by the presence of amelanotic spindle cells. Necrosis and increased mitosis are commonly seen with both variants. The amount of melanin deposition varies between cases from heavy to scant deposits.

**Immunohistochemistry**

Immunohistochemistry utilizes tumor or stromal element markers to aid in the diagnosis and staging of melanoma. Melanocytic differentiation markers are helpful in diagnosing poorly differentiated tumors, staging the primary tumor, and assessing sentinel lymph node status. These markers are generally specific to the melanocytic lineage and assist in the identification of tumor cell type. Examples include MART/Melan-A (high specificity), gp100/HMB-45, and S100 (high sensitivity). In practice, S100 is commonly used to determine if the tumor is of melanocytic origin and along with MART/Melan-A, provides an overall impression of lesion architecture. MART/Melan-A and gp100/HMB-45 can also differentiate melanomas from neurofibromas, schwannomas, and malignant peripheral nerve sheath tumors. Melanoma progression markers distinguish between benign and malignant tumors and assess the aggressiveness of the primary melanoma. Vascular endothelial growth factor (VEGF) is a potent angiogenic factor that is present in primary and metastatic melanoma lesions, but is relatively absent in benign (including atypical) nevi. The transition from the horizontal (radial) to the vertical growth phase is accompanied by the induction of VEGF by tumor cells.

**Classification and Staging**

Whereas CM is classified into 5 subtypes according to their growth pattern (superficial spreading, nodular, acral lentiginous, desmoplastic, and lentigo maligna melanoma), there is no accepted classification system for MM. Similarly, CM is staged by Breslow thickness, Clark microstaging levels and the American Joint Committee on Cancer (AJCC) criteria for CM staging, while a simple three stage system is employed for MM: stage I for localized disease, stage II for regional metastases, and stage III for distant metastases. As this system does not take into account the extent of the primary tumor, the AJCC staging criteria for the site of origin (i.e. oral cavity, paranasal sinuses) is often used.

**Prognosis**

MM has a worse prognosis than CM. The 5-year survival rate for a MM is less than 20% for stage I or II disease. In contrast, the 10-year survival rate for a stage I or II CM is 71%. The perception that MM is a more aggressive form of melanoma may be due to inherent differences in tumor progression or to the fact that mucosal regions have a richer blood supply and easier access to lymphatic drainage. Also, patients with MM tend to present 15 years later than those with CM; thus, age may contribute to the deleterious prognosis as well. Prognostic indicators for MM are slightly different than those for CM and include the clinical stage at presentation, tumor thickness greater than 5 mm, vascular invasion on histopathology, and the development of distant organ failure. The location of the primary tumor also has prognostic significance. Tumors in the nasal cavity fare better than those with either oral or pharyngeal involvement. In one study, 5-year survival rates were 30% and 0%, respectively. Oral melanomas have also been shown to have an increased incidence of nodal involvement.

**Treatment**

The standard treatment for MM is surgical excision with wide clear margins. The surgery depends upon the extent of the tumor, as well as its location in the head and neck. The goal of surgery is to obtain complete resection of the tumor with clear margins and thereby achieve local control. Patients in which local control cannot be achieved frequently develop distant metastases. It is often difficult to obtain disease-free margins in areas of the head and neck as many of the more dramatic resections would necessitate the sacrifice of important structures, such as the eye. The decision to undergo radical surgery should be tempered by the fact that patients with MM can develop distant metastases despite local control.

The role of radiation in the management of MM is controversial. Patients with sinonasal lesions are more likely to be treated with post-operative radiation due to the difficulty in obtaining a clear surgical excision in that region. However, the addition of radiation has not been shown to significantly improve local, regional nodal, or distant tumor control.

Neck dissection (removal of cervical lymph nodes) is indicated in patients presenting with evidence of cervical metastases. The role of elective management of the neck (i.e. neck dissection in the presence of no clinical or radiographic evidence of nodal metastases) is controversial. Given the higher rate of cervical metastases in oral cavity MM, an elective neck dissection (END) should be considered, although there is no evidence that END alters survival.

The benefit of systemic immunotherapy or chemotherapy has
α with DTIC has slightly better response rates but does not affect total survival. Systemic therapy should be considered in patients presenting with advanced disease (particularly as part of a clinical trial) once the risks and benefits are considered by the patient.

Epilogue
Mr. M was reviewed in a multidisciplinary clinic with a treatment plan for surgery followed by post-operative radiotherapy. He underwent a right radical neck dissection, a left selective neck dissection, a total laryngectomy and partial pharyngectomy. The lesion was exophytic and involved the right pharynx (Figure 5). Intra-operative frozen sections of margins were negative. His pharynx was reconstructed with a tubed anterolateral thigh fasciocutaneous free flap. Mr. M was left with a permanent tracheostomy and he communicates with a tracheoesophageal puncture.

References