ANATOMY

The skin is made of 2 main layers, the epidermis and dermis. The epidermis is composed of multiple layers. The stratum basale is the deepest layer. It is mitotically active with cells attached to each other by desmosomes. The basement membrane is attached to this layer by hemidesmosomes. Melanocytes live in this layer. The next superficial layer is the stratum spinosum, characterized by spiny processes on the keratinocytes. The next layer is the stratum granulosum, characterized by flattened cells with keratohyalin granules. The stratum corneum is the most superficial layer. This layer is devoid of nuclei and serves as a protective barrier. Other major cells of note that reside in the epidermis are Langerhans cells, a type of antigen presenting cell, and neuroendocrine cells which detect pressure and light touch.

The underlying basement membrane is made of 2 layers, a superficial lamina lucida and deeper lamina densa. The dermis is a thicker layer deep to the basement membrane. The main cell is the fibroblast. Collagen makes up 70% of the dermis with 85% of the collagen being type I. The dermis is made of 2 layers, the superficial papillary layer and then the deeper reticular layer.

The skin has predictable lymph drainage patterns much like the upper aerodigestive tract. Pathak et al. demonstrated the pattern of lymph drainage of melanoma in the head and neck prospectively. 92% of the 169 patients studied prospectively had correct prediction of their lymph node metastasis spread. The skin of the head and neck contains loss of surface area and there is a lack of a uniform system that clearly defines regions in the head and neck. In a retrospectively reviewed cohort of 209 patients, Vauterin et al. in 2005 divided the cutaneous head and neck primary sites (See slides 8-10).

CLINICAL EVALUATION

Skin cancer is the most common skin cancer. Cutaneous squamous cell carcinoma (cSCC) accounts for about 20-25% of non-melanoma skin cancer (NMSC), making it the second most
common behind basal cell carcinoma (BCC). The annual incidence in the USA ranges from 35-150 per 100,000 depending on geographical area. It is most common in Australia with an incidence of 300 per 100,000. The incidence of cSCC has been increasing yearly. This is thought to be because of the aging population, increased number of immunocompromised individuals, increasing ultraviolet radiation (UVR) secondary to fashion and social trends, use of tanning booths, and thinning of the ozone layer.

There are many risk factors for developing cSCC. Host and environmental risk factors include: UVR (both UVA and UVB), male sex, increasing age, Fitzpatrick grade I /II, proximity to the equator, exposure of ionizing radiation, immunosuppression, cigarette smoking, history of trauma or burns, exposure to the following substances: coal tar, creosote, arsenic, paraffin, mustard gas. Genetic and molecular factors include: xeroderma pigmentosum (XP), albinism, human papilloma virus (HPV), epidermodysplasia verruciformis, mutations in p53, p21, c-Ha-ras, K-ras.

Key historical questions that need to be asked are how long the lesion has been present, how it has changed, presence of other lesions, what is concerning to the patient about the lesion, pain, bleeding, parathesias. The presence of parathesias and formication may be a sign of perineural invasion. For the otolaryngologist, a standard head and neck exam should be performed. Pertaining to the skin exam, inspection and especially palpation of any suspicious lesions should be done. If any lesions are found, the size, depth, fixation, margins and presence of ulceration should be noted. A cranial nerve exam should be performed, focusing on trigeminal nerve and facial nerve branches. A neck exam should be done thoroughly looking for any lymphadenopathy in the neck and salivary glands. Dermatologists used a tool called the dermatoscope to help with diagnosis. This is a tool which uses LED lights and a polarized, magnified lens to detect certain features. If there is a suspicious lesion found on exam, a biopsy should be considered. A full thickness excisional biopsy should be performed as opposed to a shave biopsy, fine-needle aspiration, or partial thickness biopsy. Tumor depth, ulceration, mitotic rate, and neurovascular invasion are key findings that should be assessed on biopsy specimens. Imaging isn’t regularly obtained unless there is concern for advanced stages or aggressive nature. If palpable lymphadenopathy is present or neck disease is suspected, a computed tomography (CT) scan with contrast of the neck is recommended. This can give information about locoregional nodal staging. If there is any suspicion for underlying bony involvement, a CT of the maxillofacial area may be done. If there is any concern about the orbit or intracranial disease, a magnetic resonance imaging (MRI) scan should be obtained.

The differential diagnosis of a skin lesion is vast. Common benign lesions include actinic keratosis (AK), seborrheic keratosis, pseudoepitheliomatous hyperplasia, keratoacanthoma. The common malignant tumors that mimic cSCC include BCC, melanoma, and merkel cell carcinoma. Other mesenchymal neoplasms, adnexal neoplasms, lymphoid neoplasms are rare but ultimately biopsy can provide tissue diagnosis.

**SCREENING AND PREVENTION**

There is not a general consensus for skin cancer screening, but the American Academy of Dermatology gives yearly free screenings and the American Cancer Society recommends total skin
screening for adults over 20 years of age. Some recommend self screening exams and others recommend physician screens. Dermoscopy is a good screening tool to enhance the exam. There are other modalities including confocal scanning laser microscopy but are more for research purposes than everyday clinical practice. Some patients that should have more reason to get screened are the following: light hair and skin color, history of UVR exposure, history of ionizing radiation, history of AK or cSCC, genetic disposition, immunosuppression.

Immunosuppression is one of the most important risk factors for cSCC. The most common cause of increased incidence of cSCC is immunosuppression secondary to solid organ transplant recipients (OTR), lymphoma and leukemia, and human immunodeficiency virus (HIV). The increased risk can ranges from 65 to 250 times more than the normal population. In solid OTR, the risk of cSCC skyrockets as opposed the small increase in incidence of BCC. There is also a greater risk of recurrence and metastasis. 10-18% of cSCC in patients with Non-Hodgkin’s lymphoma or chronic lymphocytic leukemia can have nodal metastasis. Patients with HIV have about a 5 times increased risk; HIV patients’ increase in cSCC is proportional with the increased rate of BCC unlike solid OTRs.

The most important prevention method is decreasing exposure to UVR. Ways to do this is to wear protective clothing, avoiding the sun at peak hours and wearing sunscreen that blocks both UVA and UVB. SPF or sun protective factor is measure of UVB protection. Educating patients on the harms of tanning can also help. When patients have precursor lesions including AK or cSCC in situ, managing these lesions can prevent progression to cSCC. AK is a precursor lesion to cSCC that is very easily treated with most commonly cryotherapy. Other medical treatments of these lesions include, topical 5-fluorouracil, imiquimod, COX-2 inhibitors, oral isoretinoin, topical retinoids and photodynamic therapy (PDT). PDT is a therapy involving a photosensitizing agent such as 5-aminolevulinic acid or methyl aminolevulinic acid and a combination of light and oxygen to make radical oxygen species to treat these lesions.

CARCINOGENESIS

The keratinocyte is the cell that cSCC arises from. The precursor to cSCC is AK. These present as red to tan macules or scales on the skin. There is a 0.075-0.096% chance of malignant degeneration per year. Combined over 10-25 years, this risk has a cumulative 10-20% chance. SCC in situ also known as Bowen’s disease is a premalignant lesion that presents as an erythematous plaque, patch or papule and can have a 3% chance of development of invasive SCC. Invasive SCC usually presents as a large non-healing sore with central ulceration.

UVB, with a wavelength of 293 nm, is the key type of UVR that causes specific mutations in keratinocytes. There are 2 “signature mutations” that UVB creates in DNA: cyclobutane pyrimidine dimers and pyrimidine (6-4) pyrimidine photoproducts. During DNA replication, these mutations cause a miscode of either a single cytosine (C) to thymine (T) or a double CC to TT. 90% of human cSCC have these mutations in the p53 suppressor gene. Indirect DNA damage is also caused by reactive oxygen species by both UVB and UVA. UVR also plays a critical role in suppressing secondary immune reactions and suppressing memory response. It has been shown to suppress contact
hypersensitivity, Th1-driven immune reactions, induction of complement fixing antibodies, and immune response to cellular pathogens.

**HISTOPATHOLOGY (SEE SLIDE 41-50)**

Actinic keratosis is characterized by hyperkeratosis, a thickening of stratum corneum, and parakeratosis, retention of nuclei in the stratum corneum. There is an underlying proliferation of atypical basal keratinocytes between segments of follicular and eccrine ostia. Atypical keratinocytes demonstrate enlarged, hyperchromatic nuclei with pleomorphism. Atypical keratinocytes confined to basal and suprabasal layers but not all layers like SCIS. There are variants of AK including hyperplastic, pigmented, acantholytic, and lichenoid.

SCC is shows atypia of keratinocytes involving all layers of an acanthotic (hyperkeratosis) epidermis. Atypical cells confined to epidermis with intact BM. Cells may contain coarse keratohyaline granules in the cytoplasm. Common features include: mitotic figures, nuclear pleomorphism with vesicular or hyperchromatic nuclei, prominent nucleoli, randomly dispersed dyskeratotic (premature keratinization) cells.

cSCC shows atypical keratinocytes with invasion through the basement membrane and dermal invasion. Histologic grading is based on degree of keratinization and maturation of infiltrating tumor cells. Immunohistochemical markers specific for SCC include cytokeratin 5 and 6 and p63. In well differentiated cSCC, there are polyhedral shaped cells with intercellular bridges and abundant glassy, eosinophilic cytoplasm; Keratinization with parakeratotic material or “keratin pearls” is also present. In poorly differentiated SCC, there is minimal degree of keratinization, lacks keratin pearls, greater nuclear pleomorphism and also, infiltrates of lymphocytes, plasma cells, eosinophils.

There are multiple variants of cSCC. Adenoid or acantholytic SCC is more common in the head and neck of older males. It shows invasive lobules of SCC with acantholysis arranged in a tubular or alveolar-like pattern like glandular structures. There is a slightly higher rate of metastatic potential of 2% compared to 0.5% of standard invasive SCC. Spindle cell or sarcomatoid SCC occurs in the head and neck of older Caucasian males with prior sun or radiation exposure. There is invasive bundles of poorly differentiated, atypical, spindle-shaped cells with hyperchromatic, pleomorphic nuclei admixed with scattered, bizarre-shaped, giant cells. Spindle cell SCC is prone to perineural invasion (PNI), local recurrence, and regional metastasis. Desmoplastic SCC, commonly found on ear, is thicker with poorly differentiated features.

There is a 6 times greater risk of metastasis and 10 times greater risk of local recurrence versus non-desmoplastic lesions. Basosquamous carcinoma has features of BCC and SCC. There are malignant basal cells with peripheral palisading nuclei and aggregates of eosinophilic cytoplasm. There is a high rate of lymphatic and perineural invasion with frequent local recurrence and metastases. Verrucous carcinoma, associated with HPV 6, 11, 16, 18, is a low grade, well-differentiated squamous proliferation. PNI and metastasis are rare. Keratoacanthoma is a low-grade SCC with low malignant potential. It is nodular, circumscribed, keratin-filled, crateriform with
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abundant glassy, eosinophilic cytoplasm. Microabscesses can be present. These may grow very rapidly and regress spontaneously. It can be confused with invasive SCC.

STAGING AND PROGNOSIS

The staging of cSCC by the American Joint Committee on Cancer (AJCC) has evolved from the 6th edition in 2002 to the 7th edition in 2010. In the AJCC 6th edition for cSCC, the T stage was divided based on horizontal diameter with T4 invading deep extradermal structures (See slide 53). The N stage was just based on the presence of regional nodal metastasis, and the M stage was based on the presence of distant metastasis. The AJCC 7th edition made lots of changes in the T and N staging. The T stage was not based on horizontal diameter anymore; instead, the T stage was based on the presence of high-risk features. These features include: 2 mm or greater thickness, Clark level 4 or greater, PNI, locations involving the ear or non-hair bearing lip and poor differentiation. These features are more closely related to mortality. The new N stage adopted the traditional N stage for upper aerodigestive tract mucosal SCC. The updated N stage takes into account disease burden in the head and neck lymphatics. The M stage stayed the same (See slide 55-56).

This change in the T staging is based on a multitude of studies showing that survival relied more on these high-risk features rather than horizontal diameter. Brantsch et al in a study with 615 patients, showed that 16% of patients with cSCC of over 6 mm thickness had lymph node metastasis. In this same group, zero patients with cSCC of less than 2 mm thickness had lymph node metastasis. Kraus et al showed 33% of patients with cSCC with greater than 4 mm thickness accounted for over 80% of lesions with lymph node metastasis. Breuniger et al, in a study with 500 patients, showed that zero patients with cSCC less than 2 mm thickness had lymph node metastasis and 20% of patients with cSCC greater than 5 mm thickness had lymph node metastasis. Goepfert reported tumors with PNI had 47% local recurrence rate and 34.8% metastasis rate. Other factors that are not accounted for are the status of being a recurrent lesion and immunosuppression, both of which decrease favorable outcomes.

cSCC has a low rate of metastasis of about 3-5%. Tertiary centers frequently report higher numbers of metastatic tumors at about 10-15%. The parotid gland is most frequent site of metastasis. 70-80% out of the total patients with metastasis have both parotid and cervical lymph node metastasis as opposed to just 20-30% have only cervical lymph node metastasis. Over 70% of metastasis occur within the first year of treatment of the primary lesion. The N staging from the 6th to the 7th edition of the AJCC Cancer Staging has changed significantly. O’Brien et al in 2002 formulated their own staging system with a parotid (P) and neck (N) 2-tier staging of locoregional metastasis. This system was studied extensively and a multi-institute trial showed that there was a significant difference in overall survival in advanced (P2 and P3) disease versus early (P1) disease (see slide 62).

The prognosis of cSCC is usually good with the majority cured with single modality therapy. About 10% develop recurrence and 5% develop nodal spread. Prognosis decreases with the high risk factors mentioned previously. The Westmead Hospital group conducted a study on prognostic factors in cSCC. They weighed 4 factors including immunosuppression, treatment modality, extracapsular
spread (ECS) and presence of positive margins. The 5-year survival for the patients measured with this system was predictable based on the range of scores they fell into (see slide 64).

**TREATMENT**

Treatment of early disease is usually cured with single modality surgery. Wide local excision is the most common approach used. 4 mm margins will give >95% cure rate for low risk lesions. The National Comprehensive Cancer Network (NCCN) recommends 4-6 mm surgical margins. Intraoperative frozen sectioning can be done for more prompt pathological diagnosis of a cure. The pathologist uses a technique called bread-loafing to cut the sections. In the facial area, there is not as much real estate to get larger margins. Moh’s surgery was developed in 1983 where the surgeon serves as the pathologist also. The tumor is excised, margins are examined with cryostat and hematoxylin and eosin (H&E) staining. Positive margins are marked and targeted for limited excision in that area. The tumor is mapped using a serial “pie pan” method with the entire margin being examined. Moh’s surgeons report up to a 99% cure rate. Reconstruction may be needed after primary lesion excision with the principles of the reconstructive ladder taken into account, which is another topic of discussion. Reconstruction may be delayed to confirm margins to be negative.

When the tumor demonstrates aggressive features, the lymph node basins need attention. The N0 neck is a controversial topic. Most cSCC will not metastasize. Aggressive features include: recurrent lesions, >2 cm in size, rapid growth, near eyes or lips, poor differentiation, desmoplastic and spindle cell subtypes of SCC, invasion into subcutaneous tissue, PNI, lymphovascular invasion. Options include watchful waiting, sentinel lymph node biopsy (SLNB), radiation therapy and chemotherapy. Elective neck dissection in a N0 neck is not usually recommended. However, when there is palpable lymphadenopathy or radiographical evidence of lymph node spread, therapeutic neck dissection is recommended in patients who are able to undergo surgery. Different areas affected by the primary lesion generally merit neck dissection in specific basins. Lesions superior and anterior to half of the external auditory canal (EAC) warrant superficial parotidectomy and lymphadenectomy of levels II, III and IV. Lesions posterior to this generally include level V in addition to levels II through IV. Lesions involving the perioral and midface area include level I also.

SLNB is not a mainstay of treatment of cSCC as it is for malignant melanoma. SLNB has its advantages over neck dissection as it is less invasive and can avoid the morbidity of neck dissections. The benefits over the disadvantage of a false-negative must be outweighed. Ahmed et al performed a systematic review of SLNB in head and neck cSCC in 2013. A total of 73 patients from 11 publications were included. At least 1 sentinel lymph node was identified in 100% of the patients with 13.5% having a disease-positive node. 4.8% failed regionally after SLNB. These pooled data led to a 77% sensitivity, 100% specificity and 95.2% negative predictive value (NPV). This NPV mirrored the rates of SLNB in melanoma.

When the parotid will be surgically addressed, superficial parotidectomy alone is recommended. No evidence suggests that total parotidectomy is superior to superficial parotidectomy in locoregional control. Superficial parotidectomy with adjuvant XRT is adequate for metastasis to parotid with
microscopic residual disease involving facial nerve and normal facial function. Weakness of facial nerve or temporal bone invasion requires radical parotidectomy with sacrifice of involved branches and likely temporal bone resection.

Radiation therapy (XRT) is commonly used for advanced disease as adjuvant therapy. XRT alone is usually not recommended. However, in poor surgical candidates such as elderly patients with multiple medical morbidities. Indications for XRT as an adjuvant therapy is usually the following: > 4 cm or recurrent tumors, aggressive histology, PNI, close or positive margins, multiple positive nodes, and ECS. XRT improves local control, disease-specific survival and overall survival in cases of PNI. General recommendations for the parotid and neck include the above indications and clinically or radiographically evident parotid and cervical disease. In P+ but N0 disease, irradiate entire ipsilateral neck for high risk of subclinical disease.

Chemotherapy is usually combined with XRT as adjuvant therapy in advanced disease. Candidates includes ones with positive margins, multiple positive nodes and ECS. Most data for cisplatin, carboplatin and cetuximab is extrapolated from mucosa SCC of the upper aerodigestive tract. There is promising data for the role of chemotherapy in cSCC. Tanvetyanon et al. performed a retrospective cohort study with patients with stage III and IV cSCC with high risk features of multiple positive lymph nodes, positive margins or ECS. Out of the 61 patients studied, 27 had adjuvant XRT and 34 had adjuvant XRT with concurrent chemotherapy (cisplatin or carboplatin) and medial recurrence free survivals were and 15.4 and 40.3 months respectively. However, no difference in overall survival was observed.

Targeted therapies are ones that interfere with specific molecules involved in cancer cell growth and survival. These therapies have come to the forefront of research for cancer. The 2 related to SCC are epidermal growth factor receptor (EGFR) inhibition and mammalian target of rapamycin (mTOR) inhibition. EGFR is overexpressed in epithelium-derived neoplasms and overexpression is associated with worse prognosis in mucosal SCC. Cetuximab is one of these drugs that is used in mucosal head and neck SCC. Other EGFR tyrosine kinase inhibitors are gefitinib and erlotinib. Lewis et al performed a phase II study of gefitinib as neoadjuvant chemotherapy for aggressive cSCC in the head and neck. 22 patients were evaluated for response with 18.2% with a complete response and 27.3% with a partial response. The mTOR inhibitor sirolimus has been studied as a de novo therapy for OTRs. The first prospective trial of this therapy was done in renal transplant patients. Out of the 16 patients in the sirolimus group, only 1 developed a new skin cancer and in the control group of 17 patients, 8 developed a new skin cancer. Benefits of this therapy included delayed development of premalignancies, regression of pre-existing lesions, and deceleration of incidence of new skin cancers.

CONCLUSION

As the incidence of cSCC is rising, the responsibility is with the physician to help prevent and cure this treatable disease. As an otolaryngologist, a thorough skin exam of the head & neck should be done as part of the H&N exam. A relationship with a dermatologist is important as skin cancers are increasing in incidence and surveillance is important. Primary surgical excision (with negative
margins) usually provides cure as a single modality. The physician must be cognizant of features of aggressive cSCC which can metastasize locoregionally. Addressing the lymph node basins while considering other modalities including XRT and chemotherapy must be taken into account to prolong a disease free life of the patient. A tumor board with radiation oncologists and medical oncologists is vital in the care of a patient with aggressive cSCC. SLNB has promising data but more research needs to be done before it becomes standard of care.

BIBLIOGRAPHY